Martindale

The Complete Drug Reference

Thirty-eighth Edition

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VOL A_2

Pharmaceutical Press

Bronchodilators and Anti-asthma Drugs

This chapter includes many of those drugs used for their bronchodilator or anti-inflammatory properties in the management of reversible airways obstruction, such as asthma and chronic obstructive pulmonary disease.

The main bronchodilators discussed in this chapter are the sympathomimetic beta agonists (stimulants of beta-adrenoceptors), and the xanthines (mainly theophylline). The antimuscarinic bronchodilators ipratropium, oxitropium, and tiotropium are also included. The major class of anti-inflammatory drugs, the corticosteroids, are discussed separately, on p. 1597.1; other drugs considered to act on the processes of airway inflammation and which are included in this section include sodium cromoglicate and its analogues, and the various drugs that act on leukotriene synthesis and receptor binding, on platelet-activating factor (PAF), or on other aspects of the inflammatory cascade.

Anti-asthma Drug Groups

Antimuscarinics

The parasympathetic nervous system plays a role in the regulation of bronchomotor tone, and antimuscarinic drugs have bronchodilator properties. The quaternary ammonium compounds aclidinium bromide, glycopyrronium bromide, ipratropium bromide, oxitropium bromide, and tiotropium bromide are the antimuscarinic (anticholinergic) bronchodilators in current use; as well as reduced CNS effects they have less effect on mucociliary clearance than drugs such as atropine, which can produce accumulation of viscid lower airway secretions and a risk of mucus plugging in these patients. An antimuscarinic may be the bronchodilator of choice in the management of chronic obstructive pulmonary disease. In patients with asthma they are usually reserved for use in life-threatening acute asthma exacerbations.

Described in this chapter are

- Aclidinium, p. 1201.1
- Ipratropium, p. 1211.3
- Oxitropium, p. 1218.1
- Tiotropium, p. 1238.1

Beta agonists

The sympathetic nervous system plays a role in the regulation of bronchomotor tone and $beta_2$-adrenoceptors in bronchial smooth muscle produce bronchodilatation when stimulated. Short-acting selective agonists of $beta_2$-adrenoceptors ($beta_2$ agonists; $beta_2$ stimulants), of which salbutamol is the paradigmatic example, are therefore first-line drugs for the relief of asthma symptoms. They are also widely used in the management of chronic obstructive pulmonary disease, although antimuscarinic bronchodilators may be preferred or used in addition. Long-acting $beta_2$ agonists are used in asthma in patients also requiring anti-inflammatory therapy. They may also be used in some patients with chronic obstructive pulmonary disease.

Described in this chapter are

- Arformoterol, p. 1202.3
- Bambuterol, p. 1203.1
- Bitolterol, p. 1203.2
- Carmoterol, p. 1207.1
- Clenbuterol, p. 1207.2
- Fenoterol, p. 1208.2
- Formoterol, p. 1209.2
- Hexoprenaline, p. 1211.1
- Indacaterol, p. 1211.2
- Isoetarine, p. 1213.2
- Levosalbutamol, p. 1213.3
- Orciprenaline, p. 1217.3
- Pirbuterol, p. 1218.3
- Procaterol, p. 1219.1
- Reproterol, p. 1219.2
- Salbutamol, p. 1220.2
- Salmeterol, p. 1224.1
- Terbutaline, p. 1228.1
- Tretoquinol, p. 1239.1
- Tulobuterol, p. 1239.2
- Vilanterol, p. 1239.3

Corticosteroids

Corticosteroids are widely used for their anti-inflammatory (glucocorticoid) properties in the management of asthma, and may be beneficial in some patients with chronic obstructive pulmonary disease. Because of the potential adverse effects associated with prolonged systemic corticosteroid therapy, inhalation of corticosteroids with reduced systemic activity is preferred; oral corticosteroids are generally only used in short courses, and at relatively low doses, to gain control of the disease. The actions and uses of the corticosteroids are discussed in much greater detail in the section beginning on p. 1597.1.

Leukotriene inhibitors and antagonists

Leukotrienes appear to play an important role in the inflammatory process of asthma, and some drugs may modify or inhibit this action. Leukotriene synthesis may be prevented by blockade of the enzyme 5-lipoxygenase with inhibitors such as zileuton. Alternatively, leukotriene receptor antagonists such as zafirlukast may be used to block specific receptors (usually those of leukotriene D_4) and prevent their activation. These anti-leukotriene drugs have a role in the prophylactic management of asthma as an alternative when inhaled corticosteroids cannot be used in mild asthma, and as add-on therapy in more severe asthma.

Described in this chapter are

- Amlexanox, p. 1202.2
- Ibudilast, p. 1211.2
- Montelukast, p. 1214.3
- Pemirolast, p. 1218.2
- Pranlukast, p. 1218.3
- Tipelukast, p. 1239.1
- Zafirlukast, p. 1239.3
- Zileuton, p. 1240.3

Mast cell stabilisers

The role of the mast cell in starting an inflammatory cascade has long been recognised as important, and the best established of the mast cell stabilisers are sodium cromoglicate and nedocromil sodium. These compounds inhibit mast cell degranulation in response to antigens or other stimuli, and hence prevent the release of histamine, leukotrienes, and other inflammatory mediators. They are usually well tolerated and guidelines for the treatment of asthma mention their use for prophylactic therapy as an alternative, or a supplement, to corticosteroids, particularly in children. However, it is generally considered that the corticosteroids are more effective.

Described in this chapter are

- Amlexanox, p. 1202.2
- Nedocromil, p. 1216.2
- Pemirolast, p. 1218.2
- Repirinast, p. 1219.2
- Sodium Cromoglicate, p. 1225.3
- Tranilast, p. 1239.1

Xanthines

Xanthines are drugs with complex actions that include, in varying degrees, relaxation of bronchial smooth muscle and relief of bronchospasm, stimulant effects on respiration, and anti-inflammatory effects. Theophylline and its derivatives have long been used for their bronchodilator properties in the management of asthma and chronic obstructive pulmonary disease, but the narrow therapeutic range and the propensity for interactions with other drugs make theophylline a difficult drug to use, and it tends to be reserved for combination therapy in patients who cannot be managed with other bronchodilators (such as the $beta_2$ agonists) plus inhaled corticosteroids.

Described in this chapter are

- Acefylline piperazine, p. 1200.3
- Ambroxol acefyllinate, p. 1201.2
- Aminophylline, p. 1201.2
- Bamifylline, p. 1203.2
- Bufylline, p. 1203.3
- Caffeine, p. 1203.3
- Choline Theophyllinate, p. 1207.1
- Diprophylline, p. 1207.3
- Doxofylline, p. 1208.1
- Etamiphylline Camsilate, p. 1208.2
- Etofylline, p. 1208.2
- Heptaminol Acefyllinate, p. 1210.3
- Proxyphylline, p. 1219.2
- Theobromine, p. 1229.2
- Theophylline, p. 1229.3

Management of Reversible Airways Obstruction

Asthma

Asthma is a chronic inflammatory disease in which the patient has episodes of reversible airways obstruction due to bronchial hyperresponsiveness. It is a common disorder, the prevalence of which has increased sharply over the last 40 years, particularly in children, with prevalence greater than 30% in some areas. More than 10% of the population in developed countries are affected. Rates are increasing in developing countries as they become more westernised,[1] and global differences in prevalence appear to be lessening.[2] It has been suggested that asthma is probably not one illness, but a collection of different phenotypes which meet the criteria for clinical diagnosis of asthma.[3,4] Although there is no clear definition of the asthma phenotype, 3 categories have been suggested: clinical phenotypes such as severity-defined or defined by age at onset, trigger-related phenotypes such as allergy-or aspirin-induced asthma, and inflammatory phenotypes such as eosinophilic asthma.[4] Current guidelines classify by severity according to the clinical features present before treatment.[5-7] Asthma may be described as extrinsic when it is associated with exposure to a specific allergen such as pollen or house-dust mite, or to a non-specific stimulus such as a chemical irritant or exercise. It may be described as intrinsic when no external precipitating factor is identifiable.

The aetiology of asthma is poorly understood, but both genetic and environmental factors are believed to contribute to development and progression of the disease.[1,4,9]

Resistance to airflow in asthma is increased by a number of abnormalities, including contraction of the airway smooth muscle, the presence of excessive secretions within the airway lumen, and inflammatory cell infiltration. The inflammation in chronic asthma causes remodelling, found as shedding and thickening of the airway epithelium, and hypertrophy and hyperplasia of smooth muscle.[8,9] Airway remodelling or thickening may be important in more severe disease and can result in relatively irreversible narrowing of the airways.[7]

The principal symptoms of asthma are wheezing, dyspnoea (breathlessness), chest tightness, and cough, and these symptoms tend to be variable, intermittent, worse at night or early morning, and provoked by particular triggers. In an acute attack, the respiratory rate is rapid and tachycardia is common.[5-7] The peak expiratory flow (PEF) and forced expiratory volume in the first second (FEV_1) are decreased in asthma, and in a severe asthmatic attack the PEF is generally less than 50% of predicted values. Life-threatening features include exhaustion, cyanosis, bradycardia, hypotension, confusion, and coma.[5-7]

Management of asthma. As asthma is a chronic disease, management involves prophylactic measures to reduce inflammation and airway resistance and to maintain airflow, as well as specific regimens for the treatment of acute attacks. **Measurements** of lung function play an important part in determining treatment and patients are encouraged to monitor their own disease by using a simple peak flow meter to measure PEF;[5-7] spirometry is used to measure airflow limitation and reversibility in hospitals and surgeries.[5-7] Use of exhaled nitric oxide has been investigated to monitor disease control with corticosteroids;[10] however, an asthma treatment strategy using exhaled nitric oxide did not result in a large reduction in exacerbations or less use of inhaled corticosteroids.[11]

Drug therapy is preferably given by **inhalation** to deliver the drugs directly to the desired site of action. This produces higher local concentrations and permits smaller doses than would be required orally, with a consequent reduction in adverse effects. Systematic reviews[12-14] have found that hand-held inhaler devices including pressurised metered-dose inhalers (MDIs), dry powder inhalers, and breath actuated pressurised MDIs, are generally equally effective for the delivery of short-acting $beta_2$ agonists and corticosteroids in stable asthma. Choice of inhaler should be individualised, especially in children, taking into account ease of use, safety, and convenience.[6,7,14] Differences in drug delivery exist between inhaler devices and this should be considered when substituting one device for another.[7]

Spacer devices can be fitted to some MDIs to act as reservoirs for the drug to make it easier for the patient to inhale each dose correctly. Use of MDIs with spacer devices produce outcomes which are at least equivalent to nebuliser therapy.[14,15] Nebulisers tend to be reserved for patients who are unable or unwilling to use these devices, although the choice of spacer and method of use may substantially affect drug delivery.[5,16] Use of a spacer device for the inhalation of high doses of corticosteroids reduces oropharyngeal deposition, systemic absorption, and adverse effects.[5,7] Specially adapted or modified inhalation devices, as well as spacer devices, are also available to enable children to achieve a correct technique when using inhaled drug therapy, but alternative routes of delivery such as oral dosage or nebulisation may be necessary for some infants and small children.[16] Frequent intermittent or continuous nebulisation of short-acting $beta_2$ agonists are both effective in patients with severe bronchoconstriction.[14]

The standard **drugs** used in the management of asthma are the $beta_2$ agonists and corticosteroids.[5-7]

$Beta_2$ agonists relax the bronchial smooth muscle to produce bronchodilatation by selectively stimulating $beta_2$-

adrenergic receptors. Short-acting selective beta$_2$ agonists such as salbutamol or terbutaline are the initial drugs of choice for use as required to relieve acute bronchospasm; if inhaled, they can have an almost immediate bronchodilating effect. Regular use of beta$_2$ agonists is mainly restricted to long-acting beta$_2$ agonists such as salmeterol xinafoate in patients also requiring anti-inflammatory prophylactic treatment; a short-acting beta$_2$ agonist should still be used as required.[5-7]

Corticosteroids are the most effective preventer therapy available for the management of asthma.[17] They are used for their anti-inflammatory properties and to reduce bronchial hyperresponsiveness; they must be taken regularly to achieve maximum benefit. Corticosteroid therapy is recommended both for acute attacks and chronic asthma prophylaxis. Meta-analysis suggests that systemic corticosteroids speed the resolution of exacerbations and reduce the rate of relapse.[18,19] It has also been suggested that inhaled corticosteroids may be of benefit in acute asthma if multiple doses are inhaled at intervals of less than 30 minutes, over a 90 to 120-minute period.[20] In chronic asthma, regular inhaled corticosteroids are one of the cornerstones of management. Combining inhaled corticosteroids with long-acting beta$_2$ agonists may have synergistic benefits;[17,21,22] such a combination is more effective than combining inhaled corticosteroids with anti-leukotriene drugs.[23] The use of an inhaled corticosteroid, budesonide, and a rapid and long-acting beta$_2$ agonist, formoterol, in a combined inhaler as both regular maintenance therapy and as a reliever when required, has been studied.[24] Giving additional corticosteroid with each reliever inhalation in response to symptoms could be expected to provide improved control of airway inflammation,[25] and reductions in the rate of exacerbations have been reported[26,27] with relatively lower doses of inhaled corticosteroid in patients with uncontrolled persistent asthma, compared with more conventional treatment regimens using a beta$_2$ agonist as a reliever. While the place of budesonide/formoterol maintenance and reliever therapy in the management of asthma is not yet clearly defined,[25] some guidelines[6,7] include this regimen (referred to by the manufacturer, *AstraZeneca*, as Symbicort Maintenance and Reliever Therapy, or SMART) as an option for adults at Step 3 (see below).

Exercise-induced bronchoconstriction is also reduced in both adults and children by regular use of inhaled corticosteroids.[28]

Various studies have examined the role that inhaled corticosteroids might play in modifying the development of asthma in symptomatic children.[29-31] Although the short-term therapeutic efficacy varied between studies, possibly due to the differing lengths of treatment and study populations used, in all 3 studies the long-term clinical and functional outcomes did not differ in children treated with inhaled corticosteroids compared with placebo.

Xanthines such as aminophylline or theophylline may be given for their bronchodilating properties although there is evidence that the long-acting beta$_2$ agonist salmeterol produces a greater improvement in lung function, reduces the need for rescue short-acting beta$_2$ agonists, and has fewer adverse effects compared with theophylline.[32] There is disagreement about adding xanthine treatment to beta$_2$ agonists for the management of acute severe asthma (see below).

Inhaled *antimuscarinics* such as ipratropium bromide or oxitropium bromide, used with beta$_2$ agonists, are given in acute asthma; a systematic review[33] found that inhaled multiple doses of antimuscarinic reduced hospital admissions and improved lung function tests compared with beta$_2$ agonists alone.

Cromoglicate or nedocromil may be used as an alternative to corticosteroids for the prophylaxis of less severe asthma or combined with other therapy. *Anti-leukotrienes* such as the leukotriene receptor antagonist zafirlukast and the leukotriene inhibitor zileuton are another alternative or adjunct to inhaled corticosteroids. When used with inhaled corticosteroids, anti-leukotrienes bring modest improvements in lung function compared with inhaled corticosteroids alone.[34] They may also be useful in exercise-induced bronchoconstriction.[5-7] The anti-IgE monoclonal antibody *omalizumab*[17,35] is available for use in selected patients with allergen-induced asthma. A systematic review of omalizumab,[36] as adjunctive therapy to corticosteroids, found that treatment led to a reduction, and in some cases, withdrawal of regular inhaled corticosteroid, as well as a reduction in asthma exacerbations; longer term evaluation of adverse effects, direct comparison with inhaled corticosteroids, and assessment in children is needed.

CHRONIC ASTHMA

Advice for patients with chronic asthma includes avoidance of smoking, of allergens such as pollen, and of bronchoconstricting drugs such as beta blockers. Patients who have had asthma induced by aspirin and NSAIDs should also avoid these drugs. Skin testing to determine allergen sensitivity may be advisable.[5-7] US guidelines[5] suggest consideration of immunotherapy to desensitise patients with poorly controlled disease unavoidably exposed to a precipitating allergen. Although there is increasing evidence of benefit from such treatment[37] the size of the benefit overall remains somewhat uncertain, and the potential adverse effects make it controversial (see under Allergen Immunotherapy, p. 2435.1). UK guidelines[6] consider that although there is evidence of benefit from immunotherapy when compared with placebo, comparative studies with other asthma treatments are needed.

Gastro-oesophageal reflux has been suggested as another exacerbating factor;[38] symptoms of gastro-oesophageal reflux disease are about one and a half times more common among individuals with asthma than the general population,[39] although the exact nature of the association remains unclear. A 2003 systematic review of acid suppressive therapy concluded that it did not benefit asthma in most patients;[40] more recent studies on the subject support this view,[41,42] although one did note reduced exacerbations and an improvement in the asthma quality of life in patients given lansoprazole compared with placebo.[42]

Guidelines for drug therapy of chronic asthma have been issued in many countries including Australia,[43] Canada,[44,45] the UK,[6] and the USA,[5] and by the Global Initiative for Asthma (GINA).[7] Guidelines specifically for the management of childhood asthma have been issued by The European Pediatric Asthma Group.[46] In general, guidelines advocate a stepwise approach to treatment. Initial control is achieved with the early use of anti-inflammatory drugs at doses most appropriate for the severity of disease. In mild to moderate asthma, starting inhaled corticosteroids at very high doses and stepping down confers no benefit,[47,48] and relatively low initial doses are recommended.[5-7]

Guidelines vary slightly in their definition of low, moderate and high inhaled **corticosteroid doses**—for the definitions of these terms in UK, US, and global asthma guidelines see Asthma, under Choice of Corticosteroid, p. 1600.3.

In adults and older children

The *UK* recommendations for adults and children over 5 years of age with chronic asthma are as follows:

- Step 1; mild intermittent asthma
  Patients requiring only occasional relief from symptoms may be adequately managed with an inhaled short-acting beta$_2$ agonist such as salbutamol or terbutaline taken when needed.
- Step 2; regular preventer therapy
  Regular inhaled corticosteroids may be added at an appropriate starting dose for the severity of the disease if symptoms are present or an inhaled beta$_2$agonist is required three times a week or more, or if symptoms wake the patient from sleep one night a week. Patients who have had an exacerbation of asthma requiring oral corticosteroids in the last 2 years should also be considered for regular inhaled corticosteroids. *Alternatives* are cromoglicate or nedocromil, leukotriene receptor antagonists, or modified-release oral theophylline, but these are less effective.
- Step 3; initial add-on therapy
  If adequate control is not achieved, the preferred treatment is to supplement low-dose inhaled corticosteroids with a long-acting inhaled beta$_2$ agonist such as salmeterol xinafoate. If there is only suboptimal response, the long-acting beta$_2$ agonist is continued and inhaled corticosteroid increased to a moderate dose. If there is no response to a long-acting beta$_2$ agonist, it should be stopped and inhaled corticosteroid increased to a moderate dose; if control is still inadequate addition of another drug such as a leukotriene receptor antagonist or modified-release oral theophylline should be considered.
- Step 4; persistent poor control
  For patients with persistent poor control of asthma despite use of inhaled moderate-dose corticosteroids and an additional drug (usually a long-acting inhaled beta$_2$ agonist), increasing the inhaled corticosteroid to a high dose should be considered. Patients over 12 years of age may alternatively benefit from addition of either a leukotriene receptor antagonist, modified-release oral theophylline, or an oral modified-release beta$_2$ agonist. If a trial of a particular treatment option is ineffective, the drug is stopped (or in the case of an increased dose of inhaled corticosteroid, reduced).
- Step 5; continuous or frequent use of oral corticosteroids
  If further control is needed, then an oral corticosteroid such as prednisolone may also be given in single daily doses at the lowest dose providing adequate control. High-dose inhaled corticosteroids should also be maintained. Other treatments may be considered to minimise the use of corticosteroid tablets, such as a 6-week trial of treatment with long-acting beta$_2$ agonists, leukotriene receptor antagonists, or theophylline. If a trial of a particular treatment option is not effective, the drug is stopped. When other treatments have proved unsuccessful in patients over 12 years of age, a 3-month trial of immunomodulators such as methotrexate, ciclosporin, and oral gold may be considered for their anti-inflammatory, immunosuppressant, and corticosteroid-sparing properties: their use must be balanced against their potentially serious adverse effects. Referral for specialist care is advised for all patients at this step

The *US* recommendations for chronic asthma management in adults and children over 5 years are:

- Step 1
  A short-acting inhaled beta$_2$ agonist is recommended, taken as required to relieve symptoms.
- Step 2
  As in UK guidelines, if regular controller therapy is needed, then a low-dose inhaled corticosteroid is the preferred treatment. Other alternatives include cromoglicate, nedocromil, a leukotriene receptor antagonist, and theophylline.
- Step 3
  The preferred treatment for patients over 12 years who are not controlled with low-dose inhaled corticosteroids, is either addition of a long-acting inhaled beta$_2$ agonist or increasing the inhaled corticosteroid to a moderate dose. In children aged 5 to 12 years either a leukotriene receptor antagonist or modified-release oral theophylline are equally acceptable treatment options in place of a long-acting inhaled beta$_2$ agonist; however, they are secondary options for patients 12 years and over, along with the leukotriene inhibitor zileuton.
- Step 4
  An increase in the inhaled corticosteroid to a moderate dose is recommended in patients not controlled by Step 3. A long-acting inhaled beta$_2$ agonist is the preferred addition to this; alternatives include either a leukotriene receptor antagonist or modified-release theophylline, or in patients 12 years and over, the leukotriene inhibitor zileuton.
- Step 5
  High-dose inhaled corticosteroid in addition to a long-acting inhaled beta$_2$ agonist is the preferred treatment for patients on Step 5. Alternatively, children aged 5 to 11 years may benefit from either a leukotriene receptor antagonist or modified-release theophylline in place of a long-acting inhaled beta$_2$ agonist. Omalizumab may be considered for patients 12 years and over who have allergies.
- Step 6
  As in Step 5 of the UK guidelines above, an oral corticosteroid may be added to the inhaled high-dose corticosteroid and long-acting beta$_2$ agonist. Alternatively, children aged 5 to 11 years may benefit from either a leukotriene receptor antagonist or modified-release theophylline in place of a long-acting beta$_2$ agonist. Omalizumab may be considered for patients 12 years and over who have allergies.

Consultation with an asthma specialist is recommended from Step 4.

Global guidelines for the management of asthma in adults and children aged over 5 years recommend:

- Step 1, as for UK guidelines, a short-acting inhaled beta$_2$ agonist is the recommended reliever treatment. An inhaled antimuscarinic such as ipratropium, a short-acting oral beta$_2$ agonist, or immediate-release theophylline may be considered as alternatives.
- Step 2; reliever medication plus single controller
  As in UK guidelines a low-dose inhaled corticosteroid is the preferred treatment; anti-leukotrienes are considered an appropriate alternative.
- Step 3; reliever medication plus one or two controllers
  A low-dose inhaled corticosteroid with a long-acting inhaled beta$_2$ agonist (the preferred option in adolescents and adults), or else increasing the inhaled corticosteroid to a moderate (the preferred option in children over 5 years) or high dose should be considered. Alternative treatment options for all ages are a combination of low-dose inhaled corticosteroid with either an anti-leukotriene or modified-release theophylline.
- Step 4; reliever medication plus two or more controllers
  The preferred treatment at Step 4 is to combine a moderate or high dose of an inhaled corticosteroid with a long-acting inhaled beta$_2$ agonist. Addition of either an anti-leukotriene or modified-release theophylline may also provide benefit. High-dose inhaled corticosteroids should be reserved for patients who are not controlled by moderate doses combined with a long-acting inhaled beta$_2$ agonist and/or an additional controller; they are recommended only on a trial basis for 3 to 6 months.
- Step 5
  As in Step 5 of UK guidelines and Step 6 of US guidelines, an oral corticosteroid may be considered in addition to another controller medication. Omalizumab is an option for patients with allergic asthma who remain uncontrolled on combinations of other controllers including a high dose of inhaled or oral corticosteroids.

Referral to an asthma specialist is recommended from Step 4.

A short 'rescue' course of oral prednisolone may also be needed at any time and at any step for an acute exacerbation.

In children under 5 years of age

Recommendations for the management of chronic asthma in children under 5 years of age have also been issued in the UK[6] and USA,[5] and by GINA.[49] There is limited information available for this age group, however, and some recommendations are based on extrapolations from studies in older children and adults. These guidelines also provide a stepwise approach to management. UK recommendations for management of chronic asthma in children under 5 years of age are as follows:

- Step 1; mild intermittent asthma
  Inhaled short-acting $beta_2$ agonist as required.
- Step 2; regular preventer therapy
  A low-dose inhaled corticosteroid may be added if control is poor. If a corticosteroid cannot be used, an alternative to be considered is a leukotriene receptor antagonist.
- Step 3; initial add-on therapy
  Addition of a leukotriene receptor antagonist may be considered if control is poor in those already taking inhaled corticosteroids. In those taking a leukotriene receptor antagonist alone, addition of a low-dose inhaled corticosteroid should be reconsidered. Children under 2 years and those who have persistent poor control on Step 3, may be referred to a respiratory paediatrician (Step 4).

Global guidelines are similar to those in the UK.

The US makes the following recommendations for the management of chronic asthma in children under 5 years of age:

- Step 1, as for UK guidelines above.
- Step 2
  As in UK guidelines, addition of a low-dose inhaled corticosteroid is recommended. Alternative, but less preferable, treatments include the leukotriene receptor antagonist montelukast, and cromoglicate.
- Step 3
  An increase in the inhaled corticosteroid to moderate-dose should be considered.
- Step 4
  In addition to moderate-dose inhaled corticosteroid, consider either a long-acting inhaled $beta_2$ agonist or montelukast.
- Step 5
  The inhaled corticosteroid is increased to high-dose, in addition to either a long-acting $beta_2$ agonist or montelukast.
- Step 6
  In patients who remain uncontrolled, an oral corticosteroid may be added.

Consultation with an asthma specialist is recommended from step 4 onwards.

A short course of oral prednisolone may also be needed for acute exacerbations of asthma.

For all ages, treatment should be regularly reviewed and reduced in a stepwise manner if asthma is well controlled. Patients should be maintained on the lowest possible dose of inhaled corticosteroid; a reduction in dose every 3 months should be considered, decreasing the dose by about 25 to 50% each time.[6,7]

ACUTE SEVERE ASTHMA

An acute attack of severe asthma (status asthmaticus) is potentially life-threatening and treatment should be instituted as soon as possible. UK guidelines[6] provide guidance on the assessment and initial treatment of exacerbations of asthma in general practice and in the accident and emergency department. Patients with any features of a life-threatening attack, or a severe attack persisting after initial treatment with high-dose short-acting $beta_2$ agonist and an oral corticosteroid, require admission to hospital.

In adults.

Guidelines suggest the following regimen for the hospital management of adults:[6]

- Initially, oxygen should be given to all hypoxaemic patients with acute severe or life-threatening asthma to maintain an oxygen saturation of 94 to 98%.
- High doses of inhaled short-acting $beta_2$ agonists (salbutamol 5 mg or terbutaline 10 mg) and antimuscarinic (ipratropium bromide 500 micrograms) should be given via a nebuliser with oxygen, or compressed air if oxygen is not available; if neither of these is available, multiple actuations of a MDI into a large volume spacer device may be used.
- High doses of systemic corticosteroids are also required: for example, oral prednisolone 40 to 50 mg daily or intravenous hydrocortisone 100 mg every 6 hours. Alternatively, intramuscular methylprednisolone 160 mg may be given instead of a course of oral prednisolone.
- A single intravenous dose of magnesium sulfate (1.2 to 2 g infused over 20 minutes) may be considered at this stage if life-threatening features are still present. The role of magnesium sulfate has not been fully established, although there is some evidence that it has bronchodilator effects in adults. A meta-analysis concluded that its routine use was not justified, but that it appears to be safe and beneficial in some patients with severe exacerbations.[50]
- Subsequently, oxygen therapy should be continued, as should corticosteroid treatment with oral prednisolone or intravenous hydrocortisone.
- Nebulised $beta_2$ agonists and ipratropium bromide may be given every 4 to 6 hours. If the patient's condition has not improved after 15 to 30 minutes, the nebulised $beta_2$ agonist should be given more frequently (up to every 15 minutes, or in a continuous regimen such as salbutamol 10 mg hourly).
- If progress is still unsatisfactory, then an infusion of aminophylline (5 mg/kg over 20 minutes then 500 to 700 micrograms/kg per hour, monitoring blood concentrations if continued for more than 24 hours; the loading dose should not be given to patients already on maintenance oral therapy), or a parenteral $beta_2$ agonist may be considered, although there is limited evidence to support the routine use of either of these drugs.
- Patients who deteriorate further with drowsiness, unconsciousness, or respiratory arrest need transferral to an intensive care unit and intermittent positive-pressure ventilation.

Oral prednisolone treatment is continued for at least 5 days or until recovery. Once lung function is stabilised the patient can be discharged taking inhaled corticosteroids and bronchodilators.

In children.

UK guidelines suggest the following regimen for acute asthma in children aged 2 years and over:[6]

- Severe acute attacks in children are initially treated with oxygen, given via either a face mask or nasal cannula, to maintain an oxygen saturation of 94 to 98%. High-dose short-acting $beta_2$ agonists are also given, either via a nebuliser (salbutamol 2.5 mg or terbutaline 5 mg in children aged 2 to 5 years; up to 5 mg of salbutamol and up to 10 mg of terbutaline may be given in children over 5 years) using oxygen as the driving gas, or as multiple actuations of a MDI into a large volume spacer device. There is some evidence that in children with acute asthma, use of spacers rather than nebulisers improves oxygenation, and reduces adverse effects and time spent in the emergency department.[15]
- A systemic corticosteroid at a high dose is also required, either oral prednisolone (20 mg daily in children aged 2 to 5 years, and 30 to 40 mg daily in those over 5 years of age: children already receiving maintenance oral corticosteroids should receive 2 mg/kg up to a maximum of 60 mg daily), or intravenous hydrocortisone (4 mg/kg every 4 hours in more severely affected children).
- If life-threatening features are present, or response to $beta_2$ agonists is poor, nebulised ipratropium bromide (250 micrograms) may be added. Bronchodilators may be repeated every 20 to 30 minutes initially, and then weaned according to response.
- If no improvement is seen, transfer to a paediatric intensive care unit is recommended. Further treatment options to consider are intravenous salbutamol (15 micrograms/kg over 10 minutes followed by an infusion of 1 to 5 micrograms/kg per minute of a 200 microgram/mL solution); intravenous aminophylline (5 mg/kg over 20 minutes then 1 mg/kg per hour; the loading dose should not be given in children already receiving oral theophylline); and, for children over 5 years of age, a single intravenous dose of magnesium sulfate (40 mg/kg to a maximum of 2 g over 20 minutes).

Subsequent management follows a similar routine to that in adults.

For children under 2 years of age with acute asthma UK guidelines recommend beginning with oxygen and a trial of short-acting $beta_2$ agonist given by multiple actuations of an MDI into a large volume spacer or via a nebuliser (salbutamol 2.5 mg or terbutaline 5 mg). The $beta_2$ agonist is repeated every 1 to 4 hours if responding; if response is poor nebulised ipratropium (250 micrograms) is added. A short course of a high-dose oral corticosteroid (prednisolone 10 mg daily for up to 3 days) may be considered.

Global guidelines[7,49] for acute severe asthma are similar to those in the UK, except parenteral $beta_2$ agonists are not recommended for routine use in severe asthma exacerbations, although they are included as a treatment option for critically-ill patients. US guidelines also suggest that the parenteral use of $beta_2$ agonists is of unproven value. Also in contrast to the UK, the intravenous use of xanthines is not recommended in the USA. In compiling the UK guidelines the British Thoracic Society has taken the view that although most patients on maximal doses of nebulised $beta_2$ agonists and corticosteroids derive no additional benefit from intravenous aminophylline, some could obtain additional bronchodilatation; intravenous aminophylline was therefore recommended for patients with life-threatening unresponsive acute asthma attacks;[6] some evidence in children,[51] although not in adults,[52] supports this. In contrast, the most recent US guidelines issued by the National Asthma Education and Prevention Program do not recommend the use of xanthines as they are considered to offer no benefit over the optimal use of inhaled short-acting $beta_2$ agonists and increase the frequency of adverse effects.[5] In consequence, in the US guidelines, adult patients whose asthma cannot be managed with oxygen, inhaled short-acting $beta_2$ agonists and antimuscarinics, and systemic corticosteroids may be considered for treatment with intravenous magnesium sulfate or nebulisation with a mixture of helium and oxygen (heliox) in order to avoid intubation and mechanical ventilation. UK guidelines consider there is no evidence to support the use of heliox; a meta-analysis[53] concluded that the existing evidence on heliox failed to show a clear benefit, and although lung function might be improved in the most severe acute asthma patients, the number and size of studies available for analysis was small and the quality variable.

OTHER ASPECTS OF ASTHMA MANAGEMENT

Other therapeutic approaches for the management of asthma are currently under investigation.[54] Ultra-long-acting $beta_2$ agonists under development such as carmoterol, milveterol (GSK-159797; TD-3327), and indacaterol are suitable for once daily use, leading to increased convenience for patients.[55] Carbamazepine has shown potential as a treatment for asthma in addition to regular asthma therapy;[56] improved lung function and fewer exacerbations have been reported. The recombinant human B-type natriuretic peptide (BNP), nesiritide, has been reported to be an effective bronchodilator when given intravenously;[57] its clinical role, if any, remains to be determined. As well as their established antibacterial effect, it has been suggested that macrolides also have immunomodulatory effects that could be useful in the management of respiratory diseases. However, a systematic review[1] found insufficient evidence to support or refute the use of macrolides in chronic asthma although some clinical data indicated a positive effect; routine use was not recommended and further studies were warranted. Ketolides also appear to have immunomodulatory effects: a 10-day course of oral telithromycin started with standard treatment for acute asthma in adults was reported to improve asthma symptoms, regardless of infection with *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*) or *Mycoplasma pneumoniae*.[58] The mechanism of this effect is unclear, however, and further studies are needed.[59]

Interestingly, furosemide given by inhalation has been found to protect against bronchoconstriction induced by exercise[60] and external stimuli,[61,62] but was not effective in improving bronchial hyperresponsiveness in a 4-week study,[63] and provided no additional benefit when added to salbutamol for the treatment of acute asthma in a small study in children.[64] Any clinical application has yet to be determined.[65] There has been some interest in heparin given by inhalation,[65-67] and nebulised lidocaine may be of some benefit;[65,68,69] intravenous lidocaine or oral mexiletine have been shown to block reflex bronchoconstriction.[70] Inhaled magnesium sulfate may also be of some adjunctive benefit to $beta_2$ agonists in the management of acute episodes.[71]

There is increasing study of the cellular mechanisms of inflammation in asthma and ways of controlling them.[72] Phosphodiesterase type-4 is an enzyme that hydrolyses cyclic adenosine monophosphate (cyclic AMP), stimulating the release of acute inflammatory mediators and immune responses; it is found in airways smooth muscle, pulmonary nerves, and inflammatory and immune cells relevant to the pathogenesis of asthma. Phosphodiesterase type-4 inhibitors such as roflumilast are under investigation for their anti-inflammatory and bronchodilator activity.[72,73] The thromboxane A_2 antagonist, seratrodast, is being tried for its effects on pulmonary function and mucus secretion. Asthma-relevant cytokines or chemokines have been targeted in several ways. Interleukin-4 (IL-4) stimulates a range of inflammatory processes in asthma, and soluble recombinant interleukin-4 receptor (IL-4R; rhuIL-4R) is being investigated[74,75] as an antagonist to bind and neutralise interleukin-4. Investigation into the recombinant human IL-4 variant, pitrakinra, is showing promising results in late phase asthmatic responses to allergen challenge.[76] The anti-CD25 interleukin-2 antagonist daclizumab has also been investigated with some reported benefit. An anti-interleukin-5 antibody, mepolizumab, has also been investigated;[72,75] although airway and bone-marrow eosinophils were reduced, no clinical benefits were noted. Cytokines which have a potential anti-inflammatory effect are interleukin-10,[72] interleukin-12, and interferon gamma.[72,75] TNF-α may also play a role in severe asthma. The anti-TNF antibody infliximab, and the TNF receptor blocker etanercept have been shown to be effective in other inflammatory diseases.[72] Small studies using parenteral etanercept have shown some benefit on lung function and

symptoms;[77,78] promising results have also been reported with intravenous infliximab.[79]

The effects of diet and dietary supplements on asthma have also been of interest. Modification of dietary fatty acids in the first 5 years of life,[80] did not reduce the risk of asthma or allergic disease in children considered to be at high risk for developing asthma. Dietary ascorbic acid supplementation has been investigated, and although an improvement in post-exercise lung function and symptoms were noted in one small placebo-controlled study in adults with asthma and exercise-induced bronchoconstriction,[81] a systematic review including this study and 4 others considered that there was insufficient evidence to recommend a specific role for vitamin C in the treatment of asthma.[82] Maternal diet during pregnancy has also been examined; Vitamin D deficiency has been suggested as playing a possible role in immune-mediated disorders such as asthma.[83]

Exercise-induced asthma. For most patients exercise-induced asthma is an expression of poorly controlled asthma and regular treatment with inhaled corticosteroids should be reviewed.[6] Immediately before exercise, inhaled short-acting $beta_2$ agonists are the drugs of choice.[6,7] If exercise is a specific problem in patients taking inhaled corticosteroids, consideration may be given to leukotriene receptor antagonists, long-acting $beta_2$ agonists (although some tolerance may occur), cromoglicate, oral $beta_2$ agonists or theophylline.[6]

Pregnancy. It is particularly important that asthma should be well controlled during pregnancy; where this is achieved asthma has no important effects on pregnancy, labour, or the fetus.[5-7,84-87] A prospective case-control study[88] found no increase in the risk of major congenital malformations in children born to mothers being treated for asthma.

Inhalation has particular advantages as a means of giving drugs during pregnancy because the therapeutic action can be achieved without the need for plasma drug concentrations liable to have a pharmacological effect on the fetus. Systemic treatment should not be withheld if indicated, although there is insufficient information to support the use of anti-leukotrienes, except as continued treatment in women who were taking these before pregnancy for asthma not controlled by other medications.[6,85,86]

Severe exacerbations can have an adverse effect on pregnancy and should be treated promptly with conventional therapy, including oral or parenteral corticosteroids, oxygen, and nebulisation of a $beta_2$ agonist.[6,86] Prednisolone is a suitable corticosteroid for oral use since very little of the drug reaches the fetus.[85]

Occupational asthma. More than 10% of adult-onset asthma cases can be attributed to occupational exposure to pulmonary irritants.[89] Reduction or avoidance of exposure to the trigger is ideally an important component of management.[6,7,89,90] Symptoms may still persist; however, the prognosis for workers with occupational asthma is worse for those who remain exposed for more than one year after symptoms develop, compared with those removed earlier.[6]

Rhinitis and asthma. There is a significant association between allergic rhinitis and asthma.[7,91] It has been proposed that they are both manifestations of a single inflammatory process within the respiratory tract.[92] Asthma outcomes may be improved by following a combined therapeutic approach to comorbid allergic rhinitis and asthma.[91] Intranasal corticosteroids, an effective treatment for allergic rhinitis, have produced conflicting results in studies which assessed their effects on asthma symptoms.[91] Leukotriene receptor antagonists have produced benefits for patients with both allergic rhinitis and asthma and the anti-IgE antibody omalizumab may have a role in more severe cases.[91,93]

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Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD, chronic obstructive lung disease, chronic obstructive airways disease) is a common disorder characterised by airflow obstruction which is more or less continuous and not fully reversible, unlike asthma. The airflow limitation is usually progressive and is associated with chronic inflammation which is mainly caused by cigarette smoking;[1,2] passive smoking exposure[3] genetic factors, infections, environmental pollution, and occupational dust and chemical exposure[4] may also have an aetiological role. Symptoms of COPD include chronic and progressive dyspnoea, wheeze, frequent respiratory-tract infections, cough, and sputum production.[1,2] COPD may affect central or proximal airways, peripheral airways, lung parenchyma, and pulmonary vasculature to varying degrees in individuals with the disease[1,5]

- **Central airways.** Hypertrophy of the mucous glands and an increase in the number of goblet cells within the bronchial mucosa leads to an increase in mucus production (*chronic bronchitis*). Patients suffer from a chronic productive cough with excessive sputum production, and have been described as 'blue bloaters'. Airway wall changes include squamous metaplasia of the airway epithelium, loss of cilia and ciliary dysfunction, and increased smooth muscle and connective tissue.
- **Peripheral airways.** *Bronchiolitis* is present in the small airways. Goblet cell hyperplasia, squamous cell metaplasia, inflammatory cell infiltration, and fibrosis are all seen, leading to irreversible narrowing of the airways.
- **Lung parenchyma.** *Emphysema* occurs in the lung parenchyma in COPD. An abnormal permanent enlargement of air spaces distal to the terminal bronchioles is accompanied by destruction of the alveolar wall without obvious fibrosis. There is excessive airway collapse upon expiration and irreversible airways obstruction. Dyspnoea is a prominent symptom; a marked loss of weight may also be noted. Patients may hyperventilate to maintain oxygen levels in the blood and have been called 'pink puffers' in contrast to the 'blue bloaters' of the classic bronchitic presentation. Emphysema can sometimes be caused by a hereditary deficiency of alpha$_1$-proteinase inhibitor (alpha$_1$ antitrypsin), see p. 2438.2. Microscopic lesions can progress to form bullae, which are defined as an emphysematous space greater than 1 cm in diameter.
- **Pulmonary vasculature.** Initially these changes are characterised by thickening of the vessel wall and endothelial dysfunction. These are followed by increased vascular smooth muscle and inflammatory cell infiltration. In advanced stages of the disease there is collagen deposition and emphysematous destruction of the capillary bed.
- **Extrapulmonary changes.** Patients with severe COPD with hypoxaemia and hypercapnia can develop *cor pulmonale* (heart disease secondary to disease of the lungs and respiratory system) marked by pulmonary hypertension, right ventricular hypertrophy, and right heart failure.[5,6] COPD is also associated with systemic inflammation and skeletal muscle wasting.[5]

Management of COPD. Although there is less consensus than for asthma, guidelines for the treatment of COPD have been issued in several countries,[1,2,5,7-9] and some clinicians have developed clinical algorithms for management.[10] The most important therapeutic intervention is encouraging those patients who smoke to stop; this is the most effective intervention to reduce disease progression.[1,2,11] Psychological support and adjunctive drug therapy may be required (see Smoking Cessation, p. 2570.2). Prevention of respiratory infection should be considered; influenza vaccination is recommended[1,2,5,7,8] and can reduce serious illness and death in patients with COPD by about 50%.[1,5,7,8] Compared with influenza vaccination, there is less well-defined benefit from pneumococcal vaccination in patients with COPD.[8] It is generally recommended however,[1,2,7,8] and a study found most benefit in younger patients and those with more severe disease.[12]

Drug treatment is mainly symptomatic and palliative using bronchodilators, corticosteroids, and oxygen therapy.

First-line drug therapy for the treatment of COPD consists of bronchodilators to alleviate bronchospasm and any reversible component of the airways obstruction. Either an inhaled short-acting *antimuscarinic*, such as ipratropium bromide, or a short-acting *beta$_2$ agonist*, is suggested as the initial bronchodilator.[1,2,7] Individual responses to the different classes of bronchodilators are variable.[8] In mild disease inhaled bronchodilators can be used on an as-needed basis.[1,2,7,8] In moderate and more severe disease, therapeutic options include the regular use of these bronchodilators either alone[7] or in combination,[7,8] or the addition of long-acting bronchodilators such as the beta$_2$ agonists salmeterol and formoterol or the antimuscarinic tiotropium.[1,2,5,7,8] A review[13] of the role of long-acting bronchodilators in COPD found that they effectively improved lung function; however, they differed in their effects on other outcomes. Only tiotropium had consistent superiority to the short-acting bronchodilator ipratropium. A reduction in COPD exacerbations and related hospitalisations and improved symptoms and quality of life have been reported in two systematic reviews[14,15] of tiotropium compared with either placebo or ipratropium; improvements in lung function compared with either placebo, ipratropium, or a long-acting beta$_2$ agonist were also noted. Regular treatment with long-acting bronchodilators is more effective and convenient than with shorter acting drugs.[1,2] Combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilatation while avoiding the need for high doses and the associated adverse effects.[1,2,7] Ipratropium given with salmeterol has been associated with beneficial effects on quality of life and lung function compared with salmeterol alone.[16] Beneficial effects on lung function have also been reported with tiotropium plus formoterol compared with either treatment alone.[17,18] A *xanthine* such as an oral modified-release preparation of theophylline may also be considered, usually where short and long-acting bronchodilators are ineffective, or in patients unable to use inhaled therapy, as there is an increased risk of adverse effects and drug interactions as well as a need for monitoring.[1,2,7,8,19] Theophylline has been reported to reduce exacerbations compared with a long-acting beta$_2$ agonist,[20] but is less effective than inhaled corticosteroids. Theophylline may also have positive cardiac inotropic effects, see under Chronic Obstructive Pulmonary Disease, p. 1231.1, which could be of value in cor pulmonale. Roflumilast is an oral *phosphodiesterase inhibitor* that can be used for maintenance treatment in those with severe disease; its place in therapy is not yet established.

Inhaled corticosteroids have been reported to reduce the rate of exacerbations,[21-23] and guidelines recommend regular treatment with an *inhaled corticosteroid* combined with a long-acting beta$_2$ agonist for symptomatic patients with moderate to severe COPD and repeated exacerbations.[1,2,5] UK guidelines[2] include recommendations on the selection of bronchodilators and corticosteroids for regular inhaled maintenance treatment according to predicted FEV$_1$ for those who remain breathless or have exacerbations despite using short-acting beta$_2$ agonists or short-acting antimuscarinics.

Although some guidelines[7] still recommend trying oral prednisolone in selected patients with stable COPD to assess response to continued inhaled corticosteroid therapy, a large study[24] found that the response to a course of oral prednisolone was unrelated to the change in FEV$_1$ and health status over the next 3 years of treatment with either inhaled fluticasone or placebo. Other guidelines[2] have therefore concluded that a short course of oral corticosteroid is a poor predictor of long-term response to inhaled therapy, and do not recommend this assessment. A systematic review[23] also found that bronchodilator reversibility and bronchial hyper-responsiveness did not predict response to inhaled corticosteroids.

Whether inhaled corticosteroids improve the long-term outcomes of COPD is less clear. There has been some suggestion that inhaled corticosteroids reduce mortality,[25,26] although subsequent systematic reviews[23,27] did not find any significant effect. A study[28] designed to assess the effect of a combination inhaler containing an inhaled corticosteroid (fluticasone) and the long-acting beta$_2$ agonist salmeterol on survival in COPD patients did not show a significant reduction in all-cause mortality, but benefits were seen in the rate of exacerbations, lung function, and health status compared with placebo. Unexpectedly, the study investigators also reported a higher probability of pneumonia amongst patients given medications containing fluticasone. A later systematic review[27] also found an excess risk of pneumonia in patients with COPD, and a case-control study suggested the risk increased with higher doses of inhaled corticosteroids.[29] Other meta-analyses compared combined inhaled corticosteroid and long-acting beta$_2$ agonist in one inhaler with either placebo,[30] long-acting beta$_2$ agonist,[31] or inhaled corticosteroid.[32] Combination therapy led to a significant reduction in exacerbation rates compared with placebo, long-acting beta$_2$ agonist, and inhaled corticosteroid. However, another systematic review considered that the relative efficacy and safety of such a combination versus the antimuscarinic tiotropium was uncertain.[33] All-cause mortality was reduced with combination therapy compared with either placebo or inhaled corticosteroid, but no impact was seen in comparison with long-acting beta$_2$ agonists.[30-32] Again, the increased incidence of pneumonia in the inhaled corticosteroid groups was a cause of concern. The UK MHRA has warned[34] of the need to be vigilant for the development of pneumonia and other infections in patients with COPD who are using inhaled corticosteroids, as the symptoms of infection often overlap with those of exacerbation of COPD; the use of corticosteroids should be reconsidered if such infections develop. The MHRA also warned[35] that since the benefit of adding an inhaled corticosteroid to a long-acting beta$_2$ agonist was limited, such combination therapy should only be used when COPD progresses to severe disease, and that inhaled corticosteroids should not be used alone.

The effect that inhaled corticosteroids have on the rate of decline in lung function seen in COPD patients has also been studied. A pooled analysis[36] found that, although small but significant improvements in FEV$_1$ were recorded in the first 6 months of treatment with inhaled corticosteroid compared with placebo (particularly in ex-smokers and women), the rate of decline was not affected after the first 6 months. A systematic review[23] came to similar conclusions regarding lung function decline, but reported a slowing in the rate of decline in quality of life. A later 3-year placebo-controlled study did demonstrate a reduction in the yearly rate of decline in lung function with a combination of fluticasone and salmeterol, or either component alone.[37]

Long-term maintenance use of *oral* corticosteroids is not generally recommended,[1,2,5,7,8] although they have a place in the short-term management of exacerbations (see below), and withdrawal after an exacerbation may be difficult in some patients with advanced disease.[2]

In patients with severe COPD and persistent hypoxaemia, supplemental *oxygen* provided on an almost continuous long-term basis at home has been found to improve survival and alleviate complications such as cor pulmonale, polycythaemia and neuropsychological impairment.[38,39] Guidelines recommend starting oxygen therapy in patients whose resting PaO_2 is less than 55 mmHg (about 7.3 kPa), or whose arterial-oxygen saturation is less than about 88%.[1,2,5,7,8] It may also be considered when PaO_2 is between 55 and 60 mmHg (7.3 to 8 kPa) or arterial-oxygen saturation is less than about 90%, and if there is evidence of polycythaemia, pulmonary hypertension, or right heart failure.[1,2,5,7,8] Nocturnal oxygen therapy may benefit some patients who suffer from nocturnal hypoxaemia,[5,7] but not all guidelines recommend it, as evidence for clinical benefits and improvement in survival is lacking.[5] Evidence of benefit from short-term, 'as-needed' oxygen inhalation after exertion is lacking,[40] although a review of studies using ambulatory oxygen during an exercise test reported an improvement in exercise performance versus placebo;[41] selected patients might gain some benefits.[2,42]

A meta-analysis[43] of the use of *mucolytics* suggested a small reduction in exacerbations and in the total number of days of disability; benefit may be greater in patients with frequent or prolonged exacerbations. Although most guidelines do not recommend widespread use,[1,2] patients with chronic productive cough may be considered for treatment;[2] a reduction in exacerbations has been reported.[1,7] Patients who are not prescribed inhaled corticosteroids may also gain some benefit.[1,43] Improved pulmonary function has been reported in patients given aerosolised surfactant.[44]

There is some evidence that treatment with *cardiovascular drugs* can produce improvements in some pulmonary measures. Cohort and case control studies have reported a reduced COPD and pneumonia/influenza mortality risk with the use of statins.[45] Another case control study[46] also reported a reduction in pulmonary as well as cardiovascular outcomes with statins, ACE inhibitors, and angiotensin II receptor inhibitors, the largest benefits occurring with the combination of statins and either ACE inhibitors or angiotensin II receptor inhibitors. This combination was associated with a reduction in COPD hospitalisations, total mortality in both high- and low-risk groups, and myocardial infarction in the high-risk group.

A systematic review[47] to assess the effects of cardioselective beta blockers on respiratory function of patients with COPD found no adverse effects on lung function or respiratory symptoms compared with placebo, and concluded that they should not be routinely withheld from patients with COPD and cor pulmonale. Additionally, a retrospective study[48] noted a reduced mortality associated with beta blocker use in patients hospitalised for acute exacerbations of COPD.

Surgery may be used in selected patients with end-stage disease who remain symptomatic despite optimal medical treatment. Bullectomy may be used to remove a large bulla that does not contribute to gas exchange.[1,2,5,7,49] Lung transplantation (p. 1941.3) may be used in very advanced COPD,[1,2,5,7] particularly in patients with idiopathic emphysema or alpha$_1$ antitrypsin deficiency.[49] In severe COPD with hyperinflation and obvious target areas, lung volume reduction surgery may be considered; it may be a better option than medical therapy to reduce mortality in patients

with mainly upper-lobe emphysema and low exercise capacity.[1,2,5,7,50]

Much *investigational therapy* has focused, with variable results, on three key processes in COPD: oxidative tissue damage, protease-mediated tissue destruction, and leucocyte-driven chronic inflammation.[51,52] Oxidative stress has been targeted with antoxidants, particularly acetylcysteine.[53] Various mediators of the inflammatory processes have also been targeted, for example, inhibitors of interleukin-8[53,54] and phosphodiesterase type 4.[53,55,56] Other therapies which have been considered include inhibitors of cell signalling, TNF, and adhesion molecules and chemokines.[53] Retinoids have been studied in emphysema for potential positive effects on lung repair.[57] Small studies have reported improvements in dyspnoea[58,59] and exercise capacity[59] with inhaled furosemide. Inhaled formulations of trospium chloride and the long-acting antimuscarinic glycopyrronium bromide are under development for the treatment of COPD. There is also evidence that oral therapy with polyunsaturated fatty acids (including omega-3 and omega-6 fatty acids) may improve exercise capacity.[60] As well as their established antibacterial effect, it has been suggested that macrolides also have immunomodulatory effects that could be useful in the management of respiratory diseases; however, their role in COPD remains to be determined.

Exacerbations. Patients with COPD frequently suffer acute exacerbations of their symptoms, and may require hospitalisation. They are triggered mainly by respiratory viruses and bacteria, which infect the lower airway and increase inflammation.[61] Treatment options include maximal bronchodilators, antibacterials, systemic corticosteroids, and oxygen as necessary, with appropriate management of any associated cardiovascular disorder.[1,2,5,7,8,62]

For *bronchodilator* therapy a short-acting $beta_2$ agonist may be combined with a short-acting antimuscarinic such as ipratropium,[1,5,7,8] although evidence for the efficacy of this combination is lacking.[63] Some guidelines[1,2] further advocate use of a xanthine such as intravenous theophylline in unresponsive patients, although evidence of a clear benefit with systemic xanthines is inconsistent.[64]

Systemic *corticosteroids* are beneficial in acute exacerbations of COPD.[1,2,5,7,8] Studies[65,66] of severe acute exacerbation requiring hospitalisation have found systemic corticosteroids to improve lung function and reduce the length of hospital stay, and a later meta-analysis confirmed that early treatment with oral or parenteral corticosteroids reduced treatment failure and the need for additional treatment, although it was also associated with an increased risk of adverse effects.[67] Some consider that the most effective dose and duration of treatment is yet to be established,[67,68] although one study[65] found that a 2-week course was as effective as a longer course of 8 weeks. Guidelines suggest oral doses of prednisolone 25 to 50 mg daily, or equivalent, for 7 to 14 days.[1,2,5,7,8] There is also no evidence of long-term benefit.[65,66] Inhaled budesonide may be an alternative to oral corticosteroids in the treatment of exacerbations.[1]

The use of *antibacterials* for acute exacerbations has long been controversial. Meta-analysis[69] has suggested a decrease in mortality, treatment failure, and sputum purulence compared with placebo in moderately to severely ill patients, although the analysis included only a small number of studies, with important differences in design (see also Bronchitis, p. 175.3). Guidelines recommend their use on an empirical basis where signs of infection are present[1,2,5,7,8] but do not support prophylactic antibacterial cover for those with recurrent acute exacerbations.[1,2,5,7] Short courses of antibacterial therapy (5 days or less) are as effective as longer courses in mild to moderate exacerbations.[70]

Oxygen therapy is required in patients with hypoxia; the goal is to maintain oxygen saturation above 90% but prevent increasing CO_2 retention.[1,5,7] Uncontrolled oxygen therapy can result in suppression of respiratory drive, carbon dioxide narcosis, and respiratory arrest; in hospital, arterial blood gases should be used to guide treatment.[2] Some guidelines[7] suggest low initial oxygen concentrations of 24 to 28%. A 2006 systematic review[71] found a lack of evidence on the safest way to provide initial oxygen treatment in COPD exacerbations.

Respiratory stimulants such as doxapram[72] are of limited use but may be considered when non-invasive ventilation is unavailable or inappropriate.[1,2]

Despite intensive therapy, some patients progress to respiratory muscle fatigue and require ventilatory support.

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Acefylline Piperazine *(BAN, rINN)*

Acefilina piperazina; Acéfylline Pipérazine; Acefyllinum Piperazinum; Acepifylline; Piperazine Theophylline Ethanoate; Ацефиллин Пиперазин.

Piperazine bis(theophyllin-7-ylacetate) (1:1).

$(C_9H_{10}N_4O_4)_2C_4H_{10}N_2$=562.5

CAS — 18833-13-1; 18428-63-2.

ATC — R03DA09.

ATC Vet — QR03DA09.

UNII — 121910S6Z.

Profile

Acefylline piperazine is a derivative of theophylline (p. 1229.3) that has been used for its bronchodilator effects. It is not converted to theophylline in the body.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Cadiphylate; Etophylate; *Indon.*: Etaphylline.

Multi-ingredient Preparations. *India*: Cadiphylate.

Aclidinium Bromide *(USAN, rINN)*

14115700; Aclidinii Bromidum; Bromure d'Aclidinium; Bromuro de aclidinio; LAS-34273; LAS-W-330; Аклидиний Бромид.

(3*R*)-3-{[Hydroxydi(thiophen-2-yl)acetyl]oxy}-1-(3-phenoxypropyl)-1λ^5-azabicyclo[2.2.2]octan-1-ylium bromide.

$C_{26}H_{30}BrNO_4S_2$=564.6

CAS — 320345-99-1.

ATC — R03BB05.

ATC Vet — QR03BB05.

UNII — UQW7UF9N91.

Uses and Administration

Aclidinium bromide is a quaternary ammonium antimuscarinic used similarly to ipratropium (p. 1211.3) in the maintenance treatment of reversible airways obstruction, as in chronic obstructive pulmonary disease (p. 1199.1); it is not suitable for the initial treatment of acute bronchospasm. Aclidinium is given by inhalation, via a dry powder inhaler, as the bromide, although doses may be expressed as either the base or the salt; aclidinium bromide 375 micrograms is equivalent to about 322 micrograms of aclidinium.

Metered doses from the inhaler device may be expressed as the amount delivered *into* the mouthpiece (400 micrograms of aclidinium bromide per actuation) or the amount delivered *from* the mouthpiece (corresponding to 375 micrograms of aclidinium bromide per inhalation). The usual dose is one metered dose inhaled twice daily.

References.

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2. Puhr R, *et al.* Efficacy of aclidinium bromide 400 µg twice daily compared with placebo and tiotropium in patients with moderate to severe COPD. *Chest* 2012; 141: 745–52.
3. Jones PW, *et al.* Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. *Eur Respir J* 2012; 40: 830–6.
4. Kerwin EM, *et al.* Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I). *COPD* 2012; 9: 90–101.

Adverse Effects and Precautions

As for Ipratropium Bromide (p. 1212.2).

The most frequently reported adverse effects of inhaled aclidinium bromide are headache and nasopharyngitis. Other adverse effects include cough, dysphonia, rhinitis, sinusitis, and diarrhoea.

Interactions

For interactions associated with antimuscarinics in general, see Atropine, p. 1312.3. However, these interactions are not usually seen with antimuscarinics, such as aclidinium bromide, given by inhalation.

Pharmacokinetics

Aclidinium bromide is rapidly absorbed from the lung, with peak plasma concentrations occurring within 5 minutes of inhalation in healthy subjects and within 15 minutes in patients with chronic obstructive pulmonary disease. Whole lung deposition of inhaled aclidinium bromide is about 30% of the metered dose; less than 5% reaches the systemic circulation as unchanged aclidinium. Aclidinium bromide is rapidly hydrolysed in plasma.

Aclidinium bromide is rapidly and extensively metabolised by chemical and enzymatic hydrolysis (mainly by butyrylcholinesterase) to inactive metabolites. After intravenous dosing, about 1% is excreted as unchanged drug in the urine; 54 to 65% of the dose is excreted as metabolites in the urine and 20 to 33% as metabolites in the faeces. After inhalation, about 0.1% is excreted as unchanged drug in the urine; the estimated effective half-life is reported to be 5 to 8 hours, and the terminal elimination half-life about 2 to 3 hours.

References.

1. Jansat JM, *et al.* Safety and pharmacokinetics of single doses of aclidinium bromide, a novel long-acting, inhaled antimuscarinic, in healthy subjects. *Int J Clin Pharmacol Ther* 2009; 47: 460–8.
2. Jansat JM, *et al.* Safety and pharmacokinetics of multiple doses of aclidinium bromide, a novel long-acting muscarinic antagonist for the treatment of chronic obstructive pulmonary disease, in healthy participants. *J Clin Pharmacol* 2009; 49: 1239–46.
3. Ortiz S, *et al.* Safety and tolerability of aclidinium administered intravenously and absolute bioavailability of inhaled aclidinium in healthy male participants. *J Clin Pharmacol* 2012; 52: 819–27.
4. de la Motte S, *et al.* Pharmacokinetics and safety of aclidinium bromide in younger and elderly patients with chronic obstructive pulmonary disease. *Int J Clin Pharmacol Ther* 2012; 50: 403–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Eklira Genuair; *Neth.*: Eklira Genuair; *Norw.*: Eklira Genuair; *Spain*: Bretaris; Eklira Genuair; *UK*: Eklira Genuair; *USA*: Tudorza.

Ambroxol Acefyllinate *(BANM, rINNM)*

Acebrofylline; Acebrophylline; Acefilinato de ambroxol; Ambroxol Acéfylline; Ambroxoli Acefyllinas; Амброксола Ацефиллинат.

$C_{13}H_{18}Br_2N_2O_2C_9H_{10}N_4O_4$=616.3

CAS — 96989-76-3.

UNII — 0HM1E1747N.

Profile

Ambroxol has mucolytic properties (see Ambroxol Hydrochloride, p. 1654.3) but theophylline derivatives such as the acefyllinate are used as bronchodilators. Ambroxol acefyllinate is given in an oral dose of 100 mg twice daily. For doses in children see below.

Administration in children. Ambroxol acefyllinate can be used as a bronchodilator in children. Children from 1 to 6 years of age may be given an oral dose of 25 mg twice daily, and children from 6 to 12 years, 50 mg twice daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Brismucol†; Brondilat; Brondyneo; Bronfilil; Brontek; Cebronfilina†; Expectilat; Filinar; Hiflux; Teomuc; *India*: A-Xanthin; Ab-Phylline; Bestofyline-A; Mucoreg; *Ital.*: Ambromucil; Broncomnes; Surfolase; *Mex.*: Brismucol; Kasmucol; *Venez.*: Brixilon; Bronilis; Klas.

Multi-ingredient Preparations. *India*: Acedril.

Aminophylline *(BAN, pINN)*

Aminofilin; Aminofilina; Aminofylin; Aminofyllini; Aminofylin; Aminophyllinum; Euphyllinum; Metaphyllin; Teofilina y etilenodiamina, mezcla de; Teofilinas-etilendiaminas; Teofillinetilèndiamin; Teofyllinietyleenidiamiini; Teofyllinetylendiamin; Theophyllaminum; Theophylline and Ethylenediamine; Theophylline Ethylenediamine Compound; Theophylline-ethylenediamine; Theophyllinum Et Ethylenediaminum; Аминофиллин.

A mixture of theophylline and ethylenediamine (2:1), its composition approximately corresponding to the formula below.

$(C_7H_8N_4O_2)_2C_2H_4(NH_2)_2$=420.4

CAS — 317-34-0 (anhydrous aminophylline).

ATC — R03DA05.

ATC Vet — QR03DA05.

UNII — 27Y3KJK423.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *US*, and *Viet.* Some pharmacopoeias include anhydrous and hydrated aminophylline in one monograph. Some pharmacopoeias do not specify the hydration state.

Ph. Eur. 8: (Theophylline-Ethylenediamine, Anhydrous; Aminophylline BP 2014). It contains 84.0 to 87.4% of anhydrous theophylline and 13.5 to 15.0% of anhydrous ethylenediamine. A white or slightly yellowish hygroscopic powder, sometimes granular. Freely soluble in water (the solution becomes cloudy through absorption of carbon dioxide); practically insoluble in dehydrated alcohol. Store in airtight containers. Protect from light.

USP 36: (Aminophylline). It is anhydrous or contains not more than two molecules of water of hydration. It contains not less than 84.0 and not more than 87.4% of anhydrous theophylline. It consists of white or slightly yellowish granules or powder, having a slight ammoniacal odour. Upon exposure to air it gradually loses ethylenediamine and absorbs carbon dioxide with the liberation of theophylline. One g dissolves in 25 mL of water to give a clear solution; 1 g dissolved in 5 mL of water crystallises upon standing, but redissolves when a small amount of ethylenediamine is added; insoluble in alcohol and in ether. Its solutions are alkaline to litmus. Store in airtight containers.

Aminophylline Hydrate *(BANM, pINNM)*

Aminofilina dwuwodna; Aminofilina hidratada; Aminofylin hydratovaný; Aminophylline, Hydrate d'; Aminophyllini Hydratum; Aminophyllinum Dihydricum; Aminophyllinum Hydricum; Teofyllinietyleenidiamiinihydraatti; Teofyllineetylendiaminhydrat; Théophylline-éthylènediamine hydratée; Theophyllinum et ethylenediaminum hydricum; Аминофиллина Гидрат.

$(C_7H_8N_4O_2)_2C_2H_4(NH_2)_2.2H_2O$=456.5

CAS — 49746-06-7; 5897-66-5 (aminophylline dihydrate); 76970-41-7 (aminophylline monohydrate).

ATC — R03DA05.

ATC Vet — QR03DA05.

UNII — C229N9DX94 (aminophylline dihydrate); YZE0LU9ZMS (aminophylline monohydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.* Some pharmacopoeias include anhydrous and hydrated aminophylline in one monograph. Some pharmacopoeias do not specify the hydration state.

Ph. Eur. 8: (Theophylline-ethylenediamine Hydrate; Aminophylline Hydrate BP 2014). It contains 84.0 to 87.4% of anhydrous theophylline and 13.5 to 15.0% of anhydrous ethylenediamine. A white or slightly yellowish powder, sometimes granular. Freely soluble in water (the solution becomes cloudy through absorption of carbon dioxide); practically insoluble in dehydrated alcohol. Store in well-filled airtight containers. Protect from light.

USP 36: (Aminophylline). It is anhydrous or contains not more than two molecules of water of hydration. It contains not less than 84.0 and not more than 87.4% of anhydrous theophylline. It consists of white or slightly yellowish granules or powder, having a slight ammoniacal odour. Upon exposure to air it gradually loses ethylenediamine and absorbs carbon dioxide with the liberation of theophylline. One g dissolves in 25 mL of water to give a clear solution; 1 g dissolved in 5 mL of water crystallises upon standing, but redissolves when a small amount of ethylenediamine is added; insoluble in alcohol and in ether. Its solutions are alkaline to litmus. Store in airtight containers.

Incompatibility. Aminophylline solutions should not be allowed to come into contact with metals.

Solutions of aminophylline are alkaline and if the pH falls below 8, crystals of theophylline will deposit.[1] Drugs known to be unstable in alkaline solutions, or that would lower the pH below the critical value, should not be mixed with aminophylline.

1. Edward M. pH—an important factor in the compatibility of additives in intravenous therapy. *Am J Hosp Pharm* 1967; 24: 440–9.

Uses and Administration

Aminophylline has the actions and uses of theophylline (see p. 1229.3) and is used similarly as a bronchodilator in the management of asthma (p. 1195.2) and chronic obstructive pulmonary disease (p. 1199.1). Aminophylline has also been used to relieve neonatal apnoea (p. 1204.3). It was formerly used as an adjunct in the treatment of heart failure, and may occasionally have a role in patients with this condition who are also suffering from obstructive airways disease. Aminophylline is usually preferred to theophylline when greater solubility in water is required, particularly in intravenous formulations.

Aminophylline may be given in the anhydrous form or as the hydrate, and doses may be expressed as either; aminophylline hydrate 1.09 mg is equivalent to about 1 mg of aminophylline. The USP 36 specifies that aminophylline preparations should be labelled with respect to their anhydrous *theophylline* content; aminophylline 1 mg and aminophylline hydrate 1.09 mg are equivalent to about 0.86 mg theophylline. As the pharmacokinetics of theophylline are affected by several factors including age, smoking, disease, diet, and drug interactions, the dose of aminophylline must be carefully individualised and serum-theophylline concentrations monitored (see Uses and Administration of Theophylline, p. 1229.3).

In the management of **acute severe bronchospasm**, aminophylline may be given intravenously by slow injection or infusion. To reduce adverse effects, intravenous aminophylline should not be given at a rate greater than 25 mg/minute. In adults who have not been taking aminophylline, theophylline, or other xanthine-containing medication, a loading dose of 5 mg/kg ideal (lean) bodyweight or 250 to 500 mg of aminophylline may be given intravenously over 20 to 30 minutes by slow injection or infusion, followed by a maintenance infusion dose of 500 micrograms/kg per hour. Older patients and those with cor pulmonale, heart failure, or liver disease may require lower maintenance doses; smokers often need higher maintenance doses. A loading dose may not be considered necessary unless the patient's condition is deteriorating.

Intravenous aminophylline is best avoided in patients already taking theophylline, aminophylline, or other xanthine-containing medication but, if considered necessary, the serum-theophylline concentration should first be assessed and the initial loading dose should be calculated on the basis that each 600 micrograms/kg of aminophylline (equivalent to about 500 micrograms/kg theophylline) will increase serum-theophylline concentration by 1 microgram/mL.

In the management of **chronic bronchospasm** aminophylline may be given orally as modified-release preparations; a usual dose is aminophylline hydrate 225 to 450 mg twice daily. Therapy should start with the lower dose and be increased as appropriate. Retitration of the dosage is required if the patient is changed from one modified-release preparation to another as the bioavailability of modified-release aminophylline preparations may vary.

For doses of aminophylline used in children, see Administration in Children, below.

Intramuscular injection of aminophylline causes intense local pain and is not recommended.

Aminophylline has also been used as the hydrochloride.

Administration. *RECTAL ADMINISTRATION.* Absorption from aminophylline suppositories is erratic and this dose form has been associated with toxicity, hence the warnings that suppositories should not be used, especially in children. In the UK suppositories are no longer readily available; one hospital wishing to use the rectal route for apnoea in premature infants (see Neonatal Apnoea, p. 1204.3) achieved therapeutic plasma-theophylline concentrations with a specially formulated rectal gel.[1]

1. Cooney S, *et al.* Rectal aminophylline gel in treatment of apnoea in premature newborn babies. *Lancet* 1991; 337: 1351.

Administration in children. Aminophylline may be given intravenously, by slow injection or infusion, to manage **acute severe bronchospasm** in children. Doses should be calculated using ideal or lean body-weight. In children who have not been taking aminophylline, theophylline or other xanthine-containing medicine, UK licensed product information recommends a loading dose of 5 mg/kg given by slow injection or infusion over 20 to 30 minutes. Initial maintenance dose ranges are:

- 6 months up to 10 years of age: 1 mg/kg per hour
- 10 to 16 years of age: 800 micrograms/kg per hour

Although unlicensed in the UK for use in children under 6 months, the *BNFC* suggests that these doses may be used from 1 month of age. Children aged from 12 to 18 years may be given 500 to 700 micrograms/kg per hour. Serum-theophylline concentrations should be used to guide further dose adjustments.

Children who are already receiving theophylline, aminophylline or other xanthine-containing medicines, should not normally receive a loading dose of intravenous aminophylline unless serum-theophylline concentration is available to guide dosage. Loading doses are based on the expectation that each 600 micrograms/kg lean body-weight of aminophylline will result in a 1-microgram/mL increase in serum-theophylline concentration.

Oral modified-release preparations are given to children with a body-weight over 40 kg in the long-term management of **chronic bronchospasm**. An initial dose of aminophylline hydrate 225 mg twice daily may be given if the child has not previously taken xanthine preparations, increased after 1 week to 450 mg twice daily according to serum-theophylline concentrations. Different modified-release preparations are not considered interchangeable.

Aminophylline has also been used in the management of **neonatal apnoea** (see p. 1204.3). For further information on the dosage of theophylline itself in neonates, see Administration in Infants, p. 1230.2.

Cardiac arrhythmias. For mention of the use of aminophylline for bradyarrhythmias, see Theophylline, p. 1231.1.

Erectile dysfunction. For reference to the use of a cream containing aminophylline, isosorbide dinitrate, and codergocrine mesilate in the treatment of erectile dysfunction, see under Glyceryl Trinitrate, p. 1392.2.

Methotrexate neurotoxicity. For reference to the use of aminophylline or theophylline to relieve the acute neurotoxicity of methotrexate, see Other Drugs, under Treatment of Adverse Effects, p. 827.1.

Motor neurone disease. A study[1] in 25 patients with amyotrophic lateral sclerosis (see p. 2605.2) found that aminophylline improved the endurance of respiratory muscles and increased the handgrip strength of skeletal muscles; it may have some potential therapeutic benefit in such patients.

1. Berto MC, *et al.* Acute action of aminophylline in patients with amyotrophic lateral sclerosis. *Acta Neurol Scand* 2007; 115: 301–5.

Reduction of body fat. Cosmetic aminophylline cream has been promoted for its supposed ability to remove fat ('cellulite') from the thighs.[1] Concern has been raised about the potential for topical sensitisation.[2] Cosmetic use of aminophylline is banned in some countries.

1. Dickinson BL, Gora-Harper ML. Aminophylline for cellulite removal. *Ann Pharmacother* 1996; 30: 292–3.
2. Simon PA. Comment: aminophylline-containing cream. *Ann Pharmacother* 1996; 30: 1341.

Renal colic. Aminophylline has been studied[1] for its potential value as an adjunct in the management of the pain associated with renal calculi (p. 6.3).

1. Djaladat H, *et al.* The effect of aminophylline on renal colic: a randomized double blind controlled trial. *South Med J* 2007; 100: 1081–4.

Adverse Effects, Treatment, and Precautions

As for Theophylline, p. 1231.2, p. 1232.3, and p. 1233.1. Hypersensitivity has been associated with the ethylenediamine content.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies aminophylline as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

As for Theophylline, p. 1233.3.

Pharmacokinetics

Aminophylline, a complex of theophylline with ethylenediamine, readily liberates theophylline in the body. The pharmacokinetics of theophylline are discussed on p. 1236.3.

Studies in healthy subjects suggested that ethylenediamine does not affect the pharmacokinetics of theophylline after oral or intravenous dosage.[1,2]

1. Asiaksen A, *et al.* Comparative pharmacokinetics of theophylline and aminophylline in man. *Br J Clin Pharmacol* 1981; 11: 269–73.
2. Caldwell J, *et al.* Theophylline pharmacokinetics after intravenous infusion with ethylenediamine or sodium glycinate. *Br J Clin Pharmacol* 1986; 22: 351–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cardirenal; Fadafilina; Larjanfilina; *Braz.*: Aminoima†; Aminoliv; Asmafin; Asmapen; Asmodrin; Asmoquinol; Minoton; Pulmodilat†; Unifilin; *Canad.*: Phyllocontin†; *Chile*: Cardiomin; *China*: Xing You Shan (星尤善); *Cz.*: Syntophyllin; *Denm.*: Teofylamin; *Fin.*: Aminocont; *Gr.*: Euphyllin†; Phyllotemp; *Hung.*: Diaphyllin; *India*: Minophyl; *Indon.*: Phyllocontin; *Irl.*: Phyllocontin; *Ital.*: Aminomal; Tefamin; *Jpn*: Neophyllin; *Mex.*: Amofilin†; Drafilyn-Z; *Philipp.*: Theofil; *Port.*: Filotempo; *S.Afr.*: Phyllocontin; *Spain*: Eufilina†; *Swed.*: Teofyllamin; *Thai.*: Amino; Asmalia†; *Turk.*: Aminocardol; Asmafilin; Carena; Filinsel; *UK*: Phyllocontin; *Venez.*: Broncophilina.

Multi-ingredient Preparations. *Braz.*: Alergo Filinal; Dispneitrat†; *China*: Asmeton (阿斯美); Cha Xin Na Min (茶新那敏); Fufang Dan An Pian (复方胆氨片); Ke Zhi (克之); *Hong Kong*: Amiton†; Asmeton; *India*: Broncofree; Cortasthma; *Mex.*: Paliatil; *Port.*: Anti-Asmatico†; *S.Afr.*: Genasma†; Natrophylline Compound†; Repasma†; *USA*: Emergent-Ez.

Pharmacopoeial Preparations

BP 2014: Aminophylline Injection; Aminophylline Tablets; Prolonged-release Aminophylline Tablets;
USP 36: Aminophylline Delayed-release Tablets; Aminophylline Injection; Aminophylline Oral Solution; Aminophylline Rectal Solution; Aminophylline Suppositories; Aminophylline Tablets.

Amlexanox *(BAN, USAN, rINN)*

AA-673; Amlexanoxo; Amlexanoxum; Amoxanox; CHX-3673; Амлексаноксс

2-Amino-7-isopropyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylic acid.

$C_{16}H_{14}N_2O_4$=298.3

CAS — 68302-57-8.

ATC — A01AD07; R03DX01.

ATC Vet — QA01AD07; QR03DX01.

UNII — BRL1C2459K.

NOTE. The name Elics has been used as a trade mark for amlexanox.

Pharmacopoeias. In *Jpn*.

Profile

Amlexanox has a stabilising action on mast cells resembling that of sodium cromoglicate (p. 1225.3) and also acts as a leukotriene inhibitor. It is given orally in the management of asthma (p. 1195.2) and for allergic rhinitis (p. 612.1); a dose of 25 or 50 mg three times daily has been suggested. Amlexanox is also given as a metered-dose nasal spray for allergic rhinitis, and as 0.25% eye drops for allergic conjunctivitis.

Amlexanox is also applied in the management of aphthous ulcers (see Mouth Ulceration, p. 1814.2); a 5% oral paste may be used 4 times daily. Other formulations include a 2-mg biodegradable oral disc designed to deliver amlexanox locally.

References.

1. Khandwala A, *et al.* 5% amlexanox oral paste, a new treatment for recurrent minor aphthous ulcers: I. Clinical demonstration of acceleration of healing and resolution of pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; 83: 222–30.
2. Khandwala A, *et al.* 5% amlexanox oral paste, a new treatment for recurrent minor aphthous ulcers: II. Pharmacokinetics and demonstration of clinical safety. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; 83: 231–8.
3. Bell J. Amlexanox for the treatment of recurrent aphthous ulcers. *Clin Drug Investig* 2005; 25: 555–66.
4. Murray B, *et al.* The efficacy of amlexanox OraDisc on the prevention of recurrent minor aphthous ulceration. *J Oral Pathol Med* 2006; 35: 117–22.
5. Liu J, *et al.* An evaluation on the efficacy and safety of amlexanox oral adhesive tablets in the treatment of recurrent minor aphthous ulceration in a Chinese cohort: a randomized, double-blind, vehicle-controlled, unparallel multicenter clinical trial. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; 102: 475–81.
6. Meng W, *et al.* A clinical evaluation of amlexanox oral adhesive pellicles in the treatment of recurrent aphthous stomatitis and comparison with amlexanox oral tablets: a randomized, placebo controlled, blinded, multicenter clinical trial. *Trials* 2009; 10: 30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: An He (安呵); Fu Rui Ji (福瑞斯); Li Ke Bang (立克邦); Xishumai (西扑迈); *Fin.*: Aftasol†; *Irl.*: Aphtheal; *Jpn*: Solfa; *Neth.*: Miraftil; *Port.*: Aftail; *USA*: Aphthasol†.

Arformoterol Tartrate *(USAN, rINNM)* ⊗

Arformotérol, Tartrate d'; Arformoteroli Tartras; *R,R*-Formoterol Tartrate; Tartrato de arformoterol; Арформотерола тартрат.

(-)-*N*-[2-Hydroxy-5-((1*R*)-1-hydroxy-2-[[(1*R*)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl)phenyl]formamide hydrogen (2*R*,3*R*)-2,3-dihydroxybutanedioate.

$C_{19}H_{24}N_2O_4.C_4H_6O_6$=494.5

CAS — 67346-49-0 (arformoterol); 200815-49-2 (arformoterol tartrate).

UNII — 5P8VJ2I235.

Profile

Arformoterol is the *R,R*-enantiomer of the $beta_2$-adrenoceptor agonist formoterol (p. 1209.2) and has similar properties. Arformoterol is a long-acting selective $beta_2$ agonist that is used as a bronchodilator in the management of chronic obstructive pulmonary disease (p. 1199.1). It is given as the tartrate, but doses are described in terms of the base; 22 micrograms of arformoterol tartrate is equivalent to about 15 micrograms of arformoterol. Given as a nebulised solution, a usual inhaled dose of arformoterol is 15 micrograms given every 12 hours.

References.

1. Lötvall J, *et al.* The effect of formoterol over 24 h in patients with asthma: the role of enantiomers. *Pulm Pharmacol Ther* 2005; 18: 109–13.
2. Anonymous. Arformoterol (Brovana) for COPD. *Med Lett Drugs Ther* 2007; 49: 53–5.
3. Baumgartner RA, *et al.* Nebulized arformoterol in patients with COPD: a 12-week, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled trial. *Clin Ther* 2007; 29: 261–78.
4. Matera MG, Cazzola M. Ultra-long-acting β_2-adrenoceptor agonists: an emerging therapeutic option for asthma and COPD? *Drugs* 2007; 67: 503–15.
5. King P. Role of arformoterol in the management of COPD. *Int J Chron Obstruct Pulmon Dis* 2008; 3: 385–91.
6. Donohue JF, *et al.* Arformoterol and salmeterol in the treatment of chronic obstructive pulmonary disease: a one year evaluation of safety and tolerance. *Ther Adv Respir Dis* 2008; 2: 37–48.
7. Madaan A. Arformoterol tartrate in the treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease. *Drugs Today* 2009; 45: 3–9.
8. Panettieri RA, *et al.* Comparison of the efficacy and safety of arformoterol 15 µg twice daily and arformoterol 30 µg once daily in COPD: a single dose, multicenter, randomized, modified-blind, two-way crossover study. *Clin Ther* 2009; 31: 1716–23.
9. Hanania NA, *et al.* The safety and efficacy of arformoterol and formoterol in COPD. *COPD* 2010; 7: 17–31.
10. Cazzola M, *et al.* Arformoterol tartrate in the treatment of COPD. *Expert Rev Respir Med* 2010; 4: 155–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Brovana.

Bambuterol Hydrochloride

(BANM, rINNM) ⊗

Bambutérol, Chlorhydrate de; Bambuterol, hidrocloruro de; Bambuterol-hidroklorid; Bambuterolhydrochlorid; Bambuterol-hydrochlorid; Bambuterolhydroklorid; Bambuterolí hydrochloridum; Bambuterolihydrokloridi; Bambuterolio hidrochloridas; Hidrocloruro de bambuterol; KWD-2183; Бамбутерола Гидрохлорид.

(*RS*)-5-(2-*tert*-Butylamino-1-hydroxyethyl)-*m*-phenylene bis (dimethylcarbamate) hydrochloride.

$C_{18}H_{29}N_3O_5.HCl$=403.9

CAS — 81732-65-2 (bambuterol); 81732-46-9 (bambuterol monohydrochloride).

ATC — R03CC12.

ATC Vet — QR03CC12.

UNII — 786Q84QZ3F.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Bambuterol Hydrochloride). A white or almost white crystalline powder. It exhibits polymorphism. Freely soluble in water; soluble in alcohol.

Uses and Administration

Bambuterol is an inactive prodrug of terbutaline (p. 1228.1), a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has similar actions to those of salbutamol (p. 1220.2) except that it has a more prolonged duration of action (at least 24 hours). Bambuterol hydrochloride is used as a long-acting bronchodilator for persistent reversible airways obstruction in conditions such as asthma (p. 1195.2). The usual dose is 10 to 20 mg orally once daily at bedtime. Doses may need to be reduced in renal impairment (see below).

Administration in renal impairment. Licensed product information recommends that the initial dose of bambuterol hydrochloride should be halved in patients with renal impairment (glomerular filtration rate less than 50 mL/minute). Further doses should be adjusted according to response.

Asthma. References.

1. Pugleholm AM, *et al.* Therapeutic equivalence between bambuterol, 10 mg once daily, and terbutaline controlled release, 5 mg twice daily, in mild to moderate asthma. *Eur Respir J* 1993; 6: 1474–8.
2. Gunn SD, *et al.* Comparison of the efficacy, tolerability and patient acceptability of once-daily bambuterol tablets against twice-daily controlled release salbutamol in nocturnal asthma. *Eur J Clin Pharmacol* 1995; 48: 23–8.
3. Zarkovic JP, *et al.* The Bambuterol Multicentre Study Group. One-year safety study with bambuterol once daily and terbutaline three times daily in 2-12-year-old children with asthma. *Pediatr Pulmonol* 2000; 29: 424–9.

Adverse Effects and Precautions

As for Salbutamol, p. 1221.3. Bambuterol is not recommended for patients with severe hepatic impairment as its metabolism would be unpredictable. The dose of bambuterol should be reduced in renal impairment (see above). It is unsuitable for the relief of acute bronchospasm or in patients with unstable respiratory disease.

Effects on the heart. A prescription event monitoring study found an excess risk of non-fatal heart failure in elderly patients receiving bambuterol, particularly in the first month of treatment.[1] See also under Salbutamol, p. 1222.1.

1. Martin RM, *et al.* Risk of non-fatal cardiac failure and ischaemic heart disease with long acting β_2 agonists. *Thorax* 1998; 53: 558–62.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bambuterol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

As for Salbutamol, p. 1223.1. Bambuterol inhibits plasma cholinesterases and can prolong the action of drugs such as suxamethonium (see Sympathomimetics, under Suxamethonium, p. 2040.1) that are inactivated by these enzymes.

Pharmacokinetics

Nearly 20% of a dose of bambuterol is absorbed from the gastrointestinal tract after oral doses. It is slowly metabolised in the body to its active metabolite, terbutaline; peak terbutaline concentrations are reported to occur about 4 to 7 hours after a dose of bambuterol as tablets. The slow rate at which metabolism occurs determines the prolonged duration of action of bambuterol of at least 24 hours. Hydrolysis of bambuterol is catalysed by plasma cholinesterase; however, bambuterol also inhibits plasma cholinesterase and therefore partly inhibits its own metabolism. For the metabolism and excretion of terbutaline, see p. 1229.1.

References.

1. Sitar DS. Clinical pharmacokinetics of bambuterol. *Clin Pharmacokinet* 1996; 31: 246–56.
2. Nyberg L, *et al.* Pharmacokinetics of bambuterol in healthy subjects. *Br J Clin Pharmacol* 1998; 45: 471–8.
3. Bang U, *et al.* Pharmacokinetics of bambuterol in subjects homozygous for the atypical gene for plasma cholinesterase. *Br J Clin Pharmacol* 1998; 45: 479–84.
4. Ahlström H, *et al.* Pharmacokinetics of bambuterol during oral administration to asthmatic children. *Br J Clin Pharmacol* 1999; 48: 299–308.
5. Rosenborg J, *et al.* Pharmacokinetics of bambuterol during oral administration of plain tablets and solution to healthy adults. *Br J Clin Pharmacol* 2000; 49: 199–206.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Bambec; ***Braz.***: Bambair; Bambec; ***China***: Ao Duo Li (奥多利); Bambec (帮备); BangShun (邦顺); Bei He Jian (贝合健); Hui Jie (汇杰); Li Ke Fei (立可菲); Luo Xi (洛希); LuoLi (罗利); Zhu Long (祝龙); ***Denm.***: Bambec; Oxeol; ***Fr.***: Oxeol; ***Ger.***: Bambec; ***India***: Abel; Asthafree; Bambudil; Bemlo; Betaday; ***Norw.***: Bambec; ***NZ***: Bambec; ***Philipp.***: Bambec; Bambutec; Pulmitac; ***Singapore***: Bambec; ***Spain***: Bambec; ***Swed.***: Bambec; ***Thai.***: Bambec; ***UK***: Bambec.

Multi-ingredient Preparations. ***India***: Montair Plus; Monway Plus; Odimont Plus.

Bamifylline Hydrochloride

(BANM, USAN, rINNM)

AC-3810; Bamifilina, hidrocloruro de; Bamifylline, Chlorhydrate de; Bamifyllini Hydrochloridum; BAX-2739Z; 8102-CB; CB-8102; Hidrocloruro de bamifilina; Бамифиллина Гидрохлорид.

8-Benzyl-7-[2-(*N*-ethyl-*N*-2-hydroxyethylamino)ethyl]theophylline hydrochloride.

$C_{20}H_{27}N_5O_3.HCl$=421.9

CAS — 2016-63-9 (bamifylline); 20684-06-4 (bamifylline hydrochloride).

ATC — R03DA08.

ATC Vet — QR03DA08.

UNII — 66466QLM3S.

Profile

Bamifylline hydrochloride is a theophylline derivative (p. 1229.3) that is used for its bronchodilator properties in reversible airways obstruction. It is not converted to theophylline in the body. It is given in usual oral doses of 600 or 900 mg daily in 2 or 3 divided doses. It is also given rectally as suppositories, and by slow intravenous infusion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Bamifix; ***Fr.***: Trentadil; ***Ital.***: Bamiflx; Briofil.

Bitolterol Mesilate *(BANM, rINNM)* ⊗

Biltolterol, Mésilate de; Bitolterol, mesilato de; Bitolterol Mesylate (USAN); Bitolteroli Mesilas; Mesilato de bitolterol; Win-32784; Битолтерола Мезилат.

4-[2-(*tert*-Butylamino)-1-hydroxyethyl]-*o*-phenylene di-*p*-toluate methanesulphonate.

$C_{28}H_{31}NO_5.CH_4O_3S$=557.7

CAS — 30392-40-6 (bitolterol); 30392-41-7 (bitolterol mesilate).

ATC — R03AC17.

ATC Vet — QR03AC17.

UNII — 4E53T3611U.

Profile

Bitolterol is an inactive prodrug that is hydrolysed in the body to colterol, a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has similar properties to those of salbutamol (p. 1220.2), and has been used as a bronchodilator in the management of diseases with reversible airways obstruction such as asthma (p. 1195.2) or in some patients with chronic obstructive pulmonary disease (p. 1199.1); inhalation results in the rapid onset of bronchodilatation (2 to 4 minutes) with a duration of action of 5 or more hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Tornalate†.

Bufylline *(BAN)*

Ambuphylline (USAN); Bufilina; Theophylline-aminoisobutanol; Буфиллин.

2-Amino-2-methylpropan-1-ol theophyllinate.

$C_{11}H_{19}N_5O_3$=269.3

CAS — 5634-34-4.

ATC — R03DA10.

ATC Vet — QR03DA10.

UNII — VOUSV0B772.

Profile

Bufylline is a theophylline derivative (p. 1229.3) that has been used for its bronchodilator effects as an ingredient of preparations promoted for coughs and other respiratory-tract disorders. The ethiodide has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Braz.***: EMS Expectorante; Revenil Dospan; Revenil Expectorante; Revenil; Xpe Expectorante; ***S. Afr.***: Nethaprin Dospan†; Nethaprin Expectorant†.

Caffeine *(BAN)*

Anhydrous Caffeine; Cafeína; Cafeína anhidra; Caféine; Coffein; Coffeinum; Guaranina; Guaranine; Kofeiini; Kofein; Kofeina; Kofeinas; Koffein; Methyltheobromine; Metilteobromina; Teína; Théine; Кофеин.

1,3,7-Trimethylpurine-2,6(3*H*,1*H*)-dione; 1,3,7-Trimethylxanthine; 7-Methyltheophylline.

$C_8H_{10}N_4O_2$=194.2

CAS — 58-08-2.

ATC — N06BC01.

ATC Vet — QN06BC01.

UNII — 3G6A5W338E.

NOTE. Compounded preparations of caffeine may be represented by the following names:

- Co-bucaf APAP (*PEN*)—butalbital, paracetamol, and caffeine.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.* Some pharmacopoeias include caffeine and caffeine hydrate under one monograph.

Ph. Eur. 8: (Caffeine). A white or almost white, crystalline powder or silky white or almost white crystals. It sublimes readily. Sparingly soluble in water; freely soluble in boiling water; slightly soluble in dehydrated alcohol. It dissolves in concentrated solutions of alkali benzoates or salicylates.

USP 36: (Caffeine). It is anhydrous or contains one molecule of water of hydration. An odourless white powder or white, glistening needles, usually matted together. The hydrate is efflorescent in air. The hydrate is soluble 1 in 50 of water, 1 in 75 of alcohol, 1 in 6 of chloroform, and 1 in 600 of ether. The hydrate should be stored in airtight containers.

Caffeine Citrate *(BANM)*

Cafeína, citrato de; Citrated Caffeine; Coffeinum Citricum; Кофеина Цитрат.

$C_8H_{10}N_4O_2.C_6H_8O_7$=386.3

CAS — 69-22-7.

ATC — N06BC01.

ATC Vet — QN06BC01.

UNII — U26EO4675Q.

Caffeine Hydrate *(BANM)*

Cafeína monohidrato; Caféine monohydratée; Caffeine Monohydrate; Coffein-Monohydrat; Coffeinum Monohydricum; Kofeiinimonohydraatti; Kofein monohydrat; Kofeinas monohidratas; Koffein-monohidrat; Koffeinmonohydrat; Кофеин Моногидрат.

$C_8H_{10}N_4O_2.H_2O$=212.2

CAS — 5743-12-4.

ATC — N06BC01.

ATC Vet — QN06BC01.

UNII — 9765I0632G.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.* Some pharmacopoeias include caffeine and caffeine hydrate under one monograph.

Ph. Eur. 8: (Caffeine Monohydrate; Caffeine Hydrate BP 2014). A white or almost white, crystalline powder or silky white or almost white crystals. It sublimes readily. Sparingly

soluble in water; freely soluble in boiling water; slightly soluble in dehydrated alcohol. It dissolves in concentrated solutions of alkali benzoates or salicylates.

USP 36: (Caffeine). It is anhydrous or contains one molecule of water of hydration. An odourless white powder or white, glistening needles, usually matted together. The hydrate is efflorescent in air. The hydrate is soluble 1 in 50 of water, 1 in 75 of alcohol, 1 in 6 of chloroform, and 1 in 600 of ether. The hydrate should be stored in airtight containers.

Stability. References to the stability of caffeine and caffeine citrate.

1. Eisenberg MG, Kang N. Stability of citrated caffeine solutions for injectable and enteral use. *Am J Hosp Pharm* 1984; 41: 2405–6.
2. Nahata MC, *et al.* Stability of caffeine injection in intravenous admixtures and parenteral nutrition solutions. *DICP Ann Pharmacother* 1989; 23: 466–7.
3. Hopkin C, *et al.* Stability study of caffeine citrate. *Br J Pharm Pract* 1990; 12: 133.
4. Donnelly RF, Tirona RG. Stability of citrated caffeine injectable solution in glass vials. *Am J Hosp Pharm* 1994; 51: 512–14.
5. Fraser BD. Stability of caffeine citrate injection in polypropylene syringes at room temperature. *Am J Health-Syst Pharm* 1997; 54: 1106, 1108.

Uses and Administration

Caffeine is a methylxanthine that, like theophylline (p. 1229.3), inhibits the enzyme phosphodiesterase and has an antagonistic effect at central adenosine receptors. It is a stimulant of the CNS, particularly the higher centres, and it can produce a condition of wakefulness and increased mental activity. It may also stimulate the respiratory centre, increasing the rate and depth of respiration. Its bronchodilating properties are weaker than those of theophylline. Caffeine facilitates the performance of muscular work and increases the total work that can be performed by a muscle. The diuretic action of caffeine is weaker than that of theophylline.

Caffeine is used as a mild CNS stimulant in usual oral doses of 50 to 100 mg, although doses of up to 200 mg may be used. Doses should not be taken more often than every 3 hours. It is also frequently included in oral analgesic preparations with aspirin, paracetamol, or codeine in unit doses of about 15 to 65 mg but its clinical benefit is debated (see Pain, p. 1205.1). Caffeine is sometimes given with ergotamine in preparations for the treatment of migraine, usually in unit doses of 100 mg. Caffeine citrate has been used similarly. For details of doses in children, see Administration in Children, below.

Caffeine and sodium benzoate and caffeine and sodium salicylate are readily soluble in water and have been used when caffeine is to be given by injection.

Beverages of coffee, tea, and cola provide active doses of caffeine (see p. 2648.2).

General references.

1. Sawynok J. Pharmacological rationale for the clinical use of caffeine. *Drugs* 1995; 49: 37–50.
2. Keisler BD, Armsey TD. Caffeine as an ergogenic aid. *Curr Sports Med Rep* 2006; 5: 215–9.
3. Jones G. Caffeine and other sympathomimetic stimulants: modes of action and effects on sports performance. *Essays Biochem* 2008; 44: 109–23.
4. Ferré S. An update on the mechanisms of the psychostimulant effects of caffeine. *J Neurochem* 2008; 105: 1067–79.

Administration in children. Caffeine is used in the short-term treatment of neonatal apnoea of prematurity (below).

- An initial loading dose of caffeine citrate 20 mg/kg (equivalent to 10 mg/kg caffeine) is given orally or by intravenous infusion over 30 minutes. If there is inadequate response to the first loading dose, a second loading dose may be given. Licensed product information recommendations for timing of the second dose vary; re-dosing after either 4 hours or 24 hours have been suggested. If there is continued inadequate response, serum-caffeine concentrations should be measured before further doses are given.
- Beginning 24 hours after the loading dose, a maintenance dose of caffeine citrate 5 to 10 mg/kg (2.5 to 5 mg/kg caffeine) daily is given either orally or by intravenous infusion over 10 minutes.

Serum concentrations of caffeine should be measured before starting treatment in infants who have already been treated with theophylline (which is metabolised to caffeine in infants) or whose mothers consumed caffeine before delivery. Infants with impaired renal or hepatic function should also have serum concentrations of caffeine monitored, and doses reduced if necessary. Serious toxicity has been associated with serum concentrations greater than 50 micrograms/mL.

Optimal duration of treatment has not been established, however therapy is usually continued until the neonate has reached 37 weeks of gestational age when apnoea of prematurity usually resolves spontaneously. It is recommended that caffeine should be stopped when the patient has 5 to 7 days without a significant apnoeic attack.

Asthma. Caffeine's bronchodilating activity is about 40% that of theophylline[1] and oral doses of 5 or 10 mg/kg have been shown to produce an effect.[2,3] Because of its weak action other xanthines are generally recommended in asthma (p. 1195.2), but it may need to be avoided before tests of lung function.[4]

1. Gong H, *et al.* Bronchodilator effects of caffeine in coffee: a dose-response study of asthmatic subjects. *Chest* 1986; 89: 335–42.
2. Becker AB, *et al.* The bronchodilator effects and pharmacokinetics of caffeine in asthma. *N Engl J Med* 1984; 310: 743–6.
3. Bukowskyj M, Nakatsu K. The bronchodilator effect of caffeine in adult asthmatics. *Am Rev Respir Dis* 1987; 135: 173–5.
4. Welsh EJ, *et al.* Caffeine for asthma. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 13/07/10).

Dementia. A cohort study in 7017 patients aged 65 years and over examined the association between caffeine intake, cognitive decline, and incident dementia.[1] Caffeine consumption itself was found to be significantly associated with many variables also associated with cognitive decline, such as age, gender, depressive symptoms, and cardiovascular disease. Although no relationship was found between baseline caffeine intake and incident dementia in a 4-year follow-up period, caffeine consumption appeared to reduce cognitive decline in women without dementia. The authors concluded that further studies are required to ascertain whether caffeine may be of value in prolonging the period of mild cognitive impairment in women before a diagnosis of dementia.

1. Ritchie K, *et al.* The neuroprotective effects of caffeine: a prospective population study (the Three City Study). *Neurology* 2007; 69: 536–45.

Diabetes mellitus. A single dose of caffeine 250 mg proved beneficial in augmenting warning symptoms and physiological responses to experimentally-induced hypoglycaemia in diabetic patients,[1] and was suggested as a potentially useful adjunct for diabetics who have difficulty in recognising the onset of hypoglycaemia (see Diabetic Emergencies, p. 465.3). In a subsequent placebo-controlled crossover study oral caffeine 200 mg twice daily appeared to enhance the intensity of hypoglycaemic warning symptoms in patients with type 1 diabetes on a low-caffeine diet.[2] A later study[3] reported an association between caffeine and a reduction in the frequency of nocturnal hypoglycaemia in patients with type 1 diabetes, which the authors suggested may explain the increase in warning symptoms and hormonal responses previously reported in daytime hypoglycaemia. Caffeine has also been seen to impair postprandial glucose metabolism in patients with type 2 diabetes,[4] raising concern about the potential hazards of caffeine in these patients for whom decreases in insulin sensitivity might increase average glucose levels and the risk of diabetic complications.

1. Debrah K, *et al.* Effect of caffeine on recognition of and physiological responses to hypoglycaemia in insulin-dependent diabetes. *Lancet* 1996; 347: 19–24.
2. Watson JM, *et al.* Influence of caffeine on the frequency and perception of hypoglycemia in free-living patients with type 1 diabetes. *Diabetes Care* 2000; 23: 455–9.
3. Richardson T, *et al.* Influence of caffeine on frequency of hypoglycaemia detected by continuous interstitial glucose monitoring system in patients with long-standing type 1 diabetes. *Diabetes Care* 2005; 28: 1316–20.
4. Lane JD, *et al.* Caffeine impairs glucose metabolism in type 2 diabetes. *Diabetes Care* 2004; 27: 2047–8.

Diagnosis and testing. Caffeine excretion assessed by measuring its urinary metabolites or by the exhalation of labelled CO_2 in breath after doses of ^{13}C- or ^{14}C-labelled caffeine has been used to develop liver function tests and to determine the activity of specific enzymes such as xanthine oxidase, P450 cytochromes, and polymorphic *N*-acetyltransferase.[1]

Caffeine given orally has been used to assess acetylator status by determining the metabolic ratio of the metabolites 5-acetylamino-6-formylamino-1-methyluracil (AFMU) to 1-methylxanthine in urine,[2] but some have questioned its value.[3]

Caffeine has also been investigated in the diagnosis of susceptibility to malignant hyperthermia.[4] Intramuscular injection induced a temporary hypermetabolic reaction in subjects susceptible to malignant hyperthermia, but not in non-susceptible subjects or healthy controls. The authors suggested that monitoring of carbon dioxide, produced by hypermetabolism, might offer a minimally invasive test for such susceptibility.

1. Kalow W, Tang B-K. The use of caffeine for enzyme assays: a critical appraisal. *Clin Pharmacol Ther* 1993; 53: 503–14.
2. Hildebrand M, Seifert W. Determination of acetylator phenotype in caucasians with caffeine. *Eur J Clin Pharmacol* 1989; 37: 525–6.
3. Notarianni LJ, *et al.* Caffeine as a metabolic probe: NAT2 phenotyping. *Br J Clin Pharmacol* 1996; 41: 169–73.
4. Anetseder M, *et al.* Diagnosis of susceptibility to malignant hyperthermia by use of a metabolic test. *Lancet* 2002; 359: 1579–80.

ECT. In patients whose seizure duration is declining despite maximal ECT stimulation, pretreatment with high-dose intravenous caffeine increases seizure duration without affecting seizure threshold. Theophylline has been used similarly, see p. 1233.2.

References.

1. Hinkle PE, *et al.* Use of caffeine to lengthen seizures in ECT. *Am J Psychiatry* 1987; 144: 1143–8.
2. Coffey CE, *et al.* Caffeine augmentation of ECT. *Am J Psychiatry* 1990; 147: 579–85.
3. Kelsey MC, Grossberg GT. Safety and efficacy of caffeine-augmented ECT in elderly depressives: a retrospective study. *J Geriatr Psychiatr Neurol* 1995; 8: 168–72.

Neonatal apnoea. Apnoea of infancy has been defined as cessation of breathing either lasting 20 seconds or more or associated with bradycardia, cyanosis, pallor, and marked hypotonia, for which no specific cause can be identified. Premature infants (less than 37 weeks of gestation) can exhibit periodic breathing with pathological apnoea (apnoea of prematurity); this usually resolves as the infant approaches term and the neurological systems controlling ventilation mature.[1,2]

The management of neonatal apnoea for which no underlying disorder can be found may involve supportive measures such as cardiorespiratory monitoring;[1] continuous positive airways pressure and drug therapy may be required.[3]

The methylxanthines, aminophylline, theophylline, and caffeine, reduce the frequency of apnoea and the need for mechanical ventilation in preterm infants during the first seven days of therapy.[4] In preterm infants given intermittent positive airway pressure, prophylactic methylxanthine treatment increases the chances of successful extubation within one week.[5] There is evidence to suggest that this benefit might be more helpful in infants of extremely low birth-weight extubated in the first week. High doses of caffeine, 20 mg/kg daily, have been used around the time of extubation in neonates born at less than 30 weeks of gestation. Short term benefits were noted,[6] and no evidence of harm in the first year of life. A review of the use of prophylactic methylxanthines found no evidence to show that caffeine prevents apnoea in at-risk preterm infants, or that it reduces the severity of apnoea or its symptoms; prophylactic methylxanthines might, however, reduce the duration of need for positive pressure ventilation and the rate of patent ductus arteriosus ligation.[7] Caffeine has also been reported to reduce the incidence of bronchopulmonary dysplasia in infants with very low birth-weight,[3] so that positive airways pressure could be stopped earlier in infants given caffeine compared with those given placebo. A later evaluation of these infants found that caffeine therapy improved the rate of survival without neurodevelopmental disability at 18 to 21 months.[8] The incidence of cerebral palsy and cognitive delay were also reduced. Earlier stopping of positive airway pressure in the infants assigned to caffeine explained almost half of the beneficial long-term effect of caffeine, but further studies are required to ascertain other potential mechanisms of action. When assessed at 5 years, neonatal caffeine therapy was no longer associated with a significantly improved rate of survival without disability in these children.[9] Rates of cognitive impairment were much lower at 5 years than at 18 months, and similar in the 2 groups, suggesting that cognitive delay may not be a lasting outcome after preterm birth.

Caffeine has a wider therapeutic index, fewer peripheral adverse effects than theophylline, and a longer half-life enabling once-daily dosage, and is therefore preferred.[4,10] Caffeine is given as the citrate salt, and is well absorbed when given orally. For details of doses, see Administration in Children, above. The *BNFC* considers appropriate serum concentrations in neonatal apnoea to be 10 to 20 mg/litre (50 to 100 micromol/litre). Higher concentrations of 25 to 35 mg/litre (130 to 180 micromol/litre) may sometimes be required. Previous treatment with theophylline, infants born to mothers who consumed caffeine before delivery, infants showing signs of toxicity, or infants who require higher doses will require monitoring of plasma caffeine concentrations; however, routine monitoring of plasma concentrations is not always considered necessary.[11] During the first year of life, the elimination half-life of both caffeine and theophylline decreases significantly as the infant matures; regular monitoring of serum concentrations and constant dosage adjustments are therefore required if therapy is prolonged.[1]

For details of the adverse effects on the cardiovascular system associated with caffeine during treatment of neonatal apnoea, see Effects on the Cardiovascular System, p. 1205.2.

Use of doxapram has been tried for apnoea that does not respond to xanthine therapy;[1,2,12] its effects were similar to the methylxanthines.[13,14] Doxapram is poorly absorbed orally and adverse effects such as hypertension, CNS stimulation, and heart block have been reported.[15]

1. Kriter KE, Blanchard J. Management of apnea in infants. *Clin Pharm* 1989; 8: 577–87.
2. Ruggins NR. Pathophysiology of apnoea in preterm infants. *Arch Dis Child* 1991; 66: 70–73.
3. Schmidt B, *et al.* Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006; 354: 2112–21.
4. Henderson-Smart DJ, De Paoli AG. Methylxanthine treatment for apnoea in preterm infants. Available in The Cochrane Database of

Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 03/07/12).
5. Henderson-Smart DJ, Davis PG. Prophylactic methylxanthines for endotracheal extubation in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 03/07/12).
6. Steer P, *et al.* High dose caffeine citrate for extubation of preterm infants: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2004; 89: F499–F503.
7. Henderson-Smart DJ, De Paoli AG. Prophylactic methylxanthine for prevention of apnoea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 03/07/12).
8. Schmidt B, *et al.* Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007; 357: 1893–1902.
9. Schmidt B, *et al.* Caffeine for Apnea of Prematurity (CAP) Trial Investigators. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *JAMA* 2012; 307: 275–82.
10. Henderson-Smart DJ, Steer PA. Caffeine versus theophylline for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 03/07/12).
11. Natarajan G, *et al.* Therapeutic drug monitoring for caffeine in preterm neonates: an unnecessary exercise? *Pediatrics* 2007; 119: 936–40.
12. Hascoet J-M, *et al.* Risks and benefits of therapies for apnoea in premature infants. *Drug Safety* 2000; 23: 363–79.
13. Eyal F, *et al.* Aminophylline versus doxapram in idiopathic apnea of prematurity: a double-blind controlled study. *Pediatrics* 1985; 75: 709–13.
14. Pellowski A, Finer NN. A blinded, randomized, placebo-controlled trial to compare theophylline and doxapram for the treatment of apnea of prematurity. *J Pediatr* 1990; 116: 648–53.
15. Henderson-Smart DJ, Steer P. Doxapram versus methylxanthine for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 19/03/08).

Obesity. A 1999 review[1] of non-prescription weight loss supplements concluded that controlled studies have not shown fat loss in overweight individuals using caffeine without an energy-restricted diet. A later study[2] examined a herbal combination product, containing amongst its active ingredients caffeine (from kola nut) and ephedrine (from ephedra), in the treatment of overweight and obesity without other lifestyle modifications. Some beneficial effects on body-weight were reported after 12 weeks of treatment compared with placebo; however, although no serious adverse effects were seen in the healthy subjects enrolled in this study, the herbal product used contained relatively low amounts of active ingredients compared with preparations used in other similar studies. The FDA has since banned the sale of dietary supplements containing ephedra as they present an unreasonable risk to health (see Ephedra, p. 1663.1), and concerns have been raised about potential additive stimulant effects of preparations containing both caffeine and ephedrine, see Sympathomimetics under Interactions, p. 1206.2.

1. Egger G, *et al.* The effectiveness of popular, non-prescription weight loss supplements. *Med J Aust* 1999; 171: 604–8.
2. Coffey CS, *et al.* A randomized double-blind placebo-controlled clinical trial of a product containing ephedrine, caffeine, and other ingredients from herbal sources for treatment of overweight and obesity in the absence of lifestyle treatment. *Int J Obes Relat Metab Disord* 2004; 28: 1411–19.

Orthostatic hypotension. Caffeine has been of benefit in the treatment of orthostatic hypotension (p. 1634.3) due to autonomic failure in some patients, especially for postprandial hypotension.[1-3] However, efficacy has only been shown in mild cases and it is usually ineffective in severe cases.[4]

1. Onrot J, *et al.* Hemodynamic and humoral effects of caffeine in autonomic failure. *N Engl J Med* 1985; 313: 549–54.
2. Hoeldtke RD, *et al.* Treatment of orthostatic hypotension with dihydroergotamine and caffeine. *Ann Intern Med* 1986; 105: 168–73.
3. Tonkin AL. Postural hypotension. *Med J Aust* 1995; 162: 436–8.
4. Mathias CJ. Orthostatic hypotension. *Prescribers' J* 1995; 35: 124–32.

Pain. Caffeine has been widely used in analgesic preparations to enhance the effects of both non-opioid and opioid analgesics but is of debatable benefit (see under Choice of Analgesic, p. 4.2). Some investigators have failed to show that caffeine offers any benefit[1,2] but others have shown that the adjuvant use of caffeine can increase analgesic activity.[3-8] A meta-analysis of 10 studies comparing paracetamol plus caffeine with paracetamol alone in women with postpartum uterine cramp found any benefit of the combination to be minimal.[9] A literature review[10] concluded that there was some evidence that caffeine may be useful as an analgesic adjuvant in relieving headache, but that the dose may need to be at least 65 mg and that these higher doses increase the risk of nervousness and dizziness. Evidence for the effects of caffeine in other types of pain, such as postpartum, postoperative, dental, rheumatic, and cancer pain, was inconclusive.

In the UK it is generally recommended that caffeine-containing analgesic preparations should not be used not only because of doubts about caffeine enhancing the analgesic effect but because it can add to gastrointestinal adverse effects and in large doses can itself cause headache.

Whether caffeine enhances the gastrointestinal absorption of ergotamine in preparations for the relief of migraine is not clear.

1. Winter L, *et al.* A double-blind, comparative evaluation of acetaminophen, caffeine, and the combination of acetaminophen and caffeine in outpatients with post-operative oral surgery pain. *Curr Ther Res* 1983; 33: 115–22.
2. Sawynok J. Pharmacological rationale for the clinical use of caffeine. *Drugs* 1995; 49: 37–50.
3. Laska EM, *et al.* Caffeine as an analgesic adjuvant. *JAMA* 1984; 251: 1711–18.
4. Rubin A, Winter L. A double-blind randomized study of an aspirin/caffeine combination versus acetaminophen/aspirin combination versus acetaminophen versus placebo in patients with moderate to severe postpartum pain. *J Int Med Res* 1984; 12: 338–45.
5. Schachtel BP, *et al.* Caffeine as an analgesic adjuvant: a double-blind study comparing aspirin with caffeine to aspirin and placebo in patients with sore throat. *Arch Intern Med* 1991; 151: 733–7.
6. Migliardi JR, *et al.* Caffeine as an analgesic adjuvant in tension headache. *Clin Pharmacol Ther* 1994; 56: 576–86.
7. Kraetsch HG, *et al.* Analgesic effects of propyphenazone in comparison to its combination with caffeine. *Eur J Clin Pharmacol* 1996; 49: 377–82.
8. Diener HC, *et al.* The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. *Cephalalgia* 2005; 25: 776–87.
9. Zhang WY, Li Wan Po A. Analgesic efficacy of paracetamol and its combination with codeine and caffeine in surgical pain—a meta-analysis. *J Clin Pharm Ther* 1996; 21: 261–82.
10. Zhang W-Y. A benefit-risk assessment of caffeine as an analgesic adjuvant. *Drug Safety* 2001; 24: 1127–42.

POST-DURAL PUNCTURE HEADACHE. Intravenous caffeine sodium benzoate may relieve post-dural puncture headache (p. 1983.1) that persists despite conservative therapy. However, the evidence for such use has been questioned.[1]

1. Halker RB, *et al.* Caffeine for the prevention and treatment of postdural puncture headache: debunking the myth. *Neurologist* 2007; 13: 323–7.

Psoriasis. The efficacy of a 10% formulation of topical caffeine in the treatment of psoriasis has been investigated in a group of 39 patients with stable plaque psoriasis.[1] Improvements were seen at each 2-week follow-up stage, but the difference only became significant after 8 weeks. The only adverse effect noted during the study was mild itching, reported by 2 of the caffeine recipients.

1. Vali A, *et al.* Evaluation of the efficacy of topical caffeine in the treatment of psoriasis vulgaris. *J Dermatol Treat* 2005; 16: 234–7.

Adverse Effects, Treatment, and Precautions

As for Theophylline, p. 1231.2, p. 1232.3, and p. 1233.1.

Tolerance occurs rapidly to the stimulating effects of caffeine; physical signs of withdrawal including irritability, restlessness, lethargy, and headache may occur if intake is stopped abruptly.

General references.

1. Wills S. Drugs and substance misuse: caffeine. *Pharm J* 1994; 252: 822–4.
2. Fredholm BB, *et al.* Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev* 1999; 51: 83–133.

Breast feeding. The American Academy of Pediatrics[1] states that caffeine is excreted slowly by the infant and may be associated with irritability and poor sleeping pattern when ingested by breast-feeding mothers. However, no effects occur with moderate intake of caffeinated beverages (2 or 3 cups daily) and caffeine is usually compatible with breast feeding. Furthermore, a prospective cohort study of over 800 infants showed no significant consequences of maternal caffeine consumption on sleep patterns at the age of 3 months, even in those whose mothers consumed ≥300 mg daily during pregnancy and while breast feeding.[2]

Studies examining the transfer of caffeine into breast milk after oral doses of 35 to 336 mg of caffeine have recorded peak maternal plasma concentrations of 2.4 to 4.7 micrograms/mL, peak maternal saliva concentrations of 1.2 to 9.2 micrograms/mL, and peak breast-milk concentrations of 1.4 to 7.2 micrograms/mL. At these concentrations in breast milk, the calculated daily caffeine ingestion by breast-fed infants ranged from 1.3 to 3.1 mg, which was not thought to present a hazard, although irritability and a poor sleeping pattern were reported.[3-6]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/03/08)
2. Santos IS, *et al.* Maternal caffeine consumption and infant nighttime waking: prospective cohort study. *Pediatrics* 2012; 129: 860–8.
3. Tyrala EE, Dodson WE. Caffeine secretion into breast milk. *Arch Dis Child* 1979; 54: 787–800.
4. Hildebrandt R, *et al.* Transfer of caffeine to breast milk. *Br J Clin Pharmacol* 1983; 15: 612P.
5. Sagraves R, *et al.* Pharmacokinetics of caffeine in human breast milk after a single oral dose of caffeine. *Drug Intell Clin Pharm* 1984; 18: 507.
6. Berlin CM, *et al.* Disposition of dietary caffeine in milk, saliva, and plasma of lactating women. *Pediatrics* 1984; 73: 59–63.

Effects on the cardiovascular system. An increased caffeine intake has been associated with an increase in daytime blood pressure.[1] The study, in 82 healthy, normotensive adolescents, suggested that caffeine use may be a factor contributing to essential hypertension in young people.

High dose caffeine (25 mg/kg) used as a loading dose in the prevention and treatment of neonatal apnoea (see p. 1204.3) resulted in a marked reduction of cerebral and intestinal blood flow velocity in preterm infants;[2] no changes were noted in left ventricular output, blood pressure, or heart rate. The authors attributed the effect on blood flow velocity to vasoconstriction, and suggested a smaller caffeine loading dose, repeated several hours later. A later study, also in preterm infants, which examined the effect of a divided loading dose of caffeine (12.5 mg/kg repeated after 4 hours), found that cerebral blood flow velocity was decreased after the second dose; intestinal blood flow velocity and left ventricular output remained unchanged.[3] The authors concluded that the 20% reduction in cerebral blood flow velocity seen was probably not meaningful for infants with adequate cerebral oxygen supply; however, an infant's ability to respond to hypoxaemia by vasodilatation may be compromised.

For a discussion of the effects of caffeine-containing beverages on cardiovascular risk factors, see p. 2648.3.

1. Savoca MR, *et al.* Association of ambulatory blood pressure and dietary caffeine in adolescents. *Am J Hypertens* 2005; 18: 116–20.
2. Hoecker C, *et al.* Caffeine impairs cerebral and intestinal blood flow velocity in preterm infants. *Pediatrics* 2002; 109: 784–7.
3. Hoecker C, *et al.* Effects of a divided high loading dose of caffeine on circulatory variables in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2006; 91: F61–F64.

Effects on mental function. The effects of caffeine on sleep, including its potential to cause sleep disturbances and excessive daytime sleepiness, have been reviewed.[1,2]

1. James JE, Keane MA. Caffeine, sleep and wakefulness: implications of new understanding about withdrawal reversal. *Hum Psychopharmacol* 2007; 22: 549–58.
2. Roehrs T, Roth T. Caffeine: sleep and daytime sleepiness. *Sleep Med Rev* 2008; 12: 153–62.

Headache. The association of caffeine with headache has been reviewed.[1] Headache is a recognised symptom of caffeine withdrawal and even subjects who drink moderate amounts of coffee can develop headaches lasting 1 to 6 days when switched to a decaffeinated brand.[2] It has also been suggested that postoperative headache could be attributed to caffeine withdrawal as fasting patients are required to abstain from drinking tea or coffee before surgical procedures. Several studies[3-5] have found a positive association between postoperative headache and daily caffeine consumption, although there have also been negative findings.[6] A prospective study suggested that a prophylactic intravenous dose of caffeine on the day of surgery reduced the likelihood of postoperative headache in patients at risk of caffeine withdrawal.[7]

In a case-control study,[8] investigating the possible association of dietary and medicinal caffeine use with chronic daily headache (CDH), caffeine was found to be a modest risk factor for CDH onset, regardless of headache type. Patients suffering from CDH were more likely overall to have been high caffeine consumers before the onset of CDH; no association was found with current caffeine consumption.

1. Shapiro RE. Caffeine and headaches. *Curr Pain Headache Rep* 2008; 12: 311–5.
2. van Dusseldorp M, Katan MB. Headache caused by caffeine withdrawal among moderate coffee drinkers switched from ordinary to decaffeinated coffee: a 12 week double blind trial. *BMJ* 1990; 300: 1558–9.
3. Galletly DC, *et al.* Does caffeine withdrawal contribute to postanaesthetic morbidity? *Lancet* 1989; i: 1335.
4. Weber JG, *et al.* Perioperative ingestion of caffeine and postoperative headache. *Mayo Clin Proc* 1993; 68: 842–5.
5. Nikolajsen L, *et al.* Effect of previous frequency of headache, duration of fasting and caffeine abstinence on perioperative headache. *Br J Anaesth* 1994; 72: 295–7.
6. Verhoeff FH, Millar JM. Does caffeine contribute to postoperative morbidity? *Lancet* 1990; 336: 632.
7. Weber JG, *et al.* Prophylactic intravenous administration of caffeine and recovery after ambulatory surgical procedures. *Mayo Clin Proc* 1997; 72: 621–6.
8. Scher AI, *et al.* Caffeine as a risk factor for chronic daily headache: a population-based study. *Neurology* 2004; 63: 2022–7.

Overdosage. Reports and reviews of caffeine toxicity.

1. Zimmerman PM, *et al.* Caffeine intoxication: a near fatality. *Ann Emerg Med* 1985; 14: 1227–9.
2. Dalvi RR. Acute and chronic toxicity of caffeine: a review. *Vet Hum Toxicol* 1986; 28: 144–50.
3. Rivenes SM, *et al.* Intentional caffeine poisoning in an infant. *Pediatrics* 1997; 99: 736–8.
4. Anderson BJ, *et al.* Caffeine overdose in a premature infant: clinical course and pharmacokinetics. *Anaesth Intensive Care* 1999; 27: 307–11.
5. Ergenekon E, *et al.* Caffeine intoxication in a premature neonate. *Paediatr Anaesth* 2001; 11: 737–9.
6. Holstege CP, *et al.* Massive caffeine overdose requiring vasopressin infusion and hemodialysis. *J Toxicol Clin Toxicol* 2003; 41: 1003–7.
7. de Wijkerslooth LRH, *et al.* Life-threatening hypokalaemia and lactate accumulation after autointoxication with Stacker 2, a 'powerful slimming agent'. *Br J Clin Pharmacol* 2008; 66: 728–31.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies caffeine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Pregnancy. Studies of maternal caffeine intake on pregnancy outcomes have had mixed results. Although some prospective studies have found that maternal caffeine intake was associated with reduced fetal growth,[1,2] another study did not support this conclusion,[3] and a moderate reduction in caffeine intake in the second half of pregnancy was reported to have no effect on birth-weight or length of gestation.[4] Similarly, conflicting results have been reported for the effect of caffeine on miscarriage[5-8] and the risk of sudden infant death syndrome.[9,10] A report evaluating the reproductive effects of caffeine for the Food Standards Agency in the UK,[11] concluded that maternal caffeine intake during pregnancy is associated with an increased risk of fetal growth restriction. It seemed likely that the risk was increased with a caffeine intake of about 200 mg daily, but a lower threshold below which there was no increase in risk was not identified. It was also not possible to ascertain causality, although it was considered prudent to assume this. Although the literature suggested a positive association between caffeine intake and miscarriage, limitations in study design did not allow a firm conclusion to be drawn and data on other adverse effects such as preterm birth and congenital malformations were also inconclusive.

1. Cook DG, *et al.* Relation of caffeine intake and blood caffeine concentrations during pregnancy to fetal growth: prospective population based study. *BMJ* 1996; 313: 1358–62.
2. CARE Study Group. Maternal caffeine intake during pregnancy and risk of fetal growth restriction: a large prospective observational study. Abridged version: *BMJ* 2008; 337: 1334–8. Full version: http://www.bmj.com/cgi/reprint/337/nov03_2/a2332 (accessed 25/08/09)
3. Clausson B, *et al.* Effect of caffeine exposure during pregnancy on birth weight and gestational age. *Am J Epidemiol* 2002; 155: 429–36.
4. Bech BH, *et al.* Effect of reducing caffeine intake on birth weight and length of gestation: randomised controlled trial. Abridged version: *BMJ* 2007; 334: 409. Full version: http://www.bmj.com/cgi/reprint/334/7590/409 (accessed 25/08/09)
5. Mills JL, *et al.* Moderate caffeine use and the risk of spontaneous abortion and intrauterine growth retardation. *JAMA* 1993; 269: 593–7.
6. Klebanoff MA, *et al.* Maternal serum paraxanthine, a caffeine metabolite, and the risk of spontaneous abortion. *N Engl J Med* 1999; 341: 1639–44.
7. Infante-Rivard C, *et al.* Fetal loss associated with caffeine intake before and during pregnancy. *JAMA* 1993; 270: 2940–3.
8. Chattingius S, *et al.* Caffeine intake and the risk of first-trimester spontaneous abortion. *N Engl J Med* 2000; 343: 1839–45.
9. Ford RPK, *et al.* Heavy caffeine intake in pregnancy and sudden infant death syndrome. *Arch Dis Child* 1998; 78: 9–13.
10. Alm B, *et al.* Caffeine and alcohol as risk factors for sudden infant death syndrome. *Arch Dis Child* 1999; 81: 107–11.
11. Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Statement on the reproductive effects of caffeine. Available at: http://cot.food.gov.uk/pdfs/cotstatementcaffeine200804.pdf (accessed 25/08/09)

Interactions

Like theophylline (see p. 1233.3) caffeine undergoes extensive metabolism by hepatic microsomal cytochrome P450 isoenzyme CYP1A2, and is subject to many interactions with other drugs and substances that enhance or reduce its metabolic clearance.

Reviews.

1. Carrillo JA, Benitez J. Clinically significant pharmacokinetic interactions between dietary caffeine and medications. *Clin Pharmacokinet* 2000; 39: 127–53.

Alcohol. In a study of 8 healthy subjects given an oral dose of alcohol of 2.2 mL/kg, caffeine 150 mg by mouth did not antagonise the central effects of alcohol and, instead, a synergistic interaction occurred which further increased reaction time. The common practice of drinking coffee after drinking alcohol in order to sober up is not supported by these results.[1] Another study[2] found that some antagonism of the central effects of alcohol was produced by caffeine, although there was no reversal of subjective sensations of drunkenness; however the dose of caffeine in this study (400 mg) was considerably higher.

1. Oborne DJ, Rogers Y. Interactions of alcohol and caffeine on human reaction time. *Aviat Space Environ Med* 1983; 54: 528–34.
2. Azcona O, *et al.* Evaluation of the central effects of alcohol and caffeine interaction. *Br J Clin Pharmacol* 1995; 40: 393–400.

Antiarrhythmics. In 7 healthy subjects and 5 patients with cardiac arrhythmias, *mexiletine* in a single dose of 200 mg and a dose of 600 mg daily respectively, reduced the elimination of caffeine by 30 to 50%.[1] *Lidocaine, flecainide,* and *tocainide* had no effect on caffeine elimination in healthy subjects.[1]

1. Joeres R, Richter E. Mexiletine and caffeine elimination. *N Engl J Med* 1987; 317: 117.

Antibacterials. Caffeine elimination half-life has been reported to be increased and clearance decreased when given with *ciprofloxacin,*[1-3] *enoxacin,*[2,3] and *pipemidic acid,*[2,3] whereas *lomefloxacin,*[4] *norfloxacin,*[2,3] and *ofloxacin*[2,3] had little or no effect on these parameters. Enoxacin had the greatest inhibitory effect on caffeine clearance.[2,3]

1. Healy DP, *et al.* Interaction between oral ciprofloxacin and caffeine in normal volunteers. *Antimicrob Agents Chemother* 1989; 33: 474–8.
2. Harder S, *et al.* Ciprofloxacin-caffeine: a drug interaction established using in vivo and in vitro investigations. *Am J Med* 1989; 87 (suppl 5A): 89–91S.
3. Barnett G, *et al.* Pharmacokinetic determination of relative potency of quinolone inhibition of caffeine disposition. *Eur J Clin Pharmacol* 1990; 39: 63–9.
4. Healy DP, *et al.* Lack of interaction between lomefloxacin and caffeine in normal volunteers. *Antimicrob Agents Chemother* 1991; 35: 660–4.

Antidepressants. Fluvoxamine has been reported to significantly reduce the clearance and prolong the elimination half-life of caffeine.[1] The clinical importance of this interaction, attributed to inhibition of cytochrome P450 isoenzyme CYP1A2 by fluvoxamine, is unknown.

1. Culm-Merdek KE, *et al.* Fluvoxamine impairs single-dose caffeine clearance without altering caffeine pharmacodynamics. *Br J Clin Pharmacol* 2005; 60: 486–93.

Antiepileptics. The mean clearance of caffeine was increased and its half-life decreased in epileptic patients taking *phenytoin* compared with healthy controls, resulting in lower plasma-caffeine concentrations. Treatment with *carbamazepine* or *valproic acid* had no effect on the pharmacokinetics of caffeine.[1]

1. Wietholtz H, *et al.* Effects of phenytoin, carbamazepine, and valproic acid on caffeine metabolism. *Eur J Clin Pharmacol* 1989; 36: 401–6.

Antifungals. In a single-dose study in healthy subjects, *terbinafine* 500 mg by mouth decreased the clearance and increased the elimination half-life of caffeine 3 mg/kg given intravenously. *Ketoconazole* 400 mg by mouth did not prolong the elimination of caffeine to a significant extent.[1]

1. Wahlländer A, Paumgartner G. Effect of ketoconazole and terbinafine on the pharmacokinetics of caffeine in healthy volunteers. *Eur J Clin Pharmacol* 1989; 37: 279–83.

Antigout drugs. In a study in 2 healthy subjects, the plasma half-life of caffeine was essentially unchanged by 7 days of oral treatment with *allopurinol* 300 mg or 600 mg daily. However, allopurinol caused a specific, dose-dependent inhibition of the conversion of 1-methylxanthine to 1-methyluric acid.[1]

1. Grant DM, *et al.* Effect of allopurinol on caffeine disposition in man. *Br J Clin Pharmacol* 1986; 21: 454–8.

Gastrointestinal drugs. Oral *cimetidine* 1 g daily reduced the systemic clearance of caffeine and prolonged its elimination half-life in 5 healthy subjects. Although the steady-state plasma-caffeine concentration would increase by about 70%, it was thought unlikely that this would produce adverse clinical effects.[1] However, in contrast a study in 11 children given cimetidine in doses of 11 to 36 mg/kg daily for gastritis found no evidence that it altered the metabolism of a dose of ^{13}C-labelled caffeine.[2]

1. Broughton LJ, Rogers HJ. Decreased systemic clearance of caffeine due to cimetidine. *Br J Clin Pharmacol* 1981; 12: 155–9.
2. Parker AC, *et al.* Lack of inhibitory effect of cimetidine on caffeine metabolism in children using the caffeine breath test. *Br J Clin Pharmacol* 1997; 43: 467–70.

Lithium. For mention of the effect of caffeine on serum-lithium concentrations, see Xanthines, p. 432.3.

Methoxsalen. Single oral doses of 1.2 mg/kg methoxsalen have reduced the clearance of caffeine in patients with psoriasis,[1,2] consistent with a cytochrome P450 isoenzyme CYP1A2-dependent inhibition of caffeine demethylation.[2]

1. Mays DC, *et al.* Methoxsalen is a potent inhibitor of the metabolism of caffeine in humans. *Clin Pharmacol Ther* 1987; 42: 621–6.
2. Bendriss EK, *et al.* Inhibition of caffeine metabolism by 5-methoxypsoralen in patients with psoriasis. *Br J Clin Pharmacol* 1996; 41: 421–4.

Sex hormones. The clearance of caffeine has been reported to be reduced and its elimination half-life increased in women taking *oral contraceptives.*[1-3] This interaction was thought to be due to impairment of hepatic metabolism of caffeine by sex hormones and could result in increased accumulation of caffeine. Similar results have been reported[4] in a study of postmenopausal women given oestrogens for *hormone replacement therapy* and caffeine.

1. Patwardhan RV, *et al.* Impaired elimination of caffeine by oral contraceptive steroids. *J Lab Clin Med* 1980; 95: 603–8.
2. Abernethy DR, Todd EL. Impairment of caffeine clearance by chronic use of low-dose oestrogen-containing oral contraceptives. *Eur J Clin Pharmacol* 1985; 28: 425–8.
3. Balogh A, *et al.* Influence of ethinylestradiol-containing combination oral contraceptives with gestodene or levonorgestrel on caffeine elimination. *Eur J Clin Pharmacol* 1995; 48: 161–6.
4. Pollock BG, *et al.* Inhibition of caffeine metabolism by estrogen replacement therapy in postmenopausal women. *J Clin Pharmacol* 1999; 39: 936–40.

Sympathomimetics. Use of caffeine 400 mg with *phenylpropanolamine* 75 mg, both given orally as modified-release preparations, produced greater plasma-caffeine concentrations in healthy subjects than caffeine alone. Greater increases in blood pressure and more reports of physical adverse effects occurred after the combination than after either drug alone.[1]

Giving caffeine with *ephedrine* has been reported to produce significant cardiovascular, metabolic, and hormonal responses, including increased systolic blood pressure and heart rate, and raised fasting glucose and insulin.[2] These enhanced effects appear to be the result of a pharmacodynamic rather than a pharmacokinetic interaction, and led to the issue of a warning by Health Canada in 2006 not to use weight loss products containing both caffeine and ephedrine, since the combination had caused reported adverse effects ranging from dizziness, tremors, headaches, and irregularities in heart rate to seizures, psychosis, heart attacks, and stroke.[3] Those particularly at risk include individuals suffering from ischaemic heart disease, hypertension, and diabetes.[2,3]

1. Lake CR, *et al.* Phenylpropanolamine increases plasma caffeine levels. *Clin Pharmacol Ther* 1990; 47: 675–85.
2. Haller CA, *et al.* Enhanced stimulant and metabolic effects of combined ephedrine and caffeine. *Clin Pharmacol Ther* 2004; 75: 259–73.
3. Health Canada. Health Canada advises consumers not to use weight loss products containing ephedrine and caffeine (issued 23rd May 2006). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2006/2006_33-eng.php (accessed 09/07/08)

Theophylline. For the effect of caffeine on the metabolism and elimination of theophylline, see p. 1235.3.

Pharmacokinetics

Caffeine is absorbed readily after oral doses and is widely distributed throughout the body. It is also absorbed through the skin. Absorption when given rectally by suppository may be slow and erratic. Absorption after intramuscular injection may be slower than after oral doses. Caffeine passes readily into the CNS and into saliva; low concentrations are also present in breast milk. Caffeine crosses the placenta.

In adults, caffeine is metabolised almost completely in the liver via oxidation, demethylation, and acetylation, and is excreted in the urine as 1-methyluric acid, 1-methylxanthine, 7-methylxanthine, 1,7-dimethylxanthine (paraxanthine), 5-acetylamino-6-formylamino-3-methyluracil (AFMU), and other metabolites with only about 1% unchanged. Hepatic cytochrome P450 isoenzyme CYP1A2 is involved in caffeine enzymatic metabolism. Neonates have a greatly reduced capacity to metabolise caffeine, due to their immature hepatic enzyme systems, and it is largely excreted unchanged in the urine. By 9 months of age, urinary excretion is similar to that seen in adults. Elimination half-lives are about 3 to 7 hours in adults but may be about 3 to 4 days in neonates.

Metabolism and excretion. The metabolism of caffeine has been shown to be dose dependent[1,2] with clearance decreasing as the dose is increased suggesting saturable metabolism. Four- to fivefold differences in plasma half-lives of caffeine are common among healthy people. The plasma half-life of caffeine is decreased by smoking[3] and by exercise,[4] and is increased by liver disease such as cirrhosis and viral hepatitis,[3,5] and in pregnancy.[3] The plasma half-life of caffeine is not affected by old age[6] or obesity.[7] Drug interactions also affect the pharmacokinetics of caffeine (see above).

1. Cheng WSC, *et al.* Dose-dependent pharmacokinetics of caffeine in humans: relevance as a test of quantitative liver function. *Clin Pharmacol Ther* 1990; 47: 516–24.
2. Denaro CP, *et al.* Dose-dependency of caffeine metabolism with repeated dosing. *Clin Pharmacol Ther* 1990; 48: 277–85.
3. Kalow W. Variability of caffeine metabolism in humans. *Arzneimittelforschung* 1985; 35: 319–24.
4. Collomp K, *et al.* Effects of moderate exercise on the pharmacokinetics of caffeine. *Eur J Clin Pharmacol* 1991; 40: 279–82.
5. Scott NR, *et al.* The pharmacokinetics of caffeine and its dimethylxanthine metabolites in patients with chronic liver disease. *Br J Clin Pharmacol* 1989; 27: 205–13.
6. Blanchard J, Sawers SJA. Comparative pharmacokinetics of caffeine in young and elderly men. *J Pharmacokinet Biopharm* 1983; 11: 109–26.
7. Abernethy DR, *et al.* Caffeine disposition in obesity. *Br J Clin Pharmacol* 1985; 20: 61–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Guarana†; Percutafeine; *Austral.*: Cafnea; No Doz; *Austria*: Coffekapton; *Canad.*: Alert Aid†; Pep-Back; Wake Ups; Water Joe†; *Chile*: Jaquedryl; Percutafeine; *China*: Kang Yu Deng Tong (康裕登通); *Cz.*: Kinedryl; Peyona; *Fin.*: Cofi-Tabs†; *Fr.*: Lipofeine; Percutafeine; *Gr.*: Cafcit; Peyona; *Indon.*: Panadol Extra; *Irl.*: Peyona; Pro-Plus†; *Neth.*: Peyona; *Pol.*: Kofex†; Peyona; *Port.*: Peyona; *Rus.*: Vasobral (Вазобрал); *Spain*: Durvitan; Peyona; *UK*: Peyona; Pro-Plus; *Ukr.*: Cefecon N (Цефекон Н); Glycodin (Гликодин)†; *USA*: Cafcit; Caffedrine; Enerjets; Keep Alert; Lucidex; NoDoz; Stay Alert; Vivarin.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Aspirin and Caffeine Tablets; Caffeine Citrate Injection; Caffeine Citrate Oral Solution; Paracetamol and Caffeine Tablets; Paracetamol, Codeine Phosphate and Caffeine Capsules; Paracetamol, Codeine Phosphate and Caffeine Tablets; Soluble Paracetamol and Caffeine Tablets;

USP 36: Acetaminophen and Caffeine Tablets; Acetaminophen, Aspirin, and Caffeine Tablets; Butalbital, Acetaminophen, and

Caffeine Capsules; Butalbital, Acetaminophen, and Caffeine Tablets; Butalbital, Aspirin, and Caffeine Capsules; Butalbital, Aspirin, and Caffeine Tablets; Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules; Caffeine and Sodium Benzoate Injection; Caffeine Citrate Injection; Caffeine Citrate Oral Solution; Ergotamine Tartrate and Caffeine Suppositories; Ergotamine Tartrate and Caffeine Tablets; Orphenadrine Citrate, Aspirin, and Caffeine Tablets; Propoxyphene Hydrochloride, Aspirin, and Caffeine Capsules.

Carmoterol *(rINN)* ⊗

Carmotérol; Carmoterolum; CHF-4226; Quinoterol; TA-2005; Кармотерол.

8-Hydroxy-5-[(1*R*)-1-hydroxy-2-[[(1*R*)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]quinolin-2(1*H*)-one.

$C_{21}H_{24}N_2O_4$=368.4

CAS — 147568-66-9.

UNII — 9810NUL4D1.

Profile

Carmoterol is a beta$_2$ agonist under investigation in asthma and chronic obstructive pulmonary disease.

Choline Theophyllinate *(BAN, rINN)*

Choline, Théophyllinate de; Cholini Theophyllinas; Koliinioteofyllinaatti; Kolinteofyllinat; Oxtrifilina; Oxtriphylline; Teocinato de colina; Teofilinato de colina; Theophylline Cholinate; Холина Теофиллинат.

$C_{12}H_{21}N_5O_3$=283.3

CAS — 4499-40-5.

ATC — R03DA02.

ATC Vet — QR03DA02.

UNII — 3K045XR58X.

Pharmacopoeias. In *Br.*, *Chin.*, and *US*.

BP 2014: (Choline Theophyllinate). A white crystalline powder, odourless or with a faint amine-like odour. It contains between 41.9% and 43.6% of choline and between 61.7% and 65.5% of theophylline, each calculated with reference to the dried substance. Very soluble in water; soluble in alcohol; very slightly soluble in chloroform and in ether. Store at a temperature not exceeding 25 degrees. Protect from light.

USP 36: (Oxtriphylline). A white crystalline powder, having an amine-like odour. It contains not less than 61.7% and not more than 65.5% of anhydrous theophylline. Soluble 1 in 1 of water; freely soluble in alcohol; very slightly soluble in chloroform. A 1% solution in water has a pH of about 10.3. Store in airtight containers.

Profile

Choline theophyllinate is a theophylline salt that liberates theophylline (p. 1229.3) in the body; choline theophyllinate 1.57 mg is equivalent in theophylline content to about 1 mg of anhydrous theophylline. It is used as a bronchodilator for reversible airways obstruction. The usual initial oral dose for adults is 800 mg daily, in 4 divided doses. The daily dose should be adjusted according to clinical response and serum-theophylline concentrations (see Uses and Administration of Theophylline, p. 1229.3). For details of doses in children see Administration in children, below.

Administration in children. Choline theophyllinate can be given to children aged from 10 years in an initial oral dose of 100 to 200 mg; further doses are guided by symptoms and serum-theophylline concentrations. An average daily dose of 10 to 20 mg/kg is usually required.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies choline theophyllinate as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Brondecon Elixir†; *Canad.*: Choledyl; *Gr.*: Choledyl; *Swed.*: Teovent.

Multi-ingredient Preparations. *Austral.*: Brondecon Expectorant†; *Canad.*: Choledyl Expectorant; *India*: Airomol; Alkarex-PD; Efelin-PD; *NZ*: Broncelix†; Brondecon†.

Pharmacopoeial Preparations

BP 2014: Choline Theophyllinate Tablets;

USP 36: Oxtriphylline Delayed-release Tablets; Oxtriphylline Extended-release Tablets; Oxtriphylline Oral Solution; Oxtriphylline Tablets.

Clenbuterol Hydrochloride *(BANM, rINNM)* ⊗

Clenbutérol, Chlorhydrate de; Clenbuterol, hidrocloruro de; Clenbuterolhydrochlorid; Clenbuterolii hydrochloridum; Hidrocloruro de clenbuterol; Klenbuterol hydrochlorid; Klenbuterol-hidroklorid; Klenbuterolhydroklorid; Klenbuterolihydrokloridi; Klenbuterolio hidrochloridas; NAB-365 (clenbuterol); Кленбутерола Гидрохлорид.

1-(4-Amino-3,5-dichlorophenyl)-2-*tert*-butylaminoethanol hydrochloride.

$C_{12}H_{18}Cl_2N_2O$,HCl=313.6

CAS — 37148-27-9 (clenbuterol); 21898-19-1 (clenbuterol hydrochloride).

ATC — R03AC14; R03CC13.

ATC Vet — QR03AC14; QR03CC13.

UNII — GOR5747GWU.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of clenbuterol:

Angel Dust; Clen.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

In *US* for veterinary use only.

Ph. Eur. 8: (Clenbuterol Hydrochloride). A white or almost white crystalline powder. Soluble in water and in alcohol; slightly soluble in acetone. A 5% solution in water has a pH of 5.0 to 7.0.

USP 36: (Clenbuterol Hydrochloride). A white or almost white, crystalline powder. Soluble in water and in alcohol; slightly soluble in acetone. A 5% solution in water has a pH of 5.0 to 7.0. Protect from light.

Profile

Clenbuterol hydrochloride is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on beta$_2$ receptors (a beta$_2$ agonist). It has properties similar to those of salbutamol (p. 1220.2). It is used as a bronchodilator in the management of reversible airways obstruction, as in asthma (p. 1195.2) and in certain patients with chronic obstructive pulmonary disease (p. 1199.1). A usual oral dose is 20 micrograms twice daily. Clenbuterol hydrochloride has also been given by inhalation. In patients with asthma, as-required beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, clenbuterol indicates deterioration of asthma control and the need for review of therapy.

Abuse. Clenbuterol has been used illicitly in animal feeds in an attempt to promote weight gain and to increase muscle to lipid mass. Adverse effects typical of sympathomimetic activity have been attributed to such misuse both in farmers perpetrating such acts[1] and in innocent persons consuming meat products from affected animals.[2-5] Clenbuterol has been abused by sportsmen for its anabolic effects,[6] although it is doubtful as to whether it enhances performance.[7] Myocardial infarction was described in an otherwise healthy 17-year-old bodybuilder after abuse of clenbuterol.[8] Coronary artery spasm and/or temporary thrombosis were suggested as possible explanations for this adverse effect. A case of overdosage in a bodybuilder who took 108.75 mg of clenbuterol hydrochloride has been reported.[9] He presented after about 30 minutes with anxiety, palpitations, and shortness of breath. His supraventricular tachycardia was eventually controlled with esmolol after adenosine and then diltiazem had proved ineffective, but subsequent atrial fibrillation required cardioversion. Contamination of illicit heroin with clenbuterol has also been reported.[10-13]

1. Dawson J. β Agonists put meat in the limelight again. *BMJ* 1990; 301: 1238–9.
2. Martínez-Navarro JF. Food poisoning related to consumption of illicit β -agonist in liver. *Lancet* 1990; 336: 1311.
3. Maisiro S, *et al.* Beta blockers to prevent clenbuterol poisoning. *Lancet* 1995; 346: 180.
4. Brambilla G, *et al.* Food poisoning following consumption of clenbuterol-treated veal in Italy. *JAMA* 1997; 278: 635.
5. Ramos P, *et al.* Proposed guidelines for clenbuterol food poisoning. *Am J Med* 2004; 117: 362.
6. Anonymous. Muscling in on clenbuterol. *Lancet* 1992; 340: 403.
7. Spann C, Winter ME. Effect of clenbuterol on athletic performance. *Ann Pharmacother* 1995; 29: 75–7.
8. Kierzkowska B, *et al.* Myocardial infarction in a 17-year-old body builder using clenbuterol. *Circ J* 2005; 69: 1144–6.
9. Daubert GP, *et al.* Acute clenbuterol overdose resulting in supraventricular tachycardia and atrial fibrillation. *J Med Toxicol* 2007; 3: 56–60.
10. CDC. Atypical reactions associated with heroin use: five states, January-April 2005. *MMWR* 2005; 54: 793–6. Correction. *ibid.*: 852.
11. Hoffman RS, *et al.* A descriptive study of an outbreak of clenbuterol-containing heroin. *Ann Emerg Med* 2008; 52: 548–53.
12. Manini A, *et al.* A novel neuromuscular syndrome associated with clenbuterol-tainted heroin. *Clin Toxicol* 2008; 46: 1088–92.
13. Dimaano JQ, *et al.* Street drugs possibly tainted with clenbuterol. *J Emerg Nurs* 2008; 34: 582–3.

Urinary incontinence. A systematic review of the use of adrenergic agonists, including clenbuterol, in urinary incontinence, found that there was weak evidence to suggest that their use was better than placebo.[1] Although only minor adverse effects were reported, the authors noted that there was still potential for rare but serious adverse effects reported elsewhere in the literature.

1. Alhasso A, *et al.* Adrenergic drugs for urinary incontinence in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 15/01/08).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bronq-C; Clembumar; Oxibron; *Austria*: Spiropent; *Chile*: Airum; Asmeren; *Cz.*: Spiropent; *Ger.*: Spiropent; *Gr.*: Spiropent; *Hung.*: Spiropent; *Indon.*: Spiropent; *Ital.*: Monores; *Jpn*: Spiropent; *Malaysia*: Mavilex; *Mex.*: Novegam; Oxyflux; Spiropent; *Philipp.*: Spiropent; *Port.*: Broncoterol†; Cesbron†; *Spain*: Ventolase†; *Venez.*: Brodilan; Brodilin; Buclen; Clenbunal; Risopent.

Multi-ingredient Preparations. *Arg.*: Mucosolvon Compositum; Oxibron NF; *Austria*: Mucospas; *China*: Ambrocol (鼻泪舒); *Ger.*: Spasmo-Mucosolvan; *Mex.*: Ambodil-C; Balsibron-C; Brogal Compositum; Bronolban-M; Brosolan C†; Broxofar Compuesto; Broxol Plus; Broxolim-C; Ebromin P; Fludexol-CL; Loxorol; Mucosolvan Compositum; Mucovibrol C; Sekretovit Ex; Septacin Ex; Seraxol; Serbol; *Port.*: Clembroxol; Mucospas; Ventoliber; *Venez.*: Ambromuco Compositum; Arbixil; Clenbuxol; Linusix Compositum; Mucolin; Mucosolvan Compositum.

Diprophylline *(BAN, rINN)*

Difillina; Dihydroxypropyltheophyllinum; Diprofilina; Diprofilinas; Diprofillin; Diprofylin; Diprofyllini; Diprofyllin; Diprophyllin; Diprophyllinum; Dyphylline; Glyphyllinum; Hyphylline; Дипрофиллин.

7-(2,3-Dihydroxypropyl)-1,3-dimethylxanthine; 7-(2,3-Dihydroxypropyl)theophylline.

$C_{10}H_{14}N_4O_4$=254.2

CAS — 479-18-5.

ATC — R03DA01.

ATC Vet — QR03DA01.

UNII — 263TDE9RR9.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Diprophylline). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol. Protect from light.

USP 36: (Dyphylline). A white, odourless, amorphous or crystalline solid. Freely soluble in water; sparingly soluble in alcohol and in chloroform; practically insoluble in ether. A 1% solution in water has a pH of 5.0 to 7.5. Store in airtight containers.

Uses and Administration

Diprophylline is a theophylline derivative which is used similarly to theophylline (p. 1229.3) as a bronchodilator in reversible airways obstruction.

The usual oral dose of diprophylline is up to 15 mg/kg every 6 hours. It has also been given intramuscularly. Diprophylline is also an ingredient of preparations that have been promoted for coughs.

Action. Improvements in measurements of lung function after diprophylline in oral doses of 15 and 20 mg/kg were only one-third to one-half those obtained after oral theophylline 6 mg/kg.[1]

1. Furukawa CT, *et al.* Diphylline versus theophylline: a double-blind comparative evaluation. *J Clin Pharmacol* 1983; 23: 414–18.

Adverse Effects, Treatment, and Precautions

As for Theophylline, p. 1231.2, p. 1232.3, and p. 1233.1. Diprophylline is mainly excreted unchanged in the urine and should therefore be used with caution in patients with renal impairment; dose adjustments may be required. However, unlike theophylline, plasma concentrations of diprophylline are not greatly affected by changes in liver function or hepatic enzyme activity such as those produced by smoking or age.

Breast feeding. In a study of 20 women given diprophylline by intramuscular injection,[1] diprophylline was found to concentrate in breast milk, with a milk to serum concentration ratio of about 2. However, it was considered that the quantity of diprophylline a breast-fed infant would ingest was unlikely to produce any pharmacological action unless the child was very sensitive. The American Academy of Pediatrics[2] also considers that the use of diprophylline is usually compatible with breast feeeding.

1. Jarboe CH, *et al.* Dyphylline elimination kinetics in lactating women: blood to milk transfer. *J Clin Pharmacol* 1981; 21: 405–10.

2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/03/08)

Interactions

Since diprophylline does not undergo metabolism by hepatic microsomal cytochrome P450 it does not exhibit the many interactions seen with theophylline (p. 1233.3). However, the possibility of synergistic effects should be borne in mind if it is used with other xanthines.

Probenecid. Probenecid has been reported to decrease the clearance of diprophylline thus prolonging its half-life.[1-3]

1. May DC, Jarboe CH. Inhibition of clearance of dyphylline by probenecid. *N Engl J Med* 1981; 304: 791.
2. May DC, Jarboe CH. Effect of probenecid on dyphylline elimination. *Clin Pharmacol Ther* 1983; 33: 822–5.
3. Acara M, *et al.* Probenecid inhibition of the renal excretion of dyphylline in chicken, rat and man. *J Pharm Pharmacol* 1987; 39: 526–30.

Pharmacokinetics

Diprophylline is rapidly absorbed from the gastrointestinal tract and from the site of intramuscular injections. Diprophylline is not converted to theophylline in the body. It is largely excreted unchanged in the urine with an elimination half-life of about 2 hours. Diprophylline is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: A Shen Nuo Qi (阿圣诺奇); Ruo Chang (若畅); Tian Quan Xi Ning (天泉息宁); *Gr.*: Silbephylline; *Hong Kong*: Diproline†; Syneophylline†; Uni-Dyphine†; *Ital.*: Katasma; *Port.*: Neufil; *Turk.*: Astmadin; Diflin; *USA*: Dylix; Lufyllin.

Multi-ingredient Preparations. *Fr.*: Ozothine a la Diprophylline; *Hong Kong*: Broncholax†; *Israel*: Philinal†; Philinet†; *Ital.*: Cort-Inal; *Spain*: Alergical Expectorante; Bronsal; *Turk.*: Broksin; *UK*: Noradran; *USA*: Difil-G; Dilex-G; Dy-G†; Dyflex-G; Dyphylline-GG†; Jay-Phyl; Lufyllin-GG; Panfil G.

Pharmacopoeial Preparations
USP 36: Dyphylline and Guaifenesin Elixir; Dyphylline and Guaifenesin Tablets; Dyphylline Elixir; Dyphylline Injection; Dyphylline Tablets.

Doxofylline *(USAN, rINN)*

ABC-12/3; Doxofilina; Doxofyllinum; Доксофиллин.
7-(1,3-Dioxolan-2-ylmethyl)theophylline.
$C_{11}H_{14}N_4O_4$=266.3.
CAS — 69975-86-6.
ATC — R03DA11.
ATC Vet — QR03DA11.
UNII — MPM23GMO7Z.

Profile

Doxofylline is a theophylline derivative (p. 1229.3) which is used as a bronchodilator in reversible airways obstruction. It is given in oral doses of up to 1.2 g daily. It may also be given by slow intravenous injection.

References.

1. Dini FL, Cogo R. Doxofylline: a new generation xanthine bronchodilator devoid of major cardiovascular adverse effects. *Curr Med Res Opin* 2001; 16: 258–68.
2. Sankar J, *et al.* Doxofylline: the next generation methylxanthine. *Indian J Pediatr* 2008; 75: 251–4.
3. Shukla D, *et al.* Doxofylline: a promising methylxanthine derivative for the treatment of asthma and chronic obstructive pulmonary disease. *Expert Opin Pharmacother* 2009; 10: 2343–56.
4. Page CP. Doxofylline: a "novofylline". *Pulm Pharmacol Ther* 2010; 23: 231–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: An Li Nuo Er (安利诺尔); An Sai Ma (安赛玛); Chuan Ning (川苧); Fei Te Ai Si (菲特艾斯); Jian Fang Neng (健方能); Lang Ming (朗铭); Lv Meng (绿萌); Na De Lai (纳德来); Shu Zhi (舒志); Shuai An (帅安); Shuweixin (枢维新); Suo Di (索迪); Suo Ji (索霁); Suo Li An (索利安); Xi Si Nuo (喜思诺); Xin Qian Ping (新茜平); Xin Xi Ping (新西平); Yi Suo (益索); YiLi (奕利); *India*: Bestofyline; Coxylate; D-Xanthin; Doxfil; Doxfree; Doxiba; Doxma; Doxobid; Doxobron; Doxosafe; Doxovent; Efin-CR; Everdox; Filodox; Fyline; Fyly; Lunair; Monofin; Mucosma; Oxowin; Oxypur; *Ital.*: Ansimar; *Mex.*: Axofilin†; *Philipp.*: Ansimar; Dilatair; Maxivent; Puroxan; *Thai.*: Puroxan; *Ukr.*: Aerofillin (Аэрофиллин).

Multi-ingredient Preparations. *India*: Mucosma-T.

Etamiphylline Camsilate *(BANM, rINNM)*

Camsilato de dietamifilina; Camsilato de etamifilina; Camsilato de parafilina; Diétamiphylline Camphosulfonate; Etamifilina, camsilato de; Etamiphylline, Camsilate d'; Etamiphylline Camsylate; Etamiphyllini Camsilas; Etamphyllin Camsylate; Этамифиллина Камзилат.
7-(2-Diethylaminoethyl)-1,3-dimethylxanthine camphor-10-sulphonate; 7-(2-Diethylaminoethyl)theophylline camphor-10-sulphonate.
$C_{23}H_{37}N_5O_6S$=511.6.
CAS — 314-35-2 (etamiphylline); 19326-29-5 (etamiphylline camsilate).
ATC — R03DA06.
ATC Vet — QR03DA06.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Etamiphylline Camsilate). A white or almost white powder. Very soluble in water; soluble in alcohol and in chloroform; very slightly soluble in ether. A 10% solution in water has a pH of 3.9 to 5.4.

Profile

Etamiphylline camsilate is a derivative of theophylline (p. 1229.3) and has been used as a bronchodilator in reversible airways obstruction. Etamiphylline does not liberate theophylline in the body. Etamiphylline camsilate is used in veterinary medicine.

The hydrochloride salt has also been used.

Etofylline *(BAN, rINN)*

Aethophyllinum; Etofilina; Etofilinas; Etofillin; Etofylin; Etofylliini; Etofyllin; Étofylline; Etofyllinum; Hydroxyaethyltheophyllinum; Hydroxyéthylthéophylline; Oxyetophylline; Этофиллин.
7-(2-Hydroxyethyl)-1,3-dimethylxanthine; 3,7-Dihydro-7-(2-hydroxyethyl)-1,3-dimethyl-1*H*-purine-2,6-dione; 7-(2-Hydroxyethyl)theophylline.
$C_9H_{12}N_4O_3$=224.2.
CAS — 519-37-9.
ATC — C04AD04.
ATC Vet — QC04AD04.
UNII — L1649097BI.

Profile

Etofylline is a derivative of theophylline (p. 1229.3) that is an ingredient of preparations promoted for respiratory and cardiovascular disorders. It is not converted to theophylline in the body.

Etofylline nicotinate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Oxyphyllin.

Multi-ingredient Preparations. *Cz.*: Ersilan; Oxantil; *Hong Kong*: Instenon; *India*: Agrophyllin; Albutamol; Asthos; Bronchilet; Delin; Dericip; Deriphyllin; Deripil; Efelin; Eto-Salbetol; Glophyllin; Terphylin; *Rus.*: Instenon (Инстенон); *S.Afr.*: Actophlem; Alcophyllex; Dilinct; Solphyllex; Solphyllin; Theophen Comp; *Ukr.*: Instenon (Инстенон).

Fenoterol *(BAN, USAN, rINN)* ⊗

Fénotérol; Fenoterolı; Fenoterolum; Фенотерол.
1-(3,5-Dihydroxyphenyl)-2-(4-hydroxy-α-methylphenethylamino)ethanol.
$C_{17}H_{21}NO_4$=303.4.
CAS — 13392-18-2.
ATC — G02CA03; R03AC04; R03CC04.
ATC Vet — QG02CA03; QR03AC04; QR03CC04.
UNII — 22M9P70OQ9.

Fenoterol Hydrobromide *(BANM, rINNM)* ⊗

Fénotérol, Bromhydrate de; Fenoterol, hidrobromuro de; Fenoterol-hidrobromid; Fenoterolhydrobromid; Fenoterolhydrobromid; Fenoteroli Hydrobromidum; Fenoterolihydrobromidi; Fenoterolio hidrobromidas; Fenoterolu bromowodorek; Hidrobromuro de fenoterol; TH-1165a; Фенотерола Гидробромид.
1-(3,5-Dihydroxyphenyl)-2-(4-hydroxy-α-methylphenethylamino)ethanol hydrobromide.
$C_{17}H_{21}NO_4$.HBr=384.3.
CAS — 1944-12-3.
ATC — G02CA03; R03AC04; R03CC04.
ATC Vet — QG02CA03; QR03AC04; QR03CC04.
UNII — RLI45Z99RB.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Fenoterol Hydrobromide). A white or almost white, crystalline powder. Soluble in water and in alcohol. A 4% solution in water has a pH of 4.2 to 5.2. Protect from light.

Uses and Administration

Fenoterol is a direct-acting sympathomimetic with beta-adrenoceptor stimulant activity largely selective for beta$_2$ receptors (a beta$_2$ agonist). It has actions and uses similar to those of salbutamol (p. 1220.2) and is used as a bronchodilator in the management of reversible airways obstruction, as occurs in asthma (p. 1195.2) and in some patients with chronic obstructive pulmonary disease (p. 1199.1). On inhalation, fenoterol acts within a few minutes and has a duration of action of about 3 to 5 hours.

In the management of **reversible airways obstruction,** fenoterol hydrobromide may be given from a *metered-dose aerosol* in a dose of 1 or 2 inhalations of 100 micrograms up to 4 times daily, with at least 3 hours between doses; a maximum daily dose of 800 micrograms is recommended. Current asthma guidelines recommend that inhaled short-acting beta$_2$ agonists such as fenoterol be used on an 'as-required', not regular, basis. In those patients requiring more than occasional use of fenoterol, anti-inflammatory therapy is also needed. An increased requirement for, or decreased duration of effect of, fenoterol indicates deterioration of asthma control and the need for increased anti-inflammatory therapy.

Fenoterol hydrobromide is available as a *dry powder* inhaler in some countries; 1 inhalation of 200 micrograms, repeated once after 10 minutes if necessary, is given 3 or 4 times daily.

Fenoterol may be inhaled as a *nebulised solution* for acute attacks of bronchospasm; it may be given with the antimuscarinic ipratropium, in a dose of fenoterol hydrobromide 1.25 mg, up to a maximum of 4 times daily. Fenoterol hydrobromide is also given alone in a dose of 0.5 to 1.25 mg depending on severity, increased to a total daily dose of 2 mg in severe cases.

Fenoterol hydrobromide may also be given *orally* for the relief of bronchospasm at a dose of 2.5 to 5 mg three times daily.

For doses in children, see Administration in Children below.

Fenoterol hydrobromide has also been used similarly to salbutamol, in the management of **premature labour** (see p. 2131.1). A suggested dose, by intravenous infusion, has been 0.5 to 3 micrograms/minute, up to a maximum of 4 micrograms/minute. Therapy should be limited to a maximum of 48 hours, because prolonged treatment is associated with risks of serious cardiovascular effects in both the mother and fetus (see Precautions under Salbutamol, p. 1222.3).

Oral or *rectal* beta$_2$ agonist therapy is no longer recommended in premature labour, because of a lack of evidence of benefit from treatment given by these routes of administration. Formerly, fenoterol hydrobromide could be given orally in a dose of 5 mg every 3 to 6 hours, for maintenance therapy after uterine contractions were controlled by parenteral treatment.

Administration in children. In some countries fenoterol has been given via a metered-dose inhaler to children over 6 years of age, at the same doses used in adults (see Uses and Administration, above).

Adverse Effects and Precautions

As for Salbutamol, p. 1221.3.

Increased mortality. Since the introduction of metered-dose aerosols of beta agonists there have been two reported epidemics of increased morbidity and mortality in asthmatic patients associated with their use. The first occurred in the 1960s and was linked with the use of high-dose isoprenaline inhalers.[1] The use of isoprenaline was subsequently largely stopped in favour of more selective beta$_2$ agonists.

The second epidemic occurred in New Zealand in the late 1970s and 1980s and was associated with the use of fenoterol.[1-5] When use of fenoterol fell in New Zealand, so too did the asthma mortality rate.[5] Heavy or regular use of fenoterol was implicated.[6,7] Fenoterol was also implicated in increased asthma morbidity and mortality in a study in Canada,[7] as was salbutamol, and results from Japan also suggested a relation between asthma deaths and excessive use of beta agonists, particularly fenoterol.[8] However, an analysis of the New Zealand deaths could not identify such a risk with beta agonists other than fenoterol.[5]

There is still debate about this second epidemic. The individual case control studies, including the one from Canada,[7] showed an increased morbidity and mortality in patients taking fenoterol, but a meta-analysis of the accumulated data to 1992 suggested that the increase in mortality in the patients taking beta$_2$ agonists was slight and

only significant when they were given by nebulisation.[9] Also a working party of the UK CSM considered[10] that a causal link between asthma mortality and beta-agonist use could neither be confirmed nor refuted.

Not surprisingly there are different views on the cause of the increased asthma mortality. The cardiotoxicity of the beta agonist might have to be considered, although evidence for such an effect is considered by some to be slight.[11] The severity of the asthma might have been a factor in two different ways. One hypothesis is that patients used more fenoterol because they had severe asthma and were already at increased risk of dying.[12] Another proposes that heavy beta-agonist use led to an increase in asthma severity[13] which could be explained by a down regulation of beta receptors.[14]

This may appear to be only of historical interest since mortality rates have fallen and current recommendations for the use of short-acting beta$_2$ agonists, which are generally more selective than fenoterol, are for them to be taken as required rather than on a regular basis; indeed increasing use of such drugs is seen as an indication to amend the treatment schedule. Moreover, the dose of fenoterol has been reduced in recent years. However, controversy over regular use of short-acting beta$_2$ agonists continues to be fed by conflicting studies of their benefit. More recently 2 further observational studies have reported an association between use of short-acting beta$_2$ agonists and adverse effects on mortality.[15,16] A cohort study,[15] designed to evaluate the effect of respiratory medications on asthma death, found an association between the excessive use of short-acting beta$_2$ agonists and an increased risk of asthma death; no additional risk was found with fenoterol beyond the risk associated with beta$_2$ agonists as a class. It was unknown whether excessive use was a symptom or a cause of worsening asthma. A case-control study[16] similarly found a modestly increased risk of mortality associated with use of short-acting beta$_2$ agonists in the previous 1 to 5 years. However, the study had insufficient power to come to any conclusions regarding the effects of fenoterol, which was rarely prescribed alone, and concluded that evidence for a direct adverse effect of beta$_2$ agonists was inconclusive; other explanations might include lack of more appropriate asthma care, more severe disease or increasing severity of disease, or a tendency for patients whose disease was not responding to receive a wider range of treatments.

For discussion of similar concerns about the use of *long-acting* beta$_2$ agonists in asthma, see Salmeterol, p. 1224.3.

1. Pearce N, *et al.* Beta agonists and asthma mortality: déjà vu. *Clin Exp Allergy* 1991; 21: 401–10.
2. Crane J, *et al.* Prescribed fenoterol and death from asthma in New Zealand, 1981-83: case-control study. *Lancet* 1989; i: 917–22.
3. Pearce N, *et al.* Case-control study of prescribed fenoterol and death from asthma in New Zealand, 1977–81. *Thorax* 1990; 45: 170–5.
4. Grainger J, *et al.* Prescribed fenoterol and death from asthma in New Zealand, 1981–7: a further case-control study. *Thorax* 1991; 46: 105–111.
5. Pearce N, *et al.* End of the New Zealand asthma mortality epidemic. *Lancet* 1995; 345: 41–4.
6. Sears MR, *et al.* Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990; 336: 1391–6.
7. Spitzer WO, *et al.* The use of β -agonists and the risk of death and near death from asthma. *N Engl J Med* 1992; 326: 501–6.
8. Beasley R, *et al.* β -agonist therapy and asthma mortality in Japan. *Lancet* 1998; 351: 1406–7.
9. Mullen M, *et al.* The association between β -agonist use and death from asthma: a meta-analytic integration of case control studies. *JAMA* 1993; 270: 1842–5.
10. CSM. Beta-agonist use in asthma: report from the CSM Working Party. *Current Problems* 33 1992. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024451&RevisionSelectionMethod=LatestReleased (accessed 15/01/08)
11. Sears MR, Taylor DR. The β$_2$-agonist controversy: observations, explanations and relationship to asthma epidemiology. *Drug Safety* 1994; 11: 259–83.
12. Fuller RW. Use of β$_2$ agonists in asthma: much ado about nothing? *BMJ* 1994; 309: 795–6.
13. Sears MR. Asthma deaths in New Zealand. *Lancet* 1995; 345: 655–6.
14. Tattersfield AE. Use of β$_2$ agonists in asthma: much ado about nothing? *BMJ* 1994; 309: 794–5.
15. Lanes SF, *et al.* Respiratory medications and risk of asthma death. *Thorax* 2002; 57: 683–6.
16. Anderson HR, *et al.* Bronchodilator treatment and deaths from asthma: case-control study. Abridged version: *BMJ* 2005; 330: 117. Full version: http://www.bmj.com/cgi/reprint/330/7483/117 (accessed 15/01/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fenoterol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pulmonary oedema. Pulmonary oedema has occurred in women given beta agonists, including fenoterol,[1] for premature labour. The risk factors, the most important of which is fluid overload, are discussed under Precautions for Salbutamol, on p. 1222.3.

1. Hawker F. Pulmonary oedema associated with β$_2$-sympathomimetic treatment of premature labour. *Anaesth Intensive Care* 1984; 12: 143–51.

Interactions

As for Salbutamol, p. 1223.1.

Pharmacokinetics

Fenoterol is incompletely absorbed from the gastrointestinal tract and is also subject to extensive first-pass metabolism by sulfate conjugation. It is excreted in the urine and bile almost entirely as the inactive sulfate conjugate. Fenoterol is distributed into breast milk.

References.

1. Warnke K, *et al.* The pharmacokinetics of the beta 2-adrenoceptor agonist fenoterol in healthy women. *Eur J Clin Pharmacol* 1992; 43: 663–5.
2. Hochhaus G, Möllmann H. Pharmacokinetic/pharmacodynamic characteristics of the beta-2-agonists terbutaline, salbutamol and fenoterol. *Int J Clin Pharmacol Ther Toxicol* 1992; 30: 342–62.
3. Hildebrandt R, *et al.* Pharmacokinetics of fenoterol in pregnant and nonpregnant women. *Eur J Clin Pharmacol* 1993; 45: 275–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alveofen; Asmopul; Berotec; *Austria*: Berotec; *Belg.*: Berotec†; *Braz.*: Berotec; Bromifen; Bromotec; Fenatec; Fenozan†; *Cz.*: Berotec; *Denm.*: Berotec†; *Ger.*: Berotec; Partusisten; *Gr.*: Berotec; Ftagirol; *Hung.*: Berotec†; *Indon.*: Berotec; *Irl.*: Berotec†; *Ital.*: Dosberotec; *Jpn*: Berotec; *Malaysia*: Berotec; Feno; *Mex.*: Partusisten; *Neth.*: Berotec†; Partusisten; *Philipp.*: Berotec†; *Pol.*: Berotec; *Port.*: Berotec†; *Rus.*: Berotec (Беротек); Partusisten (Партусистен); *S.Afr.*: Berotec; *Singapore*: Berotec; *Switz.*: Berotec; *Thai.*: Berotec†; Iperol; *Ukr.*: Berotec (Беротек); *Venez.*: Segamol.

Multi-ingredient Preparations. *Arg.*: Berodual; Ipradual; *Austria*: Berodual; Berodualin; *Belg.*: Duovent; *Braz.*: Duovent; *Canad.*: Duovent; *Chile*: Berodual; *Cz.*: Berodual; *Denm.*: Berodual; Duovent; *Fin.*: Atrovent Comp; *Fr.*: Bronchodual; *Ger.*: Berodual; *Gr.*: Berodual; *Hung.*: Berodual; *India*: Fenovent; *Indon.*: Berodual; *Irl.*: Duovent†; *Ital.*: Duovent; *Malaysia*: Berodual; Duovent; *Mex.*: Berodual; Berosolvon; *Neth.*: Berodual; *Philipp.*: Berodual; *Pol.*: Berodual; *Port.*: Berodual; *Rus.*: Berodual (Бородуал); Ditec (Дитек)†; *S.Afr.*: Atrovent Beta; Berodual†; Duovent; Sabax Nebrafen; *Singapore*: Berodual; Duovent; *Switz.*: Berodual; *Thai.*: Aeroduol; Berodual; Inhalex; Ipratoral; Punol; *UK*: Duovent†; *Ukr.*: Berodual (Бородуал); *Venez.*: Berodual; Duovent; Respidual.

Pharmacopoeial Preparations

BP 2014: Fenoterol Pressurised Inhalation.

Fenspiride Hydrochloride *(USAN, rINNM)*

Decaspiride; Fenspirida, hidrocloruro de; Fenspiride, Chlorhydrate de; Fenspiridi Hydrochloridum; Hidrocloruro de fenspirida; JP-428; NAT-333; NDR-5998A; Фенспирида гидрохлорид.

8-Phenethyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one hydrochloride.

$C_{15}H_{20}N_2O_2$,HCl=296.8

CAS — 5053-06-5 (fenspiride); 5053-08-7 (fenspiride hydrochloride).

ATC — R03BX01; R03DX03.

ATC Vet — QR03BX01; QR03DX03.

UNII — 832NBX878V.

Profile

Fenspiride is reported to have bronchodilator and anti-inflammatory properties. It is given as the hydrochloride in asthma (p. 1195.2) and other respiratory disorders in usual oral doses of 160 to 240 mg daily in divided doses before meals. It has also been given rectally and by intramuscular or intravenous injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Pneumorel; *Hong Kong*: Pneumorel†; *Ital.*: Pneumorel; *Pol.*: Elofen; Eurespal; Fenspogal; Pulneo; *Port.*: Pneumorel; *Rus.*: Eurespal (Эреспал); *Ukr.*: Erespal (Эреспал); Inspiron (Инспирон).

Formoterol Fumarate

(BANM, USAN, rINNM) ⊗

BD-40A; CGP-25827A; Eformoterol Fumarat; Eformoterol Fumarate; Formoterol Fumarat; Formoterol Fumarate de; Formoterol fumarato de; Formoterolfumarat; Formoterol-fumarat; Formoterol fumaras; Formoterolifumarasti; Formoterolio fumaratas; Formoterolu fumaran; Fumarato de eformoterol; Fumarato de formoterol; YM-08315; Формотерола Фумарат.

(±)-2′-Hydroxy-5′-[(*RS*)-1-hydroxy-2-[[(*RS*)-*p*-methoxy-α-methylphenethyl]amino]ethyl]formanilide fumarate.

$(C_{19}H_{24}N_2O_4)_2.C_4H_4O_4$=804.9

CAS — 73573-87-2 (formoterol); 43229-80-7 (formoterol fumarate).

ATC — R03AC13.

ATC Vet — QR03AC13.

UNII — P3T5QA5J9N (formoterol fumarate); W34SHF8J2K (formoterol fumarate dihydrate).

Pharmacopoeias. *Eur.* (see p. vii); *Jpn*, and *US* include the dihydrate, $(C_{19}H_{24}N_2O_4)_2.C_4H_4O_4.2H_2O$ = 840.9.

Ph. Eur. 8: (Formoterol Fumarate Dihydrate; Formoteroli Fumaras Dihydricus). A white or almost white or slightly yellow powder. Slightly soluble in water and in isopropyl alcohol; practically insoluble in acetonitrile; soluble in methyl alcohol. A 0.1% solution in water has a pH of 5.5 to 6.5. Protect from light.

USP 36: (Formoterol Fumarate). A white or almost white or slightly yellow powder. Slightly soluble in water and in isopropyl alcohol; soluble in methyl alcohol; freely soluble in acetic acid and in dimethyl sulfoxide; practically insoluble in acetonitrile and in ether. A 0.1% solution in water has a pH of 5.5 to 6.5. Protect from light.

Stability. Nebuliser solution containing formoterol fumarate 10 micrograms/mL was found to be physically and chemically stable when mixed with the following solutions:[1]

- budesonide inhalation suspension 250 micrograms/mL
- acetylcysteine solution 100 mg/mL
- ipratropium bromide inhalation solution 200 micrograms/mL
- sodium cromoglicate inhalation solution 10 mg/mL

The authors of this study noted that when these solutions were mixed and nebulised, or given sequentially, the amount of drug delivered *in vitro* was increased compared with single-drug nebulisation. Additionally, sequential nebulisation led to higher delivery of the first drug given. The clinical implications of these results were unclear.

1. Akapo S, *et al.* Compatibility and aerosol characteristics of formoterol fumarate mixed with other nebulizing solutions. *Ann Pharmacother* 2008; 42: 1416–24.

Uses and Administration

Formoterol is a direct-acting sympathomimetic with mainly beta-adrenoceptor stimulant activity specific to beta$_2$ receptors (a beta$_2$ agonist). It has properties similar to those of salbutamol (p. 1220.2), but like salmeterol (p. 1224.1) it has a prolonged duration of action of up to 12 hours; it is therefore not considered suitable for the symptomatic relief of acute attacks of bronchospasm. It is used with regular inhaled corticosteroid when a regular long-acting beta$_2$ agonist is needed for management of chronic asthma (p. 1195.2), or for prevention of exercise-induced asthma. It is also used in chronic obstructive pulmonary disease (p. 1199.1).

Formoterol is given by inhalation as the fumarate but how the dose is expressed may depend on the formulation.

- A usual dose for **asthma** is 1 inhalational capsule of formoterol fumarate 12 micrograms twice daily. In the UK, this may be increased to 2 inhalational capsules (24 micrograms) twice daily if necessary for severe disease. In the USA, 1 inhalational capsule of 12 micrograms may be taken when required, at least 15 minutes before exercise, to prevent exercise-induced bronchoconstriction in those patients not taking regular doses; additional doses should not be taken within 12 hours.
- Metered doses from a dry powder inhaler may be expressed as the amount delivered *into* the mouthpiece (multiples of 6 micrograms per inhalation) or the amount delivered *from* the mouthpiece (corresponding to multiples of 4.5 micrograms per inhalation). Usual doses, expressed as the amount delivered *into* the mouthpiece, are 6 or 12 micrograms once or twice daily, increased if necessary in severe disease to 24 micrograms twice daily. (In the UK, a dose of 12 micrograms may be taken before exercise to prevent exercise-induced bronchoconstriction.) No more than 36 micrograms should be inhaled as a single dose, with a maximum daily dose of 72 micrograms.
- Metered doses from an aerosol inhaler may also be expressed as the amount delivered *into* the mouthpiece (12 micrograms per inhalation) or the amount delivered *from* the mouthpiece (corresponding to 10.1 micrograms per inhalation). Usual doses are 1 or 2 inhalations twice daily.

Treatment should be reassessed if this proves inadequate; in the UK, some preparations are licensed for additional short-term symptom relief, but such use is contrary to current asthma guidelines (see p. 1195.2).

In **chronic obstructive pulmonary disease**, a usual dose from inhalation capsules is formoterol fumarate 12 micrograms twice daily.

Metered doses from a dry powder inhaler, expressed as the amount delivered *into* the mouthpiece, are 12 micrograms once or twice daily while those from an aerosol

inhaler are 12 micrograms twice daily; if required, additional doses may be used for relief of symptoms. A maximum of 24 micrograms may be inhaled as a single dose, with a total maximum daily dose of 48 micrograms.

Formoterol fumarate may also be inhaled via a nebuliser in a dose of 20 micrograms twice daily.

An oral formulation of formoterol fumarate is available in some countries for reversible airways obstruction; doses of 80 micrograms have been given twice daily.

For doses of formoterol fumarate used in children, see Administration in Children, below.

Reviews.

1. Faulds D, *et al.* Formoterol: a review of its pharmacological properties and therapeutic potential in reversible obstructive airways disease. *Drugs* 1991; **42:** 115–37.
2. Bartow RA, Brogden RN. Formoterol: an update of its pharmacological properties and therapeutic efficacy in the management of asthma. *Drugs* 1998; **55:** 303–22.
3. Sovani MP, *et al.* A benefit-risk assessment of inhaled long-acting β_2-agonists in the management of obstructive pulmonary disease. *Drug Safety* 2004; **27:** 689–715.

Administration in children. Doses of formoterol fumarate inhaled from inhalational capsules in children aged 5 years or older are the same as those for adults, see Uses and Administration, p. 1209.3.

Formoterol fumarate may be given by metered-dose dry powder inhaler to children 6 years of age and over. The usual dose, expressed as the amount delivered *into* the mouthpiece, is 6 to 12 micrograms once or twice daily. Occasionally up to 48 micrograms daily may be required (maximum single dose should not exceed 12 micrograms).

In some countries, such as Japan, formoterol fumarate has been given orally to children from the age of 6 months at a dose of 4 micrograms/kg daily, in 2 or 3 divided doses.

Asthma. Formoterol is a long-acting beta$_2$ agonist (duration of action about 12 hours). Guidelines on the management of asthma, see p. 1195.2, generally recommend that the use of long-acting beta$_2$ agonists be reserved for patients with chronic asthma who have already progressed to inhaled corticosteroids; they are not a substitute for corticosteroids. Combinations of formoterol with an inhaled corticosteroid, used as both maintenance and reliever therapy, have been studied. Results are seemingly encouraging, although what role such combinations should play in therapy is not yet clearly defined. Formoterol may also be useful in controlling persistent nocturnal asthma or preventing exercise-induced attacks. There is some evidence that after prolonged use, protection against bronchoconstriction is reduced (see Tolerance, below), and high-dose therapy may be associated with an increased rate of severe exacerbations (see Asthma under Adverse Effects and Precautions, below). Although long-acting bronchodilators should not be used for acute relief of asthma, formoterol has reportedly been used successfully as part of the management of acute severe asthma in hospital.

References.

1. van der Molen T, *et al.* Effects of the long acting β agonist formoterol on asthma control in asthmatic patients using inhaled corticosteroids. *Thorax* 1996; **52:** 535–9.
2. Pauwels RA, *et al.* Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997; **337:** 1405–11. Correction. *ibid.*; 1998; **338:** 139.
3. O'Byrne PM, *et al.* Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001; **164:** 1392–7.
4. Goldsmith DR, Keating GM. Budesonide/formoterol: a review of its use in asthma. *Drugs* 2004; **64:** 1597–1618.
5. Pedersen S. Budesonide plus formoterol for reliever therapy in asthma. *Lancet* 2006; **368:** 707–8.
6. Pohunek P, *et al.* Budesonide/formoterol improves lung function compared with budesonide alone in children with asthma. *Pediatr Allergy Immunol* 2006; **17:** 458–65. Correction. *ibid.*; 551.
7. Berger WE. The use of inhaled formoterol in the treatment of asthma. *Ann Allergy Asthma Immunol* 2006; **97:** 24–33. Correction. *ibid.*; 562. [dosage error in text]
8. Hermansen MN, *et al.* Acute relief of exercise-induced bronchoconstriction by inhaled formoterol in children with persistent asthma. *Chest* 2006; **129:** 1203–9.
9. Bateman ED, *et al.* Budesonide/formoterol and formoterol provide similar rapid relief in patients with acute asthma showing refractoriness to salbutamol. *Respir Res* 2006; **7:** 13.
10. O'Byrne PM, Parameswaran K. Pharmacological management of mild or moderate persistent asthma. *Lancet* 2006; **368:** 794–803.
11. Cates CJ, Lasserson TJ. Combination formoterol and budesonide as maintenance and reliever therapy versus inhaled steroid maintenance for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 11/08/09).
12. Cates CJ, Lasserson TJ. Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 11/08/09).
13. Rodrigo GJ, *et al.* Formoterol for acute asthma in the emergency department: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2010; **104:** 247–52.

Stuttering. Inhaled formoterol 12 micrograms daily was reported to improve stuttering (p. 1078.1) in 3 children between 14 and 20 years old. In 2 males, the onset of effect was about 6 weeks, but long-term follow-up was not possible. In the female patient there was early improvement that persisted during 45 weeks of treatment.[1]

1. Pešák J. Preliminary experience with formoterol for the treatment of stuttering. *Ann Pharmacother* 2004; **38:** 1323.

Adverse Effects and Precautions

As for Salbutamol, p. 1221.3. Inhalation of formoterol may be associated with paradoxical bronchospasm, and high doses have been associated with an increase in severe exacerbations of asthma. It should not be used in patients who are not also receiving an inhaled corticosteroid.

Long-acting beta$_2$ agonists such as formoterol are not appropriate for the treatment of acute bronchospasm.

Conjunctival irritation and eyelid oedema have been reported in isolated cases.

References.

1. Wilton LV, Shakir SA. A post-marketing surveillance study of formoterol (Foradil): its use in general practice in England. *Drug Safety* 2002; **25:** 213–23.
2. Pauwels RA, *et al.* Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. *Eur Respir J* 2003; **22:** 787–94.

Asthma. A review of 3 controlled studies comparing inhaled formoterol with placebo, concluded that regular use of high-dose formoterol (48 micrograms daily) may be associated with more frequent serious asthma exacerbations.[1] The concomitant use of inhaled corticosteroids was allowed but not mandatory, and was not reported in the review, which led to debate on whether the results of the study would be applicable when current prescribing guidelines for asthma were followed.[2,3]

In contrast to this, a subsequent study,[4] designed to test the hypothesis of a dose-related increase in serious asthma exacerbations with formoterol therapy, did not show any increase in serious asthma exacerbations between different formoterol doses and placebo. Again, inhaled corticosteroid use was allowed but not mandatory, with 62.4% of patients reported as receiving regular anti-inflammatory therapy.

A systematic review[5] firmly concluded that the addition of a long-acting beta$_2$ agonist (such as formoterol) to low or high doses of inhaled corticosteroids reduced the risk of asthma exacerbations compared with ongoing treatment with similar doses of inhaled corticosteroids alone. The addition of a long-acting beta$_2$ agonist reduced by 23% the relative risk of patients requiring systemic corticosteroids for an asthma exacerbation, over 4 to 54 weeks. There is no evidence of a difference in safety between treatment with formoterol plus a corticosteroid (typically budesonide) and salmeterol plus a corticosteroid (fluticasone).[6] However, for concerns about serious adverse effects associated with long-acting beta$_2$ agonists in asthma, including systematic reviews of largely asthma-related events with formoterol, see Increased Mortality, under Salmeterol p. 1224.3.

1. Mann M, *et al.* Serious asthma exacerbations in asthmatics treated with high-dose formoterol. *Chest* 2003; **124:** 70–4.
2. Rissmiller RW, *et al.* Asthma exacerbations and formoterol. *Chest* 2004; **125:** 1590–1.
3. van der Molen T. Formoterol and asthma exacerbations. *Chest* 2004; **125:** 1591.
4. Wolfe J, *et al.* Formoterol, 24 µg bid, and serious asthma exacerbations: similar rates compared with formoterol, 12 µg bid, with and without extra doses taken on demand, and placebo. *Chest* 2006; **129:** 27–38.
5. Ducharme FM, *et al.* Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2010 (accessed 03/08/10).
6. Cates CJ, Lasserson TJ. Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 13/07/10).

Effects on skeletal muscle. Myalgia and muscle weakness associated with elevated creatine kinase has been reported during formoterol therapy.[1] Subsequent muscle biopsy suggested mitochondrial dysfunction. No inflammatory changes were seen and symptoms resolved on withdrawal of formoterol.

1. Kiernan MC, *et al.* Mitochondrial dysfunction and rod-like lesions associated with administration of β 2 adrenoceptor agonist formoterol. *Neuromuscul Disord* 2004; **14:** 375–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies formoterol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Tolerance. Regular use of formoterol produced bronchodilator desensitisation,[1-3] and tachyphylaxis to bronchoprotection against methacholine, effects that have been noted with other long-acting beta$_2$ agonists (see Salmeterol, p. 1225.2) and short-acting beta$_2$ agonists (see Salbutamol, p. 1222.3).

1. van der Woude HJ, *et al.* Decreased bronchodilating effect of salbutamol in relieving methacholine induced moderate to severe bronchoconstriction during high dose treatment with long acting β_2 agonists. *Thorax* 2001; **56:** 529–35.
2. Jones SL, *et al.* Reversing acute bronchoconstriction in asthma: the effect of bronchodilator tolerance after treatment with formoterol. *Eur Respir* 2001; **17:** 368–73.
3. Haney S, Hancox RJ. Tolerance to bronchodilation during treatment with long-acting beta-agonists, a randomised controlled trial. *Respir Re* 2005; **6:** 107. Also available at: http://respiratory-research.com/content pdf/1465-9921-6-107.pdf (accessed 15/01/08)

Interactions

As for Salbutamol, p. 1223.1.

Pharmacokinetics

Inhaled formoterol is rapidly absorbed. It is largely metabolised by glucuronidation and *O*-demethylation with about 10% being excreted in the urine as unchanged drug. The mean terminal elimination half-life after inhalation is estimated to be 10 hours.

Stereoselectivity. Formoterol occurs as a racemic mixture in which arformoterol (p. 1202.3), the *R,R*-enantiomer, is the active form.[1,2] It has been suggested that stereoselective metabolism and excretion may account for the individual variation in duration of effect seen with formoterol although the exact mechanism remains unclear.[1,3]

1. Zhang M, *et al.* Stereoselective glucuronidation of formoterol by human liver microsomes. *Br J Clin Pharmacol* 2000; **49:** 152–7.
2. Lötvall J, *et al.* The effect of formoterol over 24 h in patients with asthma the role of enantiomers. *Pulm Pharmacol Ther* 2005; **18:** 109–13.
3. Zhang M, *et al.* Stereoselective urinary excretion of formoterol and its glucuronide conjugate in human. *Br J Clin Pharmacol* 2002; **54:** 246–50

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fordilen; Oxis; Xanol; *Austral.*: Foradile; Oxis; *Austria*: Foradil; Oxis; *Belg.*: Foradil; Formagal; Formoair; Oxis; *Braz.*: Fluir; Foradil; Formare; Formocaps; Oxis; *Canad.*: Foradil; Oxeze; *China*: Atock (安通克); Oxis (奥克斯); Pan De Xin (盼得欣); *Cz.*: Atimos; Foradil; Forair†; Formano; Formovent; Oxis†; *Denm.*: Delnil; Eformax†; Foradil; Formo; Fostair; Oxez; Oxis; *Fin.*: Cycloterol; Fomeda; Foradil; Formaxa; Oxis; *Fr.*: Asmelor; Atimos; Foradil; Formoair; *Ger.*: Foradil; Forair; Formatris; FormoLich; Formotop; Oxis; *Gr.*: Broncoteril; Edufil; Foradil; Forair; Forcap; Formaxa; Formopen; Formotil; Imotec; Kinitron; Oxez; *Hong Kong*: Oxis; *Hung.*: Atimos; Diffumax†; Foradil; Fortofan†; Oxis; *India*: Deriform; Foratec; *Irl.*: Foradil; Oxis; *Israel*: Foradil; Oxis; *Ital.*: Aliterol; Atimos; Bolus; Evervent; Feronal; Foradil; Forotan; Fortasint; Kurovent; Levovent; Liferol; Oxis; *Jpn*: Atock; Oxis; *Malaysia*: Oxis; *Mex.*: Foradil; Oxis; *Neth.*: Atimos; Foradil; Formocaps†; Oxis; *Norw.*: Foradil†; Oxis; *NZ*: Foradil; Oxis; *Philipp.*: Atock; Foradil; Oxis†; *Pol.*: Atimos; Diffumax; Foradil; Forastmin; Oxis; Oxodil; Zafiron; Zomexil; *Port.*: Asmatec; Atimos; Eformax†; Foradil; Forair; Formaxa†; Oxis; *Rus.*: Atimos (Атимос); Foradil (Форадил); Oxis (Оксис); *S.Afr.*: Foradil; Foratec; Oxis; *Singapore*: Foradil; Oxis†; *Spain*: Broncoral; Foradil; Formatris; Neblik; Oxis; *Swed.*: Foradil; Formatris; Oxis; *Switz.*: Foradil; Oxis; *Thai.*: Oxis; *Turk.*: Atimos; Foradil; Forast; Foryxa; Oxis; Ventofor; *UK*: Atimos Modulite; Foradil; Oxis; *Ukr.*: Fortix (Фортикс); Zafiron (Зафирон); *USA*: Foradil; Perforomist; *Venez.*: Fluir; Foradil; Formotec.

Multi-ingredient Preparations. *Arg.*: Previa; Neumoterol; Symbicort; *Austral.*: Symbicort; *Austria*: Formodual; Foster; Symbicort; *Belg.*: Flutiform; Inuvair; Symbicort; *Braz.*: Alenia; Foraseq; Fostair; Symbicort; Vannair; *Canad.*: Symbicort; Zenhale; *Chile*: Symbicort; Vannair; *China*: Symbicort (信必可); *Cz.*: Budfor; Combair; Edoflo; Formodual†; Symbicort; *Denm.*: Assieme; Innovair; Rilast; Sinestic; Symbicort; *Fin.*: Flutiform; Innovair; Symbicort; *Fr.*: Formodual; Innovair; Symbicort; *Ger.*: Foster; Inuvair; Symbicort; *Gr.*: Foster; Inuvair; Symbicort; *Hong Kong*: Symbicort; *Hung.*: Foster; Symbicort; *India*: Avessa; Budamate; Combihale-FF; Duova; Fomtide; Foracort; Formonide; *Indon.*: Symbicort; *Irl.*: Budfor; Edoflo; Symbicort; *Israel*: Symbicort; *Ital.*: Assieme; Assiememite; Formodual; Foster; Inuver; Sinestic; Sinesticmite†; Symbicort; *Jpn*: Symbicort; *Malaysia*: Foracort; Symbicort; *Mex.*: Symbicort; *Neth.*: Assieme; Budfor; Edoflo†; Flutiform; Formodual; Foster; Iffeza: Sinestic; Symbicort; *Norw.*: Flutiform; Inuxair; Symbicort; *NZ*: Symbicort; Vannair; *Philipp.*: Symbicort; *Pol.*: Fostex; Symbicort; *Port.*: Assieme; Formodual; Foster; Symbicort; *Rus.*: Foradil Combi (Форадил Комби); Foster (Фостер); Simbicort (Симбикорт)†; Symbicort (Симбикорт); *S.Afr.*: Symbicord; *Singapore*: Symbicort; *Spain*: Formodual; Foster; Rilast; Symbicort; *Swed.*: Innovair; Symbicort; *Switz.*: Symbicort; Vannair; *Thai.*: Symbicort; *Turk.*: Combipack; Foradil Combi; Foster; Innovair; Symbicort; Ventofor-Combi; *UK*: flutiform; Fostair; Symbicort; *Ukr.*: Simbicort (Симбикорт); *USA*: Dulera; Symbicort; *Venez.*: Foraseq; Symbicort.

Heptaminol Acefyllinate (rINNM)

Acefilinato de heptaminol; Acéfyllinate d'Heptaminol; Acefyllinum Heptaminolum; Heptaminol, acefilinato de; Heptaminol Acéfylline; Heptaminol Acephyllinate; Heptaminol Theophylline Ethanoate; Heptaminol Theophylline-7-

acetate; Heptaminoli Acefyllinas; Гептаминола Ацефиллинат.
The 6-amino-2-methylheptan-2-ol salt of theophyllin-7-ylacetic acid.
$C_8H_{19}NO.C_9H_{10}N_4O_4$=383.4
CAS — 5152-72-7; 10075-18-0.
ATC — C01DX08.
ATC Vet — QC01DX08.
UNII — WL6JNI78OE.

Profile

Heptaminol acefyllinate is a derivative of theophylline (p. 1229.3) that has been used for its bronchodilator and cardiovascular effects.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Cariamyl.

Multi-ingredient Preparations. *Braz.*: Sureptil; *Spain*: Diclamina†.

Hexoprenaline Hydrochloride

(BANM, rINNM) ⊗

Hexoprenalina, hidrocloruro de; Hexoprénaline, Chlorhydrate d'; Hexoprenalini Hydrochloridum; Hidrocloruro de hexoprenalina; ST-1512; Гексопреналина Гидрохлорид.
N,N'-Hexamethylenebis[4-(2-amino-1-hydroxyethyl)pyrocatechol] dihydrochloride; *N,N'*-Hexamethylenebis[2-amino-1-(3,4-dihydroxyphenyl)ethanol] dihydrochloride.
$C_{32}H_{32}N_2O_6.2HCl$=493.4
CAS — 3215-70-1 (hexoprenaline); 4323-43-7 (hexoprenaline dihydrochloride).
ATC — R03AC06; R03CC05.
ATC Vet — QR03AC06; QR03CC05.

Hexoprenaline Sulfate *(BANM, USAN, rINNM)* ⊗

Hexoprenalina, sulfato de; Hexoprénaline, Sulfate d'; Hexoprenaline Sulphate; Hexoprenalini Sulfas; Sulfato de hexoprenalina; Гексопреналина Сульфат.
(±)-α,α'-[Hexamethylenebis(iminomethylene)]-bis[3,4-dihydroxybenzyl alcohol] sulfate (1:1).
$C_{32}H_{32}N_2O_6H_2SO_4$=518.6
CAS — 32266-10-7.
ATC — R03AC06; R03CC05.
ATC Vet — QR03AC06; QR03CC05.
UNII — U851S9102C.

Profile

Hexoprenaline is a direct-acting sympathomimetic with mainly beta-adrenergic activity selective to $beta_2$ receptors (a $beta_1$ agonist). It has properties similar to those of salbutamol (p. 1220.2) and has been used as a bronchodilator in the treatment of reversible airways obstruction as occurs with asthma (p. 1195.2) and in some patients with chronic obstructive pulmonary disease (p. 1199.1). It has sometimes been used similarly to salbutamol in the management of premature labour (p. 2131.1).

Hexoprenaline is usually given as the hydrochloride or sulfate.

For the relief of **bronchoconstriction**, a typical adult oral dose of the salts has been 0.5 to 1 mg three times daily. The salts were also formerly given by inhalation. In patients with asthma, as-required beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, hexoprenaline indicates deterioration of asthma control and the need for review of therapy.

In the management of **premature labour** an intravenous infusion of hexoprenaline sulfate, diluted in glucose 5% or sodium chloride 0.9%, can be given at an initial rate of about 300 nanograms/minute. Infusion may be preceded by slow intravenous injection of 10 micrograms as a loading dose over 5 to 10 minutes. $Beta_2$ agonist therapy should be limited to a maximum of 48 hours, because prolonged treatment is associated with risks of serious cardiovascular effects in both the mother and fetus (see Precautions under Salbutamol, p. 1222.3). Oral or rectal therapy is no longer recommended in premature labour because of a lack of evidence of benefit from treatment given by these routes of administration. A lower dose prolonged infusion of 75 nanograms/minute has been used for support during cervical cerclage.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Argocian; *Austria*: Gynipral; *Cz.*: Gynipral; *Hong Kong*: Ipradol; *Rus.*: Gynipral (Гинипрал); *S.Afr.*: Ipradol†; *Switz.*: Gynipral; *Ukr.*: Gynipral (Гинипрал).

Ibudilast *(rINN)*

AV-411; Ibudilastum; KC-404; MN-166; Ибудиласт.
1-(2-Isopropylpyrazolo[1,5-*a*]pyridin-3-yl)-2-methyl-1-propanone.
$C_{14}H_{18}N_2O$=230.3
CAS — 50847-11-5.
ATC — R03DC04.
ATC Vet — QR03DC04.
UNII — M0TTH61XC5.

Pharmacopoeias. In *Jpn*.

Profile

Ibudilast is an orally active leukotriene antagonist (p. 1195.2), phosphodiesterase inhibitor, and platelet-activating factor antagonist. It is given orally in the management of asthma (p. 1195.2) in a dose of 10 mg twice daily.

Ibudilast is also promoted for the management of dizziness secondary to impaired cerebral circulation following cerebral infarction, in doses of 10 mg three times daily.

Ibudilast is also under investigation for the treatment of multiple sclerosis and for chronic neuropathic pain.

References.
1. Kishi Y, *et al.* Ibudilast: a non-selective PDE inhibitor with multiple actions on blood cells and the vascular wall. *Cardiovasc Drug Rev* 2001; 19: 215–25.
2. Ledeboer A, *et al.* Ibudilast (AV-411): a new class therapeutic candidate for neuropathic pain and opioid withdrawal syndromes. *Expert Opin Invest Drugs* 2007; 16: 935–50.
3. Rolan P, *et al.* Ibudilast in healthy volunteers: safety, tolerability and pharmacokinetics with single and multiple doses. *Br J Clin Pharmacol* 2008; 66: 792–801.
4. Rolan P, *et al.* Ibudilast: a review of its pharmacology, efficacy and safety in respiratory and neurological disease. *Expert Opin Pharmacother* 2009; 10: 2897–2904.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Si Yi Ke (司易可); Wei Chang (维畅); *Jpn*: Ketas.

Indacaterol *(BAN, USAN, rINN)* ⊗

Indacaterol, Indacaterolum; QAB-149; Индакатерол.
5-[(1*R*)-2-[(5,6-Diethyl-2,3-dihydro-1*H*-inden-2-yl)amino]-1-hydroxyethyl]-8-hydroxyquinolin-2(1*H*)-one.
$C_{24}H_{28}N_2O_3$=392.5
CAS — 312753-06-3.
ATC — R03AC18.
ATC Vet — QR03AC18.
UNII — 8OR09251MQ.

Indacaterol Maleate *(BANM, USAN, rINNM)* ⊗

Indacatérol, Maléate d'; Indacaterol Maleas; Maleato de indacaterol; QAB-149-AFA; Индакатерола Малеат.
5-[(1*R*)-2-[(5,6-Diethyl-2,3-dihydro-1*H*-inden-2-yl)amino]-1-hydroxyethyl]-8-hydroxyquinolin-2(1*H*)-one hydrogen (2*Z*)-2-butenedioate (salt).
$C_{24}H_{28}N_2O_3.C_4H_4O_4$=508.6
CAS — 753498-25-8.
ATC — R03AC18.
ATC Vet — QR03AC18.
UNII — 2JEC1ITX7R.

Uses and Administration

Indacaterol is a long-acting $beta_2$ agonist used as a bronchodilator in the maintenance treatment of chronic obstructive pulmonary disease; it is not indicated for the relief of acute bronchospasm. It is given as the maleate but doses are expressed as the base; indacaterol maleate 1.3 mg is equivalent to about 1 mg of indacaterol. Inhalation results in a rapid onset (within 5 minutes) of bronchodilatation, which lasts for up to 24 hours.

In the UK indacaterol maleate is given as inhalation powder in capsules containing the equivalent of indacaterol 150 micrograms or 300 micrograms, and supplying indacaterol 120 micrograms or 240 micrograms, respectively, from the mouthpiece of the device. The contents of one capsule are inhaled daily, at the same time each day. In the USA a lower dose of one 75-microgram capsule daily, supplying indacaterol 57 micrograms from the mouthpiece, is licensed.

Indacaterol has also been investigated in the treatment of asthma.

References.
1. Roig J, *et al.* Indacaterol, a novel once daily inhaled β 2-adrenoreceptor agonist. *Open Respir Med J* 2009; 3: 27–30.
2. Beeh KM, Beier J. Indacaterol, a novel inhaled, once-daily, long-acting $beta_2$-agonist for the treatment of obstructive airways diseases. *Adv Therapy* 2009; 26: 691–9. Correction. *ibid.*: 812. [dose]
3. Dahl R, *et al.* INVOLVE Study Investigators. Efficacy of a new once-daily long-acting inhaled β 2-agonist indacaterol versus twice-daily formoterol in COPD. *Thorax* 2010; 65: 473–9.
4. Moen MD. Indacaterol: in chronic obstructive pulmonary disease. *Drugs* 2010; 70: 2269–80.

Adverse Effects and Precautions

As for Salbutamol, p. 1221.3 and p. 1222.3. Nasopharyngitis, cough, and upper respiratory-tract infections are common.

Interactions

As for Salbutamol, p. 1223.1.

Indacaterol is metabolised by the cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein and inhibitors of these substances may increase systemic exposure to indacaterol, although this did not affect safety in clinical studies.

Pharmacokinetics

Peak concentrations of indacaterol occur about 15 minutes after inhalation, and absolute bioavailability was on average 43%. Indacaterol is metabolised by cytochrome P450 isoenzymes, particularly CYP3A4. Uridine diphosphate glucuronosyltransferase 1A1 (UGT 1A1) also contributes to metabolism and indacaterol is a low-affinity substrate for P-glycoprotein. When indacaterol was given orally, about 90% was excreted in the faeces; renal clearance plays a minor role in excretion via the urine. The average terminal half-life was 45.5 to 126 hours, but a half-life of 40 to 52 hours was calculated after repeated dosing.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Onbrize; *Austral.*: Onbrez; *Austria*: Onbrez; *Belg.*: Onbrez; *Canad.*: Onbrez; *Cz.*: Hirobriz; Onbrez; Oslif; *Denm.*: Onbrez; *Fr.*: Onbrez; Oslif; *Ger.*: Onbrez; *Gr.*: Onbrez; *Hung.*: Onbrez; *Irl.*: Hirobriz; Onbrez; Oslif; *Israel*: Onbrez; *Jpn*: Onbrez; *Neth.*: Hirobriz; Onbrez; Oslif; *Norw.*: Onbrez; *Philipp.*: Onbrez; *Pol.*: Hirobriz; Onbrez; Oslif; *Port.*: Hirobriz; Onbrez; Oslif; *Singapore*: Onbrez; *Spain*: Hirobriz; Onbrez; Oslif; *Swed.*: Onbrez; *Switz.*: Onbrez; *Thai.*: Onbrez; *Turk.*: Onbrez; *UK*: Onbrez; *Ukr.*: Onbrez (Онбрез); *USA*: Arcapta.

Ipratropium Bromide *(BAN, USAN, rINN)*

Bromuro de Ipratropio; Ipratropii Bromidum; Ipratropii Bromidum Monohydricum; Ipratropio bromidas; Ipratropio, bromuro de; Ipratropiowy bromek; Ipratropium bromid monohydrát; Ipratropium, Bromure d'; Ipratropiumbromid; Ipratropium-bromid; Ipratropiumbromidi; Ipratropyum Bromür; Sch-1000-Br-monohydrate; Sch-1000; Ипратропия бромид.
(1*R*,3*r*,5*S*,8*r*)-8-Isopropyl-3-[(±)-tropoyloxy]tropanium bromide monohydrate.
$C_{20}H_{30}BrNO_3.H_2O$=430.4
CAS — 22254-24-6 (anhydrous ipratropium bromide); 66985-17-9 (ipratropium bromide monohydrate).
ATC — R01AX03; R03BB01.
ATC Vet — QR01AX03; QR03BB01.
UNII — J697UZZA9J.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Ipratropium Bromide). White or almost white crystalline powder. Soluble in water; slightly soluble in alcohol; freely soluble in methyl alcohol. The pH of a 1% solution in water is 5.0 to 7.5.

USP 36: (Ipratropium Bromide). A white to off-white, crystalline powder. Soluble in water; slightly soluble in alcohol; freely soluble in methyl alcohol. A 10% solution has a pH of 5 to 7. Store in airtight containers.

Stability. In a study[1] of the stability of admixtures of ipratropium and salbutamol nebuliser solutions equal ratio mixtures were found to retain more than 90% of their initial concentrations after storage for 5 days at 4 degrees or 22 degrees in the dark or at 22 degrees under continuous fluorescent lighting.

1. Jacobson GA, Peterson GM. Stability of ipratropium bromide and salbutamol nebuliser admixtures. *Int J Pharm Pract* 1995; 3: 169–73.

Uses and Administration

Ipratropium bromide is a quaternary ammonium antimuscarinic (p. 1195.1). It is used by inhalation as a bronchodilator in the treatment of reversible airways

obstruction, as in asthma and chronic obstructive pulmonary disease (see below).

In the UK the dose of ipratropium bromide from the metered-dose aerosol is expressed in terms of the amount of drug released from the valve into the mouthpiece (20 micrograms) whereas in the USA it is expressed in terms of the dose emitted from the mouthpiece (17 micrograms, equivalent to 21 micrograms released from the valve); recommended doses may therefore appear lower in the USA. For **reversible airways obstruction**, the usual UK dose from a metered-dose aerosol is 1 or 2 inhalations (20 or 40 micrograms) three or four times daily; single doses of up to 4 inhalations may be required. Comparable doses are used in the USA, but it is recommended that the daily dose should not exceed 12 inhalations. Ipratropium bromide may also be given by inhalation as a nebulised solution in doses of 250 to 500 micrograms up to 4 times daily. Dry powder inhalation capsules have been used.

Ipratropium bromide, given intranasally, is also used in the management of rhinorrhoea associated with **rhinitis**. A dose of 42 micrograms is given into each nostril by metered-dose nasal spray 2 or 3 times daily. US licensing also permits higher doses of 84 micrograms into each nostril 3 or 4 times daily, for up to 4 days when rhinorrhoea is associated with the common cold; doses of 84 micrograms may be given into each nostril 4 times daily, for up to 3 weeks when rhinorrhoea is associated with seasonal allergic rhinitis.

For details of doses in children, see Administration in Children, below.

Administration in children. Children may be given ipratropium bromide via a metered dose aerosol in the treatment of **reversible airways obstruction**. UK licensed product information recommends doses by age as follows:

- under 6 years: 1 inhalation of 20 micrograms three times daily
- 6 to 12 years: 1 or 2 inhalations of 20 micrograms three times daily
- 12 years and over: adult doses, see p. 1211.3

Ipratropium bromide may also be given by inhalation as a nebulised solution. UK licensed product information recommends the following doses:

- under 6 years, for the treatment of acute asthma only: 125 to 250 micrograms, given no more often than every 6 hours up to a total daily dose of 1 mg
- 6 to 12 years, for the treatment of acute or chronic asthma: 250 micrograms, repeated if necessary up to a total daily dose of 1 mg
- 12 years and over: adult doses, see p. 1211.3.

Ipratropium bromide is used in the management of rhinorrhoea associated with **rhinitis**. A dose of 42 micrograms may be given into both nostrils two or three times daily. In the UK this dose may be given to children from 12 years of age, but in the USA this dose is licensed in children from 6 years of age.

US licensing also permits higher doses for up to 4 days when rhinorrhoea is associated with the common cold:

- 5 to 11 years: 84 micrograms into each nostril three times daily
- 12 years and over: adult doses, see p. 1211.3

Higher doses are also permitted in the USA for up to 3 weeks when rhinorrhoea is associated with seasonal allergic rhinitis. Children 5 years of age and over may be given the same dose as adults, see p. 1211.3.

Asthma. Ipratropium bromide is currently recommended as an adjunct to $beta_2$ agonists in the management of acute severe asthma, see p. 1195.2. Antimuscarinic drugs, mainly ipratropium but also including oxitropium (p. 1218.1), glycopyrronium and atropine, have been reviewed in the treatment of both acute and chronic asthma. A systematic review and meta-analysis[1] of the efficacy of antimuscarinics in the treatment of acute asthma in children and adults, found they produced significant reductions in hospital admissions. Combined treatment with an inhaled $beta_2$ agonist also produced a significant increase in respiratory function.

Systematic reviews of antimuscarinic drugs have concluded that there is currently insufficient evidence to justify their routine use in adults[2] or children[3] with chronic asthma.

1. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. *Thorax* 2005; 60: 740–6.
2. Westby M, *et al.* Anticholinergic agents for chronic asthma in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 18/02/08).
3. McDonald NJ, *et al.* Anticholinergic therapy for chronic asthma in children over 2 years of age. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 07/05/10).

Chronic obstructive pulmonary disease. Inhaled antimuscarinics, such as ipratropium bromide, are currently recommended as bronchodilators in chronic obstructive pulmonary disease (COPD) guidelines, see p. 1199.1. A systematic review compared regular treatment with ipratropium (given for at least 4 weeks) with treatment using regular short-acting $beta_2$ agonists in stable COPD;[1] it found small benefits on lung function outcomes and quality of life with ipratropium compared with a short-acting $beta_2$ agonist; a reduction in the requirements for oral corticosteroids was also seen. Combination therapy with ipratropium and a short-acting $beta_2$ agonist was associated with some clinically meaningful lung function outcomes compared with the $beta_2$ agonist alone, but these were not reflected in subjective improvements or symptom scores.

A systematic review comparing ipratropium with a long-acting $beta_2$ agonist in stable COPD,[2] found that salmeterol had more effect than ipratropium on lung function, but no major differences were seen between symptom responses to ipratropium and salmeterol. Combination treatment with these two drugs was better than salmeterol alone in terms of quality of life.

1. Appleton S, *et al.* Ipratropium bromide versus short acting beta-2 agonists for stable chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 18/02/08).
2. Appleton S, *et al.* Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 18/02/08).

Hypersalivation. Ipratropium has been tried for its antimuscarinic properties in the management of sialorrhoea and hypersalivation of various causes,[1-4] but studies have suggested that it is of little value in reducing saliva production in patients with parkinsonism[3] or hypersalivation induced by clozapine.[4]

1. Kunwar AR, *et al.* Ipratropium bromide for treatment of bethanechol-induced sialorrhea. *Ann Pharmacother* 2003; 37: 1343.
2. Freudenreich O, *et al.* Clozapine-induced sialorrhea treated with sublingual ipratropium spray: a case series. *J Clin Psychopharmacol* 2004; 24: 98–100.
3. Thomsen TR, *et al.* Ipratropium bromide spray as treatment for sialorrhea in Parkinson's disease. *Mov Disord* 2007; 22: 2268–73.
4. Sockalingam S, *et al.* Treatment of clozapine-induced hypersalivation with ipratropium bromide: a randomized, double-blind, placebo-controlled crossover study. *J Clin Psychiatry* 2009; 70: 1114–19.

Rhinitis. Ipratropium bromide is used intranasally for the treatment of rhinorrhoea in allergic and non-allergic rhinitis (p. 612.1). It has also relieved rhinorrhoea and sneezing associated with the common cold, alone or with intranasal corticosteroids or xylometazoline.

References.

1. Georgitis JW, *et al.* Ipratropium bromide nasal spray in non-allergic rhinitis: efficacy, nasal cytological response and patient evaluation on quality of life. *Clin Exp Allergy* 1994; 24: 1049–55.
2. Hayden FG, *et al.* Effectiveness and safety of intranasal ipratropium bromide in common colds: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1996; 125: 89–97.
3. Dockhorn R, *et al.* Ipratropium bromide nasal spray 0.03% and beclomethasone nasal spray alone and in combination for the treatment of rhinorrhea in perennial rhinitis. *Ann Allergy Asthma Immunol* 1999; 82: 349–59.
4. Bonadonna P, *et al.* Cold-induced rhinitis in skiers—clinical aspects and treatment with ipratropium bromide nasal spray: a randomized controlled trial. *Am J Rhinol* 2001; 15: 297–301.
5. Kim KT, *et al.* Pediatric Atrovent Nasal Spray Study Group. Use of 0.06% ipratropium bromide nasal spray in children aged 2 to 5 years with rhinorrhea due to a common cold or allergies. *Ann Allergy Asthma Immunol* 2005; 94: 73–9.
6. Eccles R, *et al.* Effects of intranasal xylometazoline, alone or in combination with ipratropium, in patients with common cold. *Curr Med Res Opin* 2010; 26: 889–99.

Adverse Effects and Precautions

Ipratropium and other inhaled antimuscarinic bronchodilators commonly cause dry mouth and constipation, and rarely, urinary retention. They should be used with care in prostatic hyperplasia. Acute angle-closure glaucoma has been reported: the mist or solution should not be allowed to enter the eyes, particularly in patients susceptible to glaucoma. As with other bronchodilators, paradoxical bronchospasm has occurred. Tachycardia, palpitations, and arrhythmias have been reported with ipratropium. Hypersensitivity reactions, including urticaria, angioedema, rash, and anaphylaxis have occurred rarely. Nausea and vomiting, dyspepsia, headaches, and dizziness have also been reported.

Intranasal ipratropium has been associated with nasal dryness, irritation, and epistaxis.

For details of the adverse effects of, and precautions for, antimuscarinics in general, see Atropine, p. 1312.1 and p. 1312.2.

Buccal ulceration. A report[1] of inflammation and ulceration of the buccal mucosa associated with the use of an ipratropium bromide inhaler.

1. Spencer PA. Buccal ulceration with ipratropium bromide. *BMJ* 1986; 292: 380.

Effects on the cardiovascular system. A large systematic review[1] found that use of the inhaled antimuscarinics ipratropium and tiotropium for more than 30 days increased the risk of myocardial infarction and cardiovascular death in patients with chronic obstructive pulmonary disease (COPD) compared with placebo or an active control (an inhaled $beta_2$ agonist with or without an inhaled corticosteroid). The magnitude of the risk was difficult to discern as many of the studies included were small and short-term, resulting in few events. An increased risk of cardiovascular death with the use of ipratropium has also been reported in a case-control study[2] in COPD patients, and a cohort study involving 82 717 US veterans with COPD also found that exposure to ipratropium within the last 6 months was associated with an increased risk of cardiovascular events (heart failure, acute coronary syndrome, or arrhythmias).[3] However, these findings are contrary to results from other studies. A cohort study[4] comparing the safety of tiotropium to long-acting $beta_2$ agonists suggested users had a similar risk of cardiovascular events and a 4-year placebo-controlled study[5] of tiotropium in about 6000 patients with COPD reported a reduction in cardiac morbidity, although the study was not designed to assess cardiovascular events. Other analyses[6,7] of pooled data from studies in patients with obstructive lung disease suggested serious cardiovascular events did not occur more often in patients taking tiotropium than in those taking placebo or salmeterol. Further studies are considered necessary in order to confirm the cardiovascular safety of inhaled antimuscarinics.[8]

For further discussion of a possible increased risk of mortality associated with ipratropium use, see p. 1213.1.

For further information on the risk to the cardiovascular system associated with tiotropium, see Effects on the Cerebrovascular System, p. 1238.2.

1. Singh S, *et al.* Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA* 2008; 300: 1439–50. Correction. *ibid.* 2009; 301: 1227–30.
2. Lee TA, *et al.* Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. *Ann Intern Med* 2008; 149: 380–90.
3. Ogale SS, *et al.* Cardiovascular events associated with ipratropium bromide in COPD. *Chest* 2010; 137: 13–19.
4. Jara M, *et al.* Comparative safety of long-acting inhaled bronchodilators: a cohort study using the UK THIN primary care database. *Drug Safety* 2007; 30: 1151–60.
5. Tashkin DP, *et al.* UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 1543–54.
6. Kesten S, *et al.* Pooled clinical trial analysis of tiotropium safety. *Chest* 2006; 130: 1695–1703. Also available at: http://www.chestjournal.org/content/130/6/1695.full.pdf+html (accessed 07/08/09)
7. Rodrigo GJ, *et al.* Tiotropium and risk for fatal and nonfatal cardiovascular events in patients with chronic obstructive pulmonary disease: systematic review with meta-analysis. *Respir Med* 2009; 103: 1421–9.
8. Salpeter SR. Do inhaled anticholinergics increase or decrease the risk of major cardiovascular events? A synthesis of the available evidence. *Drugs* 2009; 69: 2025–33.

Effects on the eyes. Ocular complications have been reported with the use of aerosolised ipratropium. A patient with a history of glaucoma developed angle-closure glaucoma after use of ipratropium from a metered dose inhaler (MDI) with nebulised salbutamol.[1] Pupillary dilatation[2] and blurred vision[3] have been reported in association with ipratropium given through a spacer device in patients also given salbutamol therapy, and a 4-year-old child who attempted to self-administer an ipratropium MDI developed anisocoria (unequal dilatation of the pupils) and ataxia.[4] Angle-closure glaucoma,[5-7] pupillary dilatation,[7-10] and anisocoria[11,12] have been reported in patients given *nebulised* ipratropium, usually with salbutamol, through a poorly fitting face mask. The antimuscarinic effects of ipratropium can lead to impaired drainage of aqueous humour in the eyes of patients predisposed to angle-closure glaucoma; use with salbutamol may intensify this problem by increasing the production of aqueous humour.[6] Studies[13,14] suggest that patients with a history of angle-closure glaucoma might be at an increased risk of developing glaucoma when nebulised ipratropium and salbutamol are used together.

1. Hall SK. Acute angle-closure glaucoma as a complication of combined β-agonist and ipratropium bromide therapy in the emergency department. *Ann Emerg Med* 1994; 23: 884–7.
2. Weir REP, *et al.* Pupil blown by a puffer. *Lancet* 2004; 363: 1853.
3. Kizer KM, *et al.* Blurred vision from ipratropium bromide inhalation. *Am J Health-Syst Pharm* 2000; 57: 996–7.
4. Bond DW, *et al.* Mydriasis due to self-administered inhaled ipratropium bromide. *Eur J Pediatr* 2002; 161: 178.
5. Packe GE, *et al.* Nebulised ipratropium bromide and salbutamol causing closed-angle glaucoma. *Lancet* 1984; ii: 691.
6. Shah P, *et al.* Acute angle closure glaucoma associated with nebulised ipratropium bromide and salbutamol. *BMJ* 1992; 304: 40–1.
7. Mulpeter KM, *et al.* Ocular hazards of nebulized bronchodilators. *Postgrad Med J* 1992; 68: 132–3.
8. Roberts TE, Pearson DJ. Wide eyed and breathless. *BMJ* 1989; 299: 1348.
9. Woelfle J, *et al.* Unilateral fixed dilated pupil in an infant after inhalation of nebulized ipratropium bromide. *J Pediatr* 2000; 136: 423–4.
10. Openshaw H. Unilateral mydriasis from ipratropium in transplant patients. *Neurology* 2006; 67: 914–15.
11. Lust K, Livingstone I. Nebulizer-induced anisocoria. *Ann Intern Med* 1998; 128: 327.
12. Iosson N. Nebulizer-associated anisocoria. *N Engl J Med* 2006; 354: e8.
13. Watsun WTA, *et al.* Effect of nebulized ipratropium bromide on intraocular pressures in children. *Chest* 1994; 105: 1439–41.
14. Kalra L, Bone MF. The effect of nebulized bronchodilator therapy on intraocular pressures in patients with glaucoma. *Chest* 1988; 93: 739–41.

Effects on the gastrointestinal tract. Paralytic ileus developed shortly after starting ipratropium therapy in 2 patients, apparently due to the inadvertent swallowing of the drug during inhalation.[1,2] Both patients also had other predisposing factors for paralytic ileus (cystic fibrosis,[1] spastic diplegia[2]).

1. Mulherin D, FitzGerald MX. Meconium ileus equivalent in association with nebulised ipratropium bromide in cystic fibrosis. *Lancet* 1990; 335: 552.
2. Markus HS. Paralytic ileus associated with ipratropium. *Lancet* 1990; 335: 1224.

Effects on the respiratory tract. Antimuscarinics typically inhibit mucociliary clearance and inhibit secretions of the nose, mouth, pharynx, and bronchi. However, inhaled ipratropium bromide has virtually no effect on sputum viscosity or volume and, in contrast to atropine, it does not affect mucociliary function in the respiratory tract.[1,2]

1. Gross NJ. Ipratropium bromide. *N Engl J Med* 1988; 319: 486–94.
2. Mann KV, *et al.* Use of ipratropium bromide in obstructive lung disease. *Clin Pharm* 1988; 7: 670–80.

BRONCHOSPASM. Paradoxical bronchoconstriction occurring after the use of ipratropium was reported in 3 patients.[1] A further report[2] of paradoxical bronchoconstriction after nebulised salbutamol and ipratropium suggested that this adverse effect might have been caused by benzalkonium chloride present in the nebuliser solutions. Nebuliser solutions of ipratropium in some countries contain benzalkonium chloride as a preservative. Solutions available in the UK are preservative-free but licensed product information still recommends that the first doses of ipratropium nebuliser solution should be inhaled under medical supervision.

1. Connolly CK. Adverse reaction to ipratropium bromide. *BMJ* 1982; 285: 934–5.
2. Boucher M, *et al.* Possible associations of benzalkonium chloride in nebulizer solutions with respiratory arrest. *Ann Pharmacother* 1992; 26: 772–4.

Effects on the urinary tract. Treatment with nebulised ipratropium bromide has resulted in urinary retention in elderly men especially those with prostatic hyperplasia.[1,2] Micturition difficulties associated with use of ipratropium and salbutamol in a child have also been reported.[3]

1. Lozewicz S. Bladder outflow obstruction induced by ipratropium bromide. *Postgrad Med J* 1989; 65: 260–1.
2. Pras E, *et al.* Urinary retention associated with ipratropium bromide. *DICP Ann Pharmacother* 1991; 25: 939–40.
3. Hooimeijer HL, *et al.* Bemoeilijkte mictie bij een kind toegeschreven aan het gebruik van ipratropium en salbutamol. *Ned Tijdschr Geneeskd* 2007; 151: 2726–8.

Increased mortality. A case-control study found an unexpected association between death from asthma and treatment with ipratropium, which was not explained by comorbidity due to chronic obstructive pulmonary disease (COPD).[1] A retrospective cohort study[2] of elderly patients also found a slight increase in the risk of death in asthma patients using ipratropium, although this may have been due to the confounding effect of disease severity. No increase in all-cause mortality was seen in patients with COPD using ipratropium. In contrast, another case-control study reported an increased risk of death associated with use of ipratropium for COPD.[3] A longitudinal cohort study of 1100 patients with obstructive lung disease found an increased risk of premature death associated with ipratropium in both asthma and COPD patients.[4] After adjusting for confounding factors such as forced expiratory volume, smoking status, BMI, and presence of cor pulmonale, ipratropium was associated with a mortality risk ratio (RR) of 2.4 in asthmatic patients and 1.6 in COPD patients. Again, residual confounding by disease severity could not be ruled out.

For a suggestion that inhaled ipratropium can increase the risk of cardiovascular death, see Effects on the Cardiovascular System, p. 1212.2.

1. Guite HF, *et al.* Risk factors for death from asthma, chronic obstructive pulmonary disease, and cardiovascular disease after a hospital admission for asthma. *Thorax* 1999; 54: 301–7.
2. Sin DD, Tu JV. Lack of association between ipratropium bromide and mortality in elderly patients with chronic obstructive airway disease. *Thorax* 2000; 55: 194–7.
3. Lee TA, *et al.* Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. *Ann Intern Med* 2008; 149: 380–90.
4. Ringbæk T, Viskum K. Is there any association between inhaled ipratropium and mortality in patients with COPD and asthma? *Respir Med* 2003; 97: 264–72.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ipratropium bromide as probably not porphyrinogenic when used by inhalation; it may be used as a drug of first choice and no precautions are needed. It is classified as not porphyrinogenic when used intranasally.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Interactions

For interactions associated with antimuscarinics in general, see Atropine, p. 1312.3. However, these interactions are not usually seen with antimuscarinics, such as ipratropium, given by inhalation.

Salbutamol. For reference to nebulised salbutamol exacerbating the adverse effects of nebulised ipratropium in patients predisposed to angle-closure glaucoma, see under Effects on the Eyes, p. 1212.3.

Pharmacokinetics

After inhalation, around 10 to 30% of a dose is deposited in the lungs where it exerts its therapeutic effect. Only a small amount of ipratropium reaches the systemic circulation. The majority of a dose is swallowed but is poorly absorbed from the gastrointestinal tract. Ipratropium and its metabolites are eliminated in the urine and faeces.

References.

1. Ensing K, *et al.* Pharmacokinetics of ipratropium bromide after single dose inhalation and oral and intravenous administration. *Eur J Clin Pharmacol* 1989; 36: 189–94.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aerotrop; Akitropio; Atrovent; Iprabron; ***Austral.***: Aeron; Apovent†; Atrovent; Ipratrin; Ipravent; ***Austria***: Atrovent; Itrop; ***Belg.***: Atronase; Atrovent; Nebu-Trop; ***Braz.***: Alvent; Ares; Atrovent; Bromovent; Iprabon†; Ipraneo; ***Canad.***: Apo-Ipravent; Atrovent; Novo-Ipramide; ***Chile***: Aerotrop; Atrovent; ***China***: Atrovent (爱全乐); ***Cz.***: Atrovent; ***Denm.***: Atrovent; ***Fin.***: Atrovent; Ipraxa; ***Fr.***: Atrovent; Ipratrogen; ***Ger.***: Atrovent; Itrop; ***Gr.***: Atrovent; Zyrolen; ***Hong Kong***: Atrovent; Cyclovent†; Steri-Neb†; ***Hung.***: Atrovent; ***India***: Ipneb; Ipramist; Ipranase; Ipratop; Ipravent; ***Indon.***: Atrovent; ***Irl.***: Atrovent; Ipravent; Rinatec; ***Israel***: Aerovent; Apovent†; Atrovent; ***Ital.***: Atem; Rinovagos; ***Jpn***: Atrovent; ***Malaysia***: Atrovent; ***Mex.***: Atrovent; ***Neth.***: Atrovent; Ipraxa; ***Norw.***: Atrovent; Ipraxa; ***NZ***: Apo-Ipravent; Atrovent; Univent; ***Philipp.***: Atrovent; Broncho-vent; ***Pol.***: Atrovent; ***Port.***: Atrovent; Ipraxa; ***Rus.***: Atrovent (Атровент); Ipravent (Иправент); ***S.Afr.***: Atrovent; Ipvent; ***Singapore***: Atrovent; Steri-Neb Ipratropium; ***Spain***: Atroaldo; Atrovent; ***Swed.***: Atrovent; Ipraxa; ***Switz.***: Atropair; Atrovent; Rhinovent; ***Thai.***: Atrovent†; Iperol; ***Turk.***: Atrovent; ***UAE***: Atropulm; ***UK***: Atrovent; Respontin; Rinatec; ***USA***: Atrovent; ***Venez.***: Alovent.

Multi-ingredient Preparations. ***Arg.***: Berodual; Combivent; Ipradual; Iprasalb; Salbutral AC; ***Austral.***: Combivent; ***Austria***: Berodual; Berodualin; Combivent; ***Belg.***: Combivent; Duovent; Nebu-Iprasal; Otrivine Duo; ***Braz.***: Combivent; Duovent; ***Canad.***: Combivent; Duovent; Gen-Combo†; Mylan-Combo; ratio-Ipra Sal; ***Chile***: Berodual; Combivent; Salbutral AC; ***China***: Combivent (可必特); Ren Shu (仁舒); ***Cz.***: Berodual; ***Denm.***: Berodual; Combipramol†; Combivent; Duovent; Ipramol; Sapimol; Zymelin Plus; ***Fin.***: Atrodual; Atrovent Comp; Ipramol; Otrivin Comp; Sallpra†; ***Fr.***: Bronchodual; ***Ger.***: Berodual; ***Gr.***: Berodual; Berovent; Demoren; Ipramol; Otrivin Advance; ***Hong Kong***: Combivent; Ipramol; ***Hung.***: Berodual; Otrivin Duo; ***India***: Aeromist; Combimist; Duolin; Fenovent; ***Indon.***: Berodual; Combivent; ***Irl.***: Combineb; Combivent; Duovent†; Ipramol; ***Israel***: Otrivin Complete; ***Ital.***: Almeida; Biwind; Breva; Duovent; Naos; ***Malaysia***: Berodual; Combivent; Duolin; Duovent; Ipramol; ***Mex.***: Berodual; Combivent; ***Neth.***: Berodual; Combipramol†; Combivent; Ipramol; Otrivin Duo; ***Norw.***: Otrivin Comp; Zycomb; ***NZ***: Combivent; Duolin; ***Philipp.***: Adsal Plus; Berodual; Combipul; Combivent; Duavent; Pulmodual; ***Pol.***: Berodual; Otrivin Duo; ***Port.***: Berodual; Combivent; Ipramol; Otrifar; ***Rus.***: Berodual (Бередуал); Ipramol (Ипрамол); Xymelin Extra (Ксимелин Экстра); ***S.Afr.***: Adco-Combineb; Atrovent Beta; Berodual†; Combivent; Duolin; Duovent; Sabax Nebrafen; ***Singapore***: Berodual; Combivent; Duovent; ***Spain***: Combiprasal; Otriduo; ***Swed.***: Combivent; Ipramol; Otrivin Comp; Sapimol; ZyComb†; ***Switz.***: Berodual; Dospir; Ipramol; ***Thai.***: Aeroduol; Berodual; Combivent; Inhalex; Ipratéral; Punol; ***Turk.***: Combivent; ***UK***: Combivent; Duovent†; Ipramol; ***Ukr.***: Berodual (Бередуал); Xymelin Extra (Ксимелин Экстра); Zycomb (Зикомб)†; ***USA***: Combivent; Duo-Neb; ***Venez.***: Berodual; Combivent; Duolin; Duovent; Ipralin; Respidual.

Pharmacopoeial Preparations

BP 2014: Ipratropium Inhalation Powder, hard capsule; Ipratropium Nebuliser Solution; Ipratropium Pressurised Inhalation.

Isoetarine (BAN, rINN) ⊗

Isoetarinii; Isoetarin; Isoetarina; Isoétarine; Isoetarinum; Isoetharine (USAN); Win-3406; Изоэтарин.

1-(3,4-Dihydroxyphenyl)-2-isopropylaminobutan-1-ol.

$C_{13}H_{21}NO_3$=239.3

CAS — 530-08-5.

ATC — R03AC07; R03CC06.

ATC Vet — QR03AC07; QR03CC06.

UNII — YV0SN3276Q.

Isoetarine Hydrochloride (BANM, rINNM) ⊗

Etyprenaline Hydrochloride; Hidrocloruro de Isoetarina; Isoetarina, hidroclorúro de; Isoétarine, Chlorhydrate d'; Isoetarini Hydrochloridum; Isoetharine Hydrochloride; *N*-Isopropylethylnoradrenaline Hydrochloride; Изоэтарина Гидрохлорид.

$C_{13}H_{21}NO_3$,HCl=275.8

CAS — 50-96-4; 2576-92-3.

ATC — R03AC07; R03CC06.

ATC Vet — QR03AC07; QR03CC06.

UNII — 51V8U784H3.

Pharmacopoeias. In *US*.

USP 36: (Isoetharine Hydrochloride). A white to off-white, odourless, crystalline solid. Soluble in water; sparingly soluble in alcohol; practically insoluble in ether. A 1% solution in water has a pH of 4.0 to 5.6. Store in airtight containers.

Isoetarine Mesilate (BANM, rINNM) ⊗

Isoetarina, mesilato de; Isoétarine, Mésilate d'; Isoetarini Mesilas; Isoetharine Mesylate; Isoetharine Methanesulphonate; *N*-Isopropylethylnoradrenaline Mesylate; Mesilato de Isoetarina; Изоэтарина Мезилат.

$C_{13}H_{21}NO_3.CH_4O_3S$=335.4

CAS — 7279-75-6.

ATC — R03AC07; R03CC06.

ATC Vet — QR03AC07; QR03CC06.

UNII — DV74WJ5PJB.

Pharmacopoeias. In *US*.

USP 36: (Isoetharine Mesylate). White or practically white, odourless, crystals. Freely soluble in water; soluble in alcohol; practically insoluble in acetone and in ether. A 1% solution in water has a pH of 4.5 to 5.5. Store in airtight containers.

Profile

Isoetarine is a sympathomimetic with mainly beta-adrenergic activity. It has actions similar to those of salbutamol (p. 1220.2) but is less selective for $beta_2$ adrenoceptors. Isoetarine has been used by inhalation as a bronchodilator in the management of reversible airways obstruction.

Preparations

Pharmacopoeial Preparations

USP 36: Isoetharine Inhalation Solution; Isoetharine Mesylate Inhalation Aerosol.

Levosalbutamol (rINN) ⊗

Levalbuterol; Lévosalbutamol; Levosalbutamolum; Левосальбутамол.

(*R*)-α'-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol.

$C_{13}H_{21}NO_3$=239.3

CAS — 34391-04-3.

UNII — EDN2NBH5SS.

Levosalbutamol Hydrochloride (rINNM) ⊗

Hidrocloruro de levosalbutamol; Levalbuterol Hydrochloride (USAN); Lévosalbutamol, Chlorhydrate de; Levosalbutamol, hidrocloruro de; Levosalbutamoli Hydrochloridum; Левосальбутамола Гидрохлорид.

(*R*)-α'-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol hydrochloride.

$C_{13}H_{21}NO_3$,HCl=275.8

CAS — 50293-90-8.

UNII — WDQ1526QJM.

Pharmacopoeias. In *US*.

USP 36: (Levalbuterol Hydrochloride). A 1% solution has a pH of 4.5 to 5.5. Store in airtight containers at 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Levosalbutamol Sulfate (rINNM) ⊗

Levalbuterol Sulfate (USAN); Lévosalbutamol, Sulfate de; Levosalbutamol Sulphate; Levosalbutamoli Sulfas; Sulfato de levosalbutamol; Левосальбутамола Сульфат.

(*R*)-α'-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate (2:1).

$(C_{13}H_{21}NO_3)_2H_2SO_4$=576.7

CAS — 148563-16-0.

UNII — 71TH42O2CQ.

Levosalbutamol Tartrate (rINNM) ⊗

Levalbuterol Tartrate (USAN); Lévosalbutamol Tartrate de; Levosalbutamol Tartrás; Tartrato de levosalbutamol; (–)-α⁶-[[(1,1-Dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol (2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1) (salt).

$2(C_{13}H_{21}NO_3).C_4H_6O_6$=627.7

CAS — 661464-94-4.

UNII — AOS4I3E2JM.

Uses and Administration

Levosalbutamol, the *R* (-)-enantiomer of salbutamol (p. 1220.2), may be used as an alternative to racemic salbutamol for the management of asthma (p. 1195.2). It is given as the hydrochloride, sulfate, or tartrate but doses are usually expressed in terms of the base; 1.15 mg of levosalbutamol hydrochloride, 2.4 mg of levosalbutamol sulfate, and 2.63 mg of levosalbutamol tartrate are equivalent to about 1 mg of levosalbutamol. For the relief of acute bronchospasm, 1 or 2 inhalations of the equivalent of 45 micrograms of levosalbutamol can be given from a metered-dose aerosol, repeated every 4 to 6 hours as required.

Levosalbutamol may also be inhaled via a nebuliser; usual doses equivalent to levosalbutamol 630 micrograms are inhaled three times daily, increased if necessary to 1.25 mg three times daily. For children's doses, see Administration in Children below. In patients with asthma, as-required beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, levosalbutamol indicates deterioration of asthma control and the need for review of therapy.

Levosalbutamol is also under investigation in a topical formulation for the treatment of cutaneous lupus erythematosus.

General reviews.

1. Jenne JW. The debate on S-enantiomers of β-agonists: tempest in a teapot or gathering storm? *J Allergy Clin Immunol* 1998; 102: 893–5.
2. Nowak R. Single-isomer levalbuterol: a review of the acute data. *Curr Allergy Asthma Rep* 2003; 3: 172–8.
3. Berger WE. Levalbuterol: pharmacologic properties and use in the treatment of pediatric and adult asthma. *Ann Allergy Asthma Immunol* 2003; 90: 583–91.
4. Datta D, *et al.* An evaluation of nebulized levalbuterol in stable COPD. *Chest* 2003; 124: 844–9.
5. Kelly HW. Levalbuterol for asthma: a better treatment? *Curr Allergy Asthma Rep* 2007; 7: 310–14.

Action. *In vitro*, levosalbutamol had slightly higher affinity than racemic salbutamol for beta$_1$ and beta$_2$ adrenoceptors.[1] The *S*(+)-enantiomer had low affinity for these receptors. All 3 were mildly selective for beta$_2$ adrenoceptors.

1. Penn RB, *et al.* Comparison of R-, S-, and RS-albuterol interaction with human β$_1$- and β$_2$-adrenergic receptors. *Clin Rev Allergy Immunol* 1996; 14: 37–45.

Administration in children. Children aged 4 years and older may be given levosalbutamol via a metered-dose aerosol at the same dose as that used for adults, see Uses and Administration, above.

Children aged from 6 to 11 years of age may be given levosalbutamol via a nebuliser in doses from 310 to 630 micrograms three times daily.

Asthma. Controlled studies comparing levosalbutamol with racemic salbutamol for the treatment of asthma have produced variable results. Levosalbutamol provided greater bronchodilatation than the equivalent amount of the racemate in some studies.[1,2] A decrease in hospital admissions and an increase in patient-discharge rates have also been reported.[3-5] Controlled studies comparing levosalbutamol with racemic salbutamol in children with acute asthma have generally failed to show any clinical benefit over the racemate.[6-8] A review concluded that, although current studies did not provide evidence of a substantial advantage for levosalbutamol over racemic salbutamol, the data were insufficient to determine whether subsets of the patient population might benefit from single isomer therapy.[9]

1. Fleskow WW, *et al.* Pairwise comparison of levalbuterol versus racemic albuterol in the treatment of moderate-to-severe asthma. *Allergy Asthma Proc* 2004; 25: 429–36.
2. Nowak R, *et al.* A comparison of levalbuterol with racemic albuterol in the treatment of acute severe asthma exacerbations in adults. *Am J Emerg Med* 2006; 24: 259–67.
3. Carl JC, *et al.* Comparison of racemic albuterol and levalbuterol for the treatment of acute asthma. *J Pediatr* 2003; 143: 731–6.
4. Schreck DM, Babin S. Comparison of racemic albuterol and levalbuterol in the treatment of acute asthma in the ED. *Am J Emerg Med* 2005; 23: 842–7.
5. Truitt T, *et al.* Levalbuterol compared to racemic albuterol: efficacy and outcomes in patients hospitalized with COPD or asthma. *Chest* 2003; 123: 128–35.
6. Qureshi F, *et al.* Clinical efficacy of racemic albuterol versus levalbuterol for the treatment of acute pediatric asthma. *Ann Emerg Med* 2005; 46: 29–36.
7. Hardasmalani MD, *et al.* Levalbuterol versus racemic albuterol in the treatment of acute exacerbation of asthma in children. *Pediatr Emerg Care* 2005; 21: 415–19.
8. Andrews T, *et al.* High-dose continuous nebulized levalbuterol for pediatric status asthmaticus: a randomized trial. *J Pediatr* 2009; 155: 205–10.
9. Kelly HW. Levalbuterol for asthma: a better treatment? *Curr Allergy Asthma Rep* 2007; 7: 310–14.

Adverse Effects and Precautions

As for Salbutamol, p. 1221.3.

Incidence of adverse effects. Some studies have reported that beta-adrenergic adverse effects (e.g. nervousness and increased heart rate) are less frequent with inhaled levosalbutamol than with racemic salbutamol.[1-4] In general, however, little difference has been seen in clinical practice.[5] Despite preliminary evidence that the increased airway hyperresponsiveness occasionally seen with long-term racemic salbutamol (see Tolerance, p. 1222.3) may be due to the *S*(+)-enantiomer, and therefore might not occur with levosalbutamol,[6] a small study was unable to find any favourable protective effect.[7]

1. Nelson HS, *et al.* Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma. *J Allergy Clin Immunol* 1998; 102: 943–52.
2. Milgrom H, *et al.* Low-dose levalbuterol in children with asthma: safety and efficacy in comparison with placebo and racemic albuterol. *J Allergy Clin Immunol* 2001; 108: 938–45.
3. Handley DA, *et al.* Dose-response evaluation of levalbuterol versus racemic albuterol in patients with asthma. *J Asthma* 2000; 37: 319–27.
4. Tripp K, *et al.* A cumulative dose study of levalbuterol and racemic albuterol administered by hydrofluoroalkane-134a metered-dose inhaler in asthmatic subjects. *J Allergy Clin Immunol* 2008; 122: 544–9.
5. Ameredes BT, Calhoun WJ. Levalbuterol versus albuterol. *Curr Allergy Asthma Rep* 2009; 9: 401–9.
6. Perrin-Payolle M. Salbutamol in the treatment of asthma. *Lancet* 1995; 346: 1101.
7. Sjöswärd KN, *et al.* Single-isomer R-salbutamol is not superior to racemate regarding protection for bronchial hyperresponsiveness. *Respir Med* 2004; 98: 990–9.

Interactions

As for Salbutamol, p. 1223.1.

Pharmacokinetics

There is some systemic absorption of inhaled levosalbutamol. After a single dose levosalbutamol has a half-life of 3.3 hours. For details of the metabolism and excretion of salbutamol enantiomers, see Stereoselectivity, under Salbutamol p. 1223.2.

Metabolism. There is evidence that levosalbutamol is metabolised faster than *S*(+)-salbutamol.

References.

1. Boulton DW, Fawcett JP. Enantioselective disposition of salbutamol in man following oral and intravenous administration. *Br J Clin Pharmacol* 1996; 41: 35–40.
2. Lipworth BJ, *et al.* Pharmacokinetics and extrapulmonary β$_2$ adrenoceptor activity of nebulised racemic salbutamol and its R and S isomers in healthy volunteers. *Thorax* 1997; 52: 849–52.
3. Gumbhir-Shah K, *et al.* Pharmacokinetic and pharmacodynamic characteristics and safety of inhaled albuterol enantiomers in healthy volunteers. *J Clin Pharmacol* 1998; 38: 1096–1106.
4. Boulton DW, Fawcett JP. The pharmacokinetics of levosalbutamol: what are the clinical implications? *Clin Pharmacokinet* 2001; 40: 23–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Albulair; Ventoplus; *India*: Levolin; *USA*: Xopenex.

Pharmacopoeial Preparations

USP 36: Levalbuterol Inhalation Solution.

Mepolizumab (USAN, rINN)

Mépolizumab; Mepolizumabum; SB-240563; Меполизумаб; Immunoglobulin G1, anti-(human interleukin 5) (human-mouse monoclonal SB-240563 γ1-chain), disulfide with human-mouse monoclonal SB-240563 κ-chain, dimer.

CAS — 196078-29-2.

ATC — L04AC05.

ATC Vet — QL04AC05.

Profile

Mepolizumab is a humanised anti-interleukin-5 monoclonal antibody. It is under investigation in the management of asthma, as well as the treatment of hypereosinophilic syndrome (chronic eosinophilic leukaemia), and eosinophilic oesophagitis (p. 1810.1).

References.

1. Leckie MJ, *et al.* Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000; 356: 2144–8.
2. Plötz S-G, *et al.* Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis. *N Engl J Med* 2003; 349: 2334–9.
3. Braun-Falco M, *et al.* Angiolymphoid hyperplasia with eosinophilia treated with anti-interleukin-5 antibody (mepolizumab). *Br J Dermatol* 2004; 151: 1103–4.
4. Garrett JK, *et al.* Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol* 2004; 113: 115–19.
5. Rothenberg ME, *et al.* Mepolizumab HES Study Group. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med* 2008; 358: 1215–28. Correction. *ibid.*: 2530.
6. Haldar P, *et al.* Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; 360: 973–84.
7. Nair P, *et al.* Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009; 360: 985–93.
8. Straumann A, *et al.* Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut* 2010; 59: 21–30.

Montelukast Sodium

(BANM, USAN, rINNM)

L-706631; MK-476; Montelukast sódico; Montélukast Sodique; Natril Montelukastum; Натрий Монтелукаст.

Sodium 1-[[[(*R*)-*m*-[(*E*)-2-(7-chloro-2-quinolyl)-vinyl]-α-[*o*-(1-hydroxy-1-methylethyl)phenethyl]-benzyl]thio]methyl] cyclopropaneacetate.

$C_{35}H_{35}ClNNaO_3S$=608.2

CAS — 158966-92-8 (montelukast); 151767-02-1 (montelukast sodium).

ATC — R03DC03.

ATC Vet — QR03DC03.

UNII — U1O3J18SFL.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Montelukast Sodium). A white or almost white, hygroscopic powder. Freely soluble in water and in dichloromethane; freely soluble to very soluble in alcohol. Store in airtight containers. Protect from light.

USP 36: (Montelukast Sodium). A white or almost white, hygroscopic powder. Freely soluble in water and in dichloromethane; freely soluble to very soluble in alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Montelukast is a selective leukotriene receptor antagonist with actions and uses similar to those of zafirlukast (p. 1240.1) although it is reported to have a longer duration of action. It is used as the sodium salt, but doses are expressed in terms of the base; montelukast sodium 10.38 mg is equivalent to about 10 mg of montelukast.

Montelukast sodium is used in the management of asthma (see p. 1215.1) and allergic rhinitis (see p. 1215.3). It is given orally in doses equivalent to 10 mg of montelukast once daily. In chronic asthma, the dose is given in the evening. For acute prevention of exercise-induced bronchoconstriction, the dose should be given at least 2 hours before exercise and not repeated within 24 hours. Patients already taking montelukast daily for another indication, including chronic asthma, should not take additional doses for exercise-induced bronchoconstriction. Montelukast is not used to treat an acute asthma attack. In the treatment of seasonal or perennial allergic rhinitis (without asthma), the dose may be taken in either the morning or evening.

For details of doses in children, see below.

Administration in children. Montelukast sodium has been widely used in children,[1] for whom it is available as oral granules and chewable tablets. Chewable tablets are suitable for those aged 2 years and older; oral granules are suitable for infants from 6 months of age as they may be given directly into the mouth or mixed with a small amount of soft food. Oral daily doses, expressed as montelukast, are based on age:

- 6 months up to 2 years: 4 mg (as granules)
- 2 to 5 years: 4 mg (as granules or chewable tablets)
- 6 to 14 years: 5 mg (as chewable tablets)
- 15 years and over: use the adult dose, see above

In the UK, the above doses are licensed for the management of chronic asthma and from 2 years of age for the prophylaxis of exercise-induced asthma; in asthmatic children with concomitant seasonal allergic rhinitis, it is only licensed from age 15. Doses should be taken in the evening.

In the USA these doses are licensed from 1 year of age in chronic asthma, to be given as a single daily dose in the evening. In the prevention of exercise-induced bronchoconstriction in children aged 6 years and older, a dose may be given at least 2 hours before exercise, and not repeated within 24 hours. Patients already being treated with daily therapy for another indication, including chronic asthma, should not be given additional doses for exercise-induced bronchoconstriction. Montelukast is also licensed for use in allergic rhinitis (without asthma) in the USA. The above daily doses can be given either in the morning or the

evening from 2 years of age in seasonal allergic rhinitis and from 6 months of age in perennial allergic rhinitis.

1. Bisgaard H, *et al.* Safety and tolerability of montelukast in placebo-controlled pediatric studies and their open-label extensions. *Pediatr Pulmonol* 2009; **44:** 568–79.

Asthma. Use of montelukast in asthma (p. 1195.2) has been reviewed.[1-4] (further general references for leukotriene antagonists can be found under Zafirlukast, p. 1240.1). Montelukast produced modest improvements compared with placebo in chronic asthma and exercise-induced asthma in both adults[5,6] and children.[7-9] In a systematic review[10] of studies in adults and children comparing leukotriene receptor antagonists with inhaled corticosteroids for monotherapy in mild to moderate persistent asthma, in which more than half of the studies used montelukast, leukotriene antagonists were found to be less effective in maintaining asthma control. The difference was particularly marked in patients with moderate disease. Addition of montelukast to an inhaled corticosteroid has significantly improved asthma control in adults and adolescents,[11] and in children,[12,13] with mild to moderate asthma. However, in adults and adolescents the addition of an inhaled long-acting beta$_2$ agonist, such as salmeterol, is more effective;[11,14] comparative studies in children are limited.[14]

Montelukast may be used for prophylaxis in patients with chronic exercise-induced asthma.[15,16] However, it may only be effective in 50 to 80% of patients.[16] There is some evidence that montelukast may be more effective than inhaled salmeterol for the chronic treatment of exercise-induced asthma,[17,18] and although a later study[19] found similar effects on lung function with the two drugs, a more favourable effect was seen on gas exchange during moderate exercise with the use of montelukast.

Montelukast has also been studied in adults and children for the treatment of acute asthma, using either oral therapy or an investigational injectable form. However, despite some evidence of improvement in lung function, the addition of montelukast to standard therapy did not significantly affect rates of hospital admission.[20]

1. Jarvis B, Markham A. Montelukast: a review of its therapeutic potential in persistent asthma. *Drugs* 2000; **59:** 891–928.
2. Nayak A. A review of montelukast in the treatment of asthma and allergic rhinitis. *Expert Opin Pharmacother* 2004; **5:** 679–86.
3. Storms W. Update on montelukast and its role in the treatment of asthma, allergic rhinitis and exercise-induced bronchoconstriction. *Expert Opin Pharmacother* 2007; **8:** 2173–87.
4. Amlani S, *et al.* Montelukast for the treatment of asthma in the adult population. *Expert Opin Pharmacother* 2011; **12:** 2119–28.
5. Leff JA, *et al.* Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. *N Engl J Med* 1998; **339:** 147–52.
6. Reiss TF, *et al.* Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. *Arch Intern Med* 1998; **158:** 1213–20.
7. Knorr B, *et al.* Montelukast for chronic asthma in 6- to 14-year-old children: a randomized, double-blind trial. *JAMA* 1998; **279:** 1181–6.
8. Kemp JP, *et al.* Montelukast once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year-old children with asthma. *J Pediatr* 1998; **133:** 424–8.
9. Knorr B, *et al.* Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. Abstract: *Pediatrics* 2001; **108:** 754–5. Full version: http://pediatrics.aappublications.org/cgi/content/full/108/3/e48 (accessed 14/04/08)
10. Chauhan BF, Ducharme FM. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2012 (accessed 17/06/13).
11. Joos S, *et al.* Montelukast as add-on therapy to inhaled corticosteroids in the treatment of mild to moderate asthma: a systematic review. *Thorax* 2008; **63:** 453–62.
12. Phipatanakul W, *et al.* Montelukast improves asthma control in asthmatic children maintained on inhaled corticosteroids. *Ann Allergy Asthma Immunol* 2003; **91:** 49–54.
13. Johnston NW, *et al.* Attenuation of the September epidemic of asthma exacerbations in children: a randomized, controlled trial of montelukast added to usual therapy. *Pediatrics* 2007; **120:** e702–e712.
14. Ducharme FM, *et al.* Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2011 (accessed 17/06/13).
15. Grzelewski T, Stelmach I. Exercise-induced bronchoconstriction in asthmatic children: a comparative systematic review of the available treatment options. *Drugs* 2009; **69:** 1533–53.
16. Carver TW. Exercise-induced asthma: critical analysis of the protective role of montelukast. *J Asthma Allergy* 2009; **2:** 93–103.
17. Villaran C, *et al.* Montelukast versus salmeterol in patients with asthma and exercise-induced bronchoconstriction. *J Allergy Clin Immunol* 1999; **104:** 547–53.
18. Edelman JM, *et al.* Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction: a randomized, double-blind trial. *Ann Intern Med* 2000; **132:** 97–104.
19. Steinshamn S, *et al.* Effects of montelukast and salmeterol on physical performance and exercise economy in adult asthmatics with exercise-induced bronchoconstriction. *Chest* 2004; **126:** 1154–60.
20. Watts K, Chavasse RJPG. Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2012 (accessed 17/06/13).

Bronchiolitis. Bronchiolitis due to RSV infection is often followed by post-bronchiolitic reactive airways disease, characterised by asthma-like wheeze and other symptoms. Results from a placebo-controlled pilot study in infants with acute bronchiolitis suggested a reduction in symptoms after the first 2 weeks of montelukast treatment,[1] generating some interest in whether montelukast could prevent or modify more persistent asthma that has been associated with RSV.[2] However, a further similar study found no benefit with montelukast treatment compared with placebo,[3] and did not support the use of montelukast in infants with acute bronchiolitis.

1. Bisgaard H, Study Group on Montelukast and Respiratory Syncytial Virus. A randomized trial of montelukast in respiratory syncytial virus postbronchiolitis. *Am J Respir Crit Care Med* 2003; **167:** 379–83.
2. Szefler SJ, Simoes EAF. Montelukast for respiratory syncytial virus bronchiolitis: significant effect or provocative findings? *Am J Respir Crit Care Med* 2003; **167:** 290–1.
3. Amirav I, *et al.* A double-blind, placebo-controlled, randomized trial of montelukast for acute bronchiolitis. Abstract: *Pediatrics* 2008; **122:** 1361. Full version: http://pediatrics.aappublications.org/cgi/reprint/122/6/e1249 (accessed 17/08/09)

Cystic fibrosis. A small study in children with cystic fibrosis (p. 177.2) found that montelukast reduced eosinophilic inflammation.[1] A later study,[2] reported improved lung function and a reduction in coughing and wheezing, and concluded that montelukast may have measurable anti-inflammatory activity in patients with cystic fibrosis. In a small group of adult patients with cystic fibrosis[3] montelukast improved symptoms, in particular exercise tolerance and peak expiratory flow rates. The patients who benefited the most had positive *Aspergillus* serology, and the authors suggested that colonisation of the airways in cystic fibrosis by *Aspergillus* stimulates T helper cell inflammation and leukotriene synthesis. A review of leukotriene receptor antagonists in cystic fibrosis[4] concluded that clinical benefit seemed likely in a subset of patients with bronchial hyperresponsiveness similar to that seen in asthma.

A study into the pharmacokinetics of montelukast in cystic fibrosis[5] found that the dose of montelukast and the dosing interval do not need to be modified if the goal of therapy is to achieve similar serum concentrations as for asthma treatment; however the efficacy of these concentrations for the inflammatory lung disease of patients with cystic fibrosis was unknown.

1. Schmitt-Grohé S, *et al.* Anti-inflammatory effects of montelukast in mild cystic fibrosis. *Ann Allergy Asthma Immunol* 2002; **89:** 599–605.
2. Stelmach I, *et al.* Effects of montelukast treatment on clinical and inflammatory variables in patients with cystic fibrosis. *Ann Allergy Asthma Immunol* 2005; **95:** 372–80.
3. Morice AH, *et al.* Montelukast sodium in cystic fibrosis. *Thorax* 2001; **56:** 244–5.
4. Schmitt-Grohé S, Zielen S. Leukotriene receptor antagonists in children with cystic fibrosis lung disease: anti-inflammatory and clinical effects. *Pediatr Drugs* 2005; **7:** 353–63.
5. Graff GR, *et al.* Montelukast pharmacokinetics in cystic fibrosis. *J Pediatr* 2003; **142:** 53–6.

Eczema. Despite early indications from some small clinical studies and case reports[1-3] that montelukast might be of benefit in eczema (p. 1684.1) larger, more recent studies have failed to show any improvement compared with placebo.[4,5]

1. Capella GL, *et al.* A randomized trial of leukotriene receptor antagonist montelukast in moderate-to-severe atopic dermatitis of adults. *Eur J Dermatol* 2001; **11:** 209–13.
2. Hon KLE, *et al.* Brief case series: montelukast, at doses recommended for asthma treatment, reduces disease severity and increases soluble CD14 in children with atopic dermatitis. *J Dermatolog Treat* 2005; **16:** 15–18.
3. Angelova-Fischer I, Tsankov N. Successful treatment of severe atopic dermatitis with cysteinyl leukotriene receptor antagonist montelukast. *Acta Dermatovenerol Alp Panonica Adriat* 2005; **14:** 115–19.
4. Veien NK, *et al.* Montelukast treatment of moderate to severe atopic dermatitis in adults: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2005; **53:** 147–9.
5. Friedmann PS, *et al.* A double-blind, placebo-controlled trial of montelukast in adult atopic eczema. *Clin Exp Allergy* 2007; **37:** 1536–40.

Gastrointestinal disorders. Benefit has been reported[1] with the use of montelukast in patients with eosinophilic oesophagitis (see p. 1810.1). A systematic review with recommendations for the diagnosis and treatment of eosinophilic oesophagitis[2] concluded that although leukotriene receptor antagonists had been shown to induce symptomatic relief at high doses, no significant improvements in histology were noted and their use for the treatment of eosinophilic oesophagitis is not supported by the current literature.

1. Attwood SEA, *et al.* Eosinophilic oesophagitis: a novel treatment using montelukast. *Gut* 2003; **52:** 181–5.
2. Furuta GT, *et al.* American Gastroenterological Association; North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007; **133:** 1342–63. Also available at: http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508507014746.pdf (accessed 14/04/08)

Graft-versus-host disease. A pilot study in refractory, chronic graft-versus-host disease (GVHD) after allogeneic haematopoietic stem cell transplantation (p. 1937.1),[1] saw an improvement in 15 of 19 patients after montelukast was added to their standard immunosuppressive regimens; in 4 patients signs of chronic GVHD were resolved, 2 showed significant improvement, and 9 showed moderate improvement.

1. Or R, *et al.* Sparing effect by montelukast treatment for chronic graft versus host disease: a pilot study. *Transplantation* 2007; **83:** 577–81.

Mastocytosis. Montelukast has been tried, with some success, in the treatment of systemic mastocytosis (p. 1226.3) in an infant.[1]

1. Tolar J, *et al.* Leukotriene-receptor inhibition for the treatment of systemic mastocytosis. *N Engl J Med* 2004; **350:** 735–6.

Rhinitis. Montelukast is used in allergic rhinitis (p. 612.1), where large placebo-controlled studies have shown it to relieve symptoms in both seasonal allergic rhinitis,[1,2] and perennial allergic rhinitis.[3] However, a meta-analysis[4] of leukotriene antagonists (mainly montelukast) for management of allergic rhinitis concluded that while leukotriene antagonists were modestly more effective than placebo and of similar efficacy to antihistamines, in reducing nasal symptoms and improving rhinoconjunctivitis, they were less effective than corticosteroids even when used with antihistamines. A later systematic review[5] commented that some studies in allergic rhinitis using a combination of montelukast and an antihistamine had produced results comparable with intranasal corticosteroids. Also, in patients with both allergic rhinitis and asthma, montelukast had resulted in significant improvements in both when compared with placebo.

1. Philip G, *et al.* Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. *Clin Exp Allergy* 2002; **32:** 1020–8.
2. van Adelsberg J, *et al.* Randomized controlled trial evaluating the clinical benefit of montelukast for treating spring seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2003; **90:** 214–22.
3. Patel P, *et al.* Randomized, double-blind, placebo-controlled study of montelukast for treating perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2005; **95:** 551–7.
4. Wilson AM, *et al.* Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* 2004; **116:** 338–44.
5. Nayak A, Langdon RB. Montelukast in the treatment of allergic rhinitis: an evidence-based review. *Drugs* 2007; **67:** 887–901.

Sleep-disordered breathing. Montelukast with an intranasal corticosteroid has been reported to be beneficial in a small study in children with residual sleep-disordered breathing after tonsillectomy and adenoidectomy.[1]

1. Kheirandish L, *et al.* Intranasal steroids and oral leukotriene modifier therapy in residual sleep-disordered breathing after tonsillectomy and adenoidectomy in children. *Pediatrics* 2006; **117:** e61–e66.

Urticaria. Montelukast has been investigated in the treatment of urticaria (p. 1689.2) with variable results.[1] However, urticaria has also been described as a suspected adverse effect of montelukast therapy.

Montelukast has been reported to be more effective than placebo when used with the antihistamine desloratadine in the treatment of delayed pressure urticaria.[2]

1. McBayne TO, Siddall OM. Montelukast treatment of urticaria. *Ann Pharmacother* 2006; **40:** 939–42.
2. Nettis E, *et al.* Desloratadine in combination with montelukast suppresses the dermagraphometer challenge test papule, and is effective in the treatment of delayed pressure urticaria: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2006; **155:** 1279–82.

Adverse Effects and Precautions

As for Zafirlukast, p. 1240.1.

Additionally, palpitations and seizures have been reported with montelukast use. In children, eczema and infections such as varicella, gastroenteritis, and upper respiratory-tract infections have occurred.

Churg-Strauss syndrome. For discussion of the possible role of leukotriene antagonists in Churg-Strauss syndrome see under Zafirlukast, p. 1240.2.

Effects on the CNS. For information on the CNS adverse effects associated with use of anti-leukotrienes, see under Zafirlukast, p. 1240.2.

Hepatic impairment. Although there is evidence of effects on the liver in patients receiving montelukast, and although it is largely eliminated by hepatic metabolism, montelukast (unlike zafirlukast) is not considered by licensed product information to be contra-indicated in hepatic impairment, and no dose adjustment is considered necessary in mild to moderate hepatic impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies montelukast as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

Licensed product information recommends caution when potent inducers of cytochrome P450 isoenzymes, such as phenytoin, phenobarbital, or rifampicin are given with montelukast.

Corticosteroids. For a report of peripheral oedema in a patient given montelukast and *prednisone*, see Leukotriene Antagonists, p. 1620.2.

Phenobarbital. Peak serum concentrations after a single dose of montelukast 10 mg were reduced by 20% in 14 healthy subjects who took phenobarbital 100 mg daily for 14 days, and area under the serum concentration-time curve was reduced by 38%. However, it was not thought that montelukast doses would need adjustment if given with phenobarbital.[1]

1. Holland S, *et al.* Metabolism of montelukast (M) is increased by multiple doses of phenobarbital (P). *Clin Pharmacol Ther* 1998; 63: 231.

Pharmacokinetics

Peak plasma concentrations of montelukast occur 2 to 4 hours after oral doses. The mean oral bioavailability is about 64 to 73%. Montelukast is more than 99% bound to plasma proteins. It is extensively metabolised in the liver by cytochrome P450 isoenzymes, mainly by CYP2C8 and to a lesser extent by CYP3A4 and CYP2C9. The plasma half-life ranges from 2.7 to 5.5 hours. Montelukast and its metabolites are excreted principally in the faeces via the bile.

References.

1. Knorr B, *et al.* Montelukast dose selection in 6- to 14-year-olds: comparison of single-dose pharmacokinetics in children and adults. *J Clin Pharmacol* 1999; 39: 786–93.
2. Knorr B, *et al.* Montelukast dose selection in children ages 2 to 5 years: comparison of population pharmacokinetics between children and adults. *J Clin Pharmacol* 1999; 41: 612–19.
3. Migoya E, *et al.* Pharmacokinetics of montelukast in asthmatic patients 6 to 24 months old. *J Clin Pharmacol* 2004; 44: 487–94.
4. Knorr B, *et al.* Pharmacokinetics and safety of montelukast in children aged 3 to 6 months. *J Clin Pharmacol* 2006; 46: 620–7.
5. Kearns GL, *et al.* Pharmacokinetics and safety of montelukast oral granules in children 1 to 3 months of age with bronchiolitis. *J Clin Pharmacol* 2008; 48: 502–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Inspirol; Montrate; Rolast; Singulair; *Austral.*: Singulair; *Austria*: Singulair; *Belg.*: Rhinosingulair; Singulair; *Braz.*: Montelair; Singulair; *Canad.*: Singulair; *Chile*: Asventol; Brondilat; Montecross; Singulair; *China*: Singulair (顺尔宁); *Cz.*: Brogalas; Castispir; Elukan; Eonic; Miralust; Monkasta; Monlucare; Montecon; Montel; Montelar; Monteratio; Montexal; Montulind; Singulair; Telumantes; *Denm.*: Asthmont†; Elukan; Kemtelo; Kestilumar; Lukair; Metiprego; Miralust; Monspes†; Montegen; Montetrinas; Monthan; Montisartas; Montulind; Olekast†; Otelus†; Singulair; *Fin.*: Airathon; Astecon; Singulair; *Fr.*: Singulair; *Ger.*: Montelubronch; Singulair; *Gr.*: Montast; Pneumo-Kast; Singulair; Telukast; *Hong Kong*: Singulair; *Hung.*: Singulair; *India*: Airway; Astham; Breathezy; Emlucast; Kast; MK; Molly; Montair; Montal; Montasma; Montek; Montelast; Monti; Odimont; *Irl.*: Molat; Montelair; Singulair; *Israel*: Singulair; Take Air; *Ital.*: Asthmont; Kemtelo; Lukasm; Mintalos; Monstonol; Montegen; Monthan; Moolpas; Otelus; Singulair; Xigenast; *Jpn*: Kipres; *Malaysia*: Singulair; *Mex.*: Singulair; *Neth.*: Airathon; Kastlutemon; Lukastang; Montefranc; Monthan; Singulair; Spirokast; *Norw.*: Singulair; *NZ*: Singulair; *Philipp.*: Brecare; Kastair; Kastorion; Leukast; Montair; Montecad; Montekast; Montemax; Montiget; Singulair; *Pol.*: Airathon; Asmenol; Astmirex; Drimon; Eonic; Hardic; Milukante; Monkasta; Montelak; Montenorm; Montessan; Montest; Promonta; Singulair; Symlukast; Vizendo; *Port.*: Deprive†; Dilocea; Lukair; Singulair; Singulergy; Synglarin†; *Rus.*: Monkasta (Монкаста); Singulair (Сингулэр); *S.Afr.*: Lumont; Singulair; Sintrine; Topraz; *Singapore*: Singulair; *Spain*: Monkasta; Pluralais; Singulair; *Swed.*: Singulair; *Switz.*: Lukair; Singulair; *Thai.*: Montek; Singulair; *Turk.*: Airlast; Clast; Luxat; Monax; N-Fess; Nolta; Onceair; Respair; Singulair; Zespira; *UK*: Singulair; *Ukr.*: Lucast (Лукаст); Milukant (Милукант); Montel (Монтел); Singlon (Сінглон); Singulair (Сингулэр); *USA*: Singulair; *Venez.*: Airon; Inuvic; Monukast; Singulair.

Multi-ingredient Preparations. *India*: Airway-L; Alnacet-M; Arokast; Breathezy-L; Dilevocet-M; Polcet-MT; Hiskast; Kurecet-M; L-Montus; Largy-M; Lazine-M; LCRal Plus; Le-Zyncet-M; Lemont-LC; Lepit-MK; Leverest-MK; Levocet-M; Levoclic-M; Levoriz-MK; Levotin Plus; Levotra-M; Levotrin-M; Levoz-M; Levzed-MK; Luka; Luzei-M; Luzer-M; Lycit-M; M-Kast-L; Molly-Plus; Moncet; Mondeo-LC; Mondeslor; Montair Plus; Montair-LC; Montasma Plus; Montbre; Montegen-L; Montek-LC; Montlilfe; Montlu-L; Montral; Monty; Monway Plus; Mosha-L; Mucopen; Nislevo-MK; Noal-LM; Nukast; Odimont Plus; Okasma; Ontelio-L; *Philipp.*: Co-Altria; Zykast.

All cross-references refer to entries in Volume A

Nedocromil Sodium *(BANM, USAN, rINNM)*

FPL-59002 (nedocromil); FPL-59002KC (nedocromil calcium); FPL-59002KP (nedocromil sodium); Natrii Nedocromilum; Nédocromil Sodique; Nedocromilo sódico; Nedocromilum Natricum; Nedokromillnatrium; Nedokromil Sodyum; Nedokromilnatrium; Натрий Недокромил.

Disodium 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-4*H*-pyrano[3,2-g]quinoline-2,8-dicarboxylate.

$C_{19}H_{15}NNa_2O_7$=415.3

CAS — 69049-73-6 (nedocromil); 69049-74-7 (nedocromil sodium); 101626-68-0 (nedocromil calcium).

ATC — R01AC07; R03BC03; S01GX04.

ATC Vet — QR01AC07; QR03BC03; QS01GX04.

UNII — ET8IF4KS1T.

NOTE. Nedocromil Calcium is also *USAN*.

Uses and Administration

Nedocromil sodium has a stabilising action on mast cells resembling that of sodium cromoglicate (p. 1226.1) and is used similarly in the management of chronic asthma. It should not be used to treat an acute attack of asthma.

For **asthma**, nedocromil sodium is inhaled from a metered-dose aerosol. The usual dose for adults and children from 6 years of age is 4 mg inhaled four times daily which may be decreased to 4 mg twice daily after control of symptoms is achieved. Clinical improvement may not be obtained for 1 week or longer after beginning therapy.

Nedocromil sodium is also used topically in the treatment of **allergic conjunctivitis** and allergic **rhinitis**. For seasonal and perennial allergic conjunctivitis it is given as a 2% solution, instilled into each eye twice daily. This may be increased to 4 times daily if necessary, which is the usual dose in vernal keratoconjunctivitis. In seasonal allergic conjunctivitis, treatment is usually given for no more than 12 weeks. In allergic rhinitis nedocromil sodium is used as a 1% nasal spray: one spray is given into each nostril 2 to 4 times daily for up to 8 weeks. For details of doses in children, see Administration in Children, below.

General references.

1. Brogden RN, Sorkin EM. Nedocromil sodium: an updated review of its pharmacological properties and therapeutic efficacy in asthma. *Drugs* 1993; 45: 693–715.
2. Parish RC, Miller LJ. Nedocromil sodium. *Ann Pharmacother* 1993; 27: 599–606.

Administration in children. Nedocromil sodium is given by metered-dose aerosol inhalation in the management of asthma in children from 6 years of age at the adult dose, see above. Although unlicensed in the UK for younger children, the *BNFC* recommends the same dose from 5 years of age.

Similarly, for the topical treatment of seasonal allergic conjunctivitis and vernal keratoconjunctivitis, the adult dose may be given to children from 6 years of age, see above. Treatment of perennial allergic conjunctivitis with nedocromil sodium is not licensed in children in the UK, but the *BNFC* recommends adult doses from 6 years of age.

Asthma. Nedocromil sodium is generally considered to be an alternative to sodium cromoglicate in the management of asthma (p. 1195.2). Nedocromil has been shown to improve symptoms and reduce bronchodilator intake in adults[1] and children[2] with chronic asthma. However, a systematic review[3] of nedocromil for chronic asthma in children subsequently found that although a number of small studies have shown that nedocromil improves airflow limitation, reduces symptoms, and reduces bronchial hyperresponsiveness, this has not been confirmed in a larger long-term study of children with milder asthma. Its place in relation to other asthma therapies for children is also unclear. It may be used before exercise to reduce exercise-induced bronchoconstriction,[4] and appears to be as effective as sodium cromoglicate for this indication.[5]

1. Edwards AM, Stevens MT. The clinical efficacy of inhaled nedocromil sodium (Tilade) in the treatment of asthma. *Eur Respir J* 1993; 6: 35–41.
2. Armenio L, *et al.* Double blind, placebo controlled study of nedocromil sodium in asthma. *Arch Dis Child* 1993; 68: 193–7.
3. Sridhar AV, McKean M. Nedocromil sodium for chronic asthma in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 14/04/08).
4. Spooner CH, *et al.* Nedocromil sodium for preventing exercise-induced bronchoconstriction. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 14/04/08).
5. Kelly KD, *et al.* Nedocromil sodium versus sodium cromoglycate for preventing exercise-induced bronchoconsniction. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 14/04/08).

Cough. For references indicating a positive response to sodium cromoglicate but not to nedocromil sodium in the management of cough induced by ACE inhibitor therapy, see Cough, p. 1226.3.

Rhinitis and conjunctivitis. Nedocromil has been used in the management of allergic rhinitis (p. 612.1) and conjunctivitis (p. 611.1). In the management of seasonal allergic rhinitis, there is some evidence that prophylactic mometasone furoate (p. 1644.1) reduces symptoms more effectively than nedocromil.[1] In vernal keratoconjunctivitis nedocromil may be more effective than cromoglicate (see p. 1227.1), but is less effective than fluorometholone.[2]

1. Pitsios C, *et al.* Efficacy and safety of mometasone furoate vs nedocromil sodium as prophylactic treatment for moderate/severe seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2006; 96: 673–8.
2. Tabbara KF, Al-Kharashi SA. Efficacy of nedocromil 2% versus fluorometholone 0.1%: a randomised, double masked trial comparing the effects on severe vernal keratoconjunctivitis. *Br J Ophthalmol* 1999; 83: 180–4.

Adverse Effects and Precautions

Inhaled nedocromil sodium may cause headache, gastrointestinal disturbances (nausea, vomiting, dyspepsia, and abdominal discomfort). An unusual or unpleasant taste is reported rarely. Paradoxical bronchospasm may occur. Eye drops may cause transient burning and stinging.

It should not be used for the treatment of acute asthma attacks. The general cautions described under sodium cromoglicate (see p. 1227.2) also apply.

Incidence of adverse effects. A review[1] of nedocromil sodium noted that adverse effects were infrequent, mild, and short-lived. The most common effect appeared to be an unpleasant or bitter taste, which occurred in 12 to 13% of patients, although less than 1% of patients stopped treatment because of it. Other adverse effects included cough (in 7%), headache (6%), sore throat (5.7%), nausea (4%), and vomiting (1.7%).

1. Brogden RN, Sorkin EM. Nedocromil sodium: an updated review of its pharmacological properties and therapeutic efficacy in asthma. *Drugs* 1993; 45: 693–715.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nedocromil as not porphyrinogenic when used ophthalmically; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11) NC for intranasal use and for obstructive airway diseases.

Pregnancy. For discussion of the safety of nedocromil when used during pregnancy, see Sodium Cromoglicate, p. 1227.2.

Pharmacokinetics

Nedocromil sodium is poorly absorbed from the gastrointestinal tract; about 10% of the inhaled dose is absorbed from the lungs. Absorption is also poor after topical ophthalmic use, and occurs mainly through the nasal mucosa. Nedocromil sodium is excreted unchanged in the urine and faeces. The half-life is stated to range from about 1 to 3.3 hours.

The extent of absorption or bioavailability of nedocromil sodium after inhalation in healthy subjects was 7 to 9% of the dose, including 2 to 3% oral absorption and 5 to 6% absorption from the respiratory tract.[1] After inhalation of nedocromil sodium 4 mg the mean peak plasma concentration was 3.3 nanograms/mL in healthy subjects and 2.8 nanograms/mL in asthmatic patients, after about 20 and 40 minutes respectively. The mean total urinary excretion 24 hours after a single dose was 5.4% of the dose in healthy subjects and 2.3% in asthmatics.

1. Neale MG, *et al.* The pharmacokinetics of nedocromil sodium, a new drug for the treatment of reversible obstructive airways disease, in human volunteers and patients with reversible obstructive airways disease. *Br J Clin Pharmacol* 1987; 24: 493–501.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Tilade; *Austria*: Tilade; Tilarin†; Tilavist; *Braz.*: Tilade; *Canad.*: Alocril; *Cz.*: Tilade; *Denm.*: Tilade†; Tilavist; *Fin.*: Tilade; *Fr.*: Tilavist; *Ger.*: Irtan; *Gr.*: Tilade; *Irl.*: Tilade; *Israel*: Tilavist; *Ital.*: Kovilen; Kovinal; Tilade; Tilarin; Tilavist; *Mex.*: Irtan; *Neth.*: Tilade; Tilavist; *Norw.*: Tilavist; *NZ*: Tilade; *Port.*: Tilavist; *Rus.*: Tilade (Тайлед); *Singapore*: Tilade; *Spain*: Tilad; Tilavist; *Swed.*: Tilavist; *Switz.*: Tilavist†; *Turk.*: Tilade†; *UK*: Rapitil; Tilade; *USA*: Alocril.

Omalizumab *(BAN, USAN, rINN)*

CGP-51901; E-25; IGE-025; Olizumab; Omalizumabum; rhuMAb-E25; Омализумаб.

Immunoglobulin G, anti-(human immunoglobulin E Fc region)(human-mouse monoclonal E25 clone pSVIE26 γ-chain), disulfide with human-mouse monoclonal E25 clone pSVIE26 κ-chain, dimer.

CAS — 242138-07-4.

ATC — R03DX05.

ATC Vet.— QR03DX05.
UNII — 2P471X1Z11.

Uses and Administration

Omalizumab is a recombinant humanised monoclonal antibody that selectively binds to IgE. It inhibits the binding of IgE to mast cells and basophils, thus reducing the release of mediators of the allergic response. Omalizumab is used in the prophylactic management of moderate to severe, persistent allergic asthma (p. 1195.2). The dose depends on the patient's weight and pre-treatment serum-IgE concentrations; in the UK, dosage regimens range from 225 to 600 mg given every 2 weeks or 75 to 600 mg every 4 weeks, whereas in the USA regimens range from 225 to 375 mg every 2 weeks or 150 to 300 mg every 4 weeks. Omalizumab is given by subcutaneous injection, and not more than 150 mg should be given at one injection site. Total IgE concentrations rise during treatment (see Pharmacokinetics, below), remaining elevated for up to 1 year after withdrawal, and cannot be used to determine continued dosage. Dose determination after treatment interruptions lasting up to 1 year should be based on pre-treatment serum-IgE concentrations.

Omalizumab is under investigation in the prophylactic management of seasonal allergic rhinitis.

References.
1. Ädelroth E, *et al.* Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000; 106: 253–9.
2. Easthope S, Jarvis B. Omalizumab. *Drugs* 2001; 61: 253–60.
3. Casale TB, *et al.* Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. *JAMA* 2001; 286: 2956–67.
4. Chervinsky P, *et al.* Omalizumab, an anti-IgE antibody, in treatment of adults and adolescents with perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2003; 91: 160–7.
5. Hanf G, *et al.* Omalizumab inhibits allergen challenge-induced nasal response. *Eur Respir J* 2004; 23: 414–18.
6. Vignola AM, *et al.* Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy* 2004; 59: 709–17.
7. Ben-Shoshan M. Omalizumab: not only for asthma. *Recent Pat Inflamm Allergy Drug Discov* 2008; 2: 191–201.
8. Morjaria JB, Polosa R. Off-label use of omalizumab in non-asthma conditions: new opportunities. *Expert Rev Respir Med* 2009; 3: 299–308.

Administration in children. Omalizumab is used for the prophylactic management of severe persistent allergic asthma in children from 6 years of age. The dose depends on the child's weight and pre-treatment serum-IgE concentrations; dose ranges are the same as those in adults, see above.

Aspergillosis. Successful treatment of allergic bronchopulmonary aspergillosis with omalizumab has been reported in children with cystic fibrosis.[1,2] In one such report,[1] repeated improvement in symptoms and normalisation in lung function within 2 to 4 hours of giving omalizumab led to complete withdrawal of corticosteroid treatment in a 12 year old girl. Others[2] have reported similar benefits.

1. van der Ent CK, *et al.* Successful treatment of allergic bronchopulmonary aspergillosis with recombinant anti-IgE antibody. *Thorax* 2007; 62: 276–7.
2. Zirbes JM, Milla CE. Steroid-sparing effect of omalizumab for allergic bronchopulmonary aspergillosis and cystic fibrosis. *Pediatr Pulmonol* 2008; 43: 607–10.

Asthma. Omalizumab may be used for the treatment of severe persistent allergic (IgE mediated) asthma as an add-on therapy to optimised standard therapy in adults (see Asthma, p. 1195.2). It has been shown to reduce exacerbations and corticosteroid requirement compared with placebo in adults with moderate-to-severe allergic asthma.[1] It also reduced exacerbation rates in patients with inadequately controlled, severe persistent asthma,[2] and is considered to be an effective therapy in difficult-to-treat, high-risk adult patients.[3,4]

A systematic review[5] of omalizumab therapy for chronic asthma found that omalizumab was more effective than placebo at reducing exacerbations and improving quality of life. Although omalizumab had an *inhaled*-corticosteroid-sparing effect, the clinical significance of the magnitude of reduction remains open to interpretation, and other factors such as cost-effectiveness and comparative efficacy compared with other add-on therapy should be considered. In patients on *oral* corticosteroids, no significant impact was seen on either exacerbations or oral corticosteroid dose.

Omalizumab has been investigated in the treatment of childhood asthma with encouraging results.[6,7]

1. Solèr M, *et al.* The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001; 18: 254–61.
2. Humbert M, *et al.* Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005; 60: 309–16.
3. Hendeles L, Sorkness CA. Anti-immunoglobulin E therapy with omalizumab for asthma. *Ann Pharmacother* 2007; 41: 1397–1410.
4. Price D. The use of omalizumab in asthma. *Prim Care Respir J* 2008; 17: 62–72.
5. Walker S, *et al.* Anti-IgE for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 14/04/08).
6. Berger W, *et al.* Evaluation of long-term safety of the anti-IgE antibody, omalizumab, in children with allergic asthma. *Ann Allergy Asthma Immunol* 2003; 91: 182–8.
7. Milgrom H, *et al.* Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001; 108: E36. Full version: http://pediatrics.aappublications.org/cgi/reprint/108/2/e36.pdf (accessed 14/04/08)

Churg-Strauss syndrome. A response to omalizumab has been reported[1] in 2 refractory cases of Churg-Strauss syndrome (p. 1603.1) which had previously been masked by corticosteroid therapy. However, Churg-Strauss syndrome has also been reported as an adverse effect of omalizumab (see below).

1. Pabst S, *et al.* Apparent response to anti-IgE therapy in two patients with refractory "forme fruste" of Churg-Strauss syndrome. *Thorax* 2008; 63: 747–8.

Adverse Effects and Precautions

Injection site reactions are common with the use of omalizumab. Other adverse effects that have been reported include generalised pain, fatigue, arthralgia, myalgia, dizziness, earache, gastrointestinal disturbances, headache, fractures, pruritus, dermatitis, and alopecia. An increased incidence of parasitic infection has been reported in patients at high risk for helminthic infections. Viral infections, upper respiratory-tract infections, sinusitis, pharyngitis, and flu-like illness can also occur. Systemic eosinophilia such as Churg-Strauss syndrome has also been reported.

Potentially life-threatening anaphylaxis presenting as bronchospasm, hypotension, syncope, urticaria, angioedema of the throat or tongue, cough, or chest tightness has been seen after omalizumab treatment. Anaphylactic reactions may occur up to 4 days after a dose, and as early as the first dose or more than 1 year after beginning regular treatment. Serum sickness reactions have also been reported rarely with omalizumab use; symptoms usually appear 1 to 5 days after an injection and include arthritis or arthralgia, rash, urticaria, fever, and lymphadenopathy.

Severe thrombocytopenia has been reported with use of omalizumab.

Licensed product information notes an increased incidence of malignancies in patients given omalizumab.

In children, pyrexia and upper abdominal pain are commonly reported after omalizumab treatment.

Omalizumab should not be used for the treatment of acute asthma attacks, and inhaled corticosteroids should not be abruptly withdrawn on starting omalizumab therapy.

References.
1. Deniz YM, Gupta N. Safety and tolerability of omalizumab (Xolair), a recombinant humanized monoclonal anti-IgE antibody. *Clin Rev Allergy Immunol* 2005; 29: 31–48.
2. Limb SL, *et al.* Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. *J Allergy Clin Immunol* 2007; 120: 1378–81. Correction. *ibid.* 2008; 121: 178.
3. Cox L, *et al.* American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. *J Allergy Clin Immunol* 2007; 120: 1373–7.
4. Corren J, *et al.* Safety and tolerability of omalizumab. *Clin Exp Allergy* 2009; 39: 788–97.

Effects on the cardiovascular system. Interim findings from a study to assess the long-term safety of omalizumab have suggested a disproportionate increase in cardiovascular and cerebrovascular problems among patients treated with omalizumab compared with an untreated control group. Reported problems included cardiomyopathy, myocardial infarction, arrhythmias, heart failure, syncope, transient ischaemic attacks, pulmonary hypertension, and thrombosis. Further data are required before a causal relationship can be ascertained; regulatory bodies in both Canada and the USA are carrying out reviews.[1,2]

1. Health Canada. Health Canada reviewing possible association of asthma drug Xolair (omalizumab) with increased risk of cardiovascular problems (issued 13th August 2009). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2009/2009_129-eng.php (accessed 16/03/10)
2. FDA. Omalizumab (marketed as Xolair) - early communication about an ongoing safety review (issued 16th July 2009). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm172406.htm (accessed 16/03/10)

Effects on the cerebrovascular system. For a possible association between omalizumab treatment and an increase in cerebrovascular adverse effects, see above.

Pharmacokinetics

Omalizumab is absorbed after subcutaneous injection with a bioavailability of about 62%, reaching peak serum concentrations after 7 to 8 days. It is removed by IgG and IgE clearance processes in the liver, with a serum elimination half-life of about 26 days. During treatment with omalizumab, the serum concentration of free IgE decreases but that of total IgE increases because the omalizumab-IgE complex has a slower elimination rate than free IgE.

References.
1. Hayashi N, *et al.* A mechanism-based binding model for the population pharmacokinetics and pharmacodynamics of omalizumab. *Br J Clin Pharmacol* 2007; 63: 548–61.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Xolair; *Austral.*: Xolair; *Austria*: Xolair; *Belg.*: Xolair; *Braz.*: Xolair; *Canad.*: Xolair; *Chile*: Xolair; *Cz.*: Xolair; *Denm.*: Xolair; *Fr.*: Xolair; *Ger.*: Xolair; *Gr.*: Xolair; *Hong Kong*: Xolair; *Hung.*: Xolair; *Irl.*: Xolair; *Israel*: Xolair; *Ital.*: Xolair; *Jpn*: Xolair; *Malaysia*: Xolair; *Neth.*: Xolair; *Norw.*: Xolair; *NZ*: Xolair; *Philipp.*: Xolair; *Pol.*: Xolair; *Port.*: Xolair; *Rus.*: Xolair (Kcomp); *Singapore*: Xolair; *Spain*: Xolair; *Swed.*: Xolair; *Switz.*: Xolair; *Thal.*: Xolair; *Turk.*: Xolair; *UK*: Xolair; *Ukr.*: Xolair (Kcomp); *USA*: Xolair; *Venez.*: Xolair.

Orciprenaline Sulfate (BANM, rINNM) ⊗

Metaproterenol Sulfate (USAN); Metaproterenol Sulphate; Orciprenalin sulfát; Orciprenalina, sulfato de; Orciprénaline Sulfate d'; Orciprenaline Sulphate; Orciprenalini Sulfas; Orciprenalino sulfatas; Orciprenalinsulfat; Orciprenalin-szulfát; Orcyprenaliny siarczan; Orsiprenalinisulfaatti; Orsiprenalin Sülfat; Sulfato de metaproterenol; Sulfato de orciprenalina; Th-152; Орципреналина Сульфат.

1-(3,5-Dihydroxyphenyl)-2-isopropylaminoethanol sulphate; *N*-Isopropyl-*N* (β,3,5-trihydroxyphenethyl)ammonium sulphate.

$(C_{11}H_{17}NO_3)_2,H_2SO_4$=520.6

CAS — 586-06-1 (orciprenaline); 5874-97-5 (orciprenaline sulfate).

ATC — R03AB03; R03CB03.

ATC Vet — QR03AB03; QR03CB03.

UNII — GJ20HS0YF0.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Orciprenaline Sulfate). A white, slightly hygroscopic, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. Protect from light.

USP 36: (Metaproterenol Sulfate). A white to off-white crystalline powder. Freely soluble in water. A 10% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. Protect from light.

Uses and Administration

Orciprenaline sulfate is a direct-acting sympathomimetic with mainly beta-adrenoceptor stimulant activity. It has actions and uses similar to those of salbutamol (p. 1220.2) but is less selective for beta$_2$ receptors.

Orciprenaline sulfate is used as a bronchodilator in the management of reversible airways obstruction, as in asthma (p. 1195.2) and in some patients with chronic obstructive pulmonary disease (p. 1199.1). However, more selective beta$_2$ agonists such as salbutamol or terbutaline are now preferred. On inhalation, the onset of action is usually within 30 minutes and can last from 1 to 5 hours.

Orciprenaline sulfate may be inhaled as a 0.4 or 0.6% *nebulised solution* from unit-dose vials containing 10 or 15 mg, respectively. For relief of acute **bronchospasm**, one vial is inhaled up to every 4 hours; in the management of chronic disease, one vial has been given 3 or 4 times daily. In patients with asthma, 'as-required' beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, orciprenaline indicates deterioration of asthma control and the need for review of therapy.

In the chronic management of reversible airways obstruction, orciprenaline sulfate has been given *orally* in a usual adult dose of 20 mg three or four times daily.

In acute bronchospasm orciprenaline sulfate has been given *parenterally*. A dose of 250 to 500 micrograms has been given by slow intravenous injection, or 5 to 10 micrograms/minute by intravenous infusion. Alternatively, an intramuscular or subcutaneous injection of 0.5 to 1 mg has been used.

Orciprenaline sulfate has also been used similarly to isoprenaline (see p. 1412.1) for its cardiovascular effects in the treatment of **bradycardia** of various types, notably in AV heart block and sinus bradycardia. In such cases oral doses of up to 240 mg daily in divided doses, have been used. For doses of orciprenaline used in children, see Administration in Children, below.

Administration in children. In patients with asthma, 'as-required' beta agonist therapy is preferable to regular use, and chronic treatment with orciprenaline would generally be regarded as inappropriate in children. Nonetheless, an oral preparation is licensed for such use in some countries; in the USA, children aged from 6 to 9 years may be given

orciprenaline sulfate 10 mg three or four times daily for reversible bronchospasm. Children aged over 9 years, or over about 25 kg, may be given adult doses, see p. 1217.3.

Asthma. Orciprenaline sulfate is considered less suitable for the relief of reversible airways obstruction than the selective beta$_2$ agonists. The UK MHRA considers that study data show substantial therapeutic advantages for salbutamol over orciprenaline with respect to improvements in pulmonary function, dosing frequency, and adverse effects.[1,2]

1. MHRA. MHRA public assessment report. Orciprenaline sulphate (Alupent): planned withdrawal from the UK market following a risk-benefit analysis (issued November 2009). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con062531.pdf (accessed 17/03/10)
2. MHRA/CHM. Orciprenaline sulphate (Alupent): withdrawal due to unfavourable benefit-risk profile. *Drug Safety Update* 2009; 3 (4): 6. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON062549&RevisionSelectionMethod=LatestReleased (accessed 03/09/10)

Adverse Effects and Precautions

As for Salbutamol, p. 1221.3 and p. 1222.3. Adverse effects are more common because of the non-selective beta agonist effect of orciprenaline, and in particular, tachycardia and palpitations can occur before maximum bronchodilatation. For the adverse effects and precautions pertaining to non-selective beta agonists see under Sympathomimetics, p. 1508.2 and p. 1508.3.

Interactions

As for Salbutamol, p. 1223.1.

Pharmacokinetics

After oral doses orciprenaline is absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver; about 40% of an oral dose is reported to reach the circulation unchanged. It is excreted in the urine mainly as metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Alupent†; *Ger.*: Alupent; *Gr.*: Alupent; *India*: Alupent; *Indon.*: Alupent; *Irl.*: Alupent†; *Ital.*: Alupent†; *Jpn*: Alotec†; *Mex.*: Alupent; *Pol.*: Astmopent†; *Rus.*: Astmopent (Астмопент)†; *UK*: Alupent†; *USA*: Alupent†.

Multi-ingredient Preparations. *Chile*: Broncodual Compuesto; Cloval Compuesto; Pulbronc; Solvanol; Tusabron†; Vapoflu; *Gr.*: Silomat Compositum; *Indon.*: Silomat Compositum†; *Irl.*: Alupent Expectorant†; *Mex.*: Bisolpent Ex; *Philipp.*: Bisolpent; *S.Afr.*: Adco-Linctopent; Benylin Chesty; Bisolvon Linctus DA; Bronkese Compound; Flemeze; *UAE*: Orcinol†.

Pharmacopoeial Preparations
BP 2014: Orciprenaline Tablets;
USP 36: Metaproterenol Sulfate Inhalation Aerosol; Metaproterenol Sulfate Inhalation Solution; Metaproterenol Sulfate Syrup; Metaproterenol Sulfate Tablets.

Oxitropium Bromide *(BAN, rINN)*

Ba-253; Bromuro de oxitropio; Oksitropiumbromidi; Oxitropii Bromidum; Oxitropio, bromuro de; Oxitropium, Bromure d'; Oxitropiumbromid; Окситропия Бромид.
6,7-Epoxy-8-ethyl-3-[(*S*)-tropoyloxy]tropanium bromide; (3*s*,6*R*,7*S*,8*r*)-8-Ethyl-3-[(*S*)-tropoyloxy]-6,7-epoxytropanium bromide.
$C_{19}H_{26}BrNO_4$=412.3
CAS — 30286-75-0.
ATC — R03BB02.
ATC Vet — QR03BB02.
UNII — SF4NW7NH7C.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Oxitropium Bromide). A white or almost white, crystalline powder. It exhibits polymorphism. Very soluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol; practically insoluble in dichloromethane.

Profile

Oxitropium bromide is a quaternary ammonium antimuscarinic with actions similar to those of ipratropium bromide (p. 1211.3), to which it is structurally related. It is used as a bronchodilator in the treatment of reversible airways obstruction, as in asthma (p. 1195.2) and chronic obstructive pulmonary disease (p. 1199.1). Doses of 100 or 200 micrograms by inhalation from a metered-dose aerosol have been given 2 or 3 times daily. Oxitropium bromide may also be given as a nebulised solution in doses of 1.5 mg inhaled 2 or 3 times daily. *Animal* studies have shown reproductive toxicity with high doses of oxitropium, hence the recommendation that it should not be used during pregnancy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Oxivent; *Ital.*: Oxivent; *Jpn*: Tersigan.

Pemirolast Potassium *(USAN, rINNM)*

BL-5617; BMY-26517; Kalii Pemirolastum; Pemirolast potásico; Pémirolast Potassique; Калия Пемироласт.
Potassium 9-methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.
$C_{10}H_7KN_6O$=266.3
CAS — 69372-19-6 (pemirolast); 100299-08-9 (pemirolast potassium).
UNII — 497A17OUUE.

Profile

Pemirolast potassium has mast cell stabilising properties like sodium cromoglicate (p. 1225.3) and may also be a leukotriene inhibitor. It has been used in the treatment of chronic asthma (p. 1195.2) and in the prophylaxis of allergic rhinitis (p. 612.1) and conjunctivitis (p. 611.1). Pemirolast potassium has no bronchodilator properties and should not be used for the treatment of acute asthma attacks.

For asthma, the usual dose is 10 mg orally twice daily after food. For allergic rhinitis the dose is halved. Pemirolast potassium 0.1% eye drops are instilled 4 times daily in the prophylactic management of allergic conjunctivitis. For details of doses in children, see below.

Pemirolast has also been investigated for the prevention of restenosis after coronary artery stent placement.

References.
1. Hasegawa T, *et al.* Kinetic interaction between theophylline and a newly developed anti-allergic drug, pemirolast potassium. *Eur J Clin Pharmacol* 1994; 46: 55–8.
2. Anonymous. New drugs for allergic conjunctivitis. *Med Lett Drugs Ther* 2000; 42: 39–40.
3. Abelson MB, *et al.* Pemirolast potassium 0.1% ophthalmic solution is an effective treatment for allergic conjunctivitis: a pooled analysis of two prospective, randomized, double-masked, placebo-controlled, phase III studies. *J Ocul Pharmacol Ther* 2002; 18: 475–88.
4. Shulman DG. Two mast cell stabilizers, pemirolast potassium 0.1% and nedocromil sodium 2%, in the treatment of seasonal allergic conjunctivitis: a comparative study. *Adv Therapy* 2003; 20: 31–40.
5. Ohsawa H, *et al.* Preventive effect of an antiallergic drug, pemirolast potassium, on restenosis after stent placement: quantitative coronary angiography and intravascular ultrasound studies. *J Cardiol* 2003; 42: 13–22.
6. Gous P, Ropo A. A comparative trial of the safety and efficacy of 0.1 percent pemirolast potassium ophthalmic solution dosed twice or four times a day in patients with seasonal allergic conjunctivitis. *J Ocul Pharmacol Ther* 2004; 20: 139–50.
7. Yahata H, *et al.* Prophylactic effect of pemirolast, an antiallergic agent, against hypersensitivity reactions to paclitaxel in patients with ovarian cancer. *Int J Cancer* 2006; 118: 2636–8.

Administration in children. Pemirolast potassium may be used in the management of asthma in children in the following oral doses:
- 1 to 4 years: 2.5 mg twice daily after food
- 5 to 10 years: 5 mg twice daily after food
- 11 years and above: use adult doses, see above

For allergic rhinitis, the above doses are halved.

Pemirolast potassium 0.1% eye drops can be used four times daily in children over 3 years with allergic conjunctivitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ai Xin Yi Le (艾欣益乐); Alegysal (研立双); Min Si Tong (珉思通); Ni Er Ping (尼尔平); PuLiMin (普利敏); Ze Er Sheng (泽而生); *Hong Kong*: Pemirox; *Indon.*: Alegysal; *Jpn*: Alegysal; *Philipp.*: Alegysal; *Thai.*: Pemirox; *USA*: Alamast.

Pirbuterol *(BAN, rINN)* ⊗

Pirbutérol; Pirbuterolі; Pirbuterolum; Pyrbuterol; Пирбутерол.
2-*tert*-Butylamino-1-(5-hydroxy-6-hydroxymethyl-2-pyridyl) ethanol.
$C_{12}H_{20}N_2O_3$=240.3
CAS — 38677-81-5.
ATC — R03AC08; R03CC07.
ATC Vet — QR03AC08; QR03CC07.
UNII — OG645J8RVW.

Pirbuterol Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de pirbuterol; CP-24314-14; Pirbutérol, Acétate de; Pirbuterol, acetato de; Pirbuterolі Acetas; Pyrbuterol Acetate; Пирбутерола Ацетат.
$C_{12}H_{20}N_2O_3,C_2H_4O_2$=300.4
CAS — 65652-44-0.
ATC — R03AC08; R03CC07.
ATC Vet — QR03AC08; QR03CC07.
UNII — 1EH73XXR9N.

Pirbuterol Hydrochloride

(BANM, USAN, rINNM) ⊗

CP-24314-1; Hidrocloruro de pirbuterol; Pirbutérol, Chlorhydrate de; Pirbuterol, hidrocloruro de; Pirbuterolі Hydrochloridum; Pyrbuterol Hydrochloride; Пирбутерола Гидрохлорид.
$C_{12}H_{20}N_2O_3$,2HCl=313.2
CAS — 38029-10-6.
ATC — R03AC08; R03CC07.
ATC Vet — QR03AC08; QR03CC07.
UNII — J6793T658K.

Profile

Pirbuterol is a direct-acting sympathomimetic with mainly beta-adrenoceptor stimulant activity and a selective action on beta$_2$ receptors (a beta$_2$ agonist). It has properties similar to those of salbutamol (p. 1220.2).

Pirbuterol is used for its bronchodilating properties. It is given as the acetate in the management of reversible airways obstruction, as in asthma (p. 1195.2) and in some patients with chronic obstructive pulmonary disease (p. 1199.1). On inhalation, pirbuterol exerts an effect within 10 minutes, which is reported to last at least 5 hours.

Pirbuterol is given by inhalation as the acetate but doses are expressed in terms of the base: pirbuterol acetate 250 micrograms is equivalent to about 200 micrograms of pirbuterol. It is given via a metered-dose aerosol in a usual dose equivalent to pirbuterol 200 to 400 micrograms (1 to 2 inhalations) as required but not more often than every four hours. A total daily dose of 2.4 mg (12 inhalations) should not be exceeded. In patients with asthma, 'as-required' beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, pirbuterol indicates deterioration of asthma control and the need for review of therapy.

Pirbuterol has also been given orally as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Maxair†; *USA*: Maxair.

Pitrakinra *(rINN)*

AER-001; Bay-16-9996; Pitrakinrum; Питракинра.
L-Methionyl-[121-aspartic acid,124-aspartic acid]interleukin-4.

NOTE. The name Aerovant has been used as a trade mark for pitrakinra.

Profile

Pitrakinra is a dual interleukin-4 and -13 receptor antagonist that is under investigation in the treatment of asthma.

References.
1. Wenzel S, *et al.* Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: results of two phase 2a studies. *Lancet* 2007; 370: 1422–31.
2. Burmeister Getz E, *et al.* Human pharmacokinetics/pharmacodynamics of an interleukin-4 and interleukin-13 dual antagonist in asthma. *J Clin Pharmacol* 2009; 49: 1025–36.

Pranlukast *(BAN, rINN)*

ONO-1078; Pranlukastum; Пранлукаст.
N-[4-Oxo-2-(1*H*-tetrazol-5-yl)-4*H*-1-benzopyran-8-yl]-*p*-(4-phenylbutoxy)benzamide.
$C_{27}H_{23}N_5O_4$=481.5
CAS — 103177-37-3.
ATC — R03DC02.
ATC Vet — QR03DC02.
UNII — TB8Z891092.

Profile

Pranlukast is a selective antagonist of the leukotriene C_4, D_4 and E_4 receptors with similar properties to zafirlukast (p. 1239.3). It is used in the management of asthma

(p. 1195.2) and allergic rhinitis (p. 612.1), at a usual oral dose of pranlukast hydrate 225 mg twice daily.

For details of doses in children, see below.

References.
1. Tamaoki J, *et al.* Leukotriene antagonist prevents exacerbation of asthma during reduction of high-dose inhaled corticosteroid. *Am J Respir Crit Care Med* 1997; 155: 1235–40.
2. Barnes NC, *et al.* Pranlukast, a novel leukotriene receptor antagonist: results of the first European, placebo-controlled, multicentre clinical study in asthma. *Thorax* 1997; 52: 523–7.
3. Grossman J, *et al.* Results of the first US double-blind, placebo-controlled, multicenter clinical study in asthma with pranlukast, a novel leukotriene receptor antagonist. *J Asthma* 1997; 34: 321–8.
4. Keam SJ, *et al.* Pranlukast: a review of its use in the management of asthma. *Drugs* 2003; 63: 991–1019.
5. Nilsuma T, *et al.* Clinical evaluation of response to long-term treatment with Pranlukast in patients with bronchial asthma. *J Investig Allergol Clin Immunol* 2004; 14: 284–91.
6. Horiguchi T, *et al.* Comparative evaluation of the leukotriene receptor antagonist pranlukast versus the steroid inhalant fluticasone in the therapy of aged patients with mild bronchial asthma. *Arzneimittelforschung* 2007; 57: 87–91.
7. Asano K, *et al.* Impact of pharmacokinetics and pharmacogenetics on the efficacy of pranlukast in Japanese asthmatics. *Respirology* 2009; 14: 822–7.

Administration in children. Children with asthma may be given 3.5 mg/kg of pranlukast hydrate orally twice daily. The maximum daily dose is 10 mg/kg, not to exceed the usual adult daily dose of 450 mg (see p. 1218.3).

Churg-Strauss syndrome. For discussion of the potential causative role of leukotriene antagonists in Churg-Strauss syndrome, see under Zafirlukast, p. 1240.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Onon; *Mex.*: Azlaire; *Venez.*: Azlaire.

Procaterol Hydrochloride

(BANM, USAN, rINNM) ⊗

Cl-888; Hidrocloruro de procaterol; OPC-2009; Procaterol, Chlorhydrate de; Procaterol, hidrocloruro de; Procaterolі Hydrochloridum; Prokaterolhydroklorid; Prokaterolihydroklorid; Прокатерола Гидрохлорид.

(±)-*erythro*-8-Hydroxy-5-(1-hydroxy-2-isopropylaminobutyl) quinolin-2(1*H*)-one hydrochloride; (±)-8-Hydroxy-5-[(1*R*,2*S*)-1-hydroxy-2-isopropylaminobutyl]-2-quinolone hydrochloride.

$C_{16}H_{22}N_2O_3$,HCl=326.8

CAS — 72332-33-3 (procaterol); 59828-07-8 (procaterol hydrochloride).

ATC — R03AC16; R03CC08.

ATC Vet — QR03AC16; QR03CC08.

UNII — 4VD1BRT7T8.

NOTE. Commercial procaterol hydrochloride is the hemihydrate ($C_{16}H_{22}N_2O_3$,HCl.½H_2O = 335.8).

Pharmacopoeias. *Chin.* and *Jpn* include the hemihydrate.

Profile

Procaterol hydrochloride is a direct-acting sympathomimetic with mainly beta-adrenoceptor stimulant activity selective to $beta_2$ receptors ($a beta_2$ agonist). It has properties similar to those of salbutamol (p. 1220.2) and it is used as a bronchodilator in the management of reversible airways obstruction, as in asthma (p. 1195.2) or in some patients with chronic obstructive pulmonary disease (p. 1199.1). On inhalation it produces an effect within 5 minutes and the effect can last up to 8 hours.

To relieve acute bronchospasm, a usual dose of 20 micrograms of procaterol hydrochloride is given by inhalation from a metered-dose aerosol or dry powder inhaler up to 4 times daily. In patients with asthma, 'as-required' beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, procaterol indicates deterioration of asthma control and the need for review of therapy. An inhalation solution containing 100 micrograms/mL has been given via a nebuliser in usual doses of 30 to 50 micrograms. Procaterol hydrochloride can also be given orally in doses of 50 micrograms once or twice daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Bai Da Tu (佰达图); Chuan Di (川迪); Meptin (美普清); Xi Si Ning (希思宁); *Cz.*: Lontermin; *Hong Kong*: Meptin; *Indon.*: Ataroc Meptin; Vactiv; *Jpn*: Meptin; *Malaysia*: Meptin; *Philipp.*: Meptin; *Port.*: Onsudil; *Singapore*: Meptin; *Thai.*: Caterol; Meptin.

Proxyphylline *(BAN, rINN)*

Proksifilinas; Proksifyllini; Proxifilina; Proxifillin; Proxifyllin; Proxyfylin; Proxyphyllin; Proxyphyllinum; Проксифиллин.

7-(2-Hydroxypropyl)-1,3-dimethylxanthine; (*RS*)-1,3-Dimethyl-7-(2-hydroxypropyl)purine-2,6(3*H*,1*H*)-dione; 7-(2-Hydroxypropyl)theophylline.

$C_{10}H_{14}N_4O_3$=238.2

CAS — 603-00-9.

ATC — R03DA03.

ATC Vet — QR03DA03.

UNII — 13G1DMN4P0.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Proxyphylline). A white or almost white, crystalline powder. Very soluble in water; soluble in alcohol. Protect from light.

Profile

Proxyphylline is a derivative of theophylline (p. 1229.3) which is used as a bronchodilator and for its cardiovascular properties. Proxyphylline is readily absorbed from the gastrointestinal tract and it is not converted to theophylline in the body.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Santussal; *Ger.*: Antihypertonicum S; *Mex.*: Gadital.

Repirinast *(USAN, rINN)*

MY-5116; Repirinast; Repirinastum; Репиринаст.

Isopentyl 5,6-dihydro-7,8-dimethyl-4,5-dioxo-4*H*-pyrano[3,2-*c*]quinoline-2-carboxylate.

$C_{20}H_{21}NO_5$=355.4

CAS — 73080-51-0.

UNII — 4K8KA8861G.

Profile

Repirinast is an orally active anti-allergic with a stabilising action on mast cells resembling that of sodium cromoglicate (p. 1225.3). It has been given orally in the management of asthma (p. 1195.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Romet.

Reproterol Hydrochloride

(BANM, USAN, rINNM) ⊗

D-1959 (reproterol); Hidrocloruro de reproterol; Réprotérol, Chlorhydrate de; Reproterol, hidrocloruro de; Reproteroli Hydrochloridum; W-2946M; Репротерола Гидрохлорид.

7-[3-[(3,5,β-Trihydroxyphenethyl)amino]propyl]theophylline hydrochloride.

$C_{18}H_{23}N_5O_5$,HCl=425.9

CAS — 54063-54-6 (reproterol); 13055-82-8 (reproterol hydrochloride).

ATC — R03AC15; R03CC14.

ATC Vet — QR03AC15; QR03CC14.

UNII — Y41COJ8W8.

Profile

Reproterol is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors ($a beta_2$ agonist). It has properties similar to those of salbutamol (p. 1220.2).

Reproterol hydrochloride is used as a bronchodilator in the management of reversible airways obstruction, as in asthma (p. 1195.2) and in some patients with chronic obstructive pulmonary disease (p. 1199.1).

For the relief of bronchospasm, reproterol is given with sodium cromoglicate via a metered-dose aerosol, in a usual dose of 2 inhalations of reproterol hydrochloride 500 micrograms four times daily. In patients with asthma, 'as-required' beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, reproterol indicates deterioration of asthma control and the need for review of therapy. A slow intravenous injection of reproterol hydrochloride 90 micrograms, repeated after 10 minutes if necessary, has been used in the treatment of status asthmaticus. Reproterol has also been given orally.

Administration in children. For the relief of bronchospasm in children, reproterol hydrochloride is given with sodium cromoglicate via a metered-dose aerosol at the same dose used in adults (see above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Bronchospasmin; *Gr.*: Bronchospasmin.

Multi-ingredient Preparations. *Ger.*: Aarane N; Allergospasmin.

Roflumilast *(USAN, rINN)*

APTA-2217; B-9302-107; BY-217; BYK-20869; Roflumilastum; Рофлумиласт.

3-(Cyclopropylmethoxy)-*N*-(3,5-dichloro-4-pyridyl)-4-(difluoromethoxy)benzamide.

$C_{17}H_{14}Cl_2F_2N_2O_3$=403.2

CAS — 162401-32-3.

ATC — R03DX07.

ATC Vet — QR03DX07.

UNII — 0P6C6ZOP5U.

Uses and Administration

Roflumilast is a phosphodiesterase type-4 inhibitor that is used for maintenance treatment of severe chronic obstructive pulmonary disease as an adjunct to bronchodilators. An oral dose of 500 micrograms is taken once daily. It should not be used to treat acute bronchospasm.

Roflumilast is also under investigation in the treatment of asthma.

References.
1. Bateman ED, *et al.* Efficacy and safety of roflumilast in the treatment of asthma. *Ann Allergy Asthma Immunol* 2006; 96: 679–86.
2. Calverley PM, *et al.* Effect of 1-year treatment with roflumilast in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 176: 154–61.
3. Field SK. Roflumilast: an oral, once-daily selective PDE-4 inhibitor for the management of COPD and asthma. *Expert Opin Invest Drugs* 2008; 17: 811–18.
4. Calverley PMA, *et al.* M2-124 and M2-125 study groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet* 2009; 374: 685–94.
5. Fabbri LM, *et al.* M2-127 and M2-128 study groups. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. *Lancet* 2009; 374: 695–703.
6. Cazzola M, *et al.* Roflumilast in chronic obstructive pulmonary disease: evidence from large trials. *Expert Opin Pharmacother* 2010; 11: 441–9.
7. Gross NJ, *et al.* Treatment of chronic obstructive pulmonary disease with roflumilast, a new phosphodiesterase 4 inhibitor. *COPD* 2010; 7: 141–53.
8. Sanford M. Roflumilast: in chronic obstructive pulmonary disease. *Drugs* 2010; 70: 1615–27.

Adverse Effects and Precautions

The most commonly reported adverse effects with roflumilast are gastrointestinal disturbances such as diarrhoea and nausea, abdominal pain, headache, and a decrease in appetite and body-weight. These adverse effects mostly occur within the first weeks of therapy and resolve on continued treatment. Weight should be checked regularly, particularly in those who are underweight, and treatment stopped if a significant weight decrease occurs. Other less common adverse effects include hypersensitivity, rash, palpitations, tremor, dizziness, gastritis, muscle spasms and weakness, myalgia, back pain, and fatigue. Gynaecomastia, dysgeusia, urticaria, respiratory-tract infections, haematochezia (blood in the stools), and increases in liver enzymes and creatine phosphokinase have been reported rarely.

An increased risk of psychiatric disorders such as insomnia, anxiety, and depression have been reported with roflumilast, and suicidal ideation and behaviour, including successful suicide attempts, have occurred rarely. Roflumilast is not recommended in patients with a history of depression and suicidal ideation or behaviour, and caution is advised in patients who report previous or existing psychiatric symptoms or those on other drugs likely to cause psychiatric events.

Roflumilast is extensively metabolised in the liver and should be used with caution in patients with mild hepatic impairment (defined as Child-Pugh class A); it is not recommended in those with moderate or severe impairment (Child-Pugh class B or C). Due to a lack of data, roflumilast is not recommended in patients taking immunosuppressive drugs, or those with severe immunological disease, severe infectious disease, cancer, or severe heart failure (NYHA grades 3 or 4).

Roflumilast should not be used for the treatment of acute asthma attacks.

Interactions

The active *N*-oxide metabolite of roflumilast has similar potency to roflumilast and is the main contributor to overall phosphodiesterase type-4 inhibition. Roflumilast is metabolised via the cytochrome P450 isoenzymes CYP3A4 and

CYP1A2, and inhibitors or inducers of these enzymes may affect exposure to roflumilast and its *N*-oxide metabolite.

Use of roflumilast with theophylline or with an oral contraceptive containing gestodene and ethinylestradiol has resulted in increased inhibition of phosphodiesterase type-4.

Roflumilast has not been shown to inhibit or induce any cytochrome P450 isoenzymes, aside from a weak induction of CYP2B6.

Fluvoxamine. Repeated doses of fluvoxamine (an inhibitor of the cytochrome P450 isoenzymes CYP1A2 and CYP2C19) increased exposure to roflumilast in a pharmacokinetic study.[1] Although the rate of formation of the active *N*-oxide metabolite was decreased, clearance was also decreased, resulting in increased exposure to the metabolite. The authors of the study suggested that this increase could have been due to CYP2C19 inhibition of *N*-oxide metabolism by fluvoxamine, as CYP1A2 was not involved in the metabolism of roflumilast *N*-oxide. Total phosphodiesterase-4 inhibition was increased by about 60%.

1. von Richter O, *et al.* Effect of fluvoxamine on the pharmacokinetics of roflumilast and roflumilast N-oxide. *Clin Pharmacokinet* 2007; 46: 613–22.

Ketoconazole. Exposure to roflumilast was increased after single and repeated doses of ketoconazole, a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4. Formation of the active *N*-oxide metabolite was delayed and exposure was slightly decreased after a single ketoconazole dose, but unchanged after repeated dosing. The authors stated that both roflumilast and its *N*-oxide are metabolised by CYP3A4 but to different degrees. Overall phosphodiesterase type-4 inhibition was unaffected and it was considered unnecessary to adjust the roflumilast dose when giving with ketoconazole.[1]

1. Lahu G, *et al.* Effect of single and repeated doses of ketoconazole on the pharmacokinetics of roflumilast and roflumilast N-oxide. *J Clin Pharmacol* 2008; 48: 1339–49.

Rifampicin. Exposure to roflumilast decreased when it was given with rifampicin, a potent inducer of the cytochrome P450 isoenzyme CYP3A4. Exposure to the active *N*-oxide metabolite was also reduced despite increased formation, and the authors of the study suggested that rifampicin could mediate these effects by induction of CYP3A4 and CYP2C19 as both are involved in metabolism of the *N*-oxide. Overall phosphodiesterase type-4 inhibition was reduced by about 60%.[1]

1. Nassr N, *et al.* Effects of rifampicin on the pharmacokinetics of roflumilast and roflumilast N-oxide in healthy subjects. *Br J Clin Pharmacol* 2009; 68: 580–7.

Pharmacokinetics

Following an oral dose on an empty stomach, peak plasma concentrations of roflumilast occur after about 0.5 to 2 hours, and after about 4 to 13 hours for the active metabolite roflumilast *N*-oxide. Food delays the time taken to reach maximum concentration but does not affect total exposure to the active compounds. The absolute bioavailability is about 80%. Plasma-protein binding of roflumilast and roflumilast *N*-oxide is about 99% and 97%, respectively. Studies in *animals* indicate that roflumilast is readily distributed to organs and tissues without evidence of accumulation; penetration of the blood-brain barrier is low. Steady-state plasma concentrations are reached after about 4 days for roflumilast, and 6 days for the *N*-oxide. Total exposure to both compounds is increased in females, elderly patients, and in non-Caucasians, and slightly decreased in smokers.

Roflumilast is extensively metabolised in the liver both via conjugation and via cytochrome P450 isoenzymes. The main metabolite is roflumilast *N*-oxide the formation of which is mediated by CYP3A4 and CYP1A2. Roflumilast and its *N*-oxide have similar potency; however, exposure to the metabolite is about tenfold greater and it is the main contributor to overall activity. The *N*-oxide is further metabolised via CYP3A4, CYP2C19, and extra-hepatic CYP1A1.

After an oral dose, the median plasma effective half-lives of roflumilast and roflumilast N-oxide are about 17 and 30 hours, respectively. About 20% of an oral or intravenous dose is recovered in the faeces, and 70% in the urine as inactive metabolites.

References.

1. Hermann R, *et al.* Steady-state pharmacokinetics of roflumilast and roflumilast N-oxide in patients with mild and moderate liver cirrhosis. *Clin Pharmacokinet* 2007; 46: 403–16.
2. Bethke TD, *et al.* Dose-proportional intraindividual single- and repeated-dose pharmacokinetics of roflumilast, an oral, once-daily phosphodiesterase 4 inhibitor. *J Clin Pharmacol* 2007; 47: 26–36.
3. Neville KA, *et al.* Single-dose pharmacokinetics of roflumilast in children and adolescents. *J Clin Pharmacol* 2008; 48: 978–85.

All cross-references refer to entries in Volume A

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Daxas; *Cz.*: Daliresp; Daxas; Libertek; *Denm.*: Daxas; *Fr.*: Daxas; *Ger.*: Daxas; *Gr.*: Daxas; *Irl.*: Daliresp; Libertek; *Israel*: Daliresp; *Neth.*: Daliresp; Daxas; Libertek; *Norw.*: Daxas; *Pol.*: Daxas; *Port.*: Daxas; *Spain*: Daxas; Libertek; *Swed.*: Daxas; *Switz.*: Daxas; *UK*: Daxas; *Ukr.*: Daxas (Даксас); *USA*: Daliresp.

Salbutamol *(BAN, rINN)* ⊗

AH-3365; Albuterol (USAN); Salbutamoli; Salbutamolis; Salbutamolum; Sch-13949W; Szalbutamol; Сальбутамол.

2-*tert*-Butylamino-1-(4-hydroxy-3-hydroxymethylphenyl) ethanol.

$C_{13}H_{21}NO_3$=239.3

CAS — 18559-94-9.

ATC — R03AC02; R03CC02.

ATC Vet — QR03AC02; QR03CC02.

UNII — QF8SVZ843E.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Salbutamol). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in alcohol. Protect from light.

USP 36: (Albuterol). A white crystalline powder. Sparingly soluble in water; soluble in alcohol. Protect from light.

Salbutamol Sulfate *(BANM, rINNM)* ⊗

Albuterol Sulfate (USAN); Salbutamol Hemisulphate; Salbutamol; sulfate de; Salbutamol, sulfato de; Salbutamol Sulphate; Salbutamoli Sulfas; Salbutamolio sulfatas; Salbutamolisulfaatti; Salbutamolsulfat; Salbutamol-sulfát; Salbutamolu siarczan; Sulfato de albuterol; Sulfato de salbutamol; Szalbutamol-szulfát; Сальбутамола Сульфат.

$(C_{13}H_{21}NO_3)_2H_2SO_4$=576.7

CAS — 51022-70-9.

ATC — R03AC02; R03CC02.

ATC Vet — QR03AC02; QR03CC02.

UNII — 021SEF3731.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Salbutamol Sulfate). A white or almost white crystalline powder. It shows Polymorphism. Freely soluble in water; practically insoluble or very slightly soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Albuterol Sulfate). A white or practically white powder. Freely soluble in water; slightly soluble in alcohol, in chloroform, and in ether. Protect from light.

Stability. For mention of the stability of a 1:1 mixture of salbutamol and ipratropium nebuliser solutions, see under Ipratropium, p. 1211.3.

Uses and Administration

Salbutamol is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist—p. 1195.1). This results in its bronchodilating action being more prominent than its effect on the heart.

Salbutamol and salbutamol sulfate are used as bronchodilators in the management of reversible airways obstruction, as in asthma and in some patients with chronic obstructive pulmonary disease. Salbutamol also decreases uterine contractility and may be given as the sulfate to arrest premature labour (p. 2131.1).

Inhalation results in the rapid onset (within 5 minutes) of bronchodilatation, which lasts for about 3 to 6 hours. After oral doses, the onset of action is within 30 minutes, with a peak effect between 2 to 3 hours after the dose, and a duration of action of up to 6 hours; modified-release preparations that have a longer duration of action are available.

Salbutamol is used as the base or sulfate in aerosol inhalers and as the sulfate in other preparations. The dosage is expressed in terms of salbutamol base; salbutamol sulfate 1.2 mg is equivalent to about 1 mg of salbutamol.

For the relief of **acute bronchospasm**, 1 or 2 inhalations of salbutamol 100 micrograms may be given from a conventional *metered-dose aerosol* as required, up to 4 times daily. Two inhalations may also be given just before exertion for the prophylaxis of exercise-induced bronchospasm. (In the USA these inhalations may be expressed as supplying 100 micrograms, the amount delivered *into* the mouthpiece, or 90 micrograms, the amount delivered *from* the mouthpiece.) Current asthma guidelines (see p. 1195.2) recommend that inhaled short-acting $beta_2$ agonists such as salbutamol be used on an as-required, not regular, basis. In those patients requiring more than occasional use of salbutamol, anti-inflammatory therapy is also needed. An increased requirement for, or decreased duration of effect of, salbutamol indicates deterioration of asthma control and the need for increased anti-inflammatory therapy. Salbutamol sulfate is now available in chlorofluorocarbon (CFC)-free aerosols. Doses for these aerosols (expressed in terms of salbutamol) are the same as for conventional aerosols.

Salbutamol may also be inhaled as the sulfate from dry powder *inhalers* or *discs*, particularly by patients who have difficulty using aerosol formulations. Doses are similar to those given by metered-dose aerosols, although not all dry powder formulations are bioequivalent.

When inhalation is ineffective, *oral* salbutamol may be given in a dose of 2 to 4 mg three or four times daily as the sulfate; some patients may require doses of up to 8 mg three or four times daily, but such increased doses are unlikely to be tolerated or to provide much extra benefit. Elderly patients should be given the lower doses initially. Modified-release preparations are also available; a usual adult dose is 8 mg twice daily.

In more severe or unresponsive bronchospasm salbutamol sulfate may be given intermittently via a *nebuliser* in adults and children. Licensed doses are 2.5 to 5 mg of salbutamol repeated up to 4 times daily; continuous use is also possible, usually at a rate of 1 to 2 mg/hour. However, guidelines allow for more frequent use or continuous use at a higher rate in acute severe asthma (see under Asthma, p. 1195.2). Single-dose units of 0.1% or 0.2%, or a concentrated solution of salbutamol 0.5%, are available for nebulisation. Continuous use is usually as a 0.005 to 0.01% solution in sodium chloride 0.9%. Patients with acute severe asthma may require supplemental oxygen.

Alternatively, salbutamol can be given via a spacer device for acute severe asthma. Four inhalations of 100 micrograms from a metered-dose inhaler are given initially, then a further 2 inhalations are given every 2 minutes according to response, up to a maximum of 10 inhalations.

In the management of a severe attack of bronchospasm a slow *intravenous injection* of salbutamol 250 micrograms as a solution containing 50 micrograms/mL as the sulfate may be required; alternatively salbutamol may be given by intravenous infusion of a solution containing 5 mg in 500 mL (10 micrograms/mL) at a usual rate of 3 to 20 micrograms/minute according to the patient's need; higher dosages have been used in patients with respiratory failure.

Salbutamol sulfate can also be given for bronchospasm by *subcutaneous* or *intramuscular* injection in doses of salbutamol 500 micrograms every 4 hours as required.

For the arrest of uncomplicated **premature labour** between 22 and 37 weeks of gestation salbutamol sulfate is given by *intravenous infusion*, preferably with the aid of a syringe pump at a concentration of 200 micrograms/mL of salbutamol in glucose 5%. If no syringe pump is available then the infusion should be with a more dilute solution of 20 micrograms/mL in glucose 5%. The same dose is used as with the syringe pump. The recommended initial rate of infusion is 10 micrograms/minute increased at intervals of 10 minutes until there is a response; the rate is then increased slowly until contractions cease. The usual effective dose is 10 to 45 micrograms/minute. The infusion should be maintained at the rate at which contractions cease for 1 hour, then reduced by decrements of 50% at intervals of 6 hours. Therapy should be limited to a maximum of 48 hours, because prolonged treatment is associated with risks of serious cardiovascular effects in both the mother and fetus (see Precautions, p. 1222.3).

The maternal pulse should be monitored throughout the infusion and the infusion rate adjusted to avoid a maternal heart rate of more than 120 beats/minute. A close watch should also be kept on the patient's state of hydration since fluid overload is considered to be a key risk factor for pulmonary oedema.

Oral or *rectal* $beta_2$ agonist therapy is no longer recommended in premature labour, because of a lack of evidence of benefit from treatment given by these routes of administration. Formerly, salbutamol could be given orally in doses of 4 mg three or four times daily, for maintenance therapy after uterine contractions were controlled by parenteral treatment.

For doses of salbutamol used in children, see Administration in Children p. 1221.1.

Administration. $Beta_2$ agonists are used extensively in the management of reversible airways obstruction. A common, effective, and convenient method of dosage is by a pressurised aerosol inhaler. With this route relief is provided rapidly and fewer systemic adverse effects are likely to occur than with oral use. It is important that patients using conventional inhalers employ the correct technique, which involves coordinating actuation of the aerosol with inhalation; if patients have difficulty with this, alternatives are available. Spacer devices may be used with inhalers. These are added on to the inhaler and reduce the velocity of the aerosol; also more propellant may evaporate before inhalation allowing a greater proportion of the drug to

reach the lungs, and coordination of actuation of the aerosol and inhalation is less important. Breath-actuated aerosol inhalers and dry powder inhalers are also available and are actuated by the patient's inspiration and thus avoid entirely the need for coordination of actuation and inhalation; however, inhalation of the dry powder has occasionally caused irritation of the throat or coughing.

The oral route can be used although generally a form of inhaled therapy as described above is preferable. Formulations intended for oral use are commercially available, including modified-release formulations. Nebulisation is an alternative method of delivery and this may be used in the management of severe acute attacks as may parenteral therapy.

Chlorofluorocarbon (CFC) propellants in pressurised aerosol inhalers are being replaced by hydrofluoroalkane (HFA) propellants. Conventional and breath-actuated HFA preparations are available. HFA aerosols may feel and taste different to CFC aerosols.

Administration in children. For the treatment of reversible airways obstruction, including nocturnal asthma, and prevention of allergen- or exercise-induced **bronchospasm** in children, the *BNFC* suggests the following usual doses of salbutamol:

by aerosol inhalation

- 1 month to 18 years of age, 100 or 200 micrograms (1 or 2 inhalations) up to four times daily, for occasional use only

by inhalation of dry powder from inhalers or discs doses vary between preparations, although they are used in children from about 5 years of age in doses similar to those given by metered-dose aerosols

Inhaled therapy is generally considered first-line treatment, but oral therapy may be necessary if an inhaler device cannot be used. In the UK salbutamol syrup is licensed for children from 2 years of age and modified-release oral preparations from 3 years of age:

orally using an immediate-release preparation

- 1 month to 2 years of age, 100 micrograms/kg (up to a maximum dose of 2 mg) three or four times daily
- 2 to 6 years of age, 1 to 2 mg three or four times daily
- 6 to 12 years of age, 2 mg three or four times daily
- over 12 years of age, doses as for adults, see Uses and Administration, p. 1220.2

orally using a modified-release preparation

- 3 to 12 years of age, 4 mg twice daily
- over 12 years of age, as for adults, see p. 1220.2

In the management of acute mild to moderate **exacerbations** of asthma, salbutamol may be given using a metered-dose aerosol inhaler via a spacer device. For children of all ages, 1 inhalation (100 micrograms) may be given every 15 to 30 seconds up to a maximum of 10 inhalations. The dose may be repeated after 10 to 20 minutes if required. In more severe exacerbations, salbutamol can be given intermittently via a nebuliser. A dose of 2.5 mg, which can be increased to 5 mg in children over 5 years of age, can be repeated every 20 to 30 minutes or as necessary. Immediate transfer to hospital and inhalation of oxygen is also required. Children under 18 months of age often respond poorly to bronchodilators; nebulised $beta_2$ agonists have been associated with mild paradoxical bronchospasm and transient worsening of oxygen saturation.

Although parenteral salbutamol is not licensed in the UK for use in children, the *BNFC* recommends the following doses in the management of **acute severe** or life-threatening acute asthma:

by intravenous injection over 5 minutes

- 1 month to 2 years of age, 5 micrograms/kg as a single dose
- 2 to 18 years of age, 15 micrograms/kg (to a maximum of 250 micrograms) as a single dose

by continuous intravenous infusion

- 1 month to 18 years of age, 1 to 2 micrograms/kg per minute, adjusted according to response and heart rate up to 5 micrograms/kg per minute. Doses above 2 micrograms/kg per minute require close monitoring

Salbutamol can be used to treat severe **hyperkalaemia** in children (see Hyperkalaemia below). The *BNFC* recommends:

by intravenous injection over 5 minutes

- children of all ages, 4 micrograms/kg as a single dose; repeated if necessary

by inhalation of nebulised solution (although intravenous injection is preferred)

- children of all ages, 2.5 or 5 mg as a single dose; repeated if necessary

Asthma. Short-acting $beta_2$ agonists such as salbutamol are used for short-term relief in all patients with symptomatic asthma (p. 1195.2). High doses are used in acute asthma, but current recommendations for chronic asthma are for low doses to be inhaled as required rather than regularly. When patients with mild asthma find that symptomatic relief is needed more than 3 times a week, then that should be a sign for additional treatment with anti-inflammatory drugs. Increasing need for, or decreased effect of, short-acting $beta_2$ agonists indicates deteriorating asthma and the requirement for stepping up therapy. In one placebo-controlled study,[1] patients with stable asthma receiving regular high doses of a short-acting inhaled $beta_2$ agonist were able to reduce the dose considerably with no change in asthma control, lending further support to the recommendation for 'as-required' rather than regular use of these drugs. The discussion under Fenoterol on p. 1208.3 on the increased mortality that has been seen in asthma patients and the connection with asthma therapy includes a view that regular use might have contributed to the increased mortality. However, a systematic review[2] of studies of short-acting $beta_2$ agonists, most of which used salbutamol, found no clear clinical advantage or detriment from regular use compared with taking them as required.

1. Harrison TW, *et al.* Randomised placebo controlled trial of β agonist dose reduction in asthma. *Thorax* 1999; **54**: 98–102.
2. Walters EH, *et al.* Inhaled short acting beta2-agonist use in chronic asthma: regular versus as needed treatment. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 15/01/08).

Bronchiolitis. Acute bronchiolitis (inflammation of the bronchioles associated with viral respiratory-tract infection, usually due to RSV—see p. 961.3) is a poorly defined respiratory condition seen in infants and young children. The diagnostic criteria, and the usual management, vary considerably from country to country. $Beta_2$ agonists such as salbutamol are widely prescribed in the USA, but not in the UK, and attempts to establish their benefits have produced conflicting results.[1] Modest benefit (but no difference in hospital admission rate) has been reported from a meta-analysis of bronchodilator therapy in general,[2] but a meta-analysis of $beta_2$-agonist therapy in bronchiolitis did not show it to be effective.[3] Some comparative studies have suggested that nebulised adrenaline is more effective than salbutamol.[4,5] However, one study in hospitalised children found no benefit from nebulised salbutamol in terms of improved oxygenation or length of hospital stay,[6] and another[7] found no difference in efficacy between nebulised adrenaline, salbutamol, and sodium chloride 0.9%.

The use of oral salbutamol in infants with acute viral bronchiolitis has been found to be no more effective than placebo and so is not recommended.[8]

1. Everard ML. Acute bronchiolitis—a perennial problem. *Lancet* 1996; **348**: 279–80.
2. Gadomski AM, Bhasale AL. Bronchodilators for bronchiolitis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 25/01/08).
3. Flores G, Horwitz RI. Efficacy of $beta_2$-agonists in bronchiolitis: a reappraisal and meta-analysis. *Pediatrics* 1997; **100**: 233–9.
4. Reijonen T, *et al.* The clinical efficacy of nebulized racemic epinephrine and albuterol in acute bronchiolitis. *Arch Pediatr Adolesc Med* 1995; **149**: 686–92.
5. Menon K, *et al.* A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. *J Pediatr* 1995; **126**: 1004–7.
6. Dobson JV, *et al.* The use of albuterol in hospitalized infants with bronchiolitis. *Pediatrics* 1998; **101**: 361–8.
7. Patel H, *et al.* A randomized, controlled trial of the effectiveness of nebulized therapy with epinephrine compared with albuterol and saline in infants hospitalized for acute viral bronchiolitis. *J Pediatr* 2002; **141**: 818–24.
8. Patel H, *et al.* Randomized, double-blind, placebo-controlled trial of oral albuterol in infants with mild-to-moderate acute viral bronchiolitis. *J Pediatr* 2003; **142**: 509–14.

Chronic obstructive pulmonary disease. Salbutamol and other $beta_2$ agonist bronchodilators form part of the first-line treatment of chronic obstructive pulmonary disease (p. 1199.1).

Cough. For studies of inhaled salbutamol in the treatment of cough, see under Beclometasone, p. 1622.1.

Hyperkalaemia. Salbutamol can lower plasma-potassium concentrations by promoting intracellular uptake,[1,2] and this effect has been used in treating mild hyperkalaemia (p. 1779.1) associated with chronic disorders such as renal failure[3,4] and hyperkalaemic periodic paralysis.[5] However, such use is controversial: the effects of salbutamol may be inconsistent[6] and some clinicians prefer to avoid the use of $beta_2$ agonists because of fears that large doses may induce cardiac arrhythmias.[7]

Salbutamol has been used to lower plasma-potassium concentrations in children[8] and premature neonates[9] with some success. For doses of salbutamol used to treat severe hyperkalaemia in children, see Administration in Children above.

1. Bushe C. Salbutamol for hyperkalaemia. *Lancet* 1983; **ii**: 797.
2. Anonymous. Hyperkalaemia—silent and deadly. *Lancet* 1989; **i**: 1240.
3. Allon M, *et al.* Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. *Ann Intern Med* 1989; **110**: 426–9.
4. McClure RJ, *et al.* Treatment of hyperkalaemia using intravenous and nebulised salbutamol. *Arch Dis Child* 1994; **70**: 126–8.
5. Wang P, Clausen T. Treatment of attacks in hyperkalaemic familial periodic paralysis by inhalation of salbutamol. *Lancet* 1976; **i**: 221–3.
6. Wong S-L, Maltz HC. Albuterol for the treatment of hyperkalemia. *Ann Pharmacother* 1999; **33**: 103–6.
7. Halperin ML, Kamel KS. Potassium. *Lancet* 1998; **352**: 135–40.
8. Helfrich E, *et al.* Salbutamol for hyperkalaemia in children. *Acta Paediatr* 2001; **90**: 1213–16.
9. Singh BS, *et al.* Efficacy of albuterol inhalation in treatment of hyperkalemia in premature neonates. *J Pediatr* 2002; **141**: 16–20.

Lymphangioleiomyomatosis. Inhaled $beta_2$ agonists are often helpful in treating the reversible component of airway obstruction in women with pulmonary lymphangioleiomyomatosis, and a trial of treatment is warranted.[1,2] For mention of the use of medroxyprogesterone in this rare disease, see Respiratory Disorders, p. 2288.3.

1. Johnson S. Lymphangioleiomyomatosis: clinical features, management and basic mechanisms. *Thorax* 1999; **54**: 254–64.
2. Johnson SR, Tattersfield AE. Clinical experience of lymphangioleiomyomatosis in the UK. *Thorax* 2000; **55**: 1052–7.

Muscular dystrophies. There is some evidence that $beta_2$ agonists affect muscle strength and have an anabolic effect, although whether this applies when given by inhalation has been queried—see Abuse, under Precautions, p. 1223.1. Salbutamol has therefore been investigated in a small number of patients in the management of muscular dystrophies (p. 1608.1). Oral doses of modified-release salbutamol up to 12 mg daily have been used in boys aged between 5 and 11 years with Duchenne or Becker muscular dystrophies,[1,2] and doses of 8 or 16 mg twice daily have been given to adults with facioscapulohumeral dystrophy.[3,4] Although some improvements in muscle strength and muscle mass have been reported, not all muscle groups respond and the long-term effects of treatment are not known.

1. Fowler EG, *et al.* Pilot trial of albuterol in Duchenne and Becker muscular dystrophy. *Neurology* 2004; **62**: 1006–8.
2. Skura CL, *et al.* Albuterol increases lean body mass in ambulatory boys with Duchenne or Becker muscular dystrophy. *Neurology* 2008; **70**: 137–43.
3. Kissel JT, *et al.* Randomized, double-blind, placebo-controlled trial of albuterol in facioscapulohumeral dystrophy. *Neurology* 2001; **57**: 1434–40.
4. van der Kooi EL, *et al.* Strength training and albuterol in facioscapulohumeral muscular dystrophy. *Neurology* 2004; **63**: 702–8.

Premature labour. $Beta_2$ agonists such as salbutamol have been used as tocolytics in the management of premature labour (p. 2131.1), and can postpone labour for a few days, but the risk of adverse cardiovascular and metabolic events including pulmonary oedema (see p. 1222.3) means that great care and appropriate monitoring of the patient's heart rate and state of hydration are needed.

Proctalgia fugax. Inhalation of salbutamol from a metered-dose inhaler at the beginning of an attack has been shown to reduce the duration of pain in patients with proctalgia fugax.[1]

1. Eckardt VF, *et al.* Treatment of proctalgia fugax with salbutamol inhalation. *Am J Gastroenterol* 1996; **91**: 686–9.

Adverse Effects

As for Sympathomimetics, p. 1508.2. Salbutamol has mainly beta-agonist effects and, like other beta agonists, may cause fine tremor of skeletal muscle (particularly the hands), palpitations, tachycardia, nervous tension, headaches, peripheral vasodilatation, and rarely muscle cramps. Inhalation causes fewer adverse effects than systemic dosage, and the more selective $beta_2$ agonists cause fewer adverse effects than less selective beta agonists. Potentially serious hypokalaemia has been reported after large doses. Myocardial ischaemia has also been reported. Hypersensitivity reactions have occurred, including paradoxical bronchospasm, angioedema, urticaria, hypotension, and collapse.

The high doses of salbutamol used intravenously to delay premature labour have additionally been associated with nausea and vomiting, and with severe adverse cardiac and metabolic effects and pulmonary oedema.

Effects on the CNS. Visual hallucinations lasting for an hour have been reported[1] after use of nebulised salbutamol in an elderly patient. At the time of the report the manufacturers were aware of 3 cases of hallucinations in children given oral salbutamol but no such reaction had been previously reported in adults given recommended doses.

Hyperactivity and restlessness have been reported with the use of salbutamol; however, a small placebo-controlled study of 19 children,[2] failed to show a statistically significant difference in activity levels after a nebulised dose of salbutamol.

1. Khanna PB, Davies R. Hallucinations associated with the administration of salbutamol via a nebuliser. *BMJ* 1986; **292**: 1430.
2. Hadjikoumi I, *et al.* Bronchodilator therapy and hyperactivity in preschool children. *Arch Dis Child* 2002; **86**: 202–4. Also available at: http://adc.bmj.com/cgi/reprint/86/3/202 (accessed 15/01/08).

Effects on electrolytes and metabolism. Salbutamol, in common with other $beta_2$-agonists, may cause *hypokalaemia* and *hyperglycaemia*. These effects are related to the dose and route of salbutamol used; hypokalaemia is more common after parenteral and nebulised use. Hypokal-

aemia may be potentiated by therapy with corticosteroids, diuretics, or xanthines, and by hypoxia; potassium concentrations should therefore be monitored in severe asthma.

Effects on the eyes. It has been suggested that salbutamol and to a greater extent ritodrine may contribute to retinopathy in the premature infant when used for premature labour.[1]

A case of acute angle-closure glaucoma was attributed to dilatation of the pupil by stimulation of the sympathetic nervous system secondary to local absorption of nebulised salbutamol in the eye; the patient also had other risk factors for developing glaucoma.[2] For reports of glaucoma precipitated by the combined use of ipratropium bromide and salbutamol via a nebuliser, see Ipratropium Bromide, p. 1212.3.

1. Michie CA, *et al.* Do maternal β-sympathomimetics influence the development of retinopathy in the premature infant? *Arch Dis Child* 1994; 71: F149.
2. Rho DS. Acute angle-closure glaucoma after albuterol nebulizer treatment. *Am J Ophthalmol* 2000; 130: 123–4.

Effects on the heart. The main adverse cardiac effect of salbutamol is **tachycardia** due to increased sympathetic effects on the cardiovascular system. Such tachycardia is dose dependent and is more common after systemic than inhaled therapy. A meta-analysis[1] of randomised, placebo-controlled studies in patients with asthma or chronic obstructive pulmonary disease (COPD) confirmed that single doses of $beta_2$ agonists can cause an increase in heart rate and a reduction in potassium concentrations (see also Effects on Electrolytes and Metabolism, p. 1221.3). The **longer-term effects** of $beta_2$ agonists on the cardiovascular system were also assessed and an increased risk of adverse cardiovascular events due to sinus tachycardia was found. There was also a trend towards an increase in major adverse events including ventricular tachycardia, atrial fibrillation, syncope, heart failure, myocardial infarction, cardiac arrest, and sudden death. **Myocardial ischaemia** has been reported with salbutamol when used to delay premature labour.[2] Eleven of 17 reports were considered serious, including one fatality. Most of these reports involved the use of parenteral formulations; none involved the use of inhaled salbutamol formulations for the relief of bronchospasm. However, there is some evidence that high doses of inhaled salbutamol can decrease coronary flow reserve, and might exacerbate ischaemia in patients with coronary artery disease.[3] Observational studies into the association between $beta_2$ agonist use and the risk of **myocardial infarction** have produced conflicting results. Some have reported an increased risk,[4,5] whereas others have reported that this risk is increased only in patients with asthma[6] but not in those with COPD.[6,7] In patients with asthma and long QT syndrome, treatment with $beta_2$ agonists (salbutamol, salmeterol, and orciprenaline) increased the risk of cardiac events such as syncope, myocardial infarction, and sudden cardiac death. The risk was higher in the first year of $beta_2$ agonist treatment but was reduced in patients also receiving beta blockers.[8] Similarly, a case-control study[9] in hypertensive patients reported that the risk of myocardial infarction was only increased in patients with ischaemic heart disease who had recently started treatment with $beta_2$ agonists. The authors of this study felt that this increased risk was likely to have been due to latent cardiovascular disease rather than a direct effect of the $beta_2$ agonists. Case-control and cohort studies have also suggested that patients with **pre-existing heart failure** may be at increased risk of **hospitalisation** from arrhythmias[10] or exacerbation of heart failure[11,12] with the use of $beta_2$ agonists.

However, a causal relationship cannot necessarily be established from these case-control and cohort studies, because of confounding factors such as comorbidity, and because the extent of $beta_1$ agonist use could only be estimated from prescription record systems.

See also Pregnancy, below.

1. Salpeter SR, *et al.* Cardiovascular effects of β-agonists in patients with asthma and COPD: a meta-analysis. *Chest* 2004; 125: 2309–21.
2. GlaxoSmithKline, Canada. Health Canada endorsed important safety information on Ventolin I.M. injection and Ventolin I.V. infusion solution: for pregnant women & labour and delivery (issued 12th June 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/ventolin_hpc-cps-eng.pdf (accessed 09/07/08)
3. Kochiadakis GE, *et al.* Effect of inhaled salbutamol on coronary circulation in humans. *Int J Cardiol* 2007; 117: 408–10.
4. Au DH, *et al.* The risk of myocardial infarction associated with inhaled β-adrenoceptor agonists. *Am J Respir Crit Care Med* 2000; 161: 827–30.
5. Au DH, *et al.* Association between inhaled β-agonists and the risk of unstable angina and myocardial infarction. *Chest* 2002; 121: 846–51.
6. Lemaitre RN, *et al.* Inhaled beta-2 adrenergic receptor agonists and primary cardiac arrest. *Am J Med* 2002; 113: 711–16.
7. Suissa S, *et al.* Inhaled short acting β agonist use in COPD and the risk of acute myocardial infarction. *Thorax* 2003; 58: 43–6.
8. Thottathil P, *et al.* International Long QT Syndrome Investigative Group. Risk of cardiac events in patients with asthma and long-QT syndrome treated with $beta_2$ agonists. *Am J Cardiol* 2008; 102: 871–4.
9. de Vries F, *et al.* Use of B_2 agonists and risk of acute myocardial infarction in patients with hypertension. *Br J Clin Pharmacol* 2008; 65: 580–6.
10. Bouvy ML, *et al.* Use of sympathomimetic drugs leads to increased risk of hospitalization for arrhythmias in patients with congestive heart failure. *Arch Intern Med* 2000; 160: 2477–80.
11. Au DH, *et al.* Risk of mortality and heart failure exacerbations associated with inhaled β-adrenoceptor agonists among patients with known left ventricular systolic dysfunction. *Chest* 2003; 123: 1964–9.
12. Au DH, *et al.* Association between chronic heart failure and inhaled β-2-adrenoceptor agonists. *Am Heart J* 2004; 148: 915–20.

Effects on the respiratory system. Paradoxical bronchoconstriction has occasionally been reported after bronchodilating therapy. With nebuliser solutions, it has been suggested that the preservatives present could be responsible (see also under Ipratropium, p. 1213.1), or that the pH may contribute if non-neutral. In addition, regular use of $beta_2$ agonists such as salbutamol (as opposed to use on an as-needed basis) has been shown to increase airway hyperresponsiveness to various stimuli and to lead to the possible development of tolerance to the bronchoprotective effect (see below).

The increased risk of pulmonary oedema associated with salbutamol is mentioned under Pulmonary Oedema, below.

Increased mortality. The increased incidence of morbidity and mortality that occurred in asthmatic patients mainly involved fenoterol, but salbutamol has been implicated. The debate on the relevance of beta agonist therapy to this increased morbidity and mortality is discussed under Fenoterol on p. 1208.3.

Overdosage. Reports of overdosage with salbutamol[1-6] have generally only described the features that may be expected with $beta_2$ agonists such as tachycardia, CNS stimulation, tremor, hypokalaemia, and hyperglycaemia. The plasma-potassium concentration and pulse rate have been found to correlate with the plasma concentration of salbutamol.[7] Symptomatic treatment of the adverse effects has proved successful although it is unlikely to be required after repeated inhalation. In the UK, the *National Poisons Information Service* notes that activated charcoal may be considered after oral overdose in patients who have taken a potentially toxic amount and present within 1 hour. Further management is mainly supportive. Tachycardia with adequate cardiac output is best left untreated, but in extreme cases beta blockers such as metoprolol or esmolol may be used (caution is required in patients with a history of bronchospasm, see p. 1320.3). Persistent hypertension may respond to an intravenous infusion of glyceryl trinitrate or another nitrate; calcium-channel blockers are an alternative. Beta blockers should be avoided because of the risk of paradoxical hypertension and coronary vasoconstriction from unopposed alpha effects.

1. Morrison GW, Farebrother MJB. Overdose of salbutamol. *Lancet* 1973; ii: 681.
2. O'Brien IAD, *et al.* Hypokalaemia due to salbutamol overdosage. *BMJ* 1981; 282: 1515–16.
3. Prior JG, *et al.* Self-poisoning with oral salbutamol. *BMJ* 1981; 282: 1932.
4. Connell JMC, *et al.* Metabolic consequences of salbutamol poisoning reversed by propranolol. *BMJ* 1982; 285: 779.
5. Spiller HA, *et al.* A two-year retrospective study of accidental pediatric albuterol ingestions. *Pediatr Emerg Care* 1993; 9: 338–40.
6. Leikin JB, *et al.* Hypokalemia after pediatric albuterol overdose: a case series. *Am J Emerg Med* 1994; 12: 64–6.
7. Lewis LD, *et al.* A study of self poisoning with oral salbutamol—laboratory and clinical features. *Hum Exp Toxicol* 1993; 12: 397–401. Correction. *ibid.* 1994; 13: 371.

Pregnancy. Most adverse effects associated with salbutamol in pregnancy relate to the cardiovascular and metabolic effects of the very high doses given by intravenous infusion in attempts to delay premature labour (see also under Pulmonary Oedema, below). Maternal effects include myocardial ischaemia,[1,2] unifocal ventricular ectopics associated with the hypokalaemic response to intravenous salbutamol,[3] and heart failure in a hypertensive woman.[4] Similarly, serious fetal and neonatal cardiovascular complications have also been associated with tocolytic salbutamol.[5]

Metabolic acidosis after salbutamol infusions in diabetic women has also been reported.[6,7]

For reports of retinopathy in the premature infant see Effects on the Eyes above.

1. Whitehead MI, *et al.* Myocardial ischaemia after withdrawal of salbutamol for pre-term labour. *Lancet* 1979; ii: 904.
2. GlaxoSmithKline, Canada. Health Canada endorsed important safety information on Ventolin I.M. injection and Ventolin I.V. infusion solution: for pregnant women & labour and delivery (issued 12th June, 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/ventolin_hpc-cps-eng.pdf (accessed 09/07/08)
3. Chew WC, Lew LC. Ventricular ectopics after salbutamol infusion for preterm labour. *Lancet* 1979; ii: 1383–4.
4. Whitehead MI, *et al.* Acute congestive cardiac failure in a hypertensive woman receiving salbutamol for premature labour. *BMJ* 1980; 280: 1221–2.
5. Katz VL, Seeds JW. Fetal and neonatal cardiovascular complications from β-sympathomimetic therapy for tocolysis. *Am J Obstet Gynecol* 1989; 161: 1–4.
6. Chapman MG. Salbutamol-induced acidosis in pregnant diabetics. *BMJ* 1977; 1: 639–40.
7. Thomas DJB, *et al.* Salbutamol-induced diabetic ketoacidosis. *BMJ* 1977; 2: 438.

Pulmonary oedema. Pulmonary oedema has occurred in women given $beta_2$ agonists, including salbutamol,[1-4] for premature labour. The risk factors, the most important of which is fluid overload, are discussed under Precautions, below.

1. Hawker F. Pulmonary oedema associated with $beta_2$-sympathomimetic treatment of premature labour. *Anaesth Intensive Care* 1984; 12: 143–51.
2. Pisani RJ, Rosenow EC. Pulmonary edema associated with tocolytic therapy. *Ann Intern Med* 1989; 110: 714–18.
3. Hamel H, *et al.* Œdème pulmonaire et tocolyse par bêta-mimétiques. *Rev Mal Respir* 2002; 19: 241–4.
4. Chapuis C, *et al.* Œdème aigu du poumon au décours d'une tocolyse par nicardipine et salbutamol lors d'une menace d'accouchement prématuré sur grossesse gémellaire. *J Gynecol Obstet Biol Reprod (Paris)* 2005; 34: 493–6.

Tolerance. Some studies suggest that regular inhalation of a short-acting $beta_2$ agonist, although it continues to produce bronchodilatation, increases airway hyperresponsiveness and may reduce the protective effect against bronchoconstriction provoked by stimuli such as bradykinin, methacholine, or allergen.[1-6] Such tolerance is considered another argument against regular use of short-acting drugs.[1] Reduced bronchoprotective effects have also been found with long-acting $beta_2$ agonists (see Salmeterol, p. 1225.2).

It has been suggested that reduced benefit with salbutamol may be due to the *S*(+)-enantiomer,[7,8] which unlike the *R* (-)-enantiomer (levosalbutamol, p. 1213.3) does not possess bronchodilating activity. Stereoselective metabolism (see under Pharmacokinetics, p. 1223.2) means that regular use of the racemate could lead to accumulation of the *S*-enantiomer, which provides a possible mechanism for the effect. Genetic polymorphism of the $beta_2$-adrenoceptor has also been proposed as another possible mechanism.[9,10]

1. Cockcroft DW, *et al.* Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1993; 342: 833–7.
2. O'Connor BJ, *et al.* Tolerance to the nonbronchodilator effects of inhaled $beta_2$-agonists in asthma. *N Engl J Med* 1992; 327: 1204–8.
3. Cockcroft DW, *et al.* Regular use of inhaled albuterol and the allergen-induced late asthmatic response. *J Allergy Clin Immunol* 1995; 96: 44–9.
4. Inman MD, O'Byrne PM. The effect of regular inhaled albuterol on exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 1996; 153: 65–9.
5. Crowther SD, *et al.* Varied effects of regular salbutamol on airway responsiveness to inhaled spasmogens. *Lancet* 1997; 350: 1450.
6. Hancox RJ, *et al.* Tolerance to beta-agonists during acute bronchoconstriction. *Eur Respir J* 1999; 14: 283–7.
7. Perrin-Fayolle M. Salbutamol in the treatment of asthma. *Lancet* 1995; 346: 1101.
8. Handley D. The asthma-like pharmacology and toxicology of (S)-isomers of β agonists. *J Allergy Clin Immunol* 1999; 104 (suppl): S69–S76.
9. Israel E, *et al.* Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. *Lancet* 2004; 364: 1505–12.
10. Broadley KJ. β-Adrenoceptor responses of the airways: for better or worse? *Eur J Pharmacol* 2006; 533: 15–27.

Precautions

Salbutamol and other beta agonists should be given with caution in hyperthyroidism, myocardial insufficiency, arrhythmias, susceptibility to QT-interval prolongation, hypertension, and diabetes mellitus (especially on intravenous use—blood glucose should be monitored since ketoacidosis has been reported).

In *severe asthma* particular caution is also required to avoid inducing hypokalaemia as this effect may be potentiated by hypoxia or by the effect of other anti-asthma drugs on potassium (see Interactions, p. 1223.1); plasma-potassium concentrations should be monitored.

$Beta_2$ agonists such as salbutamol are not appropriate for use alone in the treatment of more than mild asthma (see Asthma, p. 1195.2). Increasing need for, or decreased duration of effect of, inhaled salbutamol and other short-acting $beta_2$ agonists indicates deterioration of asthma control and the likely requirement for increased anti-inflammatory therapy.

In *women being treated for premature labour* the risk of pulmonary oedema means that the patient's state of hydration and cardiac and respiratory function should be monitored very carefully; the volume of infusion fluid should be kept to the minimum (normally using glucose 5% as the diluent), and $beta_2$-agonist therapy should be stopped immediately and diuretic therapy started if signs of pulmonary oedema develop. Other risk factors for pulmonary oedema include multiple pregnancy and heart disease. Ischaemic heart disease or significant risk factors for ischaemic heart disease are specific contra-indications; where heart disease is suspected assessment by a physician experienced in cardiology is needed. Eclampsia and severe pre-eclampsia are also contra-indications, with special care needed in mild to moderate pre-eclampsia. Other contra-indications include intra-uterine infection, intra-uterine fetal death, antepartum haemorrhage (which requires immediate delivery), placenta praevia, and cord compression; $beta_2$ agonists should not be used for threatened miscarriage. See also Uses and Administration, p. 1220.2.

For details of the precautions to be observed with sympathomimetics in general, see p. 1508.3.

Abuse. Salbutamol inhalers have been subject to abuse, particularly by children and young adults.[1-7] This has occurred in both asthmatic and non-asthmatic individuals and has been thought to be for the effect of sympathetic stimulation and for the effect of the fluorocarbon propellants. The introduction of fluorocarbon-free inhalers should reduce the latter motivation, although not the former.

The *World Anti-Doping Agency* prohibits the use of all beta$_2$ agonists in athletes, in and out of competition,[8] on the basis of their supposed ergogenic effect. Although a therapeutic use exemption may be granted for the use of inhaled salbutamol or salmeterol, e.g. in the management of asthma, the presence of salbutamol in urine at concentrations above 1 microgram/mL is considered an adverse analytical finding, unless pharmacokinetic studies show that such concentrations are being produced after inhalation of the drug at therapeutic doses up to a maximum of 1.6 mg daily; this has been shown to be a possibility.[9] The idea that abuse of inhaled beta$_2$ agonists can improve performance in non-asthmatic individuals has been questioned.[10]

1. Brennan PO. Inhaled salbutamol: a new form of drug abuse? *Lancet* 1983; ii: 1030–1.
2. Thompson PJ, *et al.* Addiction to aerosol treatment: the asthmatic alternative to glue sniffing. *BMJ* 1983; 287: 1515–16.
3. Brennan PO. Addiction to aerosol treatment. *BMJ* 1983; 287: 1877.
4. Wickramasinghe H, Liebeschuetz HJ. Addiction to aerosol treatment. *BMJ* 1983; 287: 1877.
5. O'Callaghan C, Milner AD. Aerosol treatment abuse. *Arch Dis Child* 1988; 63: 70.
6. Rakhmanina NY, *et al.* Hypokalemia in an asthmatic child from abuse of albuterol metered dose inhaler. *Pediatr Emerg Care* 1998; 14: 145–7.
7. Boland B, *et al.* Salbutamol inhaler misuse: a persisting problem? *Addiction* 2008; 103: 1907.
8. World Anti-Doping Agency. The world anti-doping code: the 2010 prohibited list international standard. Available at: http://www.wada-ama.org/rtecontent/document/2010_Prohibited_List_Final_EN_Web.pdf (accessed 14/10/09)
9. Schweizer C, *et al.* Doping test reveals high concentrations of salbutamol in a Swiss track and field athlete. *Clin J Sport Med* 2004; 14: 312–5.
10. Kindermann W, Meyer T. Inhaled β_2 agonists and performance in competitive athletes. *Br J Sports Med* 2006; 40 (suppl 1): 143–147.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies salbutamol as not porphyrinogenic: it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

Use of salbutamol and other beta$_2$ agonists with corticosteroids, diuretics, or xanthines increases the risk of hypokalaemia, and monitoring of potassium concentrations is recommended in severe asthma, where such combination therapy is common (see also Effects on Electrolytes and Metabolism, p. 1221.3). For an outline of interactions associated with sympathomimetics in general, see p. 1508.3.

Beta$_2$ agonists. Patients receiving *salmeterol* may require salbutamol to control an acute attack of bronchospasm. One study indicated that the effects might be additive,[1] but another showed that patients receiving salmeterol had reduced sensitivity to salbutamol and might need higher doses of the latter for acute relief.[2] However, a study in asthmatics admitted to a hospital emergency department with acute exacerbations of their illness, found that previous salmeterol therapy did not reduce the efficacy of standard doses of salbutamol.[3] Others have also noted attenuation of the bronchoprotective effects of a beta$_2$ agonist (in this case, *fenoterol*) by salmeterol.[4]

1. Smyth ET, *et al.* Interaction and dose equivalence of salbutamol and salmeterol in patients with asthma. *BMJ* 1993; 306: 543–5.
2. Grove A, Lipworth BJ. Bronchodilator subsensitivity to salbutamol after twice daily salmeterol in asthmatic patients. *Lancet* 1995; 346: 201–6.
3. Korosec M, *et al.* Salmeterol does not compromise the bronchodilator response to albuterol during acute episodes of asthma. *Am J Med* 1999; 107: 209–13.
4. van Veen A, *et al.* Regular use of long-acting β_2-adrenoceptor agonists attenuates the bronchoprotective efficacy of short-acting β_2-adrenoceptor agonists in asthma. *Br J Clin Pharmacol* 2000; 50: 499P.

Beta blockers. Non-cardioselective beta blockers oppose the bronchodilator effects of beta-agonist bronchodilators and are contra-indicated in asthmatic patients as they may cause serious bronchoconstriction, even if given as eye drops. No adverse interaction normally occurs between beta-agonist bronchodilators and cardioselective beta blockers; however, bronchospasm can sometimes occur in asthmatic patients, particularly if high doses are used. In a case-control study in postoperative coronary artery bypass graft patients, use of *sotalol with salbutamol* led to an increased risk for postoperative atrial fibrillation.[1]

1. Vader C, *et al.* Interaction between sotalol and albuterol after CABG: influence on postoperative arrhythmias and length of stay at an intensive care unit. *Br J Clin Pharmacol* 2002; 53: 555P–556P.

Cardiac glycosides. Hypokalaemia produced by beta$_2$ agonists may result in an increased susceptibility to digitalis-induced arrhythmias although salbutamol intravenously and orally can also decrease serum concentrations of *digoxin* (see Beta$_2$ Agonists, p. 1357.1).

Corticosteroids. Corticosteroids and beta$_2$ agonists may both produce falls in plasma potassium concentrations; there is evidence that such falls can be exacerbated by use together.[1] The possibility of enhanced hyperglycaemic effects from such a combination should also be borne in mind.

It has been suggested that in acute severe asthma, corticosteroids may modify beta receptors, reversing the beta receptor desensitisation and downregulation caused by beta$_2$ agonists and enhancing the bronchodilator response.[2] In chronic asthma there is little evidence to support this theory; however, combination therapy with corticosteroids and beta$_2$ agonists has been found to have beneficial effects on asthma control; the exact mechanism for this remains unclear.

1. Taylor DR, *et al.* Interaction between corticosteroid and beta-agonist drugs: biochemical and cardiovascular effects in normal subjects. *Chest* 1992; 102: 519–24.
2. Taylor DR, Hancox RJ. Interactions between corticosteroids and β agonists. *Thorax* 2000; 55: 595–602.

Diuretics. Hypokalaemia is known to be a possible adverse effect during treatment with beta$_2$ agonists such as salbutamol or terbutaline, and this may be enhanced if diuretics are also given;[1,2] in addition the arrhythmogenic potential of this interaction may be clinically important in patients with ischaemic heart disease.[1]

1. Lipworth BJ, *et al.* Prior treatment with diuretic augments the hypokalemic and electrocardiographic effects of inhaled albuterol. *Am J Med* 1989; 86: 653–7.
2. Newnham DM, *et al.* The effects of frusemide and triamterene on the hypokalaemic and electrocardiographic responses to inhaled terbutaline. *Br J Clin Pharmacol* 1991; 32: 630–2.

Neuromuscular blockers. Salbutamol given intravenously has been reported to enhance the neuromuscular blockade produced by *pancuronium* and by *vecuronium* (see Sympathomimetics, p. 2033.2).

Xanthines. An enhanced hypokalaemic effect may occur when salbutamol is given with *theophylline*.[1,2] See also under Terbutaline, p. 1229.1 and Sympathomimetics, under Theophylline, p. 1236.3 for the potentiation of other effects.

1. Whyte KF, *et al.* Salbutamol induced hypokalaemia: the effect of theophylline alone and in combination with adrenaline. *Br J Clin Pharmacol* 1988; 25: 571–8.
2. Kolski GB, *et al.* Hypokalemia and respiratory arrest in an infant with status asthmaticus. *J Pediatr* 1988; 112: 304–7.

Pharmacokinetics

Salbutamol is readily absorbed from the gastrointestinal tract. When given by inhalation, 10 to 20% of the dose reaches the lower airways. The remainder is retained in the delivery system or is swallowed and absorbed from the gut.

Salbutamol is subject to first-pass metabolism in the liver and possibly in the gut wall but does not appear to be metabolised in the lung; the main metabolite is the inactive sulfate conjugate.

Salbutamol is rapidly excreted, mainly in the urine, as metabolites and unchanged drug; a smaller proportion is excreted in the faeces.

The plasma half-life of salbutamol has been estimated to range from 4 to 6 hours.

General references.

1. Walker SR, *et al.* The clinical pharmacology of oral and inhaled salbutamol. *Clin Pharmacol Ther* 1972; 13: 861–7.
2. Hetzel MR, Clark TJH. Comparison of intravenous and aerosol salbutamol. *BMJ* 1976; 2: 919.
3. Lin C, *et al.* Isolation and identification of the major metabolite of albuterol in human urine. *Drug Metab Dispos* 1977; 5: 234–8.
4. Morgan DJ, *et al.* Pharmacokinetics of intravenous and oral salbutamol and its sulphate conjugate. *Br J Clin Pharmacol* 1986; 22: 587–93.
5. Lipworth BJ, *et al.* Single dose and steady-state pharmacokinetics of 4 mg and 8 mg oral salbutamol controlled-release in patients with bronchial asthma. *Eur J Clin Pharmacol* 1989; 37: 49–52.
6. Rey E, *et al.* Pharmacokinetics of intravenous salbutamol in renal insufficiency and its biological effects. *Eur J Clin Pharmacol* 1989; 37: 367–9.
7. Hindle M, Chrystyn H. Determination of the relative bioavailability of salbutamol to the lung following inhalation. *Br J Clin Pharmacol* 1992; 34: 311–15.
8. Milliez JM, *et al.* Pharmacokinetics of salbutamol in the pregnant woman after subcutaneous administration with a portable pump. *Obstet Gynecol* 1992; 80: 182–5.
9. Narasimha Murthy S, Hiremath SR. Clinical pharmacokinetic and pharmacodynamic evaluation of transdermal drug delivery systems of salbutamol sulfate. *Int J Pharm* 2004; 287: 47–53.
10. Bønnelykke K, *et al.* Age dependent systemic exposure to inhaled salbutamol. *Br J Clin Pharmacol* 2007; 64: 241–4.

Stereoselectivity. The *R* (-)-enantiomer of salbutamol (levosalbutamol—p. 1213.3) is preferentially metabolised and is therefore cleared from the body more rapidly than the *S*(+)-enantiomer, which lacks bronchodilator activity but may be implicated in some of the adverse effects of salbutamol (see Tolerance, under Adverse Effects, p. 1222.3).

References.

1. Boulton DW, Fawcett JP. Enantioselective disposition of salbutamol in man following oral and intravenous administration. *Br J Clin Pharmacol* 1996; 41: 35–40.
2. Boulton DW, *et al.* Transplacental distribution of salbutamol enantiomers at Caesarian section. *Br J Clin Pharmacol* 1997; 44: 587–90.
3. Lipworth BJ, *et al.* Pharmacokinetics and extrapulmonary β_2 adrenoceptor activity of nebulised racemic salbutamol and its R and S isomers in healthy volunteers. *Thorax* 1997; 52: 849–52.
4. Ward JK, *et al.* Enantiomeric disposition of inhaled, intravenous and oral racemic-salbutamol in man — no evidence of enantioselective lung metabolism. *Br J Clin Pharmacol* 2000; 49: 15–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aircosalm; Airsalbu; Amocasin; Asmatol; Butamol; Cercini†; Duopack; Microterol; Nebutrax; Niblet; Respiret; Salbuden; Salbulin; Salbutol; Salbutral + Aeromed; Salbutral; Venticil; Ventimol; Ventolin; Yontal; Zoom; *Austral.*: Airomir; Asmol; Butamol; Epaq†; Respax†; Ventolin; *Austria*: Buventol†; Sultanol; *Belg.*: Airomir; Docsalbuta†; Ventolin; *Braz.*: Aerodini; Aerogold; Aerogreen; Aerojet; Aerolin; Aerotrat; Asmakil†; Asmaliv; Broncofedrin; Bronconal; Butovent; Dilamol; Neutoss; Prodotamol†; Pulmoflux; Salbutam; Salbutamax†; Tussiliv; *Canad.*: Airomir; Apo-Salvent; Ventolin; *Chile*: Aerolin; Agrilin; Airomir†; Asmavent; Bropil; Butotal; Fesema; Respolin†; Salbutral; Sinasmal; *China*: Da Fen Ke Chuang (达芬科闯); Etinoline (爱纳灵); Hui Bai Shi (惠百释); Kang Er Shu Ning (伉尔纾宁); Lv Ke (律克); Pin Chuan (品川); Sai Bi Shu (赛比舒); Sha Bo Te (沙博特); Ventolin (万托林); Xi Bei Ta (西倍他); *Cz.*: Buventol; Ecosal; Ventilastin; Ventolin; *Denm.*: Airomir; Buventol; Salamol; Salbuvent; Ventolin; Ventoline; Volmax†; *Fin.*: Airomir; Buventol; Ventilastin; Ventoline; *Fr.*: Airomir; Asmasal; Buventol†; Salbumol; Ventexxair†; Ventilastin; Ventoline; *Ger.*: Apsomol†; Broncho Fertiginhalat†; Broncho Inhalat; Bronchospray; Epaq†; Padiamol†; Pentamol; Salbu; Salbubronch; Salbuhexal†; Salbulair; SalbuSandoz†; Sultanol; Ventilastin; *Gr.*: Aerolin; Asthmotrat; Brocofrin; Buventol; Comer; Normobron; Novahaler; Salbumol; Salbunova; Salomol; *Hong Kong*: Asmaliv†; Asmol†; Asthalin; Cybutol; Etinoline; Respolin†; Salamol; Salmol; Syntalin†; Uni-Butamol†; Vantin†; Ventamol†; Ventodisks†; Ventolin; Ventomol†; Volmax†; Zenmolin; *Hung.*: Buventol; Ecosal; Ventolin; *India*: Aerotaz; Asmanil; Asthalin; Bronko; Bronkonat; Brosol; Derihaler; Durasal; Salbetol; Salmaplon; Salsol; *Indon.*: Asmacare; Azmacon; Bronchosal; Brondisal; Buventol†; Fartolin; Glisend†; Hivent; Lasal; Librentin†; Pritasma; Salbron; Salbuven; Suprasma; Ventolin; Volmax†; *Irl.*: Aerolin†; Airomir†; Asmasal; Gerivent; Salamol Steri-Neb; Salamol; Salbuvent; Ventamol; Ventolin; *Israel*: Salbutrim; Ventolin; *Ital.*: Broncovaleas; Ventmax; Ventolin; Volmax†; *Malaysia*: Airomir†; Asthalin; Beatolin; Bonair; Butavent; Buventol; Salamol; Salmax; Ventolin; Volmax; *Mex.*: Apo-Salvent; Assal; Avedox-FC; Azyrol†; Biorenyn; Bonair†; Capacit; Cobamol; Dicoterol†; Exafil; Farmarest; Oladin†; Quinfaval; Salamol†; Salbutalan; Salcomed; Tunxin; Unibron; Ventolin; Volmax†; Zibil; *Neth.*: Airomir; Salamol; Ventolin; *Norw.*: Airomir; Buventol; Ventoline; *NZ*: Airomir; Apo-Salvent†; Asmigen†; Asthalin; Buventol; Respigen; Respolin; Salamol; Salapin; Ventolin; Volmax; *Philipp.*: Activent; Adsal; Aero-Vent; Airomir; Amoltex; Asbunyl; Asfrenon; Asmacaire; Asmalin; Astagen; Asvimol; Axmaxolv; Bioneb; Brytolin; Cletal†; Efamed; Emplusal; Hivent; Librentin†; Meventil; Provexel NS; Prox-S; Resdil; Rhinol; SAL; Salbuflo; Salbumed; Salvex; Sedalin; Venalax XPT; Venalax; Ventar; Vento-Broncho; Ventolin; Ventosal†; Vimonzil; *Pol.*: Buventol; Steri-Neb Salamol†; Velaspir; Ventodisk†; Ventolin; *Port.*: Airomir; Salbulair; Ventilan; *Rus.*: Asthalin (Астмпин); Salamol (Саламол); Salben (Сальбен); Salgim (Сальгим); Saltos (Сальтос); Ventolin (Вентолин); *S.Afr.*: Airomir†; Asthavent; Cybutol; Venteze; Ventolin; Volmax; *Singapore*: Apo-Salvent; Asmol; Asthma Formula; Azmasol; Brethmol; Butahale; Buventol; Medolin; Salbuair; Salmol; Venderol; Ventamol; Ventolin; Volmax; Zenmolin; *Spain*: Aldobronquial; Buto Asma†; Buto-Air; Respiroma†; Salbuair; Ventilastin†; Ventoaldo; Ventolin; *Swed.*: Airomir; Buventol; Sabufarm; Ventilastin; Ventoline; *Switz.*: Ecovent; Salamol; Ventolin; *Thai.*: Aeromol; Antomol; Asmasal; Asmol; Asthalin; Asthamol; Asthmolin; Bronchosol; Butamol†; Buto Asma; Butovent†; Buventol; Durasal; Naso; Sabumol; Salbusian; Salbutac; Saldal; Saldol; Salmol; Salvent; Solia; Sulbuta-N; Venterol; Ventolin; Violin; Zalbu; Zebu†; *Turk.*: Asthavent; Butovent; Salbulin; Salbutam; Salbutol; Vent-o-sal; Ventodisk; Ventolin; Volmax; *UAE*: Butalin; *UK*: Airomir; Asmasal; Pulvinal Salbutamol; Salamol; Salapin; Salbulin; Ventmax; Ventolin; *Ukr.*: Salamol-Eko (Саламол-Эко); Ventolin (Вентолин); *USA*: Accuneb; ProAir; Proventil; Ventolin; VoSpire; *Venez.*: Asthalin; Butoas; Salbulis; Salbumed; Salburol; Salbutan.

Multi-ingredient Preparations. *Arg.*: Beclasma; Butocort; Butosol†; Combivent; Iprasalb; Salbutol Beclo; Salbutral AC; Ventide; *Austral.*: Combivent; *Austria*: Combivent; *Belg.*: Combivent; Nebu-Iprasal; *Braz.*: Aerocort S; Aeroflux; Aerotide; Broncocilin; Clenil Compositum; Combivent; *Canad.*: Combivent; Gen-Combo†; Mylan-Combo; ratio-Ipra Sal; *Chile*: Aero-Plus; Aerosoma†; Asmavent-B; Belomet; Butocort; Butotal B; Combivent; Herolan Aerosol; Salbutral AC; Ventide; *China*: Combivent (可必特); Ren Shu (仁舒); Shun Qi (顺奇); Yi Xi Qing (昌息晴); *Denm.*: Combipramol†; Combivent; Ipramol; Sapimol; *Fin.*: Atrodual; Ipramol; Redol Comp; Salipra†; *Gr.*: Berovent; Demoren; Ipramol; *Hong Kong*: Combivent; Ipramol;

Uni-Butamol Expectorant†; Ventidet†; Ventolin Expectorant†; *India*: Aerocort; Aeromist; Aerotide; Aerovent; Airomol; Albutamol; Alernyl-B; Alkarex-PD; Amborex-GS; Ambrex; Ambril-S; Ambril-SG; Ambro PD; Ambro S; Ambro TS; Ambrodil-S; Ambrogen-S; Ambrolax-PD; Ambrolite-S; Ambrolite-ST; Ambros-GM; Ambrosol; Amcare; Amcol; Amrolite 2S; Asmatide-BR; Ast-Ex; Asthacrom†; Asthalin AX; Asthalin Expectorant; Asthavent-BR; Asthos; Axalin-AX†; Axalin; Axol Plus; Benylin E; Brex-S; Brodil; Bronchilet; Broncophyl Plus; Broncordil P; Bronko Plus; Bronkosyrup-EX; Bronmix; Brox; Budesal; C-Cold; Carbasma; Combimist; Coriminic X; Derisone; Duolin; Durabec; Durasalyn; Eascof; Efelin-PD; Efelin; Elkof; Elkuf; Elsol-S; Eto-Salbetol; Exituss; Exol; Expectus; Instaryl-P; Instaryl; Kofarest; LCP; Mastifen-S; Mexol-G; Mituss-AX; Mituss-BR; Muco Asthalin; Mucobar-S; Mucoline; Mucoresp; Neorex; Okaril; Pulmo-Rest Expectorant†; Pulmo-Rest; Theo-Asthalin; Ventorlin Exp; *Indon.*: Combivent; Partolin Expectorant; Lasal Expectorant; Proventol Expectorant; Salbron Expectorant; Salbuven Expectorant; Teosal; Ventide†; Ventolin Expectorant; *Irl.*: Combineb; Combivent; Ipramol; *Ital.*: Almeida; Biwind; Breva; Clenil Compositum; Naos; Pienaer; *Malaysia*: Aerocort; Combivent; Duolin; Ipramol; Salbutamol Expectorant; Ventolin Expectorant†; *Mex.*: Aeroflux; Apomuxol; Broxol Air; Combivent; Dinolan; Flamebin; Fluvicil; Fluxol; Fultac Mucoflux; Musaldox; Neumyn-AS; Removil; Salamflux; Sibilex; Solbotex; Ulax-C; Ventide; *Neth.*: Combipramol†; Combivent; Ipramol; *NZ*: Combivent; Duolin; *Philipp.*: Adsal Plus; Asbunyl Plus; Asfrenon GF; Asmalin Broncho; Broncaire Expectorant; Bronchospec; Brytolin; Clarituss Plus; Combipul; Combivent; Duavent; Efamed Plus; Hicaryl; Histaril; Neovent†; Pecof; Pediavent; Pulmodual; Pulmovent; Rhinol Plus; Salbumed Plus; Salvex XP; SGX; Solmux-Broncho (Reformulated); Ventar EXP; Vento-Broncho G; Ventolin Expectorant; Venzadril; *Port.*: Combivent; Ipramol; Propavente; *Rus.*: Ascoril Expectorant (Аскорил Экспекторант); Biasten (Биастен); Ipramol (Ипрамол); Jocet (Джосет); Kasnol (Кашнол); *S.Afr.*: Adco-Combineb; Combivent; Duolin; Duro-Tuss†; *Singapore*: Combivent; *Spain*: Butosol; Combiprasal; *Swed.*: Combivent; Ipramol; Sapimol; *Switz.*: Dospir; Ipramol; *Thai.*: Almasal; Asmol Expectorant; Beclosal; Bioventt; Clenil Compositum†; Combivent; Royalin; Sabumol Ex; Salmol Expectorant; Ventolin Expectorant†; *Turk.*: Clenil Kompoze; Combivent; Ventide; *UK*: Combivent; Ipramol; *Ukr.*: Ascoril Expectorant (Аскорил Экспекторант)†; Joset (Джосет); Salbroxol (Сальброксол); *USA*: Combivent; DuoNeb; *Venez.*: Aerocort; Aeroflux; Beclosal; Broxodin; Butosol; Combivent; Duolin; Ipralin; Venticort; Ventide.

Pharmacopoeial Preparations

BP 2014: Prolonged-release Salbutamol Capsules; Prolonged-release Salbutamol Tablets; Salbutamol Inhalation Powder, predispensed; Salbutamol Inhalation Powder; Salbutamol Injection; Salbutamol Nebuliser Solution; Salbutamol Oral Solution; Salbutamol Pressurised Inhalation; Salbutamol Tablets;
USP 36: Albuterol Tablets.

Salmeterol Xinafoate

(BANM, USAN, rINNM) ⊗

GR-33343G; Salmaterol Xinafoate; Salmeterol 1-Hydroxy-2-naphthoate; Salmeterol Ksinafoat; Salmétérol, Xinafoate de; Salmeterol, xinafoato de; Salmeteroli Xinafoas; Salmeteroliksinafoaatti; Salmeterolio ksinafoatas; Salmeterolxinafoat; Salmeterol-xinafoat; Sameterolxinafoat; Xinafoato de Salmeterol; Салметерола Ксинафоат.

(RS)-5-[1-Hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl] salicyl alcohol 1-hydroxy-2-naphthoate.

$C_{25}H_{37}NO_4.C_{11}H_8O_3$=603.8

CAS — 89365-50-4 (salmeterol); 94749-08-3 (salmeterol xinafoate).

ATC — R03AC12.

ATC Vet — QR03AC12.

UNII — 6EW8Q962A5.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Salmeterol Xinafoate). A white or almost white powder. Practically insoluble in water; slightly soluble in dehydrated alcohol; soluble in methyl alcohol. Protect from light.

USP 36: (Salmeterol Xinafoate). A white or off-white powder. Practically insoluble in water (pH 8.0) and in saline solution (0.9% w/w); slightly soluble in alcohol, in isopropyl alcohol, and in chloroform; soluble in methyl alcohol. Store in airtight containers at a temperature not exceeding 30 degrees.

Uses and Administration

Salmeterol is a direct-acting sympathomimetic with beta-adrenoceptor stimulant activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). When given by inhalation, salmeterol acts as a bronchodilator. The onset of action is about 10 to 20 minutes but the full effect may not be apparent until after several doses. Unlike short-acting $beta_2$ agonists (see Salbutamol, p. 1220.2), salmeterol is therefore not suitable for the symptomatic relief of an acute attack of bronchospasm. However, it is long-acting with a duration of action of about 12 hours and is indicated where the regular use of a long-acting $beta_2$ agonist is required for persistent reversible airways obstruction, as in chronic asthma or in some patients with chronic obstructive pulmonary disease. It may be useful in protecting against nocturnal and exercise-induced asthma attacks. Short-acting $beta_2$ agonists (on an as-required basis) and regular anti-inflammatory therapy should continue to be used.

Salmeterol is used in the form of the xinafoate; doses are expressed in terms of the equivalent amount of salmeterol; salmeterol xinafoate 1.45 micrograms is equivalent to about 1 microgram of salmeterol.

The usual dose is 50 micrograms of salmeterol twice daily from a metered-dose aerosol or dry powder inhaler; if necessary, up to 100 micrograms may be inhaled twice daily. For doses of salmeterol used in children, see Administration in Children, below.

Reviews.

1. Meyer JM, *et al.* Salmeterol: a novel, long-acting $beta_2$-agonist. *Ann Pharmacother* 1993; 27: 1478–87.
2. Bennett J, Tattersfield A. Drugs in focus: 15. Salmeterol. *Prescribers' J* 1995; 35: 84–8.
3. Adkins JC, McTavish D. Salmeterol: a review of its pharmacological properties and clinical efficacy in the management of children with asthma. *Drugs* 1997; 54: 331–54.
4. Jackson CM, Lipworth B. Benefit-risk assessment of long-acting $beta_2$-agonists in asthma. *Drug Safety* 2004; 27: 243–70.
5. Sovani MP, *et al.* A benefit-risk assessment of inhaled long-acting $beta_2$-agonists in the management of obstructive pulmonary disease. *Drug Safety* 2004; 27: 689–715.

Administration in children. For persistent reversible airways obstruction that requires regular bronchodilatation, including nocturnal asthma and prevention of exercise-induced asthma, children aged 4 to 12 years may be given 50 micrograms of salmeterol twice daily by inhalation.

Asthma. Salmeterol is a long-acting $beta_2$ agonist (duration of action about 12 hours). Guidelines on the management of asthma, see p. 1195.2, generally recommend that salmeterol should be reserved for use in patients with chronic asthma who have already progressed to inhaled corticosteroids; it is not a substitute for corticosteroids. Most evidence suggests that, apart from in severe exacerbations, adding a long-acting $beta_2$ agonist to standard dose inhaled corticosteroid therapy may be more effective than increasing the dose of corticosteroid, or than combining a corticosteroid and an anti-leukotriene drug. Salmeterol may also be useful in controlling persistent nocturnal asthma or preventing exercise-induced attacks. There is some evidence that after prolonged use, duration of protection against exercise-induced bronchoconstriction is reduced (see Tolerance, p. 1225.2).

References.

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2. Shrewsbury S, *et al.* Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). *BMJ* 2000; 320: 1368–73.
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5. Heyneman CA, *et al.* Fluticasone versus salmeterol/low-dose fluticasone for long-term asthma control. *Ann Pharmacother* 2002; 36: 1944–9.
6. Bateman ED, *et al.* Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. *Am J Respir Crit Care Med* 2004; 170: 836–44.
7. Weiler JM, *et al.* Effect of fluticasone/salmeterol administered via a single device on exercise-induced bronchospasm in patients with persistent asthma. *Ann Allergy Asthma Immunol* 2005; 94: 65–72.
8. Gibson PG, *et al.* Long-acting beta2-agonists as an inhaled corticosteroid-sparing agent for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 15/01/08).
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12. The American Lung Association Asthma Clinical Research Centers. Randomized comparison of strategies for reducing treatment in mild persistent asthma. *N Engl J Med* 2007; 356: 2027–39.
13. Lasserson TJ, *et al.* Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 07/05/10).
14. Ni Chroinin M, *et al.* Addition of long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 17/03/10).
15. Ducharme FM, *et al.* Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2010 (accessed 03/08/10).

Chronic obstructive pulmonary disease. Guidelines indicate that long-acting $beta_2$ agonists such as salmeterol may be used for maintenance therapy in moderate and severe chronic obstructive pulmonary disease (see p. 1199.1). Improvement in lung function and symptoms has been seen in such patients after regular treatment with inhaled salmeterol;[1-3] a reduction in exacerbations has also been seen.[4] Additional benefit has been reported from the use of salmeterol with inhaled corticosteroids.[5-7]

1. Boyd G, *et al.* An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1997; 10: 815–21.
2. Mahler DA, *et al.* Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest* 1999; 115: 957–65.
3. Stockley RA, *et al.* Addition of salmeterol to existing treatment in patients with COPD: a 12 month study. *Thorax* 2006; 61: 122–8.
4. Appleton S, *et al.* Long-acting beta2-agonists for poorly reversible chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 15/01/08).
5. Calverley P, *et al.* Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003; 361: 449–56. Correction. *ibid.*: 1660.
6. Keating GM, McCormack PL. Salmeterol/fluticasone propionate: a review of its use in the treatment of chronic obstructive pulmonary disease. *Drugs* 2007; 67: 2383–2405.
7. Kardos P, *et al.* Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 175: 144–9.

Adverse Effects and Precautions

As for Salbutamol, p. 1221.3. Inhalation of salmeterol may be associated with paradoxical bronchospasm, and it should not be used in patients who are not also receiving an inhaled corticosteroid. Very rarely, arthralgia has been reported with salmeterol use.

Salmeterol is not appropriate for the treatment of acute bronchospasm or for patients whose asthma is deteriorating.

Effects on the cardiovascular system. A pooled analysis[1] of safety data from 7 studies of salmeterol in chronic obstructive pulmonary disease found no evidence of an increased risk of cardiovascular adverse effects. The duration of these studies had ranged from 12 weeks to 1 year. For further discussion of $beta_2$ agonist use (including salmeterol) and the risk of cardiac events such as myocardial infarction, see Effects on the Heart, under Salbutamol, p. 1222.1

1. Ferguson GT, *et al.* Cardiovascular safety of salmeterol in COPD. *Chest* 2003; 123: 1817–24.

Effects on the respiratory system. Transient paradoxical bronchoconstriction with breathlessness, wheeze, or cough has been reported in 6 asthmatic patients after inhalation of salmeterol from a metered-dose aerosol but not after inhalation of the dry powder formulation by diskhaler.[1] The fluorocarbon propellants in the metered-dose aerosol were suspected as the irritants causing bronchoconstriction.

1. Wilkinson JRW, *et al.* Paradoxical bronchoconstriction in asthmatic patients after salmeterol by metered dose inhaler. *BMJ* 1992; 305: 931–2.

Effects on the skin. Urticarial rash associated with inhaled salmeterol, of which the propellant was not the cause, has been reported. Although many urticarial reactions and a variety of rashes had been attributed to beta-agonist therapy their reproducibility had not always been documented.[1]

1. Hatton MQF, *et al.* Salmeterol rash. *Lancet* 1991; 337: 1169–70.

Increased mortality. Interim results from a large controlled study (SMART)[1] designed to evaluate the safety of salmeterol in patients with *asthma*, found a small but statistically significant increase in respiratory-related and asthma-related deaths or life-threatening episodes in the total population receiving salmeterol compared with placebo. This imbalance occurred mainly in the African-American subpopulation, and combined with difficulties in enrolment, led to early termination of the study. Various factors may have influenced the differences in outcomes seen with salmeterol; greater disease severity was noted at baseline in the African-American subgroup compared with Caucasian subjects, and nearly half of all participants were not receiving inhaled corticosteroids.

A subsequent meta-analysis[2] of 19 placebo-controlled studies of patients with asthma who were taking the long-acting $beta_2$ agonists salmeterol or formoterol (see p. 1209.2), reported an increased risk of hospitalisation for an asthma exacerbation, life-threatening asthma attacks, and asthma-related deaths compared with placebo. A subgroup analysis that examined studies in which more than 75% of patients were also receiving inhaled corticosteroids also found an increased risk of hospital admission. The applicability of this review to therapy as recommended by current guidelines has been questioned,[3] as many of the studies included in the primary analysis did not require inhaled corticosteroids to be used, and studies which compared different asthma maintenance regimens were excluded because they were not placebo-controlled.

Systematic reviews of regular treatment with salmeterol[4] or formoterol[5] for chronic asthma found an increased risk of

serious non-fatal adverse effects compared with placebo. In contrast, subsequent reviews of regular treatment with salmeterol[6] or formoterol[7] plus inhaled corticosteroids found no difference in serious adverse effects when compared with inhaled corticosteroids although results were not sufficient to conclude that there was no increased risk. Additionally, the number of deaths was too small to allow a firm conclusion to be reached on the effect of long-acting beta$_2$ agonists on mortality. A direct toxic effect of beta$_2$ agonists,[7] concomitant asthma treatments and adherence to treatment,[8,9] differences in baseline disease severity,[1,8] racial or genetic factors,[1] polymorphism,[10] tolerance,[10,11] and masking of underlying airway inflammation by long-acting beta$_2$ agonists[10] have all been proposed as possible explanations for the increased risk of adverse outcomes reported with long-acting beta$_2$ agonists.

In contrast to the above studies, a meta-analysis[12] of 66 manufacturer-sponsored studies involving 20 966 patients with persistent asthma, suggested that the addition of salmeterol to inhaled corticosteroids did not alter the risk for asthma-related hospitalisation compared with inhaled corticosteroids alone, although asthma-related intubation or death was too infrequent to draw conclusions. In addition, a case-control study[13] that included 532 patients under age 65 who had died from asthma, matched with 532 controls with a hospital admission for asthma, found no evidence of adverse effects on mortality with medium to long-term use of inhaled long-acting beta$_2$ agonists. An earlier observational cohort study also found no evidence that salmeterol contributed to deaths reported from asthma.[14]

Current asthma guidelines advocate use of a long-acting beta$_2$ agonist in addition to inhaled corticosteroids, and not as monotherapy, see Management of Asthma, p. 1195.2. A review[15] by the UK MHRA concluded that:

- epidemiological data indicated that since the introduction of long-acting beta agonists there had been a reduction in asthma-related hospitalisations in adolescents and a decrease in asthma-related mortality in all ages.
- data from controlled clinical study did not reflect the safety concern from postmarketing studies, possibly due to more consistent use of corticosteroids in controlled settings
- the data supported the use of long-acting beta agonists with inhaled corticosteroids consistent with the UK guidelines on the management of asthma and that to aid compliance in the concomitant use of a corticosteroid, a combination inhaler should be used when appropriate

A systematic review in patients with stable, moderate-to-severe *chronic obstructive pulmonary disease* found that the use of long-acting beta$_2$ agonists was not associated with a higher rate of respiratory-related mortality compared with placebo.[16]

1. Nelson HS, *et al.* The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006; 129: 15–26.
2. Salpeter SR, *et al.* Meta-analysis: effect of long-acting β-agonists on severe asthma exacerbations and asthma-related deaths. *Ann Intern Med* 2006; 144: 904–12.
3. Ernst P, *et al.* Safety and effectiveness of long-acting inhaled β-agonist bronchodilators when taken with inhaled corticosteroids. *Ann Intern Med* 2006; 145: 692–4.
4. Cates CJ. Cates MJ. Regular treatment with salmeterol for chronic asthma: serious adverse events. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 12/08/09).
5. Cates CJ, *et al.* Regular treatment with formoterol for chronic asthma: serious adverse events. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 12/08/09).
6. Cates CJ, *et al.* Regular treatment with salmeterol and inhaled steroids for chronic asthma: serious adverse events. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 12/08/09).
7. Cates CJ, *et al.* Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 12/08/09).
8. Glasgroth J. The role of long-acting β-agonists in the management of asthma: analysis, meta-analysis, and more analysis. *Ann Intern Med* 2006; 144: 936–7.
9. Nelson HS, Dorinsky PM. Safety of long-acting β-agonists. *Ann Intern Med* 2006; 145: 706.
10. Currie GP, *et al.* Long-acting β$_2$-agonists in asthma: not so SMART? *Drug Safety* 2006; 29: 647–56.
11. Weinberger M, Abu-Hasan M. Life-threatening asthma during treatment with salmeterol. *N Engl J Med* 2006; 355: 852–3.
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15. MHRA/CHM. Long-acting β$_2$ agonists for asthma: review. *Drug Safety Update* 2008: 1 (6): 9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20335106&RevisionSelectionMethod=LatestReleased (accessed 22/05/08)
16. Rodrigo GJ, *et al.* Safety of long-acting β-agonists in stable COPD: a systematic review. *Chest* 2008; 133: 1079–87.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies salmeterol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Tolerance. As with short-acting beta$_2$ agonists (see Salbutamol, p. 1222.3), there is evidence that regular use of long-acting beta$_2$ agonists such as salmeterol produces tachyphylaxis to their protective effect against bronchoconstriction, as provoked by stimuli such as allergen, methacholine, or exercise.[1-4] The authors of a study of the long-term effect of salmeterol on exercise-induced asthma concluded that the decreased bronchoprotective effect over time was due to a decrease in duration of action (to less than 9 hours) rather than tachyphylaxis,[5] but this interpretation was criticised.[6,7]

There is also some evidence to suggest that symptomatic relief by short-acting beta$_2$ agonists is significantly reduced by regular use of long-acting beta$_2$ agonists.[8,9] Receptor downregulation, induced by regular use of a long-acting beta$_2$ agonist, has been suggested as the mechanism for this reduction in response and may lead to patients requiring higher doses of beta$_2$ agonists to attain relief from an acute asthma attack.[9,10] One study suggested that the greater tachyphylaxis to short-acting beta$_2$ agonists seen with salmeterol compared with formoterol might represent the expression of partial antagonism by salmeterol at beta$_2$ receptors.[8] Whatever the mechanism, the reduced bronchoprotective effect is perhaps more of a concern with long-acting beta$_2$ agonists, since, unlike the short-acting beta$_2$ agonists, their use on a regular basis is recommended.[11] See also Beta$_2$ Agonists, under Interactions of Salbutamol, p. 1223.1.

1. Cheung D, *et al.* Long-term effects of a long-acting β$_2$-adrenoceptor agonist, salmeterol, on airway hyperresponsiveness in patients with mild asthma. *N Engl J Med* 1992; 327: 1198–1203.
2. Bhagat R, *et al.* Rapid onset of tolerance to the bronchoprotective effect of salmeterol. *Chest* 1995; 108: 1235–9.
3. Booth H, *et al.* Salmeterol tachyphylaxis in steroid treated asthmatic subjects. *Thorax* 1996; 51: 1100–4.
4. Simons FER, *et al.* Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. *Pediatrics* 1997; 99: 655–9.
5. Nelson JA, *et al.* Effect of long-term salmeterol treatment on exercise-induced asthma. *N Engl J Med* 1998; 339: 141–6.
6. Aziz I, Lipworth BJ. Exercise-induced asthma. *N Engl J Med* 1998; 339: 1783.
7. Dickey BF, Adachi R. Exercise-induced asthma. *N Engl J Med* 1998; 339: 1783–4.
8. van Veen A, *et al.* A comparison of salmeterol and formoterol in attenuating airway responses to short-acting β$_2$-agonists. *Pulm Pharmacol Ther* 2003; 16: 153–61.
9. Haney S, Hancox RJ. Tolerance to bronchodilation during treatment with long-acting beta-agonists, a randomised controlled trial. Abridged version: *Respir Res* 2005; 6: 107. Full version: http://respiratory-research.com/content/6/1/107 (accessed 15/01/08)
10. Lipworth BJ. Airway subsensitivity with long-acting β$_2$-agonists: is there cause for concern? *Drug Safety* 1997; 16: 295–308.
11. Abisheganaden J, Bonshey HA. Long-acting inhaled β$_2$-agonists and the loss of "bronchoprotective" efficacy. *Am J Med* 1998; 104: 494–7.

Interactions

As for Salbutamol, p. 1223.1.

Salmeterol is metabolised by the cytochrome P450 isoenzyme CYP3A4, and use with oral ketoconazole has resulted in an increased systemic exposure to inhaled salmeterol with the potential to increase adverse effects; similar interactions could occur with other potent inhibitors of CYP3A4. Licensed product information suggests that salmeterol and ketoconazole should not be used together. Use of salmeterol with erythromycin, a moderate inhibitor of CYP3A4, did not have a significant effect on exposure to salmeterol.

For a study suggesting a decreased effect of salbutamol in patients receiving salmeterol, as well as a report of additive effects, see Beta$_2$ Agonists under Interactions of Salbutamol, p. 1223.1.

Pharmacokinetics

After inhalation of therapeutic doses of salmeterol, only low concentrations occur in the plasma. Salmeterol is metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 to α-hydroxy-salmeterol, which is eliminated mainly in the faeces.

Reviews.

1. Cazzola M, *et al.* Clinical pharmacokinetics of salmeterol. *Clin Pharmacokinet* 2002; 41: 19–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Serevent; *Austral.*: Serevent; *Austria*: Serevent; *Belg.*: Serevent; *Braz.*: Serevent; *Canad.*: Serevent; *Chile*: Serevent; Xemos; *China*: Ping Te (平特); Qitai (祺泰); Serevent (施立稳); Si Duo Mi (司多米); *Cz.*: Serevent; *Denm.*: Serevent; *Fin.*: Serevent; *Fr.*: Serevent; *Ger.*: Aeromax†; Serevent; *Gr.*: Salment; Serevent; *Hong Kong*: Serevent; *Hung.*: Serevent; *India*: Azrol; Salmeter; Serobid; *Indon.*: Serevent†; *Irl.*: Serevent; *Israel*: Serevent; *Ital.*: Arial; Salmetedur; Serevent; *Jpn*: Serevent; *Malaysia*: Serevent†; *Mex.*: Serevent; *Neth.*: Serevent; *Norw.*: Serevent; *NZ*: Serevent; *Philipp.*: Serevent†; *Pol.*: Pulmoterol; Serevent; *Port.*: Dilamax; Serevent; Ultrabeta; *Rus.*: Serevent (Серевент); *S.Afr.*: Serevent; *Singapore*: Serevent; *Spain*: Beglan; Betamican; Inaspir; Serevent; *Swed.*: Serevent; *Switz.*: Serevent; *Thai.*: Serevent; *Turk.*: Astmerole; Serevent; *UK*: Neovent; Serevent; *USA*: Serevent; *Venez.*: Salspray; Serevent.

Multi-ingredient Preparations. *Arg.*: Crivanil Plus; Flutivent; Lirtodac Plus; Neumotide; Proair Bronquial; Seretide; *Austral.*: Seretide; *Austria*: Seretide; Viani; *Belg.*: Seretide; Viani†; *Braz.*: Seretide; *Canad.*: Advair; *Chile*: Aerometrol Plus; Aurituss; Brexotide; Flunacross-S; Fluxamol; Seretide; *China*: Seretide (舒利迭); *Cz.*: Duaspir†; Seretide; *Denm.*: Aliflus†; Seretaide; Seretide; *Fin.*: Seretide; Viani; *Fr.*: Seretide; *Ger.*: Atmadisc; Viani; *Gr.*: Byany; Rolenium; Seretide; Viani; *Hong Kong*: Seretide; *Hung.*: Seretide; Thoreus; *India*: Combitide; Esiflo; Forair; Seretide; Seroflo; *Indon.*: Seretide; *Irl.*: Seretide; Viani; *Israel*: Seretide; *Ital.*: Aliflus; Seretide; *Malaysia*: Seretide; *Mex.*: Flixovent; Seretide; *Neth.*: Aliflus; Brisair†; Seretide; *Norw.*: Seretide; *NZ*: Seretide; *Philipp.*: Salmeflo; Seretide; *Pol.*: Seretide; *Port.*: Brisomax; Maizar; Seretaide; Veraspir; *Rus.*: Seretide (Серетид); Tevacomb (Тевакомб); *S.Afr.*: Foxair; Sereflo; Seretide; *Singapore*: Seretide; *Spain*: Anasma; Brisair; Inaladuo; Plusvent; Seretide; *Swed.*: Seretide; *Switz.*: Seretide; *Thai.*: Seretide; Seroflo; *Turk.*: Respiro; Seretide; *UK*: Seretide; *Ukr.*: Seretide (Серетид); *USA*: Advair; *Venez.*: Seretide.

Seratrodast *(USAN, rINN)*

A-73001; AA-2414; Abbott-73001; ABT-001; Seratrodast; Seratrodastum; Сератродаст.

(±)-2,4,5-Trimethyl-3,6-dioxo-7-phenyl-1,4-cyclohexadiene-1-heptanoic acid.

$C_{22}H_{26}O_4$=354.4

CAS — 112665-43-7; 103186-19-2

ATC — R03DX06.

ATC Vet — QR03DX06.

UNII — 4U58JM421N.

Profile

Seratrodast is a thromboxane A$_2$ antagonist that is reported to reduce airway hyperresponsiveness. It is given orally in the prophylactic management of asthma (p. 1195.2), in single doses of 80 mg in the evening after food.

Adverse effects include gastrointestinal disturbances, drowsiness, headache, palpitations, and hepatitis. Hepatic function should be monitored and the drug should be withdrawn if hypersensitivity reactions such as rashes and pruritus occur, or if there is elevation of liver enzyme values. Seratrodast should be used with care in patients with pre-existing hepatic impairment. It is not suitable for the treatment of an acute asthmatic attack.

References.

1. Tamaoki J, *et al.* Effect of a thromboxane A$_2$ antagonist on sputum production and its physicochemical properties in patients with mild to moderate asthma. *Chest* 2000; 118: 73–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Changnuo (畅诺); Quan Kang Nuo (全康诺); *Jpn*: Bronica.

Sodium Cromoglicate *(BANM, rINNM)*

Cromoglicate de Sodium; Cromoglicato de sodio; Cromoglicato disódico; Cromolyn Sodium (USAN); Dinatrii Cromoglicas; Dinatrium-chromoglykát; Disodium Cromoglycate; FPL-670; Natrii Cromoglicas; Natrio kromoglikatas; Natriumchromoglicat; Natriumcromoglicat; Natriumkromoglikaatti; Natriumkromoglikat; Natrium-kromoglikát; Sodium, cromoglicate de; Sodium Cromoglycate; Sodyum Kromoglikat; Натрий Кромоглицинат.

Disodium 4,4′-dioxo-5,5′-(2-hydroxytrimethylenedioxy)di(4*H*-chromene-2-carboxylate).

$C_{23}H_{14}Na_2O_{11}$=512.3

CAS — 16110-51-3 (cromoglicic acid); 15826-37-6 (sodium cromoglicate).

ATC — A07EB01; D11AX17; R01AC01; R03BC01; S01GX01.

ATC Vet — QA07EB01; QD11AH03; QR01AC01; QR03BC01; QS01GX01.

UNII — O2WXR10PK.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Sodium Cromoglicate). A white or almost white, hygroscopic, crystalline powder. Soluble in water; practically insoluble in alcohol. Store in airtight containers. Protect from light.

USP 36: (Cromolyn Sodium). A white, odourless, hygroscopic, crystalline powder. Soluble in water; insoluble in alcohol and in chloroform. Store in airtight containers.

Uses and Administration

Sodium cromoglicate is used for the prevention of allergic reactions. Although its precise mode of action remains uncertain, it is believed to act mainly by preventing release of mediators of inflammation from sensitised mast cells through stabilisation of mast-cell membranes. It has no direct antihistamine or anti-inflammatory action.

Sodium cromoglicate can prevent the asthmatic response to a variety of allergic and non-allergic stimuli. It is used in the management of chronic asthma that cannot be managed with inhaled beta$_2$ agonists alone; it is not used for acute attacks of asthma.

Sodium cromoglicate is also used in the prophylaxis and treatment of seasonal and perennial allergic rhinitis and allergic conditions of the eye including acute and chronic allergic conjunctivitis and vernal keratoconjunctivitis. It has been given orally, with dietary restriction, for the prevention of food allergies, and is also used in the treatment of mastocytosis.

It is important that the regular use of sodium cromoglicate is maintained, both in the prophylactic control of asthma and in the management of other allergic conditions. Beneficial effects may take several weeks to become established.

In the prophylaxis of **asthma**, sodium cromoglicate is given by inhalation as a nebulised solution or from a metered-dose aerosol. The usual dose as nebulised solution is 20 mg by inhalation 4 times daily increased, if necessary, to 6 or 8 times daily. Once the asthma has been stabilised it may be possible to reduce the dosage. In some countries, sodium cromoglicate is available in different strengths of metered-dose aerosol. Using a metered-dose aerosol providing 5 mg per inhalation, the usual dose is 10 mg four times daily, increased to 6 to 8 times daily if necessary; it may be possible to reduce the dosage to 5 mg four times daily once the asthma has been stabilised. Additional doses may be taken before exercise. Metered-dose aerosols providing 1 mg per inhalation are also available. The usual dose is 2 mg four times daily, which can be doubled if necessary. The adequacy of the lower dosage has been questioned (see under Administration, below).

Inhalation of sodium cromoglicate may cause bronchospasm; separate inhalation of a beta$_2$ agonist such as salbutamol a few minutes beforehand should prevent this. Use of a combination product containing a beta$_2$ agonist is not recommended as this is liable to be used inappropriately for relief of bronchospasm rather than for its prophylactic effect.

For the prophylaxis of **allergic rhinitis**, sodium cromoglicate solution can be given as a nasal spray. A 4% spray that delivers about 5 mg per actuation may be given as one spray into each nostril 2 to 4 times daily. Prophylactic treatment for seasonal allergic rhinitis should begin 2 to 3 weeks before exposure to the offending allergen and should continue throughout the season. In **allergic conjunctivitis** and **vernal keratoconjunctivitis**, sodium cromoglicate is used as drops of 2 or 4%, applied 4 to 6 times daily.

In **food allergy** and in **mastocytosis**, sodium cromoglicate may be given in oral doses of 200 mg four times daily before meals. If satisfactory control is not achieved within 2 to 3 weeks the dosage may be doubled, but should not exceed 40 mg/kg daily; a reduction in dosage may be possible once symptoms have been controlled.

For details of doses in children, see Administration in Children below.

Action. Sodium cromoglicate has a range of actions at cellular level that may be important for its protective effect in asthma. It is known as a mast cell stabiliser that inhibits the release of histamine and other inflammatory mediators from sensitised mast cells. Other reported actions include a direct effect on airway nerves[1,2] and antagonism[3] of substance P, which ties up with its inhibition of the effects of platelet activating factor (PAF).[4,5]

There have been a few reports[6-8] of sodium cromoglicate producing bronchodilatation. However, in practice other drugs with accepted bronchodilating activity are used for this effect in asthma treatment schedules, see p. 1195.2.

1. Barnes PJ. Asthma as an axon reflex. *Lancet* 1986; i: 242–5.
2. Dixon M, *et al.* The effects of sodium cromoglycate on lung irritant receptors and left ventricular cardiac receptors in the anaesthetized dog. *Br J Pharmacol* 1979; 67: 569–74.
3. Page C. Sodium cromoglycate, a tachykinin antagonist? *Lancet* 1994; 343: 70.
4. Morley J, *et al.* The platelet in asthma. *Lancet* 1984; ii: 1142–4.
5. Morley J. PAF and airway hyperreactivity: prospects for novel prophylactic anti-asthma drugs. In: *PAF, Platelets, and Asthma*, Basel, Birkhäuser Verlag, 1987: 87–95.
6. Horn CR, *et al.* Bronchodilator effect of disodium cromoglycate administered as a dry powder in exercise induced asthma. *Br J Clin Pharmacol* 1984; 18: 798–801.
7. Weiner P, *et al.* Bronchodilating effect of cromolyn sodium in asthmatic patients at rest and following exercise. *Ann Allergy* 1984; 53: 186–8.
8. Yuksel B, Greenough A. Bronchodilator effect of nebulized sodium cromoglycate in children born prematurely. *Eur Respir J* 1993; 6: 387–90.

Administration. The efficacy of sodium cromoglicate 2 mg four times daily by metered-dose aerosol inhaler has been shown by controlled studies in adults and children with asthma.[1-3] However, although sodium cromoglicate 2 mg by inhalation from a metered-dose aerosol was reported[4] to be as effective as 20 mg inhaled as powder, the tenfold difference in dosage has been questioned,[7] and others have reported contrary results.[8,9] It has been suggested that an aerosol supplying 5 mg per metered dose (see Uses and Administration, above) would be preferable.[10] In a comparison of single-dose pretreatment from metered-dose inhalers, sodium cromoglicate 10 mg (2 X 5 mg puffs) was as effective as beclometasone dipropionate 200 micrograms in inhibiting bronchial responsiveness to histamine.[11]

Care is required if inhaled sodium cromoglicate is given via a spacer device; evidence suggests that these may greatly influence the amount of drug delivered, reducing it to one-third of the dose delivered by inhaler actuation in some cases.[12]

1. Geller-Bernstein C, Levin S. Sodium cromoglycate pressurised aerosol in childhood asthma. *Curr Ther Res* 1983; 34: 345–9.
2. Wheatley D. Sodium cromoglycate in aerosol form in regular users of bronchodilator drugs. *Curr Med Res Opin* 1983; 8: 333–7.
3. Rubin AE, *et al.* The treatment of asthma in adults using sodium cromoglycate pressurized aerosol: a double-blind controlled trial. *Curr Med Res Opin* 1983; 8: 353–8.
4. Blumenthal MN, *et al.* A multicenter evaluation of the clinical benefits of cromolyn sodium aerosol by metered-dose inhaler in the treatment of asthma. *J Allergy Clin Immunol* 1988; 81: 681–7.
5. Selcow JE, *et al.* Clinical benefits of cromolyn sodium aerosol (MDI) in the treatment of asthma in children. *Ann Allergy* 1989; 62: 195–9.
6. Latimer KM, *et al.* Inhibition by sodium cromoglycate of bronchoconstriction stimulated by respiratory heat loss: comparison of pressurised aerosol and powder. *Thorax* 1984; 39: 277–81.
7. Anonymous. Sodium cromoglycate aerosol. *Drug Ther Bull* 1982; 20: 27.
8. Robson RA, *et al.* Sodium cromoglycate: spincaps or metered dose aerosol. *Br J Clin Pharmacol* 1981; 11: 383–4.
9. Bar-Yishay E, *et al.* Duration of action of sodium cromoglycate on exercise induced asthma: comparison of 2 formulations. *Arch Dis Child* 1983; 58: 624–7.
10. Tullett WM, *et al.* Dose-response effect of sodium cromoglycate pressurised aerosol in exercise induced asthma. *Thorax* 1985; 40: 41–4.
11. Cockcroft DW, Murdock KY. Comparative effects of inhaled salbutamol, sodium cromoglycate, and beclomethasone dipropionate on allergen-induced early asthmatic responses, late asthmatic responses, and increased bronchial responsiveness to histamine. *J Allergy Clin Immunol* 1987; 79: 734–40.
12. Barry PW, O'Callaghan C. Inhalational drug delivery from seven different spacer devices. *Thorax* 1996; 51: 835–40.

Administration in children. Children may be given sodium cromoglicate for prophylactic management of asthma and allergic rhinitis, and in the prophylaxis and treatment of acute and chronic allergic conjunctivitis and vernal keratoconjunctivitis, using adult doses, see Uses and Administration, above. Different countries may have different licensed lower age limits and some inhalation dosage forms are unsuitable in very young children.

In food allergy and in mastocytosis, sodium cromoglicate may be given orally to children from 2 years of age. A dose of 100 mg is given four times daily before meals. If satisfactory control is not achieved within 2 to 3 weeks the dosage may be doubled but should not exceed 40 mg/kg daily; a reduction in dosage may be possible once symptoms have been controlled. For food allergy, adult doses may be given to children from 14 years of age, and from 13 years for mastocytosis, see above.

Asthma. Sodium cromoglicate is used as a prophylactic agent in the management of chronic asthma (p. 1195.2), but in practice inhaled corticosteroids are preferred if regular prophylactic treatment is indicated, i.e. if the condition cannot be managed with occasional use of an inhaled short-acting beta$_2$ agonist alone. Even in children, in whom cromoglicate has tended to be more widely used, inhaled corticosteroids are considered first-line preventers. A systematic review[1] comparing sodium cromoglicate with inhaled corticosteroids found that inhaled corticosteroids were superior in terms of asthma control and lung function for both children and adults with chronic asthma. However, guidelines still specify the use of cromoglicate or nedocromil as a valid alternative to inhaled corticosteroids in some circumstances. Another systematic review[2] found insufficient evidence to conclude that sodium cromoglicate was more effective than placebo for maintenance treatment of chronic asthma in children, although the results favoured treatment for some outcomes such as symptom scores and bronchodilator use.

Response to treatment with nebulised sodium cromoglicate was found to be age-related in a study of children under 2 years of age with recurrent or persistent wheezy bronchitis and a history of allergic symptoms.[3] It was effective in children of 12 to 24 months of age but not in those below 12 months. Similarly, nebulised sodium cromoglicate was no more effective than placebo in the treatment of a group of 31 infants with persistent wheezing aged under 1 year.[4]

1. Guevara JP, *et al.* Inhaled corticosteroids versus sodium cromoglycate in children and adults with asthma. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 14/04/08).
2. van der Wouden JC, *et al.* Inhaled sodium cromoglycate for asthma in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 14/08/09).
3. Geller-Bernstein C, Levin S. Nebulised sodium cromoglycate in the treatment of wheezy bronchitis in infants and young children. *Respiration* 1982; 43: 294–8.
4. Furfaro S, *et al.* Efficacy of cromoglycate in persistently wheezing infants. *Arch Dis Child* 1994; 71: 331–4.

Cogan's syndrome. Sodium cromoglicate eye drops improved blurred vision in a patient who had had Cogan's syndrome (p. 1603.2) for 18 years.[1] Sodium cromoglicate capsules [orally] also reduced the frequency of fever attacks in this patient.

1. Carter P, Nabarro J. Cromoglycate for Cogan's syndrome. *Lancet* 1987; i: 858.

Cough. Sodium cromoglicate has been used with modest success by aerosol inhalation to suppress the cough associated with ACE inhibitor therapy (p. 1285.3) in some patients.[1,2] However, inhalation of nedocromil sodium was not helpful in the treatment of ACE inhibitor induced cough in 6 diabetic patients.[3] A systematic review[4] considered that there was no good evidence to support the use of inhaled cromoglicate or nedocromil in the treatment of non-specific cough in children.

1. Keogh A. Sodium cromoglycate prophylaxis for angiotensin-converting enzyme inhibitor cough. *Lancet* 1993; 341: 560.
2. Hargreaves MR, Benson MK. Inhaled sodium cromoglycate in angiotensin-converting enzyme inhibitor cough. *Lancet* 1995; 345: 13–16.
3. Puolijoki H, Reklaro M. Lack of effect of nedocromil sodium in ACE-inhibitor-induced cough. *Lancet* 1995; 345: 394.
4. Chang A, *et al.* Inhaled cromones for prolonged non-specific cough in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/04/08).

Eczema. A 4% sodium cromoglicate lotion was found to be of benefit in improving symptoms and reducing topical corticosteroid use in a study[1] in children with moderately severe atopic dermatitis (p. 1684.1).

1. Stainer R, *et al.* Efficacy and acceptability of a new topical skin lotion of sodium cromoglicate (Altoderm) in atopic dermatitis in children aged 2–12 years: a double-blind, randomized, placebo-controlled trial. *Br J Dermatol* 2005; 152: 334–41.

Food allergy. Oral sodium cromoglicate has been used in the prophylaxis of food allergy reactions (p. 611.2). However, efficacy has not been unequivocally established.

Mastocytosis. Mastocytosis is a rare condition characterised by abnormal proliferation of mast cells and their accumulation in body tissues.[1-3] Signs and symptoms of the disease result from the spontaneous or induced release of mast cell mediators. Mastocytosis occurs in cutaneous or systemic forms, which are further subdivided based on clinical presentation and prognosis. Clinical algorithms and recommendations for diagnosis, treatment, and response criteria have been developed.[4-6]

- *Cutaneous mastocytosis* most often manifests as urticaria pigmentosa (disseminated red-brown macules, papules, or plaques); other symptoms include flushing, pruritus, urticaria, blistering, and dermatographism. Mastocytomas may occur as brownish solitary or multiple nodular accumulations of mast cells. In children with cutaneous mastocytosis, symptoms will resolve in about half by adolescence.
- *Systemic mastocytosis* can involve diverse organs and tissues including the bones, liver, spleen, lymph nodes, haematopoietic system, gastrointestinal tract, and also the skin. General symptoms include fatigue, weight loss, fever, and sweats. Gastrointestinal complaints such as abdominal pain and diarrhoea are common, and some patients have malabsorption, steatorrhoea, or peptic ulcer disease. Bone marrow involvement may result in bone pain, osteoporosis, fractures, bone marrow fibrosis, and myeloproliferative and myelodysplastic diseases. Other systemic effects include lymphadenopathy, hepatosplenomegaly, headache and other neuropsychiatric symptoms, syncope, and anaphylactoid reactions.

Avoidance of trigger factors is an important measure in the management of mastocytosis. Such factors include exposure to extremes of cold or heat (hot bath or sunbathing), emotional stress, mechanical irritation (vigorous towel rubbing, massage), infections, alcohol, some drugs (e.g. aspirin, NSAIDs, opioid analgesics, sympathomimetics, polymyxin B, dextran, radiographic dyes), and animal venoms.[1,2,5,7]

Treatment is aimed at relieving symptoms and does not alter the course of the disease.[1,2,4,5,7,8] H_1-antagonist antihistamines such as hydroxyzine and cyproheptadine are used to provide relief of flushing, pruritus, urticaria, blistering, and abdominal pain. Patients at risk of anaphylactoid reactions should carry adrenaline for self-

injection, and those who have repeated reactions should be given prophylactic antihistamines. H_2-antagonist antihistamines such as cimetidine, and proton pump inhibitors such as omeprazole, are used to manage gastrointestinal symptoms, particularly gastritis and peptic ulcer disease. Bisphosphonates may be helpful for osteopenia and bone pain. Sodium cromoglicate is given to manage abdominal pain, nausea, and diarrhoea. It may also provide some relief of headache, neuropsychiatric symptoms, and skin symptoms in some patients. Photochemotherapy using an oral psoralen with ultraviolet A irradiation (PUVA—see p. 1712.1) has been used to reduce cutaneous manifestations of mastocytosis, but urticaria pigmentosa usually recurs within several weeks. Topical PUVA appears to be ineffective. Mastocytomas that cause symptoms may be treated with local PUVA or potent topical corticosteroids. Although surgical removal may be considered, the majority of mastocytomas will involute spontaneously.

Other treatments have also been tried in the treatment of small numbers of patients with aggressive systemic mastocytosis. Mixed results have been reported with the use of interferon alfa.[1] There is a report of ciclosporin with methylprednisolone being used successfully.[4] Imatinib has been used successfully in systemic mastocytosis with associated eosinophilia and with a mutation of the platelet-derived growth factor receptor-α gene on chromosome 4q12.[8] Beneficial responses to cladribine have also occurred in a small number of patients with systemic disease.[8,9]

1. Hartmann K, Henz BM. Mastocytosis: recent advances in defining the disease. *Br J Dermatol* 2001; 144: 682–95.
2. Carter MC, Metcalfe DD. Paediatric mastocytosis. *Arch Dis Child* 2002; 86: 315–19.
3. Castells MC. Mastocytosis: classification, diagnosis, and clinical presentation. *Allergy Asthma Proc* 2004; 25: 33–6.
4. Valent P, *et al.* Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007; 37: 435–53.
5. de la Hoz B, *et al.* Guías clínicas para el diagnóstico, tratamiento y seguimiento de las mastocitosis. *An Sist Sanit Navar* 2008; 31: 11–32.
6. Heide R, *et al.* Dutch National Mastocytosis Work Group. Mastocytosis in children: a protocol for management. *Pediatr Dermatol* 2008; 25: 493–500.
7. Almahroos M, Kurban AK. Management of mastocytosis. *Clin Dermatol* 2003; 21: 274–7.
8. Tefferi A, Pardanani A. Systemic mastocytosis: current concepts and treatment advances. *Curr Hematol Rep* 2004; 3: 197–202.
9. Kluin-Nelemans HC, *et al.* Cladribine therapy for systemic mastocytosis. *Blood* 2003; 102: 4270–6.

Rhinitis and conjunctivitis. Many drugs, including sodium cromoglicate, are used in the management of allergic rhinitis (p. 612.1) and conjunctivitis (p. 611.1). There is some evidence that nedocromil[1] or lodoxamide[2] may be more effective than cromoglicate in the management of vernal keratoconjunctivitis.

1. El Hennawi M. A double-blind placebo controlled group comparative study of ophthalmic sodium cromoglycate and nedocromil sodium in the treatment of vernal keratoconjunctivitis. *Br J Ophthalmol* 1994; 78: 365–9.
2. Leonardi A, *et al.* Effect of lodoxamide and disodium cromoglycate on tear eosinophil cationic protein in vernal keratoconjunctivitis. *Br J Ophthalmol* 1997; 81: 23–6.

Sickle-cell disease. Sodium cromoglicate has been investigated[1,2] for its potential benefits in patients with sickle-cell disease (p. 1123.2).

1. Toppet M, *et al.* Antisickling activity of sodium cromoglicate in sickle-cell disease. *Lancet* 2000; 356: 309.
2. Karimi M, *et al.* Clinical response of patients with sickle cell anemia to cromolyn sodium nasal spray. *Am J Hematol* 2006; 81: 809–16.

Adverse Effects

Inhalation of sodium cromoglicate may cause transient bronchospasm, wheezing, cough, nasal congestion, and irritation of the throat. Nausea, headache, dizziness, an unpleasant taste, and joint pain and swelling have been reported. Other reactions include aggravation of existing asthma, urticaria, rashes, pulmonary infiltrates with eosinophilia, dysuria, and urinary frequency. Severe hypersensitivity reactions such as marked bronchospasm, laryngeal oedema, angioedema, hypotension, and anaphylaxis have been reported rarely.

Intranasal use of sodium cromoglicate may cause transient irritation of the nasal mucosa, sneezing, and occasionally epistaxis. Nausea, skin rashes, and joint pains have occurred when it is taken orally. Transient burning and stinging have occasionally been reported after use of sodium cromoglicate eye drops.

Formulation. Some of the adverse effects reported with sodium cromoglicate may be due to its formulation: there is a view that some of the irritant effects reported on inhalation may be due to the use of dry powder inhalers. It has also been suggested that in some patients receiving sodium cromoglicate via a nebuliser, hypotonicity of the nebuliser solution may induce bronchospasm,[1] although others consider this debatable.[2] Nausea, bloating, abdominal cramps, and flatulence developed in a 24-year-old lactase-deficient woman 2 hours after the use of sodium cromoglicate (*Intal*) inhalation capsules via a turbo-haler for exercise-induced asthma.[3] These symptoms recurred on rechallenge and were attributed to ingestion of lactose contained within the capsules.

1. Chin TW, Nussbaum E. Detrimental effect of hypotonic cromolyn sodium. *J Pediatr* 1992; 120: 641–3.
2. Rachelefsky GS, *et al.* Detrimental effects of hypotonic cromolyn sodium. *J Pediatr* 1992; 121: 992.
3. Brandstetter RD, *et al.* Lactose intolerance associated with Intal capsules. *N Engl J Med* 1986; 315: 1613–14.

Precautions

Sodium cromoglicate has no role in the treatment of acute asthmatic attacks. Withdrawal of sodium cromoglicate may lead to recurrence of the symptoms of asthma. Should withdrawal be necessary it has been suggested that the dose be reduced gradually over a period of one week; patients in whom sodium cromoglicate therapy has permitted a reduction of corticosteroid dosage may require restoration of full corticosteroid cover.

Systemic corticosteroid therapy that has been reduced or stopped in asthmatic patients may need to be reinstated if symptoms increase, during periods of stress such as infection, illness, trauma, or severe antigen challenge, or where airways obstruction impairs inhalation of sodium cromoglicate.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sodium cromoglicate as probably not porphyrinogenic when used intranasally; it may be used as a drug of first choice and no precautions are needed. It is classified as not porphyrinogenic when used orally, by inhalation, or ophthalmically.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/11/11)

Pregnancy. Sodium cromoglicate is generally considered a low-risk drug for use during pregnancy.[1] Experience with nedocromil is more limited, but licensed product information for both sodium cromoglicate and nedocromil states that cumulative clinical experience of use during pregnancy suggests that they have no adverse effects on fetal development. However, a prospective case-control study,[2] while finding that gestational exposure to asthma medications was safe overall, was unable to rule out an increased risk of musculoskeletal malformations associated with cromones (sodium cromoglicate and nedocromil) based on a small number of exposures.

1. Gilbert C, *et al.* Fetal safety of drugs used in the treatment of allergic rhinitis: a critical review. *Drug Safety* 2005; 28: 707–19.
2. Tata LJ, *et al.* Effect of maternal asthma, exacerbations and asthma medication use on congenital malformations in offspring: a UK population-based study. *Thorax* 2008; 63: 981–7.

Pharmacokinetics

After inhalation as a powder or aerosol, the amount of sodium cromoglicate absorbed from the respiratory tract is about 10%. Less than 7% of an intranasal dose is absorbed via the nasal mucosa, and about 0.03% of an ophthalmic dose is reported to be absorbed.

Most of an inhaled or intranasal dose is exhaled or deposited in the oropharynx, swallowed, and excreted via the gastrointestinal tract, as only about 1% of a dose is absorbed from the gut. The portion that is absorbed is excreted unchanged in the urine and bile in about equal amounts. The terminal elimination half-life has been reported to be about 20 minutes after intravenous dosage, but the elimination half-life after oral doses or inhalation is about 80 minutes.

A study[1] in patients with exercise-induced asthma concluded that the plasma concentration of cromoglicate was almost certainly not related directly to its protective effect, although another study in asthmatic children given sodium cromoglicate by dry-powder inhalation, found both blood concentration and clinical response to be correlated with inhalation technique.[2]

1. Patel KR, *et al.* Plasma concentrations of sodium cromoglycate given by nebulisation and metered dose inhalers in patients with exercise-induced asthma: relationship to protective effect. *Br J Clin Pharmacol* 1986; 21: 231–3.
2. Yahav Y, *et al.* Sodium cromoglycate in asthma: correlation between response and serum concentrations. *Arch Dis Child* 1988; 63: 592–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Claroftal; Intal; Klonalcrom; *Austral.*: Cromese†; Cromolux; Intal; Opticrom; Rynacrom; *Austria*: Acromax†; Allergo-COMOD; Cromoglin; Intal; Lomusol; Vividrin; *Belg.*: Cromabak; Cromonez-Pos†; Cromophta-Pos†; Lomudal; Lomusol; Opticrom; *Braz.*: Cromabak; Cromocato; Cromolerg; Intal; Maxicrom; Rilan; *Canad.*: Apo-Cromolyn; Cromolyn; Nalcrom; Opticrom; Rhinaris-CS; *Chile*: Oftacon†; *China*: Runbo (润博); Shuanglang (双朗); *Cz.*: Allergo-COMOD; Allergocrom Kombi; Allergocrom; Cromobene†; Cromohexal; Cusicrom†; Lecrolyn†; Nalcrom; *Denm.*: Lecrolyn; Lomudal; *Fin.*: Glinor; Lecrolyn; Lomudal; *Fr.*: Allergo-COMOD; Alloptrex†; Cromabak; Cromadoses; Cromoptic; Cromorhinol; Cromosoft†; Humex; Intercron; Lomudal; Lomusol; Multicrom; Ophtacalm; Ophtacalmfree; Opticron; *Ger.*: Allergo-COMOD; Allergocrom; Allergoval; Colimune; Crom-Ophtal; Cromo; Cromohexal†; Cromopp†; Dispacromil; DNCG; Flui-DNCG†; Intal; IsoCrom†; Lomupren†; Opticrom†; Padiacrom†; Pentatop; Vividrin; *Gr.*: Allergojovis; Allergostop; Allergotin; Botastin; Crolidin; Cromabak; Cromo-POS; Cromodal; Cromolergin UD; Doxalpha; Duobetic; Erystamine-K; Fluvet; Indoprex; Iopanchol; Kaosyl; Lomudal; Nalcrom; Smarodax; Spaziron; Ufocollyre; Vekfanol; Vividrin; Zineli; Zulboral; *Hong Kong*: Cromabak; Cromal†; Cromolyn†; Dadcrome; Mitayaku; Stadaglicin†; *Hung.*: Cromohexal†; Cromosandoz; Intal†; Lecrolyn; Opticrom; Taleum; *India*: Actal; Allercrom; Chromotop; Cromal; Cromate; Fintal; Ifiral; *Indon.*: Crom-Ophtal; *Irl.*: Cromogen†; Hay-Crom; Intal; Nalcrom; Opticrom; Rynacrom†; Vividrin; *Israel*: Cromo-COMOD; Cromolyn; Cromoptic; Cronase; Lomudal; Opticrom; *Ital.*: Brunicrom; Cromabak; Gastrofrenal; Lomudal; Nalcrom; Sificrom; *Jpn*: Intal; *Malaysia*: Allergocrom; Cromal; Cusicrom; Opticrom; Stadaglicin†; *Mex.*: Alercrom; Alleoftal; Cryl; Intal; Livari; Maxicrom; Oftavit; Opticrom; Rynacrom; Spralyn; *Mon.*: Cromedil; Zallyre†; *Neth.*: Allerg-Abak; Allergo-COMOD; Lomudal; Lomusol; Nalcrom; Opticrom; Prevalin; Vividrin†; *Norw.*: Lecrolyn; Lomudal; *NZ*: Cromolux; Intal; Nalcrom; Opticrom†; Optrex Hayfever Allergy†; Rexacrom; Rynacrom†; Vicrom; *Philipp.*: Cromabak; Ifiral; Lecrolyn†; Vividrin; *Pol.*: Allergo-COMOD; Allergocrom; Cromogen†; Cromohexal; Cromosol†; Cromoxal; Cropoz G†; Cusicrom; Lecrolyn†; Nalcrom†; Polcrom; Vividrin; *Port.*: Cromabak; Davicrome†; Fenolip; Intal; Opticrom; *Rus.*: Crom-Allerg (Кром-Аллерг); Cromoglin (Кромоглин); Cromohexal (Кромогексал); Cropoz (Кропоз)†; Hay-Crom (Хай-кром); Ifiral (Ифирал); Intal (Интал); Lecrolyn (Лекролин); Nalcrom (Налкром); *S.Afr.*: Cromabak; Cromohexal; Stop-Allerg; Vividrin; *Singapore*: Allergocrom; Cromabak; Cromax; Intal; Opticrom; Rynacrom; Stadaglicin†; Vividrin; *Spain*: Alergocrom†; Cusicrom; Prenal†; Nebulasma†; Nebulcrom; Renocil†; Rinilyn†; Rinofrenal†; *Swed.*: Lecrolyn; Lomudal; Pollyferm; *Switz.*: Allergo-COMOD; Cromabak; Cromodyn; Cromosol ophta; Cromosol UD; Lomudal; Lomusol; Nalcrom; Opticrom; Vividrin†; *Thai.*: Intal; Opticrom; Rynacrom; Vividrin; *Turk.*: Allergo-COMOD; Allergocrom; Allersol; Cromabak; Intal; Opticrom†; Rynacrom; Vividrin; *UK*: Catacrom; Clariteyes†; Clarityn†; Hay-Crom; Hayfever Eye Drops†; Intal; Murine Hayfever; Nalcrom; Opticrom; Optrex Allergy; Pollenase Allergy; Rynacrom; Vivicrom†; Vividrin; *Ukr.*: Cromo Sandoz (Кромо Сандоз); Cromoglin (Кромоглин); Cromohexal (КромоГЕКСАЛ)†; Cromopharm (Кромофарм); *USA*: Crolom; Gastrocrom; Intal†; Nasalcrom†; Opticrom; *Venez.*: Cromisol; Cromoftal.

Multi-ingredient Preparations. *Arg.*: Hyalcrom; Rinogel; *Ger.*: Aarane N; Allergospasmin; *India*: Asthacrom†; *Ital.*: Cromozil; Rinofrenal; Visuglican; *Rus.*: Ditec (Дитек)†; *Spain*: Prenal Compositum†; Rinofrenal Plus†; *Turk.*: Rynacrom Compound.

Pharmacopoeial Preparations

BP 2014: Sodium Cromoglicate Eye Drops; Sodium Cromoglicate Inhalation Powder, hard capsule;

USP 36: Cromolyn Sodium Inhalation Powder; Cromolyn Sodium Inhalation Solution; Cromolyn Sodium Nasal Solution; Cromolyn Sodium Ophthalmic Solution.

Suplatast Tosilate *(rINN)*

IPD-1151T; Suplatast, Tosilate de; Suplatast, tosilato de; Suplatast Tosylate; Suplatasti Tosilas; Suplatastum Tosilas; Tosilato de suplatast; Супластат Тозилат.

(±)-(2-{[*p*-(3-Ethoxy-2-hydroxypropoxy)phenyl]carbamoyl}ethyl)dimethylsulphonium *p*-toluenesulphonate; (3-{[4-(3-Ethoxy-2-hydroxypropoxy)phenyl]amino}-3-oxopropyl)dimethylsulphonium *p*-toluenesulphonate.

$C_{23}H_{33}NO_7S_2$=499.6

CAS — 94055-76-2.

UNII — C9J89787U1.

Profile

Suplatast tosilate is an anti-allergic given orally in the prophylactic management of asthma and other allergic conditions.

References.

1. Sano Y, *et al.* Anti-inflammatory effect of suplatast tosilate on mild asthma. *Chest* 1997; 112: 862–3.
2. Nihei Y, *et al.* Suplatast tosilate (IPD), a new immunoregulator, is effective in vitiligo treatment. *J Dermatol* 1998; 25: 250–5.
3. Tamaoki J, *et al.* Effect of suplatast tosilate, a Th2 cytokine inhibitor, on steroid-dependent asthma: a double-blind randomised study. *Lancet* 2000; 356: 273–8.
4. Shioya T, *et al.* Effect of suplatast tosilate, a Th2 cytokine inhibitor, on cough variant asthma. *Eur J Clin Pharmacol* 2002; 58: 171–6.
5. Matsuda Y, *et al.* Improvement of alanine aminotransferase by administration of suplatast tosilate plus ursodeoxycholic acid in patients with resistance to ursodeoxycholic acid monotherapy on hepatitis C virus-related chronic liver disease. *Intern Med* 2002; 41: 774–9.
6. Sakuma-Oyama Y, *et al.* A case of recurrent cutaneous eosinophilic vasculitis: successful adjuvant therapy with supiatast tosilate. *Br J Dermatol* 2003; 149: 901–3.
7. Sano T, *et al.* Higashishikoku Asthma Research Group. Add-on effects of suplatast tosilate in bronchial asthma patients treated with inhaled corticosteroids. *Lung* 2003; 181: 227–35.

The symbol † denotes a preparation no longer actively marketed

8. Teraki Y, Fukuda T. Pemphigoid nodularis associated with psoriatic erythroderma: successful treatment with suplatast tosilate. *Br J Dermatol* 2008; 158: 424–6.
9. Yoshihara S, *et al.* Early intervention with suplatast tosilate for prophylaxis of pediatric atopic asthma: a pilot study. *Pediatr Allergy Immunol* 2009; 20: 486–92.
10. Węda M, *et al.* Effect of suplatast tosilate on antileukotriene non-responders with mild-to-moderate persistent asthma. *Allergol Int* 2009; 58: 389–93.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: IPD.

Terbutaline Sulfate

(BANM, USAN, rINNM) ⊗

KWD-2019; Sulfato de terbutalina; Terbutaliinisulfaatti; Terbutalin Sülfat; Terbutalina, sulfato de; Terbutaline, Sulfate de; Terbutaline Sulphate; Terbutalini Sulfas; Terbutalino sulfatas; Terbutalinsulfat; Terbutalin-sulfát; Terbutalin-szulfát; Тербуталина Сульфат.

2-*tert*-Butylamino-1-(3,5-dihydroxyphenyl)ethanol sulphate.

$(C_{12}H_{19}NO_3)_2,H_2SO_4$=548.6

CAS — 23031-25-6 (terbutaline); 23031-32-5 (terbutaline sulfate).

ATC — R03AC03; R03CC03.

ATC Vet — QR03AC03; QR03CC03.

UNII — 576PU70Y8E.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Terbutaline Sulfate). A white or almost white crystalline powder. It exhibits polymorphism. Freely soluble in water; slightly soluble in alcohol.

USP 36: (Terbutaline Sulfate). A white to grey-white crystalline powder; odourless or has a faint odour of acetic acid. Soluble in water and in 0.1N hydrochloric acid; insoluble in chloroform; slightly soluble in methyl alcohol. Store at 15 degrees to 30 degrees. Protect from light.

Uses and Administration

Terbutaline sulfate is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has actions and uses similar to those of salbutamol (p. 1220.2).

Terbutaline is given as the sulfate for its bronchodilating properties in reversible airways obstruction, as occurs in asthma (p. 1195.2) and in some patients with chronic obstructive pulmonary disease (p. 1199.1). It also decreases uterine contractility and may be used to arrest premature labour (p. 2131.1).

On inhalation, the bronchodilating effect of terbutaline usually begins within 5 minutes and lasts for up to 6 hours. The onset of action after oral doses is 30 to 45 minutes and its duration is up to 8 hours; the maximum effect occurs 1 to 4 hours after the dose.

Current asthma guidelines (see p. 1195.2) recommend that inhaled short-acting $beta_2$ agonists such as terbutaline be used on an 'as-required', not regular, basis. In those patients requiring more than occasional use of terbutaline, anti-inflammatory therapy is also needed. An increased requirement for, or decreased duration of effect of, terbutaline indicates deterioration of asthma control and the need for increased anti-inflammatory therapy.

- To relieve **acute bronchospasm** the usual dose is 1 inhalation of terbutaline sulfate 250 or 500 micrograms as required from a breath-actuated metered-dose *powder inhaler*. The maximum recommended daily dose varies; in the UK a maximum of 2 mg is suggested, whereas in some other countries higher doses of up to 4 mg are allowed.
- When inhalation is ineffective, terbutaline sulfate may be given *orally*; the usual initial dose is 2.5 or 3 mg three times daily increased up to 5 mg three times daily as necessary. Modified-release tablets are also available; the usual adult dose is 5 or 7.5 mg twice daily.
- Severe or unresponsive bronchospasm may require the use of terbutaline sulfate intermittently via a *nebuliser*. A usual dose is 2.5 to 10 mg inhaled up to 4 times daily. Single-dose units or a suitable dilution of a concentrated solution containing terbutaline sulfate 1% are used for this purpose.

Guidelines also allow for $beta_2$ agonists to be given more frequently or by continuous dosage at a higher rate in acute severe asthma (see under Asthma, p. 1195.2).

- In the treatment of severe forms of bronchospasm, terbutaline sulfate may be given by subcutaneous, intramuscular, or slow intravenous *injection*; a dose of 250 to 500 micrograms may be given up to 4 times daily. Terbutaline sulfate may also be given by *intravenous infusion*, as a solution containing 3 to 5 micrograms/mL at a rate of 0.5 to 1 mL/minute.

Terbutaline sulfate is also used to arrest uncomplicated **premature labour** between 22 and 37 weeks of gestation. It is given by *intravenous infusion* in glucose 5%, preferably by syringe pump when the concentration is 100 micrograms/mL. If no syringe pump is available then the concentration of the infusion should be 10 micrograms/mL. The recommended initial rate of infusion is 5 micrograms/minute, increased by 2.5 micrograms/minute at intervals of 20 minutes until contractions stop. Usually, a rate of up to 10 micrograms/minute is sufficient; rates in excess of 20 micrograms/minute should not be used and if that maximum rate does not delay labour then the infusion should be stopped. The maternal pulse should be monitored throughout the infusion which should be adjusted to avoid a maternal heart rate of more than 135 beats/minute. A close watch should also be kept on the patient's state of hydration since fluid overload is considered to be a key risk factor for pulmonary oedema. Once contractions have ceased, the infusion should be continued for 1 hour, then the dose may be decreased by 2.5 micrograms/minute at 20-minute intervals to the lowest maintenance dose that produces continued suppression of contractions. Therapy should be limited to a maximum of 48 hours, because prolonged treatment is associated with risks of serious cardiovascular effects in both the mother and fetus (see Precautions under Salbutamol, p. 1222.3).

Oral or *rectal* $beta_2$ agonist therapy is no longer recommended in premature labour, because of a lack of evidence of benefit from treatment given by these routes of administration. Formerly, terbutaline sulfate could be given orally in a dose of 5 mg three times daily, for maintenance therapy after uterine contractions were controlled by parenteral treatment.

For terbutaline sulfate doses used for bronchospasm in children, see Administration in Children, below.

Administration in children. For the treatment of reversible airways obstruction, including nocturnal asthma, and prevention of exercise-induced **bronchospasm** in children, the *BNFC* recommends a dose of 500 micrograms of terbutaline sulfate, inhaled via a metered-dose *powder inhaler*, up to four times daily in children aged 5 years and over. *Oral* doses, although not recommended, may be given as follows:

- 1 month to 7 years of age: 75 micrograms/kg (maximum dose 2.5 mg) three times daily
- 7 to 15 years of age: 2.5 mg two or three times daily
- over 15 years of age: as for adults (see Uses and Administration, above)

Severe or unresponsive bronchospasm may require the use of terbutaline sulfate inhaled via a *nebuliser*. UK licensed product information gives doses based on weight and age:

- under 3 years of age, average body-weight 10 kg: 2 mg given 2 to 4 times daily
- 3 to 5 years of age, average body-weight 15 kg: 3 mg given 2 to 4 times daily
- 6 to 7 years of age, average body-weight 20 kg: 4 mg given 2 to 4 times daily
- 8 years of age and over, average body-weight 25 kg or more: 5 mg given 2 to 4 times daily

In the treatment of severe bronchospasm, terbutaline sulfate may be given by subcutaneous or slow intravenous *injection*; in children 2 to 15 years of age, the *BNFC* recommends a dose of 10 micrograms/kg (maximum dose 300 micrograms) up to four times daily. Children over 15 years of age may be given the adult dose.

Terbutaline sulfate may also be given by continuous *intravenous infusion*; the *BNFC* recommends an initial dose of 2 to 4 micrograms/kg, then 1 to 10 micrograms/kg per hour according to response and heart rate. Although the injection is unlicensed in the UK for children under 2 years of age, the *BNFC* allows this dose for children from 1 month of age.

Cardiac disorders. A case report on the use of oral terbutaline for chronotropic support, in the setting of acute rejection after heart transplantation, found it to be effective and without any significant adverse effects.[1]

1. Coons JC, *et al.* Terbutaline for chronotropic support in heart transplantation. *Ann Pharmacother* 2004; 38: 586–9.

Hypoglycaemia. Giving terbutaline 5 mg orally at night reduced the risk of nocturnal hypoglycaemia in a study in patients with type 1 diabetes.[1] A later study[2] reproduced these results in 21 patients with type 1 diabetes; however, hyperglycaemia was seen the next morning. There is some evidence[3] to suggest that reducing the dose of terbutaline to 2.5 mg at night might allow for control of nocturnal hypoglycaemia without morning hyperglycaemia, but further study is needed.

1. Saleh TY, Cryer PE. Alanine and terbutaline in the prevention of nocturnal hypoglycemia in IDDM. *Diabetes Care* 1997; 20: 1231–6.
2. Raju B, *et al.* Nocturnal hypoglycaemia in type 1 diabetes: an assessment of preventive bedtime treatments. *J Clin Endocrinol Metab* 2006; 91: 2087–92.
3. Cooperberg BA, *et al.* Terbutaline and the prevention of nocturnal hypoglycemia in type 1 diabetes. *Diabetes Care* 2008; 31: 2271–2.

Myasthenia gravis. Results of a pilot study[1] suggested that oral terbutaline 2.5 mg three times daily was of modest benefit as an adjunct in the management of myasthenia gravis (p. 684.1).

1. Solíven B, *et al.* Terbutaline in myasthenia gravis: a pilot study. *J Neurol Sci* 2009; 277: 150–4.

Systemic capillary leak syndrome. Systemic capillary leak syndrome is a rare disorder marked by shifts of plasma from the intravascular to the extracellular space, and is often fatal. Acute attacks are treated with intravenous fluid resuscitation, but there is some anecdotal evidence that treatment with terbutaline combined with aminophylline or theophylline, both orally, may be useful in preventing further attacks.[1-3] Infusion of epoprostenol has also been used in acute management.[4]

1. Droder RM, *et al.* Control of systemic capillary leak syndrome with aminophylline and terbutaline. *Am J Med* 1992; 92: 523–6.
2. Amoura Z, *et al.* Systemic capillary leak syndrome: report on 13 patients with special focus on course and treatment. *Am J Med* 1997; 103: 514–19.
3. Tahirkheli NK, Greipp PR. Treatment of the systemic capillary leak syndrome with terbutaline and theophylline: a case series. *Ann Intern Med* 1999; 130: 905–9.
4. Fellows IW, *et al.* Epoprostenol in systemic capillary leak syndrome. *Lancet* 1988; ii: 1143.

Urticaria. Patients with various types of urticaria unresponsive to conventional therapy with antihistamines (see p. 1689.2) have obtained benefit from treatment with a combination of terbutaline and ketotifen; the urticarias have included chronic idiopathic urticaria,[1] dermographism,[1] and cold urticaria.[1,2] Terbutaline on its own was relatively ineffective and the mechanism of the combination was believed to be due to a stabilising effect on mast cells.[1]

Treatment of cold urticaria with a combination of terbutaline and aminophylline has also been studied.[3] The efficacy of this combined therapy was reported to vary considerably between patients, but complete remission of the urticarial response was eventually seen in 37 of the 42 patients. Treatment was stopped in 3 patients in the first week due to cardiac adverse effects.

1. Saihan EM. Ketotifen and terbutaline in urticaria. *Br J Dermatol* 1981; 104: 205–6.
2. Edge JA, Osborne JP. Terbutaline and ketotifen in cold urticaria in a child. *J R Soc Med* 1989; 82: 439–40.
3. Husz S, *et al.* Treatment of cold urticaria. *Int J Dermatol* 1994; 33: 210–13.

Adverse Effects, Treatment, and Precautions

As for Salbutamol, p. 1221.3.

An increased tendency for bleeding after caesarean section has been reported in patients being treated with terbutaline for preterm labour. Should bleeding occur, an intravenous injection of propranolol 1 to 2 mg may be given (caution is required in patients with a history of bronchospasm, see p. 1320.3).

Overdosage. An overdose of terbutaline due to transcutaneous absorption has been reported after inappropriate topical application to skin infected with tinea.[1] Transcutaneous absorption should be considered especially when children with facial eczema or dermatitis are given terbutaline via a nebuliser and mask.

For general effects of $beta_2$ agonists after overdose, see Salbutamol p. 1222.2.

1. Ingrams GJ, Morgan FB. Transcutaneous overdose of terbutaline. *BMJ* 1993; 307: 484.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies terbutaline as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pulmonary oedema. Pulmonary oedema has occurred in women given $beta_2$ agonists, including terbutaline, for premature labour.[1] The risk factors, the most important of which is fluid overload, are discussed under Precautions for Salbutamol, p. 1222.3.

1. Perry KG, *et al.* Incidence of adverse cardiopulmonary effects with low-dose continuous terbutaline infusion. *Am J Obstet Gynecol* 1995; 173: 1273–7.

Tolerance. As with other $beta_2$ agonists (see p. 1222.3) there is some evidence[1] that tolerance may develop to terbutaline when it is used regularly.

1. Hancox RJ, *et al.* Tolerance to beta-agonists during acute bronchoconstriction. *Eur Respir J* 1999; 14: 283–7.

Tooth erosion. The pH of some inhaled powder formulations of terbutaline, as well as of some corticosteroids, was found to be below 5.5, and it was suggested that this might contribute to the dissolution of enamel surfaces of teeth.[1] A later cohort study[2] found no association between asthma and tooth erosion; however only about 10% of

the medication prescribed for asthma in the cohort had a pH lower than 5.5.

1. O'Sullivan EA, Curzon MEJ. Drug treatments for asthma may cause erosive tooth damage. *BMJ* 1998; 317: 820.
2. Dugmore CR, Rock WP. Asthma and tooth erosion: is there an association? *Int J Paediatr Dent* 2003; 13: 417–24.

Interactions

As for Salbutamol, p. 1223.1.

Histamine. For the effect of terbutaline on histamine given exogenously, see p. 2525.3.

Xanthines. The metabolic and cardiovascular responses to terbutaline infusion were significantly enhanced by *theophylline* in a study in 7 healthy subjects; in particular the fall in serum potassium was greater when both drugs were given.[1] Careful monitoring of serum potassium is recommended in severe asthma where theophylline and $beta_2$-agonists may be given together.

Terbutaline conversely has an effect on theophylline. Terbutaline can reduce serum-theophylline concentrations by increasing its systemic clearance. This may, or may not, have clinical implications, as improved clinical scores have still occurred with combined therapy despite the theophylline concentration being lower than when used alone; if respiratory symptoms persist, an increase in dosage may be contemplated while monitoring theophylline adverse effects and concentration.[2]

1. Smith SR, Kendall MJ. Potentiation of the adverse effects of intravenous terbutaline by oral theophylline. *Br J Clin Pharmacol* 1986; 21: 451–3.
2. Garty M, *et al.* Increased theophylline clearance in asthmatic patients due to terbutaline. *Eur J Clin Pharmacol* 1989; 36: 25–8.

Pharmacokinetics

On inhalation of terbutaline, less than 10% of the drug is absorbed from the airways. The remainder is swallowed where it is variably absorbed from the gastrointestinal tract. Fasting bioavailability after oral doses is reported to be about 14 to 15% and is reduced by food. Terbutaline undergoes extensive first-pass metabolism by sulfate (and some glucuronide) conjugation in the liver and the gut wall. It is excreted in the urine and faeces partly as the inactive sulfate conjugate and partly as unchanged terbutaline, the ratio depending upon the route by which it is given. The terminal half-life after single and multiple dosing is reported to be between 16 and 20 hours. There is some placental transfer. Trace amounts are distributed into breast milk.

Stereoselectivity. Terbutaline, like many other sympathomimetics, exists in two stereoisomeric forms but only the (-)-enantiomer of terbutaline is pharmacologically active. Pharmacokinetic studies have been conducted on the two enantiomers and on the racemate.

The oral bioavailability of (-)-terbutaline was 14.8%, which was similar to that of the racemate; the bioavailability of (+)-terbutaline was much lower at 7.5%. The difference in bioavailability between the two enantiomers was mainly due to a difference in absorption (about 75% and 50% respectively) although a small difference in subsequent first-pass metabolism also occurred, with the (+)-isomer undergoing slightly more metabolism. It appeared that the (+)-isomer governed the elimination behaviour, both first-pass metabolism and renal clearance, of the racemate whereas the (-)-isomer determined the absorption.[1]

Other studies have also shown stereoselective sulfate conjugation of terbutaline with sulfation of the (+)-enantiomer being double that of the (-)-enantiomer.[2] The primary site of terbutaline sulfation for both enantiomers appears to be in the gut and is significantly correlated with the activity of catechol sulfotransferase.[3]

1. Borgström L, *et al.* Pharmacokinetic evaluation in man of terbutaline given as separate enantiomers and as the racemate. *Br J Clin Pharmacol* 1989; 27: 49–56.
2. Walle T, Walle UK. Stereoselective sulphate conjugation of racemic terbutaline by human liver cytosol. *Br J Clin Pharmacol* 1990; 30: 127–33.
3. Pacifici GM, *et al.* (+) and (-) terbutaline are sulphated at a higher rate in human intestine than in the liver. *Eur J Clin Pharmacol* 1993; 45: 483–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bricanyl; *Austral.*: Bricanyl; *Austria*: Bricanyl; *Belg.*: Bricanyl; *Braz.*: Adrenyl; Bricanyl; Terbutil; *Canad.*: Bricanyl; *China*: Bi Ai (比艾); Bricanyl (博利康尼); Bricasol (喘康速); Bu Rui Ping (布瑞平); Chuan Ting (川婷); Fei Ke Tan (菲科坦); Hui Bang (慧邦); Su Shun (苏顺); *Cz.*: Bricanyl; *Denm.*: Bricanyl; Dracanyl†; Terbasmin; *Fin.*: Bricanyl; *Fr.*: Bricanyl; *Ger.*: Aerodur; Bricanyl; Terbul†; *Gr.*: Bricanyl; Dracanyl; *Hong Kong*: Anvelin†; Ataline; Bricanyl; Dhatalin; Framagon†; Lanterbine†; Terbron†; Terbuline†; Terbuta; Uni-Breth†; Vicktaline†; Vida-Butaline†; *Hung.*: Bricanyl; *India*: Asmaril; BGT; Bricanyl; *Indon.*: Astherin†; Brasmatic†; Bricasma; Porasma; Lasmalin; Nairet; Neosma; Pulmobron; Relivan; Sedakter; Tabas; Terasma†; Tismalin; Yarisma; *Irl.*: Bricanyl; *Israel*: Bricalin; Terbulin; *Ital.*: Bricanyl; *Malaysia*: Ataline; Bricanyl; Britaline; Bucanil; Butaline; Tolbin; *Mex.*: Terbuken; *Neth.*: Bricanyl; Terbasmin†; *Norw.*: Bricanyl; *NZ*: Bricanyl; *Philipp.*: Alloxygen; Astebron; Bricalin; Bricanyl; Bronchodam; Pulmolin; Pulmonyl; Pulmoxcel; Terbulin; *Port.*: Bricanyl; *S.Afr.*: Bricanyl; *Singapore*: Asmalin; Ataline†; Bricanyl; Butylin; Dhatalin; Terbuline; Tolbin; *Spain*: Tedipulmo†; Terbasmin; *Swed.*: Bricanyl; *Switz.*: Bricanyl; *Thai.*: Asmadon; Asmaline; Asthmasian; Asthmic; B-lene; Bricanyl†; Broncholine; Bronchonyl; Bronco Asmo†; Bucanyl; Bucaril; Butalin; Cencanyl†; Fasma†; Framagon; P-Canyl; Proasma-T; Sulterline†; Terbu; Terbulin; Terbuline; Terbuno†; Terbusin; Tolbin; Vacanyl; *Turk.*: Bricanyl; *UK*: Bricanyl; *USA*: Brethine†.

Multi-ingredient Preparations. *Braz.*: Bricanyl Composto; *Hong Kong*: Terbuta-Expect†; Uni-Breth Expectorant†; *India*: Adcold-BR; Adcold-SBG; Alpha-Zedex; Altec; Ambrol Plus; Ambrol-TG; Ambrolax; Ambrosin-T; Ambroter; Ambrowin; Amriz; Anacuf; Arcuf Plus; Arikof-P; Arolin-XN; Ascodryl; Ascoril Expectorant; Ascoril; Asi-Ril; Asma-ZED; Asmotone Plus; Asthakind; Atoril; Axol-XL; Bluetus; Brachy; Bricarex A; Bricarex; Bricof; Bro-Zedex; Brocin; Brocoter-A; Brocoter; Bromcough; Bronchosolvin; Broncorex; Broncozone; Bronkex; Bronq; Bronsim; Browin Junior; Browin-TG; Broxter; Brozeet; Cadicoff Exp; Caiscot-AX; Capex-Bron Exp; Capex-DMR; Cinkof; Clear Chest; Cleartuss-T; Cleded-AT; Cledex-AT; Coburyax; Codril-AT; Cof QX; Cofaid-EX; Cofal; Coftex-BT; Cogof-A; Coldman; Combicold; Corico-CS; Corid-B; Corophen-A; Cos-P; Coscoril; Cosome-A; Cosyp-E; Cratex; Cufdex-EX; Cufokin; Decofed-X; Deletus-BX; Dilo-BM; Eascof Exp; Efelin-X; Eledyl; Elsol-T; Esma-PD; Estharil Plus; Etoxin-B Exp; Etoxin-B; Euphomin Plus; Ex-GTM; Exiplon-BR; Exolit; Expect-T; Grilinctus-BM; Historil; Indikof-B; Ingahist-X; Intacof-S; Kafban; Kazibrox-BT; Kickkof; Kofarest Expectorant; Kofban-EX; Koforil; Kuff-Q; Kuff-X; Kufgen-X; Kufkair; Libitus Plus; Litcoff-P; Litcoff; Mags; Marex; Medkof; Megaril; Mucaryl-AX; Mucomelt-XP; Mucopen; Mucoresp Plus; Mucorid; Mucosma-T; Mucosol; Munorm; Muscarin; Mutech; New Zephrol; Nomorcuf; Norvent; NSI-Ril; NT-Kuf-AM; NT-Kuf-M; Nutuss-A; Nutuss-BR; Okaril Plus; Oox; Optex-AT; Suprivent-A; Suprivent; Tergil-T†; Tergil†; Terpect; Terpect; Terphylate; Terphylin; Theobric; Toscof; Tuspel Plus; *Indon.*: Bricasma Expectorant†; Terasma Expectorant†; *Irl.*: Bricanyl Expectorant†; *Malaysia*: Tolbin Expectorant; *Mex.*: Bricanyl EX; *Philipp.*: Bricanyl Expectorant; *S.Afr.*: Benylin Bronchospect†; Bronchoped; *Spain*: Terbasmin Expectorante; *Thai.*: Asmaline Expectorant; Asthnyl; Benyl; Bricanyl Expectorant†; Broncet; Broncholac Bronchonyl; Cofbron; Terbu Expectorant; Terbulin Expectorant; Terbusin Expectorant; Terline; Tolbin; *Turk.*: Bricanyl Expektoran; *Ukr.*: Bro-Zedex (Бро-Зедекс)†.

Pharmacopoeial Preparations

BP 2014: Terbutaline Tablets;

USP 36: Terbutaline Oral Suspension; Terbutaline Sulfate Inhalation Aerosol; Terbutaline Sulfate Injection; Terbutaline Sulfate Tablets.

Theobromine *(BAN)*

Santheose; Teobromilni; Teobromin; Teobromina; Teobrominas; Theobromin; Theobromine; Theobrominum; Теобромин.

3,7-Dihydro-3,7-dimethylpurine-2,6(1*H*)-dione; 3,7-Dimethylxanthine.

$C_7H_8N_4O_2$=180.2

CAS — 83-67-0.

ATC — C03BD01; R03DA07.

ATC Vet — QC03BD01; QR03DA07.

UNII — OBD44SWZSP.

Pharmacopoeias. In *Eur.* (see p. vii)

Ph. Eur. 8: (Theobromine). A white or almost white powder. Very slightly soluble in water and in dehydrated alcohol; slightly soluble in ammonia. It dissolves in dilute solutions of alkali hydroxides and in mineral acids.

Profile

Theobromine has the general properties of the other xanthines (see Theophylline, below). It has a weaker activity than theophylline or caffeine and has practically no stimulant effect on the CNS. Large doses can cause nausea and vomiting. Theobromine has been used for its bronchodilating properties and in the treatment of cardiovascular disorders. Theobromine and calcium salicylate (theosalicin), theobromine and sodium acetate, and theobromine and sodium salicylate (themisalum, theobromsal) have all been used similarly to theobromine.

Theobromine is the chief xanthine in the beverage cocoa (p. 2648.2). It is also present in chocolate and in small amounts in tea. Theobroma oil may contain up to 2% theobromine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Cellenergy.

Theophylline *(BAN)*

Anhydrous Theophylline; Teocina; Teofilin; Teofillna; Teofilinas; Teofillin; Teofillina; Teofyllin; Teofyllina; Theofylin; Theophyllin; Theophylline; Theophyllinum; Теофиллин.

3,7-Dihydro-1,3-dimethylpurine-2,6(1*H*)-dione; 1,3-Dimethylxanthine.

$C_7H_8N_4O_2$=180.2

CAS — 58-55-9.

ATC — R03DA04.

ATC Vet — QR03DA04.

UNII — C137DTR5RG (theophylline); 0I55T2BTYK (anhydrous theophylline).

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.* Some pharmacopoeias include anhydrous and hydrated theophylline in one monograph.

Ph. Eur. 8: (Theophylline). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol. It dissolves in solutions of alkali hydroxides, in ammonia, and in mineral acids.

USP 36: (Theophylline). It contains one molecule of water of hydration or is anhydrous. It is a white, odourless, crystalline powder. Slightly soluble in water, more soluble in hot water; sparingly soluble in alcohol, in chloroform, and in ether; freely soluble in solutions of alkali hydroxides and in ammonia.

Theophylline Hydrate *(BANM)*

Teofilina monohidrato; Teofilinas monohidratas; Teofyllinimonohydraatti; Teofyllinmonohydrat; Theofylin monohydrát; Theophyllin-Monohydrat; Theophylline Monohydrate; Theophylline monohydratée; Theophyllinum Monohydricum; Теофиллина гидрат.

$C_7H_8N_4O_2.H_2O$=198.2

CAS — 5967-84-0.

ATC — R03DA04.

ATC Vet — QR03DA04.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *US*, and *Viet.* Some pharmacopoeias include anhydrous and hydrated theophylline in one monograph.

Ph. Eur. 8: (Theophylline Monohydrate; Theophylline Hydrate BP 2014). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol. It dissolves in solutions of alkali hydroxides, in ammonia, and in mineral acids.

USP 36: (Theophylline). It contains one molecule of water of hydration or is anhydrous. It is a white, odourless, crystalline powder. Slightly soluble in water, more soluble in hot water; sparingly soluble in alcohol, in chloroform, and in ether; freely soluble in solutions of alkali hydroxides and in ammonia.

Stability. Alcohol-free theophylline liquid repackaged in clear or amber polypropylene oral syringes could be stored at room temperature under continuous fluorescent lighting for at least 180 days without significant change in the concentration of theophylline.[1] However, it was recommended that solutions be protected from light because of the potential for discoloration.

Extemporaneous oral preparations of theophylline 5 mg/mL in commercial suspension vehicles were found[2] to be stable for up to 90 days in amber plastic bottles stored at 23 degrees to 25 degrees.

1. Johnson CE, Drabik BT. Stability of alcohol-free theophylline liquid repackaged in plastic oral syringes. *Am J Hosp Pharm* 1989; 46: 980–1.
2. Johnson CE, *et al.* Stability of anhydrous theophylline in extemporaneously prepared alcohol-free oral suspensions. *Am J Health-Syst Pharm* 2005; 62: 2518–20.

Uses and Administration

Theophylline is a xanthine (p. 1195.2) and relaxes bronchial smooth muscle, relieves bronchospasm, and has a stimulant effect on respiration. It stimulates the myocardium and CNS, decreases peripheral resistance and venous pressure, and causes diuresis. It is still not clear how theophylline exerts these effects. Inhibition of phosphodiesterase with a resulting increase in intracellular cyclic adenosine monophosphate (cyclic AMP) occurs, and may play a role. Other proposed mechanisms of action include adenosine receptor antagonism, prostaglandin antagonism, and effects on intracellular calcium. In addition, theophylline may also have an anti-inflammatory effect.

Theophylline is used as a bronchodilator in the management of reversible airways obstruction, such as in asthma. Although selective $beta_2$ adrenoceptor stimulants ($beta_2$ agonists) such as salbutamol are generally the preferred bronchodilators for initial treatment, theophylline is commonly used as an adjunct to $beta_2$ agonist and corticosteroid therapy in patients requiring an additional bronchodilating effect. Some patients with chronic obstructive pulmonary disease also have a beneficial

response to theophylline therapy. Theophylline is also used to relieve apnoea in neonates. It was formerly used as an adjunct in the treatment of heart failure, and may occasionally have a role in patients with this condition who are also suffering from obstructive airways disease.

Theophylline may be given in the anhydrous form or as the hydrate. Doses of theophylline are usually expressed as anhydrous theophylline; theophylline hydrate 1.1 mg is equivalent to about 1 mg of theophylline.

The pharmacokinetics of theophylline may be altered by factors including age, smoking, disease, diet, and drug interactions (see under Precautions p. 1233.1, Interactions p. 1233.3, and Pharmacokinetics p. 1236.3). Theophylline doses should therefore be adjusted for each individual patient according to clinical response, adverse effects, and serum-theophylline concentrations.

- Optimum **therapeutic serum concentrations** of theophylline are traditionally considered to range from 10 to 20 micrograms/mL (55 to 110 micromoles/litre) and toxic effects are more common above 20 micrograms/mL. A range of 5 to 15 micrograms/mL may be effective, and associated with fewer adverse effects.

For long-term use, once a maintenance dose has been established, monitoring of serum-theophylline concentrations at 6- to 12-monthly intervals has been recommended.

In the management of **acute severe bronchospasm**, theophylline may be given by *intravenous infusion* where available, though usually aminophylline is preferred (see p. 1201.3). (Anhydrous theophylline 1 mg is equivalent to about 1.18 mg anhydrous aminophylline or 1.28 mg aminophylline hydrate.)

- In patients who have not received theophylline, aminophylline, or other xanthine-containing medications in the previous 24 hours, a suggested loading dose of 4 to 5 mg/kg may be given by intravenous infusion over 20 to 30 minutes followed by a suggested maintenance dose of 400 to 600 micrograms/kg per hour. Lower doses should be used in the elderly and those with cor pulmonale, heart failure, or liver disease; smokers may require a higher maintenance dose. Dosage should be calculated in terms of lean or ideal body-weight.
- Intravenous theophylline therapy is best avoided in patients already taking theophylline, aminophylline, or other xanthine-containing medication but, if considered necessary, serum-theophylline concentrations should be measured to determine a loading dose. Loading doses are based on the expectation that each 500 micrograms of theophylline/kg of lean body-weight will result in an increase of serum-theophylline concentration of 1 microgram/mL.

In the treatment of **acute bronchospasm** that has not required intravenous therapy, theophylline has been given *orally* in conventional dosage forms; modified-release preparations are not suitable.

- In adults not currently taking theophylline or xanthine-containing products a suggested loading dose is 5 mg/kg, to produce an average peak serum concentration of 10 micrograms/mL. Doses should again be reduced in the elderly and those with cor pulmonale, heart failure, or liver disease; smokers may require a higher maintenance dose.

In the long-term management of **chronic bronchospasm**, theophylline may be given orally in doses ranging from 300 to 1000 mg daily in divided doses as conventional tablets, capsules, liquid preparations, or modified-release preparations. For conventional dosage forms the divided doses are generally given every 6 to 8 hours. However, modified-release preparations are more commonly used as they reduce adverse effects and the need for frequent dosing, especially in patients with a rapid theophylline clearance.

- A usual dose of modified-release theophylline is 175 to 500 mg every 12 hours, though the bioavailability of different modified-release theophylline preparations may not be comparable and retitration of dosage is required if the patient is changed from one modified-release preparation to another. Larger doses may be given in either the evening or the morning to achieve optimum therapeutic effect when symptoms are most severe. Modified-release preparations which are given once daily are also available; usual doses are 400 or 600 mg daily.
- Initially, low doses of theophylline should be given and they should be gradually adjusted according to clinical response and serum-theophylline measurements. In the USA a preferred approach to initial dosage titration in adults may be to begin with 300 mg daily, in divided doses, for 3 days; if well tolerated, the total daily dose is increased to 400 mg for 3 days, and then, if tolerated and required, to 600 mg. For doses of theophylline used in children, see Administration in Children, below.

Intramuscular injection and dosage by suppository are not recommended due to severe local irritation and slow unreliable absorption.

Theophylline is an ingredient of some preparations promoted for coughs.

There are topical cosmetic preparations containing theophylline derivatives, particularly aminophylline, that have been promoted for the local reduction of body fat (p. 1202.2).

Theophylline monoethanolamine (theophylline olamine), theophylline calcium salicylate, theophylline and sodium acetate (theophylline sodium acetate), theophylline sodium glycinate (theophylline sodium aminoacetate), theophylline calcium glycinate, and theophylline glycinate have all been used similarly to theophylline.

General references.

1. Vasallo R, Lipsky JJ. Theophylline: recent advances in the understanding of its mode of action and uses in clinical practice. *Mayo Clin Proc* 1998; 73: 346–54.
2. Barnes PJ. Theophylline: new perspectives for an old drug. *Am J Respir Crit Care Med* 2003; 167: 813–18.

Administration. Various methods have been proposed for estimating theophylline pharmacokinetic parameters to enable optimisation of initial dosage but none should be substituted for the subsequent determination of serum-theophylline concentrations and clearance at steady state.[1-3]

It was noted in 1997 that dosage requirements for theophylline had declined relative to those of historical controls, apparently due to a downward shift in theophylline clearance in the US population (perhaps due to environmental changes, such as a decrease in exposure to tobacco smoke).[4] It was suggested that earlier dosage guidelines for theophylline needed to be revised in the light of these data, so that the initial oral dose did not exceed 300 mg daily—for an approach to initial dosage titration consonant with this view, see Uses and Administration, p. 1229.3.

1. Erdman SM, *et al.* An updated comparison of drug dosing methods part II: theophylline. *Clin Pharmacokinet* 1991; 20: 280–92.
2. Hogue SL, Phelps SJ. Evaluation of three theophylline dosing equations for use in infants up to one year of age. *J Pediatr* 1993; 123: 651–6.
3. Lee TC, *et al.* Theophylline population pharmacokinetics from routine monitoring data in very premature infants with apnoea. *Br J Clin Pharmacol* 1996; 41: 191–200.
4. Asmus MJ, *et al.* Apparent decrease in population clearance of theophylline: implications for dosage. *Clin Pharmacol Ther* 1997; 62: 483–9.

Administration in children. In the management of **acute severe bronchospasm** in children, theophylline may be given by *intravenous infusion* where available, although aminophylline is preferred (see p. 1202.1). In children who have not had theophylline, aminophylline or other xanthine-containing medicine in the previous 24 hours, a suggested loading dose of 4 to 5 mg/kg may be given by intravenous infusion over 20 to 30 minutes. Initial maintenance doses are designed to achieve a serum-theophylline concentration of 10 micrograms/mL. The following doses, based on lean or ideal body-weight, have been suggested:

- 1 to 9 years of age: 800 micrograms to 1 mg/kg per hour
- 9 to 12 years of age: 700 to 770 micrograms/kg per hour

Serum-theophylline concentrations should be used to guide further dose adjustments. See Administration in Infants, below for doses used in children under 1 year of age. Children 12 years of age and over can receive similar doses to adults, see Uses and Administration, p. 1229.3.

If intravenous theophylline therapy is considered necessary in children who are already being given theophylline, aminophylline or other xanthine-containing medicine, serum-theophylline concentrations should be measured to determine a loading dose. Loading doses are based on the expectation that each 500 micrograms of theophylline/kg of lean body-weight will result in a 1-microgram/mL increase in serum-theophylline concentration.

In the treatment of **acute bronchospasm** that has not required intravenous therapy, theophylline has been given *orally* using immediate-release preparations to children aged 1 year old and above, using doses similar to those used in adults, see Uses and Administration, p. 1229.3. For doses used in children under 1 year of age, see Administration in Infants, below.

Oral modified-release preparations of theophylline are given to children from 6 months of age in the long-term management of **chronic bronchospasm**. Dose and dosage frequency depend on the preparation being used, and licensed product information should be consulted; different formulations are not considered interchangeable.

ADMINISTRATION IN INFANTS. Theophylline clearance is reduced in premature neonates and infants under 1 year of age due to an immature hepatic microsomal enzyme system (see under Metabolism and Excretion in Pharmacokinetics, p. 1237.1). Postconceptional age may have a slight influence on theophylline clearance but postnatal age is thought to be more significant.[1]

Theophylline dosage guidelines for infants under 1 year of age were issued by the FDA[2] in 1985, but some clinicians considered that higher doses might be necessary.[1,3,4] Subsequent guidelines for *oral* theophylline,[5] issued in 1995, suggested a modified regimen: premature infants should be given initial doses of 1 mg/kg every 12 hours if less than 24 days postnatal age, or 1.5 mg/kg every 12 hours if more than 24 days; in full-term infants up to 1 year of age initial daily dosage (to be given in 3 or 4 divided doses) could be calculated on the basis of the equation:

$$\text{Daily dose (mg/kg)} = (0.2 \times \text{age in weeks}) + 5.0$$

Subsequent dosage should be adjusted based on steady-state serum-theophylline concentrations, which might take as long as 5 days to be achieved in premature neonates if a loading dose is not used.[5] The recommended serum concentrations were 5 to 10 micrograms/mL in neonates and 10 to 15 micrograms/mL in older infants. If a loading dose is considered necessary, 5 mg/kg (or 1 mg/kg for each 2 micrograms/mL increase in serum-theophylline concentration in those already being given theophylline) has been suggested.

Other equations and models of population pharmacokinetics have been proposed for the calculation of appropriate theophylline doses in neonates.[6-8]

Theophylline may be given by *intravenous infusion*, where available, in the management of **acute severe bronchospasm** in infants, although aminophylline is preferred (see p. 1202.1). In infants who have not had theophylline, aminophylline or other xanthine-containing medicine in the previous 24 hours, a suggested loading dose of 4 to 5 mg/kg may be given by intravenous infusion over 20 to 30 minutes. In neonates the following initial maintenance doses have been suggested by the *American Hospital Formulary Service*[9] to achieve a serum-theophylline concentration of 7.5 micrograms/mL:

- neonate, postnatal age 24 days or less: 1 mg/kg every 12 hours
- neonate, postnatal age over 24 days: 1.5 mg/kg every 12 hours

To achieve a serum-theophylline concentration of 10 micrograms/mL the following initial maintenance doses have been suggested by the *Canadian Pharmacists Association*:

- neonate: 170 micrograms/kg per hour
- 6 weeks to 6 months of age: 430 micrograms/kg per hour
- 6 months to 1 year of age: 500 to 600 micrograms/kg per hour

Serum-theophylline concentrations should be used to guide further dose adjustments.

Theophylline may be given prophylactically to reduce some of the adverse renal consequences of perinatal asphyxia (see p. 1231.2).

Theophylline has been used in **neonatal apnoea**, although caffeine is preferred. See Neonatal Apnoea, under Caffeine p. 1204.3.

1. Gilman JT. Gal P. Inadequacy of FDA dosing guidelines for theophylline use in neonates. *Drug Intell Clin Pharm* 1986; 20: 481–4.
2. Anonymous. Use of theophylline in infants. *FDA Drug Bull* 1985; 15: 16–17.
3. Murphy JE, *et al.* New FDA guidelines for theophylline dosing in infants. *Clin Pharm* 1986; 5: 16.
4. Kriter KE, Blanchard J. Management of apnea in infants. *Clin Pharm* 1989; 8: 577–87.
5. Hendeles L, *et al.* Revised FDA labeling guideline for theophylline oral dosage forms. *Pharmacotherapy* 1995; 15: 409–27.
6. Hogue SL, Phelps SJ. Evaluation of three theophylline dosing equations for use in infants up to one year of age. *J Pediatr* 1993; 123: 651–6.
7. Lee TC, *et al.* Theophylline population pharmacokinetics from routine monitoring data in very premature infants with apnoea. *Br J Clin Pharmacol* 1996; 41: 191–200.
8. Gagnon AJ. Aminophylline dosing in the treatment of apnea of prematurity—a commentary. *Pharmacotherapy* 1996; 16: 317–18.
9. McEvoy GK (ed). AHFS Drug Information. online] Bethesda, MD: American Society of Health-System Pharmacists. Available at: http://www.medicinescomplete.com (accessed 13/10/09)

Administration in hepatic impairment. Theophylline clearance is reduced by 50% or more in patients with hepatic insufficiency such as cirrhosis, acute hepatitis, or cholestasis. Careful attention to dose reduction and frequent monitoring of serum-theophylline concentrations are required.

Asthma. Theophylline and its derivatives may be used in the treatment of chronic asthma (p. 1195.2) as an adjunct to $beta_2$ agonists and corticosteroid therapy when an additional bronchodilator is indicated. Modified-release preparations can be useful in the control of nocturnal asthma. Evidence for use in acute severe attacks is more mixed,[1,2] and guidelines differ in their recommendations.

Evidence suggests[3,4] that adding low-dose oral theophylline to inhaled corticosteroids is as effective as increasing the dose of corticosteroid in patients with moderate asthma and persistent symptoms. A systematic review[5] of studies that compared theophylline with long-acting $beta_2$ agonists found that they were both effective for control of nocturnal asthma, but that long-acting $beta_2$ agonists may be more effective in reducing asthma

symptoms, including night waking and the need for rescue medication, and are associated with fewer adverse effects.

1. Mitra A, *et al.* Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 19/03/08).
2. Parameswaran K, *et al.* Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 19/03/08).
3. Wang Y, *et al.* Comparison of inhaled corticosteroid combined with theophylline and double-dose inhaled corticosteroid in moderate to severe asthma. *Respirology* 2005; 10: 189–95.
4. Lim S, *et al.* Comparison of high dose inhaled steroids, low dose inhaled steroids plus low dose theophylline, and low dose inhaled steroids alone in chronic asthma in general practice. *Thorax* 2000; 55: 837–41.
5. Tee AKH, *et al.* Long acting beta-agonists versus theophylline for maintenance treatment of asthma. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 19/03/08).

Cardiac arrhythmias. Theophylline and aminophylline have been tried in various bradyarrhythmias, usually when other treatment has failed or is contra-indicated.[1-6] Aminophylline appears to be of little value in bradyasystolic cardiac arrest.[7,8]

1. Viskin S, *et al.* Aminophylline for bradyasystolic cardiac arrest refractory to atropine and epinephrine. *Ann Intern Med* 1993; 118: 279–81.
2. Sra JS, *et al.* Comparison of cardiac pacing with drug therapy in the treatment of neurocardiogenic (vasovagal) syncope with bradycardia or asystole. *N Engl J Med* 1993; 328: 1085–90.
3. Bertolet BD, *et al.* Theophylline for the treatment of atrioventricular block after myocardial infarction. *Ann Intern Med* 1995; 123: 509–11.
4. Alboni P, *et al.* Effects of permanent pacemaker and oral theophylline in sick sinus syndrome: the THEOPACE study: a randomized controlled trial. *Circulation* 1997; 96: 260–6.
5. Ling CA, Crouch MA. Theophylline for chronic symptomatic bradycardia in the elderly. *Ann Pharmacother* 1998; 32: 837–9.
6. Cawley MJ, *et al.* Intravenous theophylline — an alternative to temporary pacing in the management of bradycardia secondary to AV nodal block. *Ann Pharmacother* 2001; 35: 303–7.
7. Abu-Laban RB, *et al.* Aminophylline in bradyasystolic cardiac arrest: a randomised placebo-controlled trial. *Lancet* 2006; 367: 1577–84.
8. Hayward E, *et al.* Aminophylline in bradyasystolic cardiac arrest. *Emerg Med J* 2007; 24: 582–3.

Cheyne-Stokes respiration. Oral theophylline considerably reduced Cheyne-Stokes respiration (periodic breathing) and episodes of central apnoea in 2 studies in patients with stable heart failure and left ventricular systolic dysfunction.[1,2] This was associated with an improvement in arterial-oxygen saturation during sleep. One study[1] saw no significant change in cardiac function, although pulmonary function did improve. Theophylline was also effective in a patient with Cheyne-Stokes respiration possibly related to diabetic autonomic neuropathy[3] (the use of the term Cheyne-Stokes respiration to describe this patient's respiratory disorder has been questioned[4,5]).

1. Javaheri S, *et al.* Effect of theophylline on sleep-disordered breathing in heart failure. *N Engl J Med* 1996; 335: 562–7.
2. Hu K, *et al.* The effect of theophylline on sleep-disordered breathing in patients with stable chronic congestive heart failure. *Chin Med J* 2003; 116: 1711–16.
3. Pesek CA, *et al.* Theophylline therapy for near-fatal Cheyne-Stokes respiration: a case report. *Ann Intern Med* 1999; 130: 427–30.
4. Sin DD, Bradley TD. Theophylline therapy for near-fatal Cheyne-Stokes respiration. *Ann Intern Med* 1999; 131: 713.
5. Geigel EJ, Chediak AD. Theophylline therapy for near-fatal Cheyne-Stokes respiration. *Ann Intern Med* 1999; 131: 713–14.

Chronic obstructive pulmonary disease. In the treatment of chronic obstructive pulmonary disease (p. 1199.1), the bronchodilators of first choice are usually either an antimuscarinic such as ipratropium bromide, or a $beta_2$ agonist such as salbutamol, given by inhalation. However the addition of an oral xanthine such as theophylline may be of value in some patients to maximise respiratory function and for its positive cardiac inotropic effects.

A systematic review[1] of studies comparing oral theophylline with placebo in patients with moderate to severe chronic obstructive pulmonary disease (COPD), found that theophylline treatment improved lung function, ventilatory capacity, and arterial blood gas tensions. A decrease in thoracic gas entrapment and hyperinflation, and an increase in respiratory muscle function and diaphragmatic strength could be responsible for the improvement in symptoms. Improvements in arterial blood gas tensions may result from an increased tidal volume caused by either a direct positive inotropic effect on the respiratory muscles, or a central stimulatory action, or both. The authors concluded that theophylline produced an improvement in lung function similar to that reported for long acting $beta_2$ agonists in COPD patients, and that with close monitoring beneficial effects may be obtained from theophylline therapy in those patients who remain symptomatic from COPD despite first-line bronchodilator therapy. Theophylline has been reported to exert an inhibitory effect on airway inflammation in COPD, particularly at plasma concentrations below 10 micrograms/mL.[2] During acute exacerbations of COPD, low-dose theophylline was noted to have an effect on inflammatory markers, prompting the suggestion that it may increase the anti-inflammatory effect of systemic corticosteroids given for exacerbations and improve corticosteroid responsiveness.[3]

1. Ram FSF, *et al.* Oral theophylline for chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 19/03/08).
2. Barnes PJ. Theophylline for COPD. *Thorax* 2006; 61: 742–4.
3. Cosio BG, *et al.* Low-dose theophylline enhances the anti-inflammatory effects of steroids during exacerbations of COPD. *Thorax* 2009; 64: 424–9.

Contrast nephropathy. For mention of theophylline as a potential protectant against kidney damage induced by iodinated contrast media, see Effects on the Kidneys, under Amidotrizoic Acid, p. 1582.2.

ECT. For mention of the use of theophylline as an adjunct to electroconvulsive therapy, see under Precautions, p. 1233.2.

Erythrocytosis. When pharmacological treatment is required for secondary erythrocytosis (p. 1283.1), UK guidelines[1,2] recommend an ACE inhibitor or an angiotensin II receptor antagonist as the usual drugs of first choice. Although theophylline appears to be less effective than an ACE inhibitor in post-transplantation erythrocytosis[3] an oral daily dose of 8 mg/kg has produced beneficial effects.[4,5] Theophylline may be of use given either alone or with an ACE inhibitor in those who fail to respond to first-line therapy. Theophylline treatment may also reduce erythrocytosis associated with chronic obstructive pulmonary disease.[6]

1. McMullin MF, *et al.* General Haematology Task Force of the British Committee for Standards in Haematology. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. *Br J Haematol* 2005; 130: 174–95. Also available at: http://www.bcshguidelines.com/pdf/polycythaemia_05.pdf (accessed 19/03/08)
2. McMullin MF, *et al.* National Cancer Research Institute, Myeloproliferative Disorder Subgroup. British Committee for Standards in Haematology. Amendment to the guideline for diagnosis and investigation of polycythaemia/erythrocytosis. *Br J Haematol* 2007; 138: 821–2. Also available at: http://www.bcshguidelines.com/pdf/polycythaemia_amendment_07.pdf (accessed 19/03/08)
3. Ok E, *et al.* Comparison of the effects of enalapril and theophylline on polycythemia after renal transplantation. *Transplantation* 1995; 59: 1623–45.
4. Bakris GL, *et al.* Effects of theophylline on erythropoietin production in normal subjects and in patients with erythrocytosis after renal transplantation. *N Engl J Med* 1990; 323: 86–90.
5. Ilan Y, *et al.* Erythrocytosis after renal transplantation: the response to theophylline treatment. *Transplantation* 1994; 57: 661–4.
6. Oren R, *et al.* Effect of theophylline on erythrocytosis in chronic obstructive pulmonary disease. *Arch Intern Med* 1997; 157: 1474–8.

Methotrexate neurotoxicity. For reference to the use of aminophylline or theophylline to relieve the acute neurotoxicity of methotrexate, see Other Drugs, under Treatment of Adverse Effects, p. 827.1.

Perinatal asphyxia. Perinatal asphyxia frequently results in damage to the kidneys;[1] vasomotor nephropathy or acute renal failure may develop as a result of decreased perfusion to the kidneys.[2] Theophylline has been studied for the prevention of renal dysfunction associated with perinatal asphyxia in both term and preterm neonates.[1-3] Beneficial effects have been seen after early use of intravenous theophylline, including significant decreases in serum creatinine[1-3] and urinary β2-microglobulin (an indicator of tubular performance),[1,3] and a significant increase in creatinine clearance.[1-3] A single dose of 8 mg/kg theophylline, by slow intravenous injection in the first hour of life, was given to neonates at term.[1-3] Lower doses were used for preterm neonates; 1 mg/kg daily for 3 consecutive days.[2]

1. Bhat MA, *et al.* Theophylline for renal function in term neonates with perinatal asphyxia: a randomised, placebo-controlled trial. *J Pediatr* 2006; 149: 180–4.
2. Cattarelli D, *et al.* A randomised, double blind, placebo controlled trial of the effect of theophylline in prevention of vasomotor nephropathy in very preterm neonates with respiratory distress syndrome. *Arch Dis Child Fetal Neonatal Ed* 2006; 91: F80–F84.
3. Jenik AG, *et al.* A randomized, double-blind, placebo-controlled trial of the effects of prophylactic theophylline on renal function in term neonates with perinatal asphyxia. *Pediatrics* 2000; 105: e45. Also available at: http://pediatrics.aappublications.org/cgi/content/full/105/4/e45 (accessed 19/03/08)

Adverse Effects

The commonest adverse effects of theophylline and xanthine derivatives, irrespective of the route, are gastrointestinal irritation and stimulation of the CNS. Serum concentrations of theophylline greater than 20 micrograms/mL (110 micromol/litre) are associated with an increased risk of adverse effects (but see below).

Theophylline may cause nausea, vomiting, abdominal pain, diarrhoea, and other gastrointestinal disturbances, insomnia, headache, anxiety, irritability, restlessness, tremor, and palpitations. Overdosage may also lead to agitation, diuresis and repeated vomiting (sometimes haematemesis) and consequent dehydration, cardiac arrhythmias including tachycardia, hypotension, electrolyte disturbances including profound hypokalaemia, hyperglycaemia, hypomagnesaemia, metabolic acidosis, rhabdomyolysis, convulsions, and death. Severe toxicity may not be preceded by milder symptoms. Convulsions, cardiac arrhythmias, severe hypotension, or cardiac arrest may follow rapid intravenous injection, and fatalities have been reported. The drug is too irritant for intramuscular use. Proctitis may follow repeated use of suppositories.

Adverse effects are uncommon at **serum-theophylline concentrations** of 5 to 10 micrograms/mL or above, and are greatly increased in frequency and severity at concentrations greater than 20 micrograms/mL.[1-3] The severity of toxicity is generally correlated with age, underlying disease, and serum-theophylline concentration, but a distinction has been made between acute and chronic theophylline intoxication; symptoms appear to occur at a lower theophylline concentration in chronic toxicity than after acute ingestion of large amounts.[1,2,4,5] Young infants and the elderly (over 60 years) appear to be at particular risk from chronic intoxication with theophylline.[4,7] Older patients with chronic intoxication may be at greater risk of major toxic effects, such as arrhythmias, seizures, and death, than those with acute intoxication.[5]

Common clinical manifestations of theophylline toxicity after overdosage of aminophylline or theophylline include nausea, vomiting, diarrhoea, agitation, tremor, hypertonicity, hyperventilation, supraventricular and ventricular arrhythmias, hypotension, and seizures. Metabolic disturbances such as hypokalaemia, hyperglycaemia, hypophosphataemia, hypercalcaemia, metabolic acidosis, and respiratory alkalosis often occur.[1-3] Other toxic effects reported include dementia,[8] toxic psychosis,[9] symptoms of acute pancreatitis,[10] rhabdomyolysis[11-13] with associated renal failure,[11] and acute compartment syndrome.[14]

Serious toxic symptoms may not be preceded by minor symptoms. In acute intoxication with modified-release preparations the onset of major toxic symptoms may be delayed for up to 24 hours[1] and prolonged monitoring of such patients is required. Patients have recovered despite serum-theophylline concentrations in excess of 200 micrograms/mL[12,14] but fatalities have occurred with much lower serum concentrations.[10,15,16] Mortality in severe poisoning may be as high as 10%.

1. Dawson AH, Whyte IM. The assessment and treatment of theophylline poisoning. *Med J Aust* 1989; 151: 689–93.
2. Minton NA, Henry JA. Acute and chronic human toxicity of theophylline. *Hum Exp Toxicol* 1996; 15: 471–81.
3. Hardy CC, Smith J. Adverse reactions profile: theophylline and aminophylline. *Prescribers' J* 1997; 37: 96–101.
4. Olson KR, *et al.* Theophylline overdose: acute single ingestion versus chronic repeated overmedication. *Am J Emerg Med* 1985; 3: 386–94.
5. Shannon M. Life-threatening events after theophylline overdose: a 10-year prospective analysis. *Arch Intern Med* 1999; 159: 989–94.
6. Shannon M, Lovejoy FH. Effect of acute versus chronic intoxication on clinical features of theophylline poisoning in children. *J Pediatr* 1992; 121: 125–30.
7. Shannon M. Predictors of major toxicity after theophylline overdose. *Ann Intern Med* 1993; 119: 1161–7.
8. Drummond L. Aminophylline toxicity in the elderly. *BMJ* 1982; 285: 779–80.
9. Wasser WG, *et al.* Theophylline madness. *Ann Intern Med* 1981; 95: 191.
10. Burgan THS, *et al.* Fatal overdose of theophylline simulating acute pancreatitis. *BMJ* 1982; 284: 939–40.
11. Macdonald JB, *et al.* Rhabdomyolysis and acute renal failure after theophylline overdose. *Lancet* 1985; i: 932–3.
12. Rumpf KW, *et al.* Rhabdomyolysis after theophylline overdose. *Lancet* 1985; i: 1451–2.
13. Modi KB, *et al.* Theophylline poisoning and rhabdomyolysis. *Lancet* 1985; ii: 160–1.
14. Lloyd DM, *et al.* Acute compartment syndrome secondary to theophylline overdose. *Lancet* 1990; ii: 312.
15. Whyte KF, Addis GJ. Toxicity of salbutamol and theophylline together. *Lancet* 1983; ii: 618–19.
16. Davies RJ, Hawkey CJ. Fatal theophylline toxicity precipitated by in situ pulmonary artery thrombosis. *Postgrad Med J* 1989; 65: 49–50.

Effects on carbohydrate metabolism. Hyperglycaemia is frequent in theophylline intoxication, and is thought to be secondary to theophylline-induced adrenal catecholamine release.[1,2] Whether the effects on blood glucose are significant at more modest serum concentrations of theophylline is unclear, although in 29 preterm infants, mean plasma-glucose concentrations were significantly higher after treatment with intravenous aminophylline and oral theophylline than in those not treated. Two of 15 treated infants developed clinically significant hyperglycaemia and glycosuria. It was recommended that plasma-glucose concentrations be monitored in preterm infants receiving theophylline.[3]

1. Kearney TE, *et al.* Theophylline toxicity and the beta-adrenergic system. *Ann Intern Med* 1985; 102: 766–9.
2. Shannon M. Hypokalemia, hyperglycemia and plasma catecholamine activity after severe theophylline intoxication. *J Toxicol Clin Toxicol* 1994; 32: 41–7.
3. Srinivasan G, *et al.* Plasma glucose changes in preterm infants during oral theophylline therapy. *J Pediatr* 1983; 103: 473–6.

Effects on electrolytes. Hypokalaemia is a common metabolic disturbance in theophylline intoxication, but it has also been reported[1] in patients with plasma-theophylline concentrations within the therapeutic range. It is considered to be secondary to theophylline-induced adrenal catecholamine release, with cellular influx of potassium ions.[2] It is recommended[1] that plasma-potassium is moni-

tored during intravenous theophylline therapy particularly if other drugs predisposing to hypokalaemia are also given (see also Interactions, p. 1233.3). Hypophosphataemia[1,3] and hyponatraemia[1] can also occur at therapeutic plasma-theophylline concentrations. Hypomagnesaemia[4] and hypercalcaemia[5] have occurred in theophylline overdose.

1. Zantvoort FA, *et al.* Theophylline and serum electrolytes. *Ann Intern Med* 1986; 104: 134–5.
2. Minton NA, Henry JA. Acute and chronic human toxicity of theophylline. *Hum Exp Toxicol* 1996; 15: 471–81.
3. Laaban J-P, *et al.* Hypophosphatemia complicating management of acute severe asthma. *Ann Intern Med* 1990; 112: 68–9.
4. Hall KW, *et al.* Metabolic abnormalities associated with intentional theophylline overdose. *Ann Intern Med* 1984; 101: 457–62.
5. McPherson ML, *et al.* Theophylline-induced hypercalcemia. *Ann Intern Med* 1986; 105: 52–4.

Effects on the heart. *ARRHYTHMIAS.* Theophylline or aminophylline can precipitate sinus tachycardia and supraventricular and ventricular premature contractions at therapeutic serum-theophylline concentrations[1] and in overdose.[2,3] Multifocal atrial tachycardia has also been associated with both theophylline overdose[2] and serum-theophylline concentrations within the generally accepted therapeutic range of 10 to 20 micrograms/mL.[4] Use of theophylline with oral beta-adrenoceptor stimulants is associated with a significant increase in the mean heart rate.[5,6]

1. Josephson GW, *et al.* Cardiac dysrhythmias during the treatment of acute asthma: a comparison of two treatment regimens by a double blind protocol. *Chest* 1980; 78: 429–35.
2. Greenberg A, *et al.* Severe theophylline toxicity: role of conservative measures, antiarrhythmic agents, and charcoal hemoperfusion. *Am J Med* 1984; 76: 854–60.
3. Minton NA, Henry JA. Acute and chronic human toxicity of theophylline. *Hum Exp Toxicol* 1996; 15: 471–81.
4. Levine JH, *et al.* Multifocal atrial tachycardia: a toxic effect of theophylline. *Lancet* 1985; i: 12–14.
5. Coleman JJ, *et al.* Cardiac arrhythmias during the combined use of β-adrenergic agonist drugs and theophylline. *Chest* 1986; 90: 45–51.
6. Conradson T-B, *et al.* Arrhythmogenicity from combined bronchodilator therapy in patients with obstructive lung disease and concomitant ischemic heart disease. *Chest* 1987; 91: 5–9.

Effects on the kidneys. For a report of rhabdomyolysis-induced acute renal failure occurring after aminophylline overdose, see the general discussion on toxicity, p. 1231.3.

Effects on mental function. As mentioned in the general discussion on toxicity on p. 1231.3, theophylline toxicity has been associated with reports of dementia and toxic psychosis, as well as the more common adverse effects of anxiety and restlessness.

LEARNING AND BEHAVIOUR PROBLEMS. Several small studies[1-3] have suggested that theophylline may be associated with learning and behaviour problems in children, especially those with a low IQ. However, the FDA has concluded[4] that such studies provide insufficient evidence to support an adverse effect of theophylline on learning behaviour or school performance. Other studies have found no marked behavioural adverse effects that could be attributed to theophylline,[5,6] and a meta-analysis[7] suggested that methylxanthine treatment might even have a small positive effect on behaviour. Additionally, academic achievement generally appeared to be unaffected by either asthma or by treatment with appropriate doses of theophylline.[8]

1. Purukawa CT, *et al.* Learning and behaviour problems associated with theophylline therapy. *Lancet* 1984; i: 621.
2. Springer C, *et al.* Clinical, physiologic, and psychologic comparison of treatment by cromolyn or theophylline in childhood asthma. *J Allergy Clin Immunol* 1985; 76: 64–9.
3. Schlieper A, *et al.* Effect of therapeutic plasma concentrations of theophylline on behavior, cognitive processing, and affect in children with asthma. *J Pediatr* 1991; 118: 449–55.
4. Anonymous. Theophylline and school performance. *FDA Drug Bull* 1988; 18: 32–3.
5. Bender B, Milgrom H. Theophylline-induced behavior change in children: an objective evaluation of parents' perceptions. *JAMA* 1992; 267: 2621–4.
6. Bender BG, *et al.* Neuropsychological behavioral changes in asthmatic children treated with beclomethasone dipropionate versus theophylline. *Pediatrics* 1998; 101: 355–60.
7. Stein MA, *et al.* Behavioral and cognitive effects of methylxanthines: a meta-analysis of theophylline and caffeine. *Arch Pediatr Adolesc Med* 1996; 150: 284–8.
8. Lindgren S, *et al.* Does asthma or treatment with theophylline limit children's academic performance? *N Engl J Med* 1992; 327: 926–30.

Effects on the nervous system. *CONVULSIONS.* The risk of convulsions with acute theophylline toxicity is low at serum theophylline concentrations less than 60 micrograms/mL;[1] seizures are most likely in patients with peak concentrations above 100 micrograms/mL.[2] However, the risk of seizures is much greater after chronic overdosage;[1,2] seizure activity has been reported at serum concentrations just above or even within the therapeutic range.[3] Elderly patients or those with previous brain injury or neurological disease may be at increased risk,[2-4] although some have questioned the association.[1] The outcome of seizures appears to be variable: death and severe neurological deficit have occurred,[2,3] but other series have recorded recovery without serious morbidity.[4]

1. Paloucek FP, Rodvold KA. Evaluation of theophylline overdoses and toxicities. *Ann Emerg Med* 1988; 17: 135–44.
2. Olson KR, *et al.* Theophylline overdose: acute single ingestion versus chronic repeated overmedication. *Am J Emerg Med* 1985; 3: 386–94.
3. Bahls FH, *et al.* Theophylline-associated seizures with "therapeutic" or low toxic serum concentrations: risk factors for serious outcome in adults. *Neurology* 1991; 41: 1309–12.
4. Covelli HD, *et al.* Predisposing factors to apparent theophylline-induced seizures. *Ann Allergy* 1985; 54: 411–15.

Effects on the skin. For reports of cutaneous reactions to theophylline and aminophylline, see under Hypersensitivity, below.

Effects on the urinary tract. Although diuresis is more commonly seen, urinary retention has been reported in male patients during therapy with aminophylline[1] or theophylline.[2]

1. Owens GR, Tannenbaum R. Theophylline-induced urinary retention. *Ann Intern Med* 1981; 94: 212–13.
2. Prakash M, Washburne JD. Theophylline and urinary retention. *Ann Intern Med* 1981; 94: 823.

Hypersensitivity. Hypersensitivity reactions have been reported after oral or intravenous doses of aminophylline. Reactions include erythematous rash with pruritus,[1,2] erythroderma,[2] and exfoliative dermatitis.[3] Aminophylline can produce both type I (immediate) and type IV (delayed) hypersensitivity reactions, the latter being due to the ethylenediamine component and can be confirmed by skin patch tests.[1-3] If hypersensitivity to ethylenediamine is confirmed it is recommended that aminophylline is avoided and treatment continued with theophylline or another theophylline salt.[1,3,4] Hypersensitivity reactions to theophylline have been reported rarely but type I reactions have occurred.[4] An erythematous, maculopapular rash has been reported[5] during treatment with a modified-release theophylline preparation, which did not occur when another modified-release theophylline product was given.

1. Hardy C, *et al.* Allergy to aminophylline. *BMJ* 1983; 286: 2051–2.
2. Mohsenifar Z, *et al.* Two cases of allergy to aminophylline. *Ann Allergy* 1982; 49: 281–2.
3. Nierenberg DW, Glazener FS. Aminophylline-induced exfoliative dermatitis: cause and implications. *West J Med* 1982; 137: 328–31.
4. Gibb WRG. Delayed-type hypersensitivity to theophylline/aminophylline. *Lancet* 1985; i: 49.
5. Mendel S, *et al.* Dermatologic reaction to a sustained-release theophylline product. *Clin Pharm* 1985; 4: 334–5.

Hyperuricaemia. In a study of 112 asthmatic patients receiving modified-release theophylline 200 to 400 mg 12-hourly, there was a significant correlation of serum-uric acid concentrations and serum-theophylline concentrations.[1] Gout has been reported in a woman receiving theophylline and aminophylline;[2] her serum-uric acid concentration was increased while receiving the xanthines, but subsequently fell when they were stopped, and rose again when treatment was resumed.

1. Morita Y, *et al.* Theophylline increases serum uric acid levels. *J Allergy Clin Immunol* 1984; 74: 707–12.
2. Toda K, *et al.* Gout due to xanthine derivatives. *Br J Rheumatol* 1997; 36: 1131–2.

Necrotising enterocolitis. Although there have been reports of neonatal necrotising enterocolitis associated with oral theophylline or aminophylline,[1,2] a study of 275 infants concluded that theophylline did not significantly contribute to its development.[3] It has been suggested that the high osmolality of liquid feeds and drugs including oral theophylline preparations may be involved in the aetiology of necrotising enterocolitis.[4]

1. Robinson MJ, *et al.* Xanthines and necrotising enterocolitis. *Arch Dis Child* 1980; 55: 494–5.
2. Williams AJ. Xanthines and necrotising enterocolitis. *Arch Dis Child* 1980; 55: 973–4.
3. Davis JM, *et al.* Role of theophylline in pathogenesis of necrotizing enterocolitis. *J Pediatr* 1986; 109: 344–7.
4. Watkinson M, *et al.* Hyperosmolar preparations for neonates. *Pharm J* 1987; 241: 488.

Withdrawal syndromes. Episodes of apnoea beginning 28 hours after birth and increasing in frequency and severity over the next 4 days occurred in a neonate whose mother had taken aminophylline and theophylline throughout pregnancy. Measurement of serum-theophylline concentration showed the increasing apnoea coincided with falling theophylline concentration. The infant's apnoea resolved on giving theophylline; treatment was stopped after 4 months.[1]

Worsening asthma control may occur when theophylline is withdrawn; there is some evidence of a rebound deterioration in lung function due to the development of tolerance.[2]

1. Borowitz DA, *et al.* Apnea associated with theophylline withdrawal in a term neonate. *Am J Dis Child* 1982; 136: 73–4.
2. Bennett JA, *et al.* The airway effects of stopping regular oral theophylline in patients with asthma. *Br J Clin Pharmacol* 1998; 45: 402–4.

Treatment of Adverse Effects

After theophylline or aminophylline overdosage, elimination may be enhanced by repeated oral doses of activated charcoal regardless of the route of overdose (see below). An osmotic laxative may also be considered. Treatment is symptomatic and supportive; ECG monitoring is recommended. Serum-theophylline concentrations should be monitored and if modified-release preparations have been taken monitoring should be prolonged. Metabolic abnormalities, particularly hypokalaemia, should be corrected; hypokalaemia may be so severe as to require intravenous infusion of potassium. In the non-asthmatic patient severe tachycardia, hypokalaemia, and hyperglycaemia may be reversed by a non-selective beta blocker (see also below). Patients with asthma or chronic obstructive pulmonary disease (COPD) who, after correction of hypokalaemia, have severe tachycardia, may be treated with intravenous verapamil. Alternatively direct current (DC) cardioversion may be considered. Ventricular arrhythmias causing haemodynamic compromise should also be treated with DC cardioversion. Isolated convulsions may be controlled by intravenous diazepam or a barbiturate; phenytoin may be less effective. In the most refractory cases general anaesthesia, and neuromuscular blockade, with ventilation, may be required.

Charcoal haemoperfusion or haemodialysis may be required.

Reviews.

1. Dawson AH, Whyte IM. The assessment and treatment of theophylline poisoning. *Med J Aust* 1989; 151: 689–93.
2. Skinner MH. Adverse reactions and interactions with theophylline. *Drug Safety* 1990; 5: 275–85.
3. Minton NA, Henry JA. Treatment of theophylline overdose. *Am J Emerg Med* 1996; 14: 606–12.

Activated charcoal. Multiple-dose oral activated charcoal is considered the cornerstone of treatment for theophylline and xanthine poisoning. It reduces the absorption of oral theophylline, and also enhances the elimination of theophylline from the body even after absorption or intravenous doses of xanthine. Aggressive antiemetic therapy may be required to allow use and retention of activated charcoal, since theophylline toxicity causes protracted vomiting. A cathartic such as sorbitol may be given with the activated charcoal to aid elimination of theophylline, but can cause fluid and electrolyte disturbances. For oral theophylline overdose the use of gastric lavage before oral activated charcoal may not be better than activated charcoal alone.

References.

1. Neuvonen PJ, *et al.* Comparison of activated charcoal and ipecac syrup in prevention of drug absorption. *Eur J Clin Pharmacol* 1983; 24: 557–62.
2. Berlinger WG, *et al.* Enhancement of theophylline clearance by oral activated charcoal. *Clin Pharmacol Ther* 1983; 33: 351–4.
3. Mahutte CK, *et al.* Increased serum theophylline clearance with orally administered activated charcoal. *Am Rev Respir Dis* 1983; 128: 820–2.
4. Park GD, *et al.* Effects of size and frequency of oral doses of charcoal on theophylline clearance. *Clin Pharmacol Ther* 1983; 34: 663–6.
5. Goldberg MJ, *et al.* The effect of sorbitol and activated charcoal on serum theophylline concentrations after slow-release theophylline. *Clin Pharmacol Ther* 1987; 41: 108–11.
6. Al-Shareef AH, *et al.* The effects of charcoal and sorbitol (alone and in combination) on plasma theophylline concentrations after a sustained-release formulation. *Hum Exp Toxicol* 1990; 9: 179–82.
7. Minton NA, *et al.* Prevention of drug absorption in simulated theophylline overdose. *Hum Exp Toxicol* 1995; 14: 170–4.

Beta blockers. Infusion of propranolol after theophylline overdose in 2 patients was associated with improvement in hyperglycaemia, hypokalaemia, tachycardia, and hypotension. Beta-adrenergic blockade may therefore be of benefit in the management of the metabolic changes of theophylline poisoning, especially in the non-asthmatic patient.[1,2] However, in asthmatic patients, beta blockers should be reserved for those with severe hypokalaemia or cardiac arrhythmias when mechanical ventilation is available as beta blockers can cause bronchoconstriction.[1,2] Propranolol reduces the clearance of theophylline (see under Interactions, p. 1235.2) and it has been suggested that a non-interacting beta blocker may be more appropriate.[3] Esmolol has been used successfully to manage cardiovascular symptoms of overdosage.[4]

1. Kearney TE, *et al.* Theophylline toxicity and the beta-adrenergic system. *Ann Intern Med* 1985; 102: 766–9.
2. Amin DN, Henry JA. Propranolol administration in theophylline overdose. *Lancet* 1985; i: 520–1.
3. Parrar KT, Dunn AM. Beta-blockers in treatment of theophylline overdose. *Lancet* 1985; i: 983.
4. Seneff M, *et al.* Acute theophylline toxicity and the use of esmolol to reverse cardiovascular instability. *Ann Emerg Med* 1990; 19: 671–3.

Endoscopy. Absorption is delayed after overdosage with modified-release oral preparations of aminophylline or theophylline and may be further prolonged by the formation of tablet aggregates, or bezoars, in the stomach.[1-3] Of 11 patients admitted with overdosage, one vomited a bezoar, 2 had bezoars removed at gastroscopy, and in one a bezoar was found at necropsy.[3] If bezoar formation occurs gastric lavage and activated charcoal will have little

if any effect and the patient may appear to stabilise before experiencing increasing serum-theophylline concentration and clinical deterioration;[1,2] fatalities have been reported.[1] Endoscopy should be considered in cases of modified-release theophylline overdosage in which clinical signs and serial concentration measurements suggest continuing drug absorption.[2]

1. Coupe M. Self-poisoning with sustained-release aminophylline: a mechanism for observed secondary rise in serum theophylline. *Hum Toxicol* 1986; 5: 341–2.
2. Cereda J-M, *et al.* Endoscopic removal of pharmacobezoar of slow release theophylline. *BMJ* 1986; 293: 1143.
3. Smith WDF. Endoscopic removal of a pharmacobezoar of slow release theophylline. *BMJ* 1987; 294: 125.

Haemodialysis and haemoperfusion. Extracorporeal theophylline removal techniques after overdosage of aminophylline or theophylline have been reviewed.[1] Neither peritoneal dialysis nor exchange transfusion produced a significant increase in the total body clearance of theophylline, whereas haemodialysis could be expected to double clearance, and haemoperfusion results in four- to sixfold increases in clearance. Charcoal haemoperfusion should be considered if the plasma-theophylline concentration exceeds 100 micrograms/mL in an acute intoxication, or 60 micrograms/mL in chronic overdose (40 micrograms/mL if there is significant respiratory or heart failure, or liver disease) though plasma concentrations alone should not determine its use (see under Adverse Effects, p. 1231.3). If there is intractable vomiting, arrhythmias, or seizures charcoal haemoperfusion should be started without delay. In most patients a 4-hour haemoperfusion allows significant clinical improvement, but treatment should continue until plasma concentrations are below 15 micrograms/mL. Plasma concentrations should be followed at least every 4 hours for the first 12 hours post-perfusion, as rebound increases have been noted on terminating perfusion. Haemodialysis may rarely be an alternative if haemoperfusion is not available, or in series with haemoperfusion if significant rhabdomyolysis is present. There has been a case report[2] of continuous venovenous haemofiltration used to treat severe theophylline toxicity.

1. Heath A, Knudsen K. Role of extracorporeal drug removal in acute theophylline poisoning: a review. *Med Toxicol* 1987; 2: 294–308.
2. Henderson JH, *et al.* Continuous venovenous haemofiltration for the treatment of theophylline toxicity. *Thorax* 2001; 56: 242–3.

Precautions

Theophylline or aminophylline should be given with caution to patients with peptic ulceration, porphyria, hyperthyroidism, hypertension, cardiac arrhythmias or other cardiovascular disease, or epilepsy, as these conditions may be exacerbated. They should also be given with caution to patients with heart failure, hepatic dysfunction, acute febrile illness, and to neonates and the elderly, since in all of these circumstances theophylline clearance may be decreased, resulting in increases in serum-theophylline concentrations and serum half-life. Conversely, smoking and alcohol consumption increase theophylline clearance. Many drugs interact with theophylline; for details see Interactions, below.

Intravenous injections of theophylline or aminophylline must be given very slowly to prevent dangerous CNS and cardiovascular adverse effects resulting from the direct stimulant effect.

Dosage requirements of theophylline vary widely between subjects; in view of the many factors affecting theophylline pharmacokinetics, serum concentration monitoring is necessary to ensure concentrations are within the therapeutic range.

Patients should not be transferred from one modified-release theophylline or aminophylline preparation to another without clinical assessment and the measurement of serum-theophylline concentrations because of bioavailability differences.

Acute febrile illness. A reduction in theophylline clearance has been noted in patients presenting with acute respiratory illness[1] and appears to be associated with the severity of the underlying pulmonary disease and the rate of change in the patient's condition.[2] Caution has been advised in giving theophylline to patients with chronic obstructive pulmonary disease with acute exacerbations, since these patients appear most likely to exhibit altered theophylline metabolism.[2]

Similarly, a decrease in theophylline clearance and an increase in the incidence of adverse effects has been reported during acute viral infections such as influenza in children receiving theophylline therapy for chronic asthma.[3,4] Another study in asthmatic children found that acute febrile illness accompanied by increased C-Reactive Protein (CRP) level may affect theophylline metabolism.[5] The authors postulated that cytokines released in the process of acute illness were responsible. Influenza vaccination has also been reported to reduce theophylline clearance (see under Interactions, p. 1236.3). The mechanism by which theophylline metabolism is reduced in these patients may be related to increased interferon production during the acute febrile response. A dosage reduction of one half has been recommended[6] in children receiving chronic theophylline therapy who are febrile for more than 24 hours. Further dose adjustments should be based on serum-theophylline concentrations until the patients have recovered from their acute illness and are restabilised on their usual dosage. However, conflicting results have been reported and in one controlled study RSV infection was found to have no significant effect on theophylline disposition in children.[7]

1. Vozeh S, *et al.* Changes in theophylline clearance during acute illness. *JAMA* 1978; 240: 1882–4.
2. Richer M, Lam YWF. Hypoxia, arterial pH and theophylline disposition. *Clin Pharmacokinet* 1993; 25: 283–99.
3. Chang KC, *et al.* Altered theophylline pharmacokinetics during acute respiratory viral illness. *Lancet* 1978; i: 1132–3.
4. Kraemer MJ, *et al.* Altered theophylline clearance during an influenza B outbreak. *Pediatrics* 1982; 69: 476–80.
5. Yamaguchi A, *et al.* Higher incidence of elevated body temperature or increased C-reactive protein level in asthmatic children showing transient reduction of theophylline metabolism. *J Clin Pharmacol* 2000; 40: 284–9.
6. American Academy of Pediatrics Committee on Drugs. Precautions concerning the use of theophylline. *Pediatrics* 1992; 89: 781–3.
7. Muslow EA, *et al.* Lack of effect of respiratory syncytial virus infection on theophylline disposition in children. *J Pediatr* 1992; 121: 466–71.

Age. For the effects of age on the metabolism and excretion of theophylline see under Pharmacokinetics, p. 1237.1. Dosage regimens for infants are discussed under Administration in Infants, in Uses and Administration, p. 1230.2.

Breast feeding. From one study of 3 women it was estimated that less than 1% of the total theophylline eliminated was found in breast milk.[1] Another study of 5 women estimated that a breast-fed infant would receive less than 10% of the maternal dose of theophylline.[2] These amounts were considered unlikely to cause toxicity, but it has been reported that irritability in one infant seemed to occur on the intermittent days when the mother took aminophylline. The American Academy of Pediatrics[3] states that theophylline is usually compatible with breast feeding, although it noted that irritability has been reported in infants whose mothers were receiving theophylline.

1. Stec GP, *et al.* Kinetics of theophylline transfer to breast milk. *Clin Pharmacol Ther* 1980; 28: 404–8.
2. Yurchak AM, Jusko WJ. Theophylline secretion into breast milk. *Pediatrics* 1976; 57: 518–20.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. (Retired May 2010) Correction. *Ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/03/08)

ECT. Patients receiving theophylline are at risk of prolonged seizures during ECT, and status epilepticus has been reported.[1,2] The ability of theophylline to prolong seizures has led to it being used as an adjunct in ECT.[3] Caffeine has been used similarly, see p. 1204.2.

1. Peters SG, *et al.* Status epilepticus as a complication of concurrent electroconvulsive and theophylline therapy. *Mayo Clin Proc* 1984; 59: 568–70.
2. Rasmussen KG, Zorumski CF. Electroconvulsive therapy in patients taking theophylline. *J Clin Psychiatry* 1993; 54: 427–31.
3. Leentjens AFG, *et al.* Facilitation of ECT by intravenous administration of theophylline. *Convuls Ther* 1996; 12: 232–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies theophylline as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. It has been recommended[1] that serum-theophylline concentrations are measured at monthly intervals throughout pregnancy and 1 and 4 weeks after delivery since the pharmacokinetics of theophylline may be altered. An increase in the volume of distribution of theophylline, a decrease in plasma-protein binding, and a continuing decrease in clearance throughout pregnancy have been noted in some patients, especially during the later part of pregnancy,[2-4] but other studies have noted an increase in theophylline clearance during pregnancy.[1,5] Some studies have found that after delivery there is a return of clearance values to those existing before pregnancy,[2] while others have not.[4]

In a study of 12 neonates whose mothers received various theophylline preparations throughout their pregnancies[6] maternal, cord, and neonatal heelstick theophylline concentrations ranged from 2.3 to 19.6 micrograms/mL. Transient jitteriness was seen in 2 neonates and tachycardia in one, at cord theophylline concentrations of 11.7 to 17 micrograms/mL. There were no instances of vomiting, seizure, arrhythmias, diarrhoea, or feeding disturbances, which had been reported previously.

1. Rubin PC. Prescribing in pregnancy: general principles. *BMJ* 1986; 293: 1415–17.
2. Carter BL, *et al.* Theophylline clearance during pregnancy. *Obstet Gynecol* 1986; 68: 555–9.
3. Frederiksen MC, *et al.* Theophylline pharmacokinetics in pregnancy. *Clin Pharmacol Ther* 1986; 40: 321–8.
4. Gardner MJ, *et al.* Longitudinal effects of pregnancy on the pharmacokinetics of theophylline. *Eur J Clin Pharmacol* 1987; 31: 289–95.
5. Romero R, *et al.* Pharmacokinetics of intravenous theophylline in pregnant patients at term. *Am J Perinatol* 1983; 1: 31–5.
6. Labovitz B, Spector S. Placental theophylline transfer in pregnant asthmatics. *JAMA* 1982; 247: 786–8.

Renal impairment. Theophylline is eliminated mainly by hepatic metabolism and usual doses of aminophylline or theophylline can be given to patients with renal impairment. In patients undergoing haemodialysis the clearance of theophylline is increased and its elimination half-life reduced; mean values of 84.8 and 83 mL/minute and 2.5 and 2.3 hours respectively have been reported.[1,2] Haemodialysis removes up to 40% of a dose of theophylline.[1] Peritoneal dialysis has little effect on the pharmacokinetics of theophylline removing about 3.2% of a dose.[1]

1. Lee C-SC, *et al.* Comparative pharmacokinetics of theophylline in peritoneal dialysis and hemodialysis. *J Clin Pharmacol* 1983; 23: 274–80.
2. Anderson JR, *et al.* Effects of hemodialysis on theophylline kinetics. *J Clin Pharmacol* 1983; 23: 428–32.

Smoking. Certain components of tobacco smoke, notably aromatic hydrocarbons, induce hepatic drug-metabolising enzymes and cigarette smoking has been reported[1-3] to increase theophylline clearance and shorten its elimination half-life. The effect of smoking may override factors that tend to decrease theophylline clearance, such as old age.[4] The duration of enzyme induction after stopping smoking is uncertain; theophylline clearance decreased by 38% after one week of abstinence from smoking in one study,[5] while others have found changes in clearance persisting for at least 3 months.[1] Tobacco chewing has also been reported to increase theophylline clearance,[6] but nicotine chewing gum appears to have no effect.[5]

1. Hunt SN, *et al.* Effect of smoking on theophylline disposition. *Clin Pharmacol Ther* 1976; 19: 546–51.
2. Jusko WJ, *et al.* Enhanced biotransformation of theophylline in marihuana and tobacco smokers. *Clin Pharmacol Ther* 1978; 24: 406–10.
3. Grygiel JJ, Birkett DJ. Cigarette smoking and theophylline clearance and metabolism. *Clin Pharmacol Ther* 1981; 30: 491–6.
4. Cusack B, *et al.* Theophylline kinetics in relation to age: the importance of smoking. *Br J Clin Pharmacol* 1980; 10: 109–14.
5. Lee BL, *et al.* Cigarette abstinence, nicotine gum, and theophylline disposition. *Ann Intern Med* 1987; 106: 553–5.
6. Rockwood R, Henann N. Smokeless tobacco and theophylline clearance. *Drug Intell Clin Pharm* 1986; 20: 624–5.

Interactions

The toxic effects of theophylline, aminophylline, and other xanthines are additive. Use with other xanthine medications should therefore be avoided; if intravenous aminophylline is to be given for acute bronchospasm in patients who have been taking maintenance theophylline therapy, serum-theophylline concentrations should be measured first and the initial dose reduced as appropriate (see Uses and Administration, p. 1229.3).

Theophylline clearance may be reduced by interaction with other drugs including allopurinol, some antiarrhythmics, cimetidine, disulfiram, fluvoxamine, interferon alfa, macrolide antibacterials and quinolones, oral contraceptives, tiabendazole, and viloxazine, and the dose of theophylline may need to be reduced. Phenytoin and some other antiepileptics, ritonavir, rifampicin, and sulfinpyrazone may increase theophylline clearance, and require an increase in dose or dosing frequency of theophylline.

Xanthines can potentiate hypokalaemia caused by hypoxia or associated with the use of beta$_2$-adrenoceptor stimulants (beta$_2$ agonists), corticosteroids, and diuretics. There is a risk of synergistic toxicity if theophylline is given with halothane or ketamine, and it may antagonise the effects of adenosine and of competitive neuromuscular blockers; lithium elimination may be enhanced with a consequent loss of effect. The interaction between theophylline and beta blockers is complex (see p. 1235.2) but use together tends to be avoided on pharmacological grounds since beta blockers produce bronchospasm.

Theophylline is metabolised by several hepatic cytochrome P450 isoenzymes, of which the most important seems to be CYP1A2.[1] Many drugs affect the metabolic clearance of theophylline and aminophylline,[2] but the variability in theophylline pharmacokinetics makes the clinical significance of these interactions difficult to predict. Giving theophylline with drugs that inhibit its metabolism should be avoided but, if unavoidable, the dose of theophylline should be halved.[3] There is some evidence to suggest that less of a dose reduction is required in the presence of severe liver dysfunction,[4] aside from that already required by impaired hepatic metabolism, see

Administration in Hepatic Impairment, p. 1230.3. Subsequent doses should be adjusted based on serum-theophylline monitoring.[3] Even when introducing medication for which no interaction is suspected, a check on the serum-theophylline concentration within 24 hours of beginning the new drug has been advised.[3]

Theophylline reduces liver plasma flow[3] and may therefore prolong the half-life and increase steady-state concentrations of hepatically eliminated drugs but it is claimed to have no effect on antipyrine clearance.[6]

1. Ha HR, *et al.* Metabolism of theophylline by cDNA-expressed human cytochromes P-450. *Br J Clin Pharmacol* 1995; 39: 321–6.
2. Upton RA. Pharmacokinetic interactions between theophylline and other medication. *Clin Pharmacokinet* 1991; 20: 66–80 (part I) and 135–50 (part II).
3. American Academy of Pediatrics Committee on Drugs. Precautions concerning the use of theophylline. *Pediatrics* 1992; 89: 781–3.
4. Orlando R, *et al.* Liver dysfunction markedly decreases the inhibition of cytochrome P450 1A2-mediated theophylline metabolism by fluvoxamine. *Clin Pharmacol Ther* 2006; 79: 489–99.
5. Onrot J, *et al.* Reduction of liver plasma flow by caffeine and theophylline. *Clin Pharmacol Ther* 1986; 40: 506–10.
6. Dössing M, *et al.* Effect of theophylline and salbutamol on hepatic drug metabolism. *Hum Toxicol* 1989; 8: 225–8.

Antiarrhythmics. An increase in serum-theophylline concentration from 93.2 to 194.2 micromol/litre with symptoms of tachycardia, nervousness, and tremors occurred in a patient 9 days after starting *amiodarone* therapy.[1] Elevated theophylline concentrations and/or decreased clearance have also been reported following addition of *mexiletine* to theophylline therapy.[2-6] Amiodarone and mexiletine probably interact with theophylline through inhibition of its hepatic metabolism. *Tocainide* has also been found to impair theophylline metabolism resulting in a reduction in theophylline clearance but the effect was substantially smaller than that of mexiletine.[7] In one patient stabilised on theophylline therapy, an increase in the plasma-theophylline concentration with subsequent toxicity was noted after starting treatment with *propafenone*.[8]

See also under Calcium-channel Blockers, p. 1235.3.

1. Soto J, *et al.* Possible theophylline-amiodarone interaction. *DICP Ann Pharmacother* 1990; 24: 1115.
2. Stanley R, *et al.* Mexiletine-theophylline interaction. *Am J Med* 1989; 86: 733–4.
3. Ueno K, *et al.* Interaction between theophylline and mexiletine. *DICP Ann Pharmacother* 1990; 24: 471–2.
4. Hurwitz A, *et al.* Mexiletine effects on theophylline disposition. *Clin Pharmacol Ther* 1991; 50: 299–307.
5. Loi C-M, *et al.* Inhibition of theophylline metabolism by mexiletine in young male and female nonsmokers. *Clin Pharmacol Ther* 1991; 49: 571–80.
6. Ueno K, *et al.* Mechanism of interaction between theophylline and mexiletine. *DICP Ann Pharmacother* 1991; 25: 727–30.
7. Loi C-M, *et al.* The effect of tocainide on theophylline metabolism. *Br J Clin Pharmacol* 1993; 35: 437–40.
8. Lee BL, Dohrmann ML. Theophylline toxicity after propafenone treatment: evidence for drug interaction. *Clin Pharmacol Ther* 1992; 51: 353–5.

Antibacterials. *IMIPENEM.* Seizures have been reported in 3 patients receiving theophylline who were given imipenem,[1] although serum concentrations of theophylline were not affected.

1. Semel JD, Allen N. Seizures in patients simultaneously receiving theophylline and imipenem or ciprofloxacin or metronidazole. *South Med J* 1991; 84: 465–8.

ISONIAZID. Isoniazid inhibits oxidative enzymes in the liver and has been found to impair the elimination of theophylline. Both clearance and volume of distribution of theophylline were reduced with an increase in serum-theophylline concentrations in healthy subjects after 14 days of pretreatment with isoniazid[1] and theophylline toxicity has been reported[2] in a patient one month after adding theophylline to isoniazid therapy.

1. Samigun, *et al.* Lowering of theophylline clearance by isoniazid in slow and rapid acetylators. *Br J Clin Pharmacol* 1990; 29: 570–3.
2. Torrent J, *et al.* Theophylline-isoniazid interaction. *DICP Ann Pharmacother* 1989; 23: 143–5.

MACROLIDES. There are conflicting reports of the effect of *erythromycin* on the pharmacokinetics of theophylline. Significant decreases in the clearance of theophylline and prolonged elimination half-life have been reported[1-3] but other studies have found no interaction.[4,5] It has also been noted that the serum concentrations and bioavailability of erythromycin may be reduced by theophylline[6,7] (see also p. 294.3). The clearance of theophylline is also markedly decreased by *troleandomycin*,[8-10] but there have been reports that for clinical purposes the pharmacokinetics of theophylline do not seem to be significantly altered by *dirithromycin*,[11-13] *josamycin*,[9,14] *midecamycin*,[10,15,16] *rokitamycin*,[17] *roxithromycin*,[18] or *spiramycin*.[19] *Clarithromycin* also seems unlikely to have a significant effect in most patients, but in a few theophylline dosage may need to be adjusted.[20,21] In one case report, serum-theophylline concentrations fell over a few days after the withdrawal of *azithromycin*.[22] The reduction in theophylline clearance by some macrolides was thought to be due to inhibition of the cytochrome P450 isoenzyme CYP1A2; however, it has been suggested that CYP1A2 inhibition does not play a significant role and the mechanism for the interaction may be due to a combination of CYP3A inactivation and the inhibition of theophylline uptake into hepatocytes.[23]

1. Zarowitz BJM, *et al.* Effect of erythromycin base on theophylline kinetics. *Clin Pharmacol Ther* 1981; 29: 601–5.
2. Renton KW, *et al.* Depression of theophylline elimination by erythromycin. *Clin Pharmacol Ther* 1981; 30: 422–6.
3. May DC, *et al.* The effects of erythromycin on theophylline elimination in normal males. *J Clin Pharmacol* 1982; 22: 125–30.
4. Maddux MS, *et al.* The effect of erythromycin on theophylline pharmacokinetics at steady state. *Chest* 1982; 81: 563–5.
5. Hildebrandt R, *et al.* Lack of clinically important interaction between erythromycin and theophylline. *Eur J Clin Pharmacol* 1984; 26: 485–9.
6. Illopoulou A, *et al.* Pharmacokinetic interaction between theophylline and erythromycin. *Br J Clin Pharmacol* 1982; 14: 495–9.
7. Paulsen O, *et al.* The interaction of erythromycin with theophylline. *Eur J Clin Pharmacol* 1987; 32: 493–8.
8. Weinberger M, *et al.* Inhibition of theophylline clearance by troleandomycin. *J Allergy Clin Immunol* 1977; 59: 228–31.
9. Brazier JL, *et al.* Retard d'élimination de la théophylline dû à la troléandomycine: absence d'effet de la josamycine. *Therapie* 1980; 35: 545–9.
10. Lavarenne J, *et al.* Influence d'un nouveau macrolide, la midécamycine, sur les taux sanguins de théophylline. *Therapie* 1981; 36: 451–6.
11. Bachmann K, *et al.* Changes in the steady-state pharmacokinetics of theophylline during treatment with dirithromycin. *J Clin Pharmacol* 1990; 30: 1001–5.
12. Bachmann K, *et al.* Steady-state pharmacokinetics of theophylline in COPD patients treated with dirithromycin. *J Clin Pharmacol* 1993; 33: 861–5.
13. McConnell SA, *et al.* Lack of effect of dirithromycin on theophylline pharmacokinetics in healthy volunteers. *J Antimicrob Chemother* 1999; 43: 733–6.
14. Ruff F, *et al.* Macrolide et théophylline: absence d'interaction josamycine-théophylline. *Nouv Presse Med* 1981; 10: 175.
15. Principi N, *et al.* Effect of miocamycin on theophylline kinetics in children. *Eur J Clin Pharmacol* 1987; 31: 701–4.
16. Couet W, *et al.* Lack of effect of pontinomycin on the plasma pharmacokinetics of theophylline. *Eur J Clin Pharmacol* 1989; 37: 101–4.
17. Ishioka T. Effect of a new macrolide antibiotic, 3''-O-propionylleucomycin A_5 (rokitamycin) on serum concentrations of theophylline and digoxin in the elderly. *Acta Ther* 1987; 13: 17–24.
18. Saint-Salvi B, *et al.* A study of the interaction of roxithromycin with theophylline and carbamazine. *J Antimicrob Chemother* 1987; 20 (suppl B): 121–9.
19. Debruyne D, *et al.* Spiramycin has no effect on serum theophylline in asthmatic patients. *Eur J Clin Pharmacol* 1986; 30: 505–7.
20. Bachand RT. Comparative study of clarithromycin and ampicillin in the treatment of patients with acute bacterial exacerbations of chronic bronchitis. *J Antimicrob Chemother* 1991; 27 (suppl A): 91–100.
21. Gillum JG, *et al.* Effect of combination therapy with ciprofloxacin and clarithromycin on theophylline pharmacokinetics in healthy volunteers. *Antimicrob Agents Chemother* 1996; 40: 1715–16.
22. Pollak PT, Slayter KL. Reduced serum theophylline concentrations after discontinuation of azithromycin: evidence for an unusual interaction. *Pharmacotherapy* 1997; 17: 827–9.
23. Polasek TM, Miners JO. Macrolide-theophylline interactions: no role for the inhibition of cytochrome P4501A2. *Br J Clin Pharmacol* 2008; 66: 898–900.

QUINOLONES. The fluoroquinolone antibacterials vary in their propensity to interact with theophylline. *Enoxacin* shows the most marked interaction and has been reported[1] to cause serious nausea and vomiting, tachycardia, and headaches, associated with unexpectedly high plasma-theophylline concentrations in patients with respiratory-tract infections. Studies,[2-5] mainly in healthy subjects, have found that enoxacin decreases theophylline clearance by up to 74%[3] with an increase in the elimination half-life and serum-theophylline concentration.

Ciprofloxacin[2,6-8] and *pefloxacin*[2] interact with theophylline to a lesser extent than enoxacin, decreasing theophylline clearance by about 30%. Eight clinically important interactions between ciprofloxacin and theophylline had been reported to the UK CSM[9] including 1 death. A ciprofloxacin-induced seizure has been reported[10] which may have been due to the combined inhibitory effects of the 2 drugs on GABA binding. It has been recommended that ciprofloxacin should not be used in patients treated with theophylline.[9]

Norfloxacin[4,11-13] and *ofloxacin*[4,11,14] have been reported to have minor effects on the pharmacokinetics of theophylline. Although their effects were usually considered not to be clinically significant, the US FDA had received 9 reports of theophylline toxicity associated with use with norfloxacin, including 1 death.[15] *Fleroxacin*,[16] *flumequine*,[17] *lomefloxacin*,[8,18,19] *moxifloxacin*,[20] and *rufloxacin*[21] have been reported to have no significant effect on the pharmacokinetics of theophylline in small studies in healthy subjects.

The mechanism of interaction involves a reduction in the metabolic clearance of theophylline due to inhibition of hepatic microsomal enzymes. However, the exact mechanism is unknown and it is difficult to predict which patients will be at risk. Extreme caution should be used when giving quinolones with theophylline, particularly in the elderly[15] and it may be advisable to use a non-interacting fluoroquinolone, although theophylline concentrations should still be monitored.

Of the non-fluorinated quinolones, *nalidixic acid*[2] has been reported not to affect theophylline clearance whereas *pipemidic acid* has markedly inhibited theophylline clearance.[19]

1. Wijnands WJA, *et al.* Enoxacin raises plasma theophylline concentrations. *Lancet* 1984; ii: 108–9.
2. Wijnands WJA, *et al.* The influence of quinolone derivatives on theophylline clearance. *Br J Clin Pharmacol* 1986; 22: 677–83.
3. Beckmann J, *et al.* Enoxacin—a potent inhibitor of theophylline metabolism. *Eur J Clin Pharmacol* 1987; 33: 227–30.
4. Sano M, *et al.* Inhibitory effect of enoxacin, ofloxacin and norfloxacin on renal excretion of theophylline in humans. *Eur J Clin Pharmacol* 1989; 36: 323–4.
5. Koup JR, *et al.* Theophylline dosage adjustment during enoxacin coadministration. *Antimicrob Agents Chemother* 1990; 34: 803–7.
6. Nix DE, *et al.* Effect of multiple dose oral ciprofloxacin on the pharmacokinetics of theophylline and indocyanine green. *J Antimicrob Chemother* 1987; 19: 263–9.
7. Schwartz J, *et al.* Impact of ciprofloxacin on theophylline clearance and steady-state concentrations in serum. *Antimicrob Agents Chemother* 1988; 32: 75–7.
8. Robson RA, *et al.* Comparative effects of ciprofloxacin and lomefloxacin on the oxidative metabolism of theophylline. *Br J Clin Pharmacol* 1990; 29: 491–3.
9. Bem JL, Mann RD. Danger of interaction between ciprofloxacin and theophylline. *BMJ* 1988; 296: 1131.
10. Karki SD, *et al.* Seizure with ciprofloxacin and theophylline combined therapy. *DICP Ann Pharmacother* 1990; 24: 595–6.
11. Sano M, *et al.* Comparative pharmacokinetics of theophylline following two fluoroquinolones co-administration. *Eur J Clin Pharmacol* 1987; 32: 431–2.
12. Ho G, *et al.* Evaluation of the effect of norfloxacin on the pharmacokinetics of theophylline. *Clin Pharmacol Ther* 1988; 44: 35–8.
13. Davis RL, *et al.* Effect of norfloxacin on theophylline metabolism. *Antimicrob Agents Chemother* 1989; 33: 212–14.
14. Gregoire SL, *et al.* Inhibition of theophylline clearance by coadministered ofloxacin without alteration of theophylline effects. *Antimicrob Agents Chemother* 1987; 31: 375–8.
15. Grasela TH, Dreis MW. An evaluation of the quinolone-theophylline interaction using the Food and Drug Administration spontaneous reporting system. *Arch Intern Med* 1992; 152: 617–21.
16. Parent M, *et al.* Safety of fleroxacin coadministered with theophylline to young and elderly volunteers. *Antimicrob Agents Chemother* 1990; 34: 1249–53.
17. Lacarelle B, *et al.* The quinolone, flumequine, has no effect on theophylline pharmacokinetics. *Eur J Clin Pharmacol* 1994; 46: 477–8.
18. LeBel M, *et al.* Influence of lomefloxacin on the pharmacokinetics of theophylline. *Antimicrob Agents Chemother* 1990; 34: 1254–6.
19. Staib AH, *et al.* Interaction of quinolones with the theophylline metabolism in man: investigations with lomefloxacin and pipemidic acid. *Int J Clin Pharmacol Ther Toxicol* 1989; 27: 289–93.
20. Stass H, Kubitza D. Lack of pharmacokinetic interaction between moxifloxacin, a novel 8-methoxyfluoroquinolone, and theophylline. *Clin Pharmacokinet* 2001; 40 (suppl 1): 63–70.
21. Kinzig-Schippers M, *et al.* Absence of effect of rufloxacin on theophylline pharmacokinetics in steady state. *Antimicrob Agents Chemother* 1998; 42: 2359–64.

RIFAMPICIN. Rifampicin induces hepatic oxidative enzymes and an oral dose of 600 mg daily for 6 to 14 days has been shown to increase mean plasma-theophylline clearance by 25 to 82% due to enhancement of hepatic theophylline metabolism. This increase in clearance is sufficient to require dosage adjustment in some patients,[1-4] including children.[5]

1. Straughn AB, *et al.* Effect of rifampin on theophylline disposition. *Ther Drug Monit* 1984; 6: 153–6.
2. Robson RA, *et al.* Theophylline-rifampicin interaction: non-selective induction of theophylline metabolic pathways. *Br J Clin Pharmacol* 1984; 18: 445–8.
3. Boyce EG, *et al.* The effect of rifampin on theophylline kinetics. *J Clin Pharmacol* 1986; 26: 696–9.
4. Adebayo GE, *et al.* Attenuation of rifampicin-induced theophylline metabolism by diltiazem/rifampicin coadministration in healthy volunteers. *Eur J Clin Pharmacol* 1989; 37: 127–31.
5. Brocks DR, *et al.* Theophylline-rifampin interaction in a pediatric patient. *Clin Pharm* 1986; 5: 602–4.

TETRACYCLINES. Tetracycline weakly inhibited theophylline clearance after 5 days of therapy in 5 non-smoking adults with chronic obstructive airways disease[1] and theophylline toxicity has been reported[2] in a patient given a 10-day course of tetracycline during theophylline therapy. *Doxycycline* has been reported not to have any significant effect on theophylline pharmacokinetics in healthy subjects.[3]

1. Gotz VP, Ryerson GG. Evaluation of tetracycline on theophylline disposition in patients with chronic obstructive airways disease. *Drug Intell Clin Pharm* 1986; 20: 694–7.
2. McCormack JP, *et al.* Theophylline toxicity induced by tetracycline. *Clin Pharm* 1990; 9: 546–9.
3. Jonkman JHG, *et al.* No influence of doxycycline on theophylline pharmacokinetics. *Ther Drug Monit* 1985; 7: 92–4.

Antidepressants. Significantly reduced clearance and increased plasma concentrations of theophylline have been reported when given with *viloxazine*.[1,2] The dosage of theophylline should be decreased and its plasma concentrations monitored when viloxazine is also prescribed.[2] The interaction probably involves competition between the two drugs for hepatic microsomal enzymes.

Fluvoxamine has also been associated with a significant reduction in theophylline clearance[3,4] and theophylline toxicity has occurred in patients when fluvoxamine was added to their therapy.[5,6] This is due to potent liver enzyme inhibition[7] by fluvoxamine, and has been the subject of a warning by the UK CSM[8] in which they issued the standard advice of avoiding the two drugs if at all possible and, where they could not be avoided, of giving half the dose of theophylline and monitoring plasma concentrations. A small study evaluating the effect of liver cirrhosis on the interaction between fluvoxamine and theophylline saw a decrease in fluvoxamine-induced inhibition of theophylline clearance as the severity of liver cirrhosis increased.[4] The authors suggest that theophylline may require less of a dose reduction in the presence of severe liver dysfunction, aside from that already required by impaired hepatic metabolism (see Administration in Hepatic Impairment, p. 1230.3).

St John's wort may have decreased theophylline concentrations and increased the theophylline dosage requirement in one case report.[9] However, a study[10] in 12 healthy subjects found that 15 days of treatment with St John's wort did not significantly change theophylline pharmacokinetics.

For a mention of the effect of theophylline on the renal clearance of *lithium*, see Xanthines, under Interactions of Lithium, p. 432.3.

1. Thomson AH, *et al.* Theophylline toxicity following coadministration of viloxazine. *Ther Drug Monit* 1988; 10: 359–60.
2. Perault MC, *et al.* A study of the interaction of viloxazine with theophylline. *Ther Drug Monit* 1989; 11: 520–2.
3. Donaldson KM, *et al.* The effect [of] fluvoxamine at steady state on the pharmacokinetics of theophylline after a single dose in healthy male volunteers. *Br J Clin Pharmacol* 1994; 37: 492P.
4. Orlando R, *et al.* Liver dysfunction markedly decreases the inhibition of cytochrome P450 1A2-mediated theophylline metabolism by fluvoxamine. *Clin Pharmacol Ther* 2006; 79: 489–99.
5. Sperber AD. Toxic interaction between fluvoxamine and sustained release theophylline in an 11-year-old boy. *Drug Safety* 1991; 6: 460–2.
6. Thomson AH, *et al.* Interaction between fluvoxamine and theophylline. *Pharm J* 1992; 249: 137.
7. Rasmussen BB, *et al.* Selective serotonin reuptake inhibitors and theophylline metabolism in human liver microsomes: potent inhibition by fluvoxamine. *Br J Clin Pharmacol* 1995; 39: 151–9.
8. CSM/MCA. Fluvoxamine increases plasma theophylline levels. *Current Problems* 1994; 20: 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20156136&RevisionSelectionMethod=LatestReleased (accessed 20/05/08)
9. Nebel A, *et al.* Potential metabolic interaction between St John's wort and theophylline. *Ann Pharmacother* 1999; 33: 502.
10. Morimoto T, *et al.* Effect of St. John's wort on the pharmacokinetics of theophylline in healthy volunteers. *J Clin Pharmacol* 2004; 44: 95–101.

Antiepileptics. *Phenytoin* markedly decreases the elimination half-life and increases the clearance of theophylline, probably due to hepatic enzyme induction, at therapeutic or subtherapeutic serum-phenytoin concentrations[1–4] and even in heavy smokers.[2] An early report suggested that the serum concentration of phenytoin may be decreased simultaneously,[5] perhaps due to enzyme induction by theophylline[3] or reduced phenytoin absorption.[6] The interaction has been reported to occur within 5 to 14 days of taking phenytoin and theophylline, and theophylline clearance has increased by up to 350%, and reductions in serum half-life have ranged from 25 to 70% of initial values.[3,4]

Carbamazepine has also been seen to increase theophylline elimination. In one patient, theophylline serum half-life was decreased by about 24 to 60%, and clearance was increased by about 35 to 100% when carbamazepine was given.[2] In an 11-year-old girl theophylline-serum half-life was almost halved with loss of asthma control after 3 weeks of concurrent carbamazepine therapy.[7] In turn, there has been a report that theophylline may reduce serum concentrations of carbamazepine—see p. 517.3.

Although *phenobarbital* was not found to have a significant effect on the pharmacokinetics of a single dose of theophylline given intravenously,[8] enhanced theophylline clearance has been seen in patients after longer periods of treatment with phenobarbital.[9,10] The magnitude of the changes in theophylline elimination appears to be smaller with phenobarbital than phenytoin. *Pentobarbital* in high doses has also been reported to increase theophylline metabolism.[11] A more recent study[12] has also shown that therapeutic doses of pentobarbital (100 mg daily) increase plasma clearance of theophylline by a mean of 40%, although this was subject to marked interindividual variations. Renal clearance was not affected, suggesting hepatic enzyme induction as the probable mechanism.

1. Marquis J-P, *et al.* Phenytoin-theophylline interaction. *N Engl J Med* 1982; 307: 1189–90.
2. Reed RC, Schwartz HJ. Phenytoin-theophylline-quinidine interaction. *N Engl J Med* 1983; 308: 724–5.
3. Sklar SJ, Wagner JC. Enhanced theophylline clearance secondary to phenytoin therapy. *Drug Intell Clin Pharm* 1985; 19: 34–6.
4. Miller M, *et al.* Influence of phenytoin on theophylline clearance. *Clin Pharmacol Ther* 1984; 35: 666–9.
5. Taylor JW, *et al.* The interaction of phenytoin and theophylline. *Drug Intell Clin Pharm* 1980; 14: 638.
6. Hendeles L, *et al.* Decreased oral phenytoin absorption following concurrent theophylline administration. *J Allergy Clin Immunol* 1979; 63: 156.
7. Rosenberry KR, *et al.* Reduced theophylline half-life induced by carbamazepine therapy. *J Pediatr* 1983; 102: 472–4.
8. Piafsky KM, *et al.* Effect of phenobarbital on the disposition of intravenous theophylline. *Clin Pharmacol Ther* 1977; 22: 336–9.
9. Jusko WJ, *et al.* Factors affecting theophylline clearances: age, tobacco, marijuana, cirrhosis, congestive heart failure, obesity, oral contraceptives, benzodiazepines, barbiturates, and ethanol. *J Pharm Sci* 1979; 68: 1358–66.
10. Saccar CL, *et al.* The effect of phenobarbital on theophylline disposition in children with asthma. *J Allergy Clin Immunol* 1985; 75: 716–19.
11. Gibson GA, *et al.* Influence of high-dose phenobarbital on theophylline pharmacokinetics: a case report. *Ther Drug Monit* 1985; 7: 181–4.
12. Dahlqvist R, *et al.* Induction of theophylline metabolism by pentobarbital. *Ther Drug Monit* 1989; 11: 408–10.

Antifungals. There have been reports that *ketoconazole* does not appear significantly to alter the pharmacokinetics of theophylline.[1,2] Licensed product information for *fluconazole* has, however, stated that plasma clearance of theophylline may be decreased by fluconazole. A 16% reduction in theophylline clearance has been reported[3] after oral fluconazole but fluconazole was considered to have only a minor inhibitory effect on theophylline metabolism and theophylline disposition was not significantly affected. Theophylline metabolism has been inhibited to a similar degree by *terbinafine*.[4]

1. Brown MW, *et al.* Effect of ketoconazole on hepatic oxidative drug metabolism. *Clin Pharmacol Ther* 1985; 37: 290–7.
2. Heusner JJ, *et al.* Effect of chronically administered ketoconazole on the elimination of theophylline in man. *Drug Intell Clin Pharm* 1987; 21: 514–17.
3. Konishi H, *et al.* Effect of fluconazole on theophylline disposition in humans. *Eur J Clin Pharmacol* 1994; 46: 309–12.
4. Trépanier EF, *et al.* Effect of terbinafine on theophylline pharmacokinetics in healthy volunteers. *Antimicrob Agents Chemother* 1998; 42: 695–7.

Antigout drugs. Oral *allopurinol* 300 mg daily for 7 days was found to have no effect on the pharmacokinetics of theophylline after a single intravenous dose of aminophylline[1,2] or after oral theophylline given to steady state.[1] However, oral allopurinol 600 mg daily for 28 days has been found to inhibit the metabolism of theophylline,[3] increasing the mean half-life by 25% after 14 days and 29% after 28 days and there has been a report of allopurinol increasing peak plasma-theophylline concentrations by 38% in one patient within 2 days of use together.[4]

Probenecid has been reported[5] to have no effect on the hepatic metabolism or total body clearance of theophylline in a single-dose study in healthy subjects.

Sulfinpyrazone 800 mg daily for 7 days increased the total plasma clearance of theophylline by 22% in healthy subjects due to selective induction of certain cytochrome P450 isoenzymes.[6]

1. Grygiel JJ, *et al.* Effects of allopurinol on theophylline metabolism and clearance. *Clin Pharmacol Ther* 1979; 26: 660–7.
2. Vozeh S, *et al.* Influence of allopurinol on theophylline disposition in adults. *Clin Pharmacol Ther* 1980; 27: 194–7.
3. Manfredi RL, Vesell ES. Inhibition of theophylline metabolism by long-term allopurinol administration. *Clin Pharmacol Ther* 1981; 29: 224–9.
4. Barry M, Feely J. Allopurinol influences aminophenazone elimination. *Clin Pharmacokinet* 1990; 19: 167–9.
5. Chen TWD, Patton TF. Effect of probenecid on the pharmacokinetics of aminophylline. *Drug Intell Clin Pharm* 1983; 17: 465–6.
6. Birkett DJ, *et al.* Evidence for a dual action of sulphinpyrazone on drug metabolism in man: theophylline-sulphinpyrazone interaction. *Br J Clin Pharmacol* 1983; 15: 567–9.

Antineoplastics. There has been a report of increased clearance of theophylline in 3 patients given *aminoglutethimide*.[1]

The clearance of theophylline (given as theophylline, aminophylline, or choline theophyllinate) was reported to decrease by an average of 19% in 8 patients with severe *corticosteroid-dependent asthma* given low-dose weekly intramuscular injections of *methotrexate*.[2] A high degree of interpatient variability was seen. Three patients reported nausea; one of whom required a decrease in theophylline dose. The authors reported that the most likely explanation for the change in theophylline clearance was inhibition of microsomal enzyme activity.

For reference to a possible interaction between theophylline and *lomustine*, see Lomustine, p. 818.2.

1. Lenning PE, *et al.* Effect of aminoglutethimide on antipyrine, theophylline, and digitoxin disposition in breast cancer. *Clin Pharmacol Ther* 1984; 36: 796–802.
2. Glynn-Barnhart AM, *et al.* Effect of low-dose methotrexate on the disposition of glucocorticoids and theophylline. *J Allergy Clin Immunol* 1991; 88: 180–6.

Antivirals. A single injection of recombinant human *interferon alfa* reduced theophylline clearance by 33 to 81% in 8 of 9 subjects, resulting in a 1.5- to sixfold increase in the theophylline elimination half-life.[1] Injection of interferon alfa once daily for 3 days in 11 healthy subjects also reduced theophylline clearance and increased elimination half-life,[2] but the magnitude of the changes were of a similar order to normal intra-individual variation and the interaction was considered of minor clinical significance.

Licensed product information for *ritonavir* states that it substantially increases the clearance of theophylline; theophylline dosage may need to be increased to maintain efficacy.

There is evidence[3] that *aciclovir* inhibits theophylline metabolism, resulting in accumulation.

1. Williams SJ, *et al.* Inhibition of theophylline metabolism by interferon. *Lancet* 1987; ii: 939–41.
2. Jonkman JHG, *et al.* Effects of α-interferon on theophylline pharmacokinetics and metabolism. *Br J Clin Pharmacol* 1989; 27: 795–802.
3. Maeda Y, *et al.* Inhibition of theophylline metabolism by aciclovir. *Biol Pharm Bull* 1996; 19: 1591–5.

Benzodiazepines. For reference to the antagonism of benzodiazepine sedation by aminophylline, see Xanthines, under Interactions of Diazepam, p. 1070.3.

Beta blockers. *Propranolol* reduced theophylline clearance by 36% in healthy subjects given aminophylline intravenously. *Metoprolol* did not reduce clearance in the group as a whole, but a reduction was noted in some smokers whose theophylline clearance was initially high.[1] Propranolol is thought to exert a dose-dependent selective inhibitory effect on the separate cytochrome P450 isoenzymes involved in theophylline demethylation and 8-hydroxylation.[2] The less lipophilic beta blockers *atenolol*[3,4] and *nadolol*[4] had no significant effect on the pharmacokinetics of theophylline.

In general, however, beta blockers should be avoided in patients taking theophylline as they can dangerously exacerbate bronchospasm in patients with a history of asthma or chronic obstructive pulmonary disease.

1. Conrad KA, Nyman DW. Effects of metoprolol and propranolol on theophylline elimination. *Clin Pharmacol Ther* 1980; 28: 463–7.
2. Miners JO, *et al.* Selectivity and dose-dependency of the inhibitory effect of propranolol on theophylline metabolism in man. *Br J Clin Pharmacol* 1985; 20: 219–23.
3. Cerasa LA, *et al.* Lack of effect of atenolol on the pharmacokinetics of theophylline. *Br J Clin Pharmacol* 1988; 26: 800–2.
4. Corsi CM, *et al.* Lack of effect of atenolol and nadolol on the metabolism of theophylline. *Br J Clin Pharmacol* 1990; 29: 265–8.

Caffeine. Abstention from dietary methylxanthines by healthy subjects has resulted in faster elimination of theophylline.[1] While the addition of extra caffeine to the diet has been reported not to alter theophylline disposition,[2] some studies in healthy subjects have indicated that the ingestion of moderate amounts of caffeine (120 to 900 mg daily), which could be consumed by drinking several cups of coffee daily, can have a pronounced influence on the pharmacokinetics of theophylline.[3,4] In these latter studies the mean theophylline clearance was reduced by 23 and 29% with a corresponding increase in the elimination half-lives.

1. Monks TJ, *et al.* Influence of methylxanthine-containing foods on theophylline metabolism and kinetics. *Clin Pharmacol Ther* 1979; 26: 513–24.
2. Monks TJ, *et al.* The effect of increased caffeine intake on the metabolism and pharmacokinetics of theophylline in man. *Biopharm Drug Dispos* 1981; 2: 31–7.
3. Jonkman JHG, *et al.* The influence of caffeine on the steady-state pharmacokinetics of theophylline. *Clin Pharmacol Ther* 1991; 49: 248–55.
4. Sato J, *et al.* Influence of usual intake of dietary caffeine on single-dose kinetics of theophylline in healthy human subjects. *Eur J Clin Pharmacol* 1993; 44: 295–8.

Calcium-channel blockers. *Verapamil* has been reported[1] to decrease the clearance of theophylline by a mean of 14% in healthy subjects and although this was not considered to be clinically significant, symptoms of theophylline toxicity, associated with near doubling of the serum-theophylline concentration have occurred in a 76-year-old woman taking theophylline after 6 days of therapy with verapamil.[2] Studies in healthy subjects and asthmatic patients have produced conflicting results of the effect of *nifedipine* on the pharmacokinetics of theophylline. Reduced clearance[1] and an increase in the volume of distribution[3,4] of theophylline have been reported and both decreased[4] and increased[3] serum-theophylline concentrations; theophylline toxicity has been reported.[6,7] However, most studies have concluded that the effects of nifedipine are unlikely to be of clinical importance.[1,4,5,8]

Serum concentrations of theophylline have been reported to be increased by *diltiazem*[5] and reduced by *felodipine*;[9] neither of these effects were considered to be clinically significant.

1. Robson RA, *et al.* Selective inhibitory effects of nifedipine and verapamil on oxidative metabolism: effects on theophylline. *Br J Clin Pharmacol* 1988; 25: 397–400.
2. Burnakis TG, *et al.* Increased serum theophylline concentrations secondary to oral verapamil. *Clin Pharm* 1983; 2: 458–61.
3. Jackson SHD, *et al.* The interaction between iv theophylline and chronic oral dosing with slow release nifedipine in volunteers. *Br J Clin Pharmacol* 1986; 21: 389–92.
4. Adebayo GI, Mabadeje AFB. Effect of nifedipine on antipyrine and theophylline disposition. *Biopharm Drug Dispos* 1990; 11: 157–64.
5. Smith SR, *et al.* The influence of nifedipine and diltiazem on serum theophylline concentration-time profiles. *J Clin Pharm Ther* 1989; 14: 403–8.
6. Parrillo SJ, Venditto M. Elevated theophylline blood levels from institution of nifedipine therapy. *Ann Emerg Med* 1984; 13: 216–17.
7. Harrod CS. Theophylline toxicity and nifedipine. *Ann Intern Med* 1987; 106: 480.
8. Spedini C, Lombardi C. Long-term treatment with oral nifedipine plus theophylline in the management of chronic bronchial asthma. *Eur J Clin Pharmacol* 1986; 31: 105–6.
9. Bratel T, *et al.* Felodipine reduces the absorption of theophylline in man. *Eur J Clin Pharmacol* 1989; 36: 481–5.

Cannabis. A search of the literature[1] revealed 2 studies, both published in the 1970s, that showed that marijuana smoking increased the clearance of theophylline.

1. Brown D. Influence on theophylline clearance. *Pharm J* 1994; 253: 595.

Corticosteroids. In 3 patients with acute severe asthma given aminophylline intravenously, serum-theophylline concentrations rose rapidly from the therapeutic range to between 40 and 50 micrograms/mL when *hydrocortisone* was given intravenously.[1] In studies in healthy subjects, no significant changes in serum-theophylline concentrations were noted when hydrocortisone, *methylprednisolone*,[2] or *prednisone*[3] were given, although there was a trend towards increased theophylline clearance during corticosteroid therapy.[2,3] In preterm neonates, exposure to

betamethasone in utero stimulated the hepatic metabolism of theophylline,[4,5] but did not affect dosage requirements.

The possibility that adverse effects such as hypokalaemia may be potentiated by use of theophylline with corticosteroids should be borne in mind.

1. Buchanan N, *et al.* Asthma—a possible interaction between hydrocortisone and theophylline. *S Afr Med J* 1979; 56: 1147–8.
2. Leavengood DC, *et al.* The effect of corticosteroids on theophylline metabolism. *Ann Allergy* 1983; 50: 249–51.
3. Anderson JL, *et al.* Potential pharmacokinetic interaction between theophylline and prednisone. *Clin Pharm* 1984; 3: 187–9.
4. Jager-Roman E, *et al.* Increased theophylline metabolism in premature infants after prenatal betamethasone administration. *Dev Pharmacol Ther* 1982; 5: 127–35.
5. Baird-Lambert J, *et al.* Theophylline metabolism in preterm neonates during the first weeks of life. *Dev Pharmacol Ther* 1984; 7: 239–44.

Disulfiram. In a study involving 20 recovering alcoholic patients, disulfiram decreased the plasma clearance and prolonged the elimination half-life of theophylline in a dose-dependent manner.[1] It was concluded that disulfiram exerts a dose-dependent inhibitory effect on the hepatic metabolism of theophylline and that, in order to minimise the risk of toxicity if given together, the dosage of theophylline may need to be reduced by up to 50%.

1. Lol C-M, *et al.* Dose-dependent inhibition of theophylline metabolism by disulfiram in recovering alcoholics. *Clin Pharmacol Ther* 1989; 45: 476–86.

Diuretics. Although increased mean serum-theophylline concentrations were noted in 10 patients given continuous intravenous aminophylline infusions after intravenous injection of *furosemide*,[1] in 8 patients with chronic stable asthma, mean peak serum-theophylline concentrations were reduced from 12.14 micrograms/mL with placebo to 7.16 micrograms/mL when furosemide was given. Reduced concentrations were noted for up to 6 hours after furosemide.[2] Decreased theophylline concentrations were also noted in 4 neonates receiving oral or intravenous theophylline when given furosemide.[3] Serum-theophylline concentrations returned to normal when furosemide and theophylline were given more than 2 hours apart.

The possibility that adverse effects such as hypokalaemia may be potentiated if theophylline is given with diuretics should be borne in mind.

1. Conlon PF, *et al.* Effect of intravenous furosemide on serum theophylline concentration. *Am J Hosp Pharm* 1981; 38: 1345–7.
2. Carpentiere G, *et al.* Furosemide and theophylline. *Ann Intern Med* 1985; 103: 957.
3. Toback JW, Gilman ME. Theophylline-furosemide inactivation. *Pediatrics* 1983; 71: 140–1.

Gastrointestinal drugs. Oral *antacids* do not appear to affect the total absorption of theophylline from the gut.[1-5] However, some studies have shown a reduction in the rate of absorption from both immediate-[1] and modified-release theophylline preparations[2] after antacids. Also an increase in peak serum-theophylline concentrations has been noted with certain modified-release formulations.[3]

Cimetidine inhibits the oxidative metabolism of theophylline reducing its clearance by 20 to 35% and prolonging its serum half-life;[6-8] toxic effects have been reported.[6] It has been recommended that the dose of aminophylline should be reduced by about one-third if given with cimetidine.[6] This inhibition of theophylline metabolism may be enhanced by liver disease,[9] but there is wide interindividual variation. The reduction in clearance may be greater in smokers.[10] Studies have suggested that *ranitidine* does not significantly inhibit theophylline metabolism,[11-14] even at very high doses.[15] However, there have been occasional reports of theophylline toxicity after use with ranitidine.[16-18] *Famotidine*[19] has also been reported to not alter theophylline disposition but one small study found a significant decrease in theophylline clearance in some patients with chronic obstructive pulmonary disease.[20]

Omeprazole, lansoprazole, and *pantoprazole* generally have insignificant or no effect on theophylline clearance.[21,22] In CYP2C19 poor metabolisers there may be an increase in omeprazole concentrations and subsequent induction of CYP1A, a major enzyme of theophylline metabolism. A pharmacokinetic study[23] of this induction in 5 poor metabolisers given omeprazole did find a trend towards an increase in theophylline clearance.

1. Arnold LA, *et al.* Effect of an antacid on gastrointestinal absorption of theophylline. *Am J Hosp Pharm* 1979; 36: 1059–62.
2. Shargel L, *et al.* Effect of antacid on bioavailability of theophylline from rapid and timed-release drug products. *J Pharm Sci* 1981; 70: 599–602.
3. Darzentas LJ, *et al.* Effect of antacid on bioavailability of a sustained-release theophylline preparation. *Drug Invest Clin Pharm* 1983; 17: 555–7.
4. Myhre KL Walstad RA. The influence of antacid on the absorption of two different sustained-release formulations of theophylline. *Br J Clin Pharmacol* 1983; 15: 683–7.
5. Muir JF, *et al.* Lack of effect of magnesium-aluminium hydroxide on the absorption of theophylline given as a pH-dependent sustained-release preparation. *Eur J Clin Pharmacol* 1993; 44: 85–8.
6. Bauman JH, *et al.* Cimetidine-theophylline interaction: report of four patients. *Ann Allergy* 1982; 48: 100–102.
7. Vestal RE, *et al.* Cimetidine inhibits theophylline clearance in patients with chronic obstructive pulmonary disease: a study using stable isotope methodology during multiple oral dose administration. *Br J Clin Pharmacol* 1983; 15: 411–18.
8. Roberts RK, *et al.* Cimetidine-theophylline interaction in patients with chronic obstructive airways disease. *Med J Aust* 1984; 140: 279–80.
9. Gugler R, *et al.* The inhibition of drug metabolism by cimetidine in patients with liver cirrhosis. *Klin Wochenschr* 1984; 62: 1126–31.
10. Grygiel JJ, *et al.* Differential effects of cimetidine on theophylline metabolic pathways. *Eur J Clin Pharmacol* 1984; 26: 335–40.
11. Breen KJ, *et al.* Effects of cimetidine and ranitidine on hepatic drug metabolism. *Clin Pharmacol Ther* 1982; 31: 297–300.
12. Seggev JS, *et al.* No evidence for interaction between ranitidine and theophylline. *Arch Intern Med* 1987; 147: 179–80.
13. Adebayo GI. Effects of equimolar doses of cimetidine and ranitidine on theophylline elimination. *Biopharm Drug Dispos* 1989; 10: 77–85.
14. Boehning W. Effect of cimetidine and ranitidine on plasma theophylline in patients with chronic obstructive airways disease treated with theophylline and corticosteroids. *Eur J Clin Pharmacol* 1990; 38: 43–5.
15. Kelly HW, *et al.* Ranitidine at very large doses does not inhibit theophylline elimination. *Clin Pharmacol Ther* 1986; 39: 577–81.
16. Fernandes E, Melewicz FM. Ranitidine and theophylline. *Ann Intern Med* 1984; 100: 459.
17. Gardner ME, Sikorski GW. Ranitidine and theophylline. *Ann Intern Med* 1985; 102: 559.
18. Hegman GW, Gilbert RP. Ranitidine-theophylline interaction—fact or fiction? *DICP Ann Pharmacother* 1991; 25: 21–5.
19. Chremos AN, *et al.* Famotidine does not interfere with the disposition of theophylline in man: comparison to cimetidine. *Clin Pharmacol Ther* 1986; 39: 187.
20. Dal Negro R, *et al.* Famotidine and theophylline pharmacokinetics: an unexpected cimetidine-like interaction in patients with chronic obstructive pulmonary disease. *Clin Pharmacokinet* 1993; 24: 255–8.
21. Kokufu T, *et al.* Effects of lansoprazole on pharmacokinetics and metabolism of theophylline. *Eur J Clin Pharmacol* 1995; 48: 391–5.
22. Dilger K, *et al.* Lack of drug interaction between omeprazole, lansoprazole, pantoprazole and theophylline. *Br J Clin Pharmacol* 1999; 48: 438–44.
23. Cavuto NJ, *et al.* Effect of omeprazole on theophylline clearance in poor metabolizers of omeprazole. *Clin Pharmacol Ther* 1995; 57: 215.

General anaesthetics. There have been several reports[1,2] of increased cardiotoxicity when patients taking theophylline were anaesthetised with *halothane*. There was also an early report of seizures and tachycardia attributed to an interaction between theophylline and *ketamine*.[3]

1. Barton MD. Anesthetic problems with aspirin-intolerant patients. *Anesth Analg* 1975; 54: 376–80.
2. Richards W, *et al.* Cardiac arrest associated with halothane anesthesia in a patient receiving theophylline. *Ann Allergy* 1988; 61: 83–4.
3. Hirschman CA, *et al.* Ketamine-aminophylline-induced decrease in seizure threshold. *Anesthesiology* 1982; 56: 464–7.

Leukotriene inhibitors and antagonists. *Zileuton* prolongs the half-life and reduces the clearance of theophylline;[1] dosage of theophylline should be reduced to avoid toxicity when both drugs are given together, and plasma-theophylline concentrations should be monitored. Use of *zafirlukast* with theophylline decreased zafirlukast plasma concentrations but had no effect on theophylline plasma concentrations in clinical studies. However, toxic serum-theophylline concentrations occurred in one patient when zafirlukast was added to therapy, and recurred on rechallenge.[2] A dose of *montelukast* 10 mg daily did not affect the pharmacokinetics of theophylline, but doses of 200 mg and 600 mg daily reduced the maximum plasma concentration, area under the concentration-time curve, and elimination half-life of theophylline.[3]

1. Granneman GR, *et al.* Effect of zileuton on theophylline pharmacokinetics. *Clin Pharmacokinet* 1995; 29 (suppl 2): 77–83.
2. Katial RK, *et al.* A drug interaction between zafirlukast and theophylline. *Arch Intern Med* 1998; 158: 1713–15.
3. Malmstrom K, *et al.* Effect of montelukast on single-dose theophylline pharmacokinetics. *Am J Ther* 1998; 5: 189–95.

Methoxsalen. In a single-dose pharmacokinetic study in 3 healthy subjects, the rate of elimination of theophylline was decreased after a single oral dose of methoxsalen, while urinary excretion of unchanged theophylline increased.[1] Methoxsalen probably inhibits the metabolism of cytochrome P450 isoenzyme CYP1A2,[2] and it has been suggested that theophylline dose reductions are likely to be required when used with systemic methoxsalen but seem unlikely to be necessary with topical PUVA therapy.

1. Apseloff G, *et al.* Inhibition and induction of theophylline metabolism by 8-methoxypsoralen: in vivo study in rats and humans. *Drug Metab Dispos* 1990; 18: 298–303.
2. Tantcheva-Poór I, *et al.* Liver cytochrome P450 CYP1A2 is markedly inhibited by systemic but not by bath PUVA in dermatological patients. *Br J Dermatol* 2001; 144: 1127–32.

Neuromuscular blockers. For reference to resistance to neuromuscular block with pancuronium in patients receiving aminophylline, see Xanthines, p. 2033.3.

Oral contraceptives. Oral contraceptives have been reported to decrease the clearance of theophylline by about 30%, and serum concentrations may be increased,[1-3] due to the inhibitory effects of oral contraceptives on hepatic P450 isoenzymes.

1. Tornatore KM, *et al.* Effect of chronic oral contraceptive steroids on theophylline disposition. *Eur J Clin Pharmacol* 1982; 23: 129–34.
2. Gardner MJ, *et al.* Effects of tobacco smoking and oral contraceptive use on theophylline disposition. *Br J Clin Pharmacol* 1983; 16: 271–80.
3. Roberts RK, *et al.* Oral contraceptive steroids impair the elimination of theophylline. *J Lab Clin Med* 1983; 101: 821–5.

Roflumilast. Use of theophylline with roflumilast may result in an increased inhibition of phosphodiesterase type-4, see Interactions, under Roflumilast, p. 1219.3.

Sympathomimetics. The effect of beta-adrenoceptor agonists on the pharmacokinetics of theophylline is unclear. Whereas some studies have found that *orciprenaline*[1] or *terbutaline*[2] had no effect on theophylline disposition, others have shown an increase in theophylline clearance after *isoprenaline*[3,4] or *terbutaline*.[5,6]

Use of theophylline with beta-adrenoceptor agonists can potentiate adverse effects including hypokalaemia,[7,8] hyperglycaemia,[7] tachycardia,[7,8] hypertension,[7] and tremor.[9] Of 9 patients reported to the UK CSM with hypokalaemia during such combined therapy, 4 had clinical sequelae of cardiorespiratory arrest, intestinal pseudo-obstruction, or confusion. Monitoring of serum-potassium concentrations was recommended in patients with severe asthma given both beta-adrenoceptor agonists and xanthine derivatives.[10]

The possibility of an interaction with *phenylpropanolamine* should also be borne in mind, as it has been shown to reduce the clearance of theophylline significantly.[11]

1. Conrad KA, Woodworth JR. Orciprenaline does not alter theophylline elimination. *Br J Clin Pharmacol* 1981; 12: 756–7.
2. Snidow J, *et al.* Acute effects of short-term subcutaneous terbutaline on theophylline disposition. *Eur J Clin Pharmacol* 1987; 32: 191–3.
3. Hemstreet MP, *et al.* Effect of intravenous isoproterenol on theophylline kinetics. *J Allergy Clin Immunol* 1982; 69: 360–4.
4. Griffith JA, Kozloski GD. Isoproterenol-theophylline interaction possible potentiation by other drugs. *Clin Pharm* 1990; 9: 54–7.
5. Danziger Y, *et al.* Reduction of serum theophylline levels by terbutaline in children with asthma. *Clin Pharmacol Ther* 1985; 37: 469–71.
6. Garty M, *et al.* Increased theophylline clearance in asthmatic patients due to terbutaline. *Eur J Clin Pharmacol* 1989; 36: 25–8.
7. Smith SR, Kendall MJ. Potentiation of the adverse effects of intravenous terbutaline by oral theophylline. *Br J Clin Pharmacol* 1986; 21: 451–3.
8. Whyte KF, *et al.* Salbutamol induced hypokalaemia: the effect of theophylline alone and in combination with adrenaline. *Br J Clin Pharmacol* 1988; 25: 571–8.
9. van der Vet APH, *et al.* Pharmacodynamics (lungfunction tests, tremor measurements and cAMP determinations) of a single dose of 0.5 mg terbutaline subcutaneously during sustained-release theophylline medication in patients with asthmatic bronchitis. *Int J Clin Pharmacol Ther Toxicol* 1986; 24: 569–73.
10. CSM. β_2 agonists, xanthines and hypokalaemia. *Current Problems 28* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024446&RevisionSelectionMethod=LatestReleased (accessed 20/05/08)
11. Wilson HA, *et al.* Phenylpropanolamine significantly reduces the clearance of theophylline. *Am Rev Respir Dis* 1991; 143: A629.

Tiabendazole. Tiabendazole has been reported[1,2] to increase serum-theophylline concentrations and to decrease theophylline clearance. It has been recommended[2] that theophylline dosage should be reduced by 50% when tiabendazole therapy is started.

1. Sugar AM, *et al.* Possible thiabendazole-induced theophylline toxicity. *Am Rev Respir Dis* 1980; 122: 501–3.
2. Lew G, *et al.* Theophylline-thiabendazole drug interaction. *Clin Pharm* 1989; 8: 225–7.

Ticlopidine. Theophylline elimination half-life was increased and plasma clearance was decreased in 10 healthy subjects after the use of oral ticlopidine 500 mg daily for 10 days.[1]

1. Colli A, *et al.* Ticlopidine-theophylline interaction. *Clin Pharmacol Ther* 1987; 41: 358–62.

Vaccines. Transient inhibition of the hepatic metabolism of theophylline, possibly secondary to interferon production, resulting in increased theophylline serum half-life and concentration has been reported after BCG vaccination[1] and influenza vaccination.[2,3] Other studies have not been able to confirm the interaction with influenza vaccine.[4-7] The differing findings are probably due to differences in vaccine; modern purified subvirion vaccines which do not induce interferon production do not appear to alter theophylline metabolism.[8,9]

1. Gray JD, *et al.* Depression of theophylline elimination following BCG vaccination. *Br J Clin Pharmacol* 1983; 16: 735–7.
2. Renton KW, *et al.* Decreased elimination of theophylline after influenza vaccination. *Can Med Assoc J* 1980; 123: 288–90.
3. Walker S, *et al.* Serum theophylline levels after influenza vaccination. *Can Med Assoc J* 1981; 125: 243–4.
4. Goldstein RS, *et al.* Decreased elimination of theophylline after influenza vaccination. *Can Med Assoc J* 1982; 126: 470.
5. Fischer RG, *et al.* Influence of trivalent influenza vaccine on serum theophylline levels. *Can Med Assoc J* 1982; 126: 1312–13.
6. Britton L, Ruben FL. Serum theophylline levels after influenza vaccination. *Can Med Assoc J* 1982; 126: 1375.
7. Patriarca PA, *et al.* Influenza vaccination and warfarin or theophylline toxicity in nursing-home residents. *N Engl J Med* 1983; 308: 1601–2.
8. Stulin BM, Hashisaki PA. Influenza vaccination and theophylline pharmacokinetics in patients with chronic obstructive lung disease. *West J Med* 1983; 139: 651–4.
9. Winstanley PA, *et al.* Lack of effect of highly purified subunit influenza vaccination on theophylline metabolism. *Br J Clin Pharmacol* 1985; 20: 47–53.

Pharmacokinetics

Theophylline is rapidly and completely absorbed from liquid preparations, capsules, and uncoated tablets; the rate, but not the extent, of absorption is decreased by food, and food may also affect theophylline clearance. Peak serum-theophylline concentrations occur 1 to 2 hours after ingestion of liquid preparations, capsules, and uncoated tablets. Modified-release preparations exhibit considerable

variability in their absorption characteristics and in the effect of food and are generally not considered to be interchangeable. If a patient needs to be transferred from one such preparation to another then the dose should be retitrated. Rectal absorption is rapid from enemas, but may be slow and erratic from suppositories. Absorption after intramuscular injection is slow and incomplete.

Theophylline is about 40 to 60% bound to plasma proteins, but in neonates, or adults with liver disease, binding is reduced. Optimum therapeutic serum concentrations for bronchodilatation are generally considered to range from 10 to 20 micrograms/mL (55 to 110 micromol/litre) although some consider a lower range appropriate (see Therapeutic Drug Monitoring, below).

Theophylline is metabolised in the liver to 1,3-dimethyluric acid, 1-methyluric acid (via the intermediate 1-methylxanthine), and 3-methylxanthine. Demethylation to 3-methylxanthine (and possibly to 1-methylxanthine) is catalysed by the cytochrome P450 isoenzyme CYP1A2; hydroxylation to 1, 3-dimethyluric acid is catalysed by CYP2E1 and CYP3A3. Both the demethylation and hydroxylation pathways of theophylline metabolism are capacity-limited, resulting in non-linear elimination. The metabolites are excreted in the urine. In adults, about 10% of a dose of theophylline is excreted unchanged in the urine, but in neonates around 50% is excreted unchanged, and a large proportion is excreted as caffeine. Considerable interindividual differences in the rate of hepatic metabolism of theophylline result in large variations in clearance, serum concentrations, and half-lives. Hepatic metabolism is further affected by factors such as age, smoking, disease, diet, and drug interactions. The serum half-life of theophylline in an otherwise healthy, non-smoking asthmatic adult is 7 to 9 hours, in children 3 to 5 hours, in cigarette smokers 4 to 5 hours, in neonates and premature infants 20 to 30 hours, and in elderly non-smokers 10 hours. The serum half-life of theophylline may be increased in patients with heart failure or liver disease. Steady state is usually achieved within 48 hours with a consistent dosing schedule.

Theophylline crosses the placenta; it is also distributed into breast milk.

Absorption. *FOOD.* Food has substantial but variable effects on the absorption of theophylline from modified-release formulations but it is difficult to predict whether a particular formulation will be affected.[1] Some formulations are not affected by the presence of food but for others increases or decreases in the rate and/or extent of absorption have been reported. The composition and fluid content of the food appears to be important and a rapid release of theophylline ('dose-dumping') has occurred with some formulations after a meal, especially one with a high fat content.

A diet high in protein and low in carbohydrate has been reported to increase theophylline clearance, and a low-protein, high-carbohydrate diet to decrease theophylline clearance.[2-6] The consumption of methylxanthines, particularly caffeine, in the diet may decrease theophylline clearance (see Caffeine, under Interactions, p. 1235.3).

1. Jonkman JHG. Food interactions with sustained-release theophylline preparations: a review. *Clin Pharmacokinet* 1989; 16: 162–79.
2. Kappas A, *et al.* Influence of dietary protein and carbohydrate on antipyrine and theophylline metabolism in man. *Clin Pharmacol Ther* 1976; 20: 643–53.
3. Feldman CH, *et al.* Effect of dietary protein and carbohydrate on theophylline metabolism in children. *Pediatrics* 1980; 66: 956–62.
4. Feldman CH, *et al.* Interaction between nutrition and theophylline metabolism in children. *Ther Drug Monit* 1982; 4: 69–76.
5. Juan D, *et al.* Effects of dietary protein on theophylline pharmacokinetics and caffeine and aminopyrine breath tests. *Clin Pharmacol Ther* 1986; 40: 187–94.
6. Juan D, *et al.* Impairment of theophylline clearance by a hypocaloric low-protein diet in chronic obstructive pulmonary disease. *Ther Drug Monit* 1990; 12: 111–14.

Metabolism and excretion. *AGE.* From about 1 year of age until adolescence, children have a rapid theophylline clearance.[1] Premature infants and those under 1 year of age have a slower clearance[2,3] due to immature metabolic pathways.[3-5] In neonates the capacity of hepatic cytochrome P450 enzymes is much reduced compared with older children and adults, and *N*-demethylation and oxidation reactions play a minor role in the metabolism of theophylline.[4-6] Neonates are, however, capable of methylating theophylline at the N7 position to form caffeine, which is present at about one-third the concentration of theophylline at steady state.[5,6] The proportion of theophylline excreted unchanged is also increased in premature neonates and decreases with age as hepatic enzyme systems develop.[6] More rapid clearance on the first day of life in premature neonates has been reported.[7]

Some studies have found a progressive decline in clearance throughout adult years[8] whereas others have not.[9] Similarly, some studies have noted a decreased clearance in the elderly[10,11] but others have found no significant change.[12,13]

1. Zaske DE, *et al.* Oral aminophylline therapy: increased dosage requirements in children. *JAMA* 1977; 237: 1453–5.
2. Aranda JV, *et al.* Pharmacokinetic aspects of theophylline in premature newborns. *N Engl J Med* 1976; 295: 413–16.
3. Kraus DM, *et al.* Alterations in theophylline metabolism during the first year of life. *Clin Pharmacol Ther* 1993; 54: 351–9.
4. Grygiel JJ, Birkett DJ. Effect of age on patterns of theophylline metabolism. *Clin Pharmacol Ther* 1980; 28: 456–62.
5. Tserng K-Y, *et al.* Theophylline metabolism in premature infants. *Clin Pharmacol Ther* 1981; 29: 594–600.
6. Tserng K-Y, *et al.* Developmental aspects of theophylline metabolism in premature infants. *Clin Pharmacol Ther* 1983; 33: 522–8.
7. Stile IL, *et al.* Pharmacokinetics of theophylline in premature infants on the first day of life. *Clin Ther* 1986; 8: 336–41.
8. Randolph WC, *et al.* The effect of age on theophylline clearance in normal subjects. *Br J Clin Pharmacol* 1986; 22: 603–5.
9. Wiffen JK, *et al.* Does theophylline clearance alter within the adult age range? *Br J Clin Pharmacol* 1984; 17: 219P.
10. Antal EJ, *et al.* Theophylline pharmacokinetics in advanced age. *Br J Clin Pharmacol* 1981; 12: 637–45.
11. Jackson SHD, *et al.* The relationship between theophylline clearance and age in adult life. *Eur J Clin Pharmacol* 1989; 36: 29–34.
12. Bauer LA, Blouin RA. Influence of age on theophylline clearance in patients with chronic obstructive pulmonary disease. *Clin Pharmacokinet* 1981; 6: 469–74.
13. Fox RW, *et al.* Theophylline kinetics in a geriatric group. *Clin Pharmacol Ther* 1983; 34: 60–7.

ELIMINATION KINETICS. There is evidence that the elimination of theophylline is dose-dependent and that at high serum concentrations, a small change in dose of a theophylline preparation could cause a disproportionate increase in serum-theophylline concentration, due to a reduction in clearance.[1-3] However, it is not clear that this effect is clinically significant when serum-theophylline concentrations are within the therapeutic range.[4-8] It has also been suggested that repeated oral dosing of theophylline might result in a decrease of clearance compared with pre-treatment values.[9]

1. Weinberger M, Ginchansky E. Dose-dependent kinetics of theophylline disposition in asthmatic children. *J Pediatr* 1977; 91: 820–4.
2. Tang-Liu DD-S, *et al.* Nonlinear theophylline elimination. *Clin Pharmacol Ther* 1982; 31: 358–69.
3. Butcher MA, *et al.* Dose-dependent pharmacokinetics with single daily dose slow release theophylline in patients with chronic lung disease. *Br J Clin Pharmacol* 1982; 13: 241–3.
4. Koëter GH, *et al.* Pharmacokinetics of sustained release theophylline in low and high multidose regimens. *Br J Clin Pharmacol* 1981; 12: 647–51.
5. Rovei V, *et al.* Pharmacokinetics of theophylline: a dose-range study. *Br J Clin Pharmacol* 1982; 14: 769–78.
6. Gundert-Remy U, *et al.* Non-linear elimination processes of theophylline. *Eur J Clin Pharmacol* 1983; 24: 71–8.
7. Brown PJ, *et al.* Lack of dose dependent kinetics of theophylline. *Eur J Clin Pharmacol* 1983; 24: 525–7.
8. Milavetz G, *et al.* Dose dependency for absorption and elimination rates of theophylline: implications for studies of bioavailability. *Pharmacotherapy* 1984; 4: 216–20.
9. Efthimiou H, *et al.* Influence of chronic dosing on theophylline clearance. *Br J Clin Pharmacol* 1984; 17: 525–30.

GENDER. A higher theophylline clearance and shorter elimination half-life has been reported in healthy premenopausal women than in healthy men, probably due to sex-related differences in hepatic metabolism.[1] Changes in the pharmacokinetics of theophylline in women have also been reported according to the stage of the menstrual cycle;[2,3] another study[4] found no changes.

1. Nafziger AN, Bertino JS. Sex-related differences in theophylline pharmacokinetics. *Eur J Clin Pharmacol* 1989; 37: 97–100.
2. Bruguerolle B, *et al.* Influence of the menstrual cycle on theophylline pharmacokinetics in asthmatics. *Eur J Clin Pharmacol* 1990; 39: 59–61.
3. Nagata K, *et al.* Increased theophylline metabolism in the menstrual phase of healthy women. *J Allergy Clin Immunol* 1997; 100: 39–43.
4. Matsuki S, *et al.* Pharmacokinetic changes of theophylline and amikacin through the menstrual cycle in healthy women. *J Clin Pharmacol* 1999; 39: 1256–62.

Pregnancy and breast feeding. For mention of the pharmacokinetics of theophylline during pregnancy and breast feeding, see under Precautions, p. 1233.2.

Protein binding. Albumin is the major plasma binding protein for theophylline, binding is pH-dependent, and the percentage of theophylline bound at physiological pH is reported to range from about 35 to 45%.[1,2] Some studies have found the plasma protein binding of theophylline to be concentration dependent,[3] but others have not confirmed this.[1,4] Protein binding has been reported to be slightly but significantly higher in patients with bronchial asthma than in healthy controls.[5] Reduced protein binding occurs in patients with hypoalbuminaemia;[6,7] it has also been found in obese subjects[8] (possibly due to elevated concentrations of free fatty acids, which can displace theophylline from binding sites).

1. Buss D, *et al.* Determinants of the plasma protein binding of theophylline in health. *Br J Clin Pharmacol* 1983; 15: 399–405.
2. Brøtz O, *et al.* Binding of theophylline in human serum determined by ultrafiltration and equilibrium dialysis. *Br J Clin Pharmacol* 1983; 15: 393–7.
3. Gundert-Remy U, Hildebrandt R. Binding of theophylline and its metabolites to human plasma proteins. *Br J Clin Pharmacol* 1983; 16: 573–4.
4. Buss DC, *et al.* Protein binding of theophylline. *Br J Clin Pharmacol* 1985; 19: 529–31.
5. Trnavská Z. Theophylline protein binding. *Arzneimittelforschung* 1990; 40: 166–9.
6. Leopold D, *et al.* The ex vivo plasma protein binding of theophylline in renal disease. *Br J Clin Pharmacol* 1985; 19: 823–5.
7. Connelly TJ, *et al.* Characterization of theophylline binding to serum proteins in pregnant and nonpregnant women. *Clin Pharmacol Ther* 1990; 47: 68–72.
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Therapeutic drug monitoring. Dosage requirements of theophylline preparations vary widely between subjects and even vary with time in individuals, since serum-theophylline concentrations are influenced by factors including disease states, other drugs, diet, smoking, and age. Serious toxicity is related to serum concentration and may not be preceded by minor symptoms. For these reasons it is recommended that serum-theophylline concentrations should be monitored.

The generally accepted optimal serum concentration is between 10 and 20 micrograms/mL,[1-4] but this should be regarded as a guide and not a rigid barrier and clinical decisions should never be based solely on the serum concentration.[1] The therapeutic range in the treatment of neonatal apnoea is usually considered to be 5 to 15 micrograms/mL although some babies may respond at lower concentrations.[5] Some now consider that this is a more appropriate range in asthma (except perhaps acute severe asthma).[6] It has been suggested that pulmonary function tests provide a better guide in long-term therapy with theophylline.[7]

Serum-theophylline concentrations were originally measured by spectrophotometry but this is subject to considerable interference from other drugs. High performance liquid chromatography is now the method of choice when extreme accuracy is important and the enzyme multiplied immunoassay technique (EMIT) has become popular because of its rapidity and adaptability to processing large batches.[2] Devices are also available that provide serum-theophylline measurements within several minutes using monoclonal antibody technology.[2,8]

The use of salivary concentrations for monitoring theophylline dosage requirements has been tried, because it is noninvasive, but poor correlations between salivary- and serum-theophylline concentrations mean it has not gained general usage.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Crisasma; Drilyna; Nefoben; Teodosis†; Teosona Sol; Teosona; ***Austral.***: Nuelin; ***Austria***: Euphyllin; Respicur; Theospirex; Unifyl; ***Belg.***: Euphyllin; Theolair; Xanthium; ***Braz.***: Codrinan; Talofilina; Teofilab; Teolong; Teophyl†; Teoston; ***Canad.***: Apo-Theo; Novo-Theophyl†; Pulmophylline; Theolair; Uniphyl; ***Chile***: Elixine; ***China***: An Fei Lin (安菲林); Asmalon (埃斯玛隆); Bi Chuan (比川); Etipramid (迪帕米); Protheo (强乐辉); Quelesu (确乐苏); Shi Er Ping (时尔平); Xi Fu Lin (西弗林); Yan Er (延尔); Cz.: Afonilum; Euphyllin; Spophyllin†; Theoplus; ***Denm.***: Nuelin; Theo-Dur; UniXan; ***Fin.***: Nuelin; Retafyllin; Theofol; ***Fr.***: Euphylline; Theostat; *Xanthium*; ***Ger.***: Aerobin†; Afonilum†; afpred-THEO†; Bronchoparat; Bronchoretard; Euphylong; Solosin†; Theo; Tromphyllin; Uniphyllin; ***Gr.***: Aberten; Bronchogeril; Cefaphyllin; Euphyllin†; Mediphyllin Chrono; Neo-Antiasthman; Novaphylline; Quibron-R; Theo-Bros; Theo-Dur; Theoplus; Uni-Dur; Uniphyllin; ***Hong Kong***: CP-Theo; Euphylong; Nuelin; Slo-Theo; Slow-Theo; Theotrim†; ***Hung.***: Egifilin; Euphylong; Retafyllin; Theophtard; Theospirex; ***India***: Biryth; Broncordil; Delin; Duralyn; Lontif; Lungfyl; Od-Phyllin; Phylobid; Phyloday; Theo PA; Theobid; Theoday; Theoped; Unicontin; ***Indon.***: Bronchophylin; Brondilex†; Bronsolvan; Bufabron; Euphyllin; Quibron-T†; Retaphyl; Theobron; ***Irl.***: Nuelin; Slo-Phyllin†; Uniphyllin Continus; Zepholin; ***Israel***: Glyphyllin†; Theotard; Theotrim; ***Ital.***: Aminomal; Diffumal; Euphyllina; Frivent; Respicur; Theo-Dur; Theolair; ***Jpn***: Theodur; Theolong; ***Malaysia***: Apo-Theo; Nuelin; Retafyllin; ***Mex.***: Elixofilina; Fluidasa; Pharmafil†; ***Mon.***: Dilatrane; Pneumogeine†; Tedralan; ***Neth.***: Euphylong†; Theolair; ***Norw.***: Nuelin; Theo-Dur; ***NZ***: Nuelin; ***Philipp.***: Asmasolon; Brondil (Reformulated); Nuelin; Phenedrine; Theo-Dur†; ***Pol.***: Afonilum; Euphyllin; Theoplus†; Theospirex; Theovent; ***Port.***: Eufilina; Unicontin; ***Rus.***: Teotard (Теотард); Theopec (Теопек); ***S.Afr.***: Adco-Alcophyllin; Euphyllin; Microphyllin; Nuelin; Pulmophyllin†; Theophen; Theoplus; Uniphyl; ***Singapore***: Apo-Theo; Nuelin; Spophyllin; Theolin; Xanthium; ***Spain***: Elixifilin; Eufilina; Histafilin†; Pulmeno; Ter-

omol; Theo-Dur; Theolair; Theoplus†; *Swed.*: Theo-Dur; *Switz.*: Euphyllin; Theolair†; Unifyl; *Thai.*: Almarion; Asmasolon; Bronodaay†; Duralyn; Pranol; Nuelin; Polyasma; Retafyllin†; S-Phylline; Sinmaline; Sinoline; Temaco; Theocap; Theolin; Theori; Theotrim; Xanthium; *Turk.*: Bronkolin; Pirasmin; Pirazmen; Talotren; Teobag; Teokap; Teosel; Theo-Dur†; Xanthium; *UAE*: Theophar; *UK*: Nuelin; Slo-Phyllin; Unitphyllin Continus; *Ukr.*: Neofillin (Неофиллин); Theotard (Теотард); *USA*: Accurbron; Aerolate; Asmalix; Elixophyllin; Theo-24; Theochron; Uniphyl†; *Venez.*: Nuelin; Teobid.

Multi-ingredient Preparations. *Arg.*: Dexa Teosona; Dexa-Aminofilin; Sedacris; *Braz.*: Bronquitos; Endotussin†; Pranol; Marax; *Canad.*: ratio-Theo-Bronc; *Chile*: Cellenergy; *China*: Antong (安通); Xu Hong (旭宏); Yi Xi Qing (易息晴); *Cz.*: Oxantil; *Fin.*: Theofol Comp; *Ger.*: Broncho-Euphyllin; *Gr.*: Aminabel; Baladex; Gulamyl; Normavix; Repusan; Silantuss; Tycod; *Hong Kong*: Noscaphylline†; Sedral†; Uni-Theodal†; *India*: Agrophyllin; Alergin; Ambro TS; Ambrolax-PD; Ambrolite-ST; Asmapax; Asmatide-BR; Azofen-T; Broncophyl Plus; Broncordil P; Bronko Plus; Carbasma; Delin; Dericip Plus; Dericip; Deriphyllin; Deripil; Durasalyn; Glophyllin; Marax; Mucoresp; Multimix; Multimix; Multrimix; Tergil-T†; Theo-Asthalin; Theobric; *Indon.*: Asmadex; Asmano; Asmasolon; Asthma Soho; Neo Napacin†; Prinasma†; Teosal; Theochodil; Tusapres; *Ital.*: Altadrine Firming†; Binfolipase; *Malaysia*: Asthma; Theophylline Expectorant; *Mex.*: Aminoefedrison; *Philipp.*: Mucophylline; *Pol.*: Baladex; *Rus.*: Insanovin (Инсановин); Theophedrinum-N (Теофедрин-Н); *S.Afr.*: Actophlem; Adco-Metaxol; Alcophyllex; Diatussin; Solphyllex; Solphyllin; Theophen Comp; *Spain*: Teolixir Compositum†; *Thai.*: Almasal; Asiabron; Asma-Dec; Bronchil; Brondil†; Brondry; Chintasma; Forasma; Mila-Asma; Polyphed; Qualiton; *Turk.*: Fenastma; *UK*: Do-Do ChestEze; *USA*: Broncomar; Elixophyllin-GG; Elixophyllin-KI; Glyceryl-T; Hydrophed; Marax; Neoasma; Quadrinal; Tedrigen; Theodrine; Theomax DF; *Venez.*: Metoxifilin.

Pharmacopoeial Preparations

BP 2014: Prolonged-release Theophylline Tablets;
USP 36: Theophylline and Guaifenesin Capsules; Theophylline and Guaifenesin Oral Solution; Theophylline Capsules; Theophylline Extended-release Capsules; Theophylline in Dextrose Injection; Theophylline Oral Solution; Theophylline Oral Suspension; Theophylline Sodium Glycinate Elixir; Theophylline Sodium Glycinate Tablets; Theophylline Tablets; Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets.

Tiotropium Bromide *(BAN, rINN)*

Ba-679; Ba-679BR; Bromuro de tiotropio; Tiotropii Bromidum; Tiotropio, bromuro de; Tiotropium, Bromure de; Tiotropyum Bromür; Тиотропия бромид.

6β,7β-Epoxy-3β-hydroxy-8-methyl-1α*H*,5α*H*-tropanium bromide di-2-thienylglycolate.

$C_{19}H_{22}BrNO_4S_2$=472.4

CAS — 186691-13-4 (tiotropium); 139404-48-1 (anhydrous tiotropium bromide or tiotropium bromide hydrate); 136310-93-5 (anhydrous tiotropium bromide); 411207-31-3 (tiotropium bromide monohydrate).

ATC — R03BB04.

ATC Vet — QR03BB04.

UNII — XX112XZP0J (tiotropium bromide); L64SXO195N (tiotropium bromide monohydrate).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tiotropium Bromide Monohydrate). A white or yellowish-white powder or crystals. Sparingly soluble in water; soluble in methyl alcohol; practically insoluble in dichloromethane.

Uses and Administration

Tiotropium bromide is a quaternary ammonium antimuscarinic that is structurally related to ipratropium but has a prolonged bronchodilator action. It is used similarly to ipratropium (p. 1211.3) in the maintenance treatment of reversible airways obstruction, as in chronic obstructive pulmonary disease (below); tiotropium is not suitable for the initial treatment of acute bronchospasm. Tiotropium bromide can be given as inhalation powder in capsules containing 22.5 micrograms of tiotropium bromide monohydrate, equivalent to 18 micrograms of tiotropium, and supplying 10 micrograms of tiotropium from the mouthpiece of the inhaler device. The contents of one capsule are inhaled daily, at the same time each day.

Tiotropium bromide can also be given as inhalation solution via a metered-dose inhaler. Each metered dose contains 3.124 micrograms of tiotropium bromide monohydrate equivalent to 2.5 micrograms of tiotropium. Two metered doses are inhaled daily, at the same time each day.

References.

1. Hvizdos KM, Goa KL. Tiotropium bromide. *Drugs* 2002; 62: 1195–1203.

Chronic obstructive pulmonary disease. In chronic obstructive pulmonary disease (COPD; p. 1199.1) tiotropium bromide has been shown to be effective at improving dyspnoea,[1-3] health-related quality of life,[1,3,4] symptom-limited exercise tolerance,[2] lung function measurements,[3,4] and reducing exacerbations[1,3-6] compared with placebo.

Tiotropium has also been found to be more effective than ipratropium at improving dyspnoea, health-related quality of life,[7] and lung function,[7,8] and reducing exacerbations;[7] consideration of tiotropium as first-line maintenance treatment in COPD has been suggested.[9,10]

Similarly, tiotropium has produced better bronchodilatation, reduced dyspnoea, and improved health-related quality of life scores compared with salmeterol,[11] although its benefits in comparison with a combination of salmeterol and fluticasone are unclear.[12]

Combining tiotropium therapy with an inhaled corticosteroid and a long-acting beta$_2$ agonist did not statistically influence rates of COPD exacerbations but did improve lung function, quality of life, and hospitalisation rates in patients with moderate to severe COPD.[13]

A systematic review[14] and a meta-analysis[15] confirmed that tiotropium reduces exacerbations and related hospitalisations, improves quality of life and symptoms in stable COPD. Tiotropium may also have slowed the decline in forced expiratory volume (FEV) seen in COPD, an observation that was supported by a subgroup analysis of a study in patients with moderate COPD,[16] suggesting that treatment with tiotropium should begin at an early stage of the disease. Further studies are required to evaluate the effect of tiotropium on FEV and to clarify its role in relation to long-acting beta$_2$ agonists.

The role of tiotropium in the management of COPD has been extensively reviewed.[9,17-20]

1. Casaburi R, *et al.* A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002; 19: 217–24.
2. Maltais F, *et al.* Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. *Chest* 2005; 128: 1168–78.
3. Brusasco V, *et al.* Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax* 2003; 58: 399–404.
4. Tashkin DP, *et al.* UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 1543–54.
5. Niewoehner DE, *et al.* Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med* 2005; 143: 317–26.
6. Tashkin DP. Preventing and managing exacerbations in COPD—critical appraisal of the role of tiotropium. *Int J Chron Obstruct Pulmon Dis* 2010; 5: 41–53.
7. Vincken W, *et al.* Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. *Eur Respir J* 2002; 19: 209–16.
8. van Noord JA, *et al.* A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease. *Thorax* 2000; 55: 289–94.
9. Chen AM, *et al.* Long-acting bronchodilator therapy for the treatment of chronic obstructive pulmonary disease. *Ann Pharmacother* 2008; 42: 1832–42.
10. Troosters T, *et al.* UPLIFT Investigators. Tiotropium as a first maintenance drug in COPD: secondary analysis of the UPLIFT trial. *Eur Respir J* 2010; 36: 65–73.
11. Donohue JF, *et al.* A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 2002; 122: 47–55.
12. Welsh EJ, *et al.* Combination inhaled steroid and long-acting beta2-agonist versus tiotropium for chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2010 (accessed 14/07/10).
13. Aaron SD, *et al.* Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2007; 146: 545–55.
14. Barr RG, *et al.* Tiotropium for stable chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 18/02/08).
15. Barr RG, *et al.* Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis. *Thorax* 2006; 61: 854–62. Correction. *ibid.*: 62: 191.
16. Decramer M, *et al.* UPLIFT investigators. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. *Lancet* 2009; 374: 1171–8.
17. Gross NJ. Tiotropium bromide. *Chest* 2004; 126: 1946–53.
18. Olin JL. Tiotropium: an inhaled anticholinergic for chronic obstructive pulmonary disease. *Am J Health-Syst Pharm* 2005; 62: 1263–9.
19. Somand H, Remington TL. Tiotropium: a bronchodilator for chronic obstructive pulmonary disease. *Ann Pharmacother* 2005; 39: 1467–75.
20. Burns G, Bianchi S. Chronic obstructive pulmonary disease: the evidence for use of tiotropium. *Br J Hosp Med* 2006; 67: 85–91.

Adverse Effects and Precautions

As for Ipratropium Bromide (p. 1212.2).

Pharyngitis, sinusitis, rhinitis, and epistaxis have also been reported after inhalation.

Patients with moderate to severe renal impairment (creatinine clearance 50 mL/minute or less) should be closely monitored as tiotropium bromide is mainly excreted by the kidneys.

Effects on the cardiovascular system. For discussion of the possible increased risk of cardiovascular events with inhaled antimuscarinic use, see Ipratropium, p. 1212.2.

Effects on the cerebrovascular system. In March 2008 the FDA reported[1] that the manufacturer of tiotropium bromide (*Boehringer Ingelheim*) had informed them that they had identified a possible increased risk of stroke in patients taking tiotropium bromide. From pooled analysis of 29 clinical studies in patients with chronic obstructive pulmonary disease preliminary estimates of the risk of stroke were 8 per 1000 patients treated for one year with tiotropium compared with 6 per 1000 patients given placebo for one year. However, a self-controlled case series (where cases act as their own controls to reduce confounding), found no evidence that tiotropium bromide was associated with an increased risk of stroke in almost 1000 stroke patients.[2] Similarly, results from UPLIFT,[3] a large, 4-year, placebo-controlled study of tiotropium in about 6000 patients with chronic obstructive pulmonary disease, also showed no increased risk of stroke with tiotropium. Further analysis of the final results of UPLIFT by the FDA[4] confirmed that the data do not support an increased risk of stroke, heart attack, or cardiovascular death.

For further information on the risk to the cardiovascular system associated with tiotropium, see Effects on the Cardiovascular System, under Ipratropium Bromide, p. 1212.2.

1. FDA. Early communication about ongoing safety review of tiotropium (marketed as Spiriva HandiHaler) (issued 18th March 2008; updated 7th October 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm070655 (accessed 03/08/10)
2. Grosso A, *et al.* Inhaled tiotropium bromide and risk of stroke. *Br J Clin Pharmacol* 2009; 68: 731–6.
3. Tashkin DP, *et al.* UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 1543–54.
4. FDA. Follow-up to the October 2008 updated early communication about an ongoing safety review of tiotropium (marketed as Spiriva HandiHaler) (issued 14th January 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm197429.htm (accessed 03/08/10)

Effects on the skin. Subacute cutaneous lupus erythematosus has been reported in a patient inhaling tiotropium.[1] Skin lesions developed one week after introduction of the drug, resolved when the drug was stopped, and recurred on rechallenge.

Inhaled tiotropium has also been associated with a photosensitive lichenoid eruption in another patient,[2] 22 months after starting treatment. The lesions resolved when the drug was stopped; patch testing however, gave a negative result. Rechallenge was not attempted.

1. Pham H-C, Saurat J-H. Inhalation route inducing subacute cutaneous lupus erythematosus with tiotropium. *Arch Dermatol* 2005; 141: 911–12.
2. Pérez-Pérez L, *et al.* Photosensitive lichenoid eruption and inhaled tiotropium bromide. *Dermatology* 2007; 214: 97–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tiotropium bromide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

For interactions associated with antimuscarinics in general, see Atropine, p. 1312.3. However, these interactions are not usually seen with antimuscarinics, such as tiotropium, given by inhalation.

Pharmacokinetics

After inhalation, some tiotropium bromide is absorbed from the lung, with the majority deposited in the gastrointestinal tract. In healthy subjects a systemic bioavailability of about 20% is reported after dry powder inhalation, and about 33% after inhalation of the solution. Tiotropium is about 72% bound to plasma proteins. It is excreted largely unchanged in the urine, although it may undergo some metabolism by non-enzymatic cleavage and by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. The terminal elimination half-life is between 5 and 6 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Spiriva; *Austral.*: Spiriva; *Austria*: Spiriva; *Belg.*: Spiriva; *Braz.*: Spiriva; *Canad.*: Spiriva; *Chile*: Spiriva; *China*: Spiriva (思力华); *Cz.*: Spiriva; *Denm.*: Spiriva; *Fin.*: Spiriva; *Fr.*: Spiriva; *Ger.*: Spiriva; *Gr.*: Spiriva; *Hong Kong*: Spiriva; *Hung.*: Spiriva; *India*: Tiova; *Indon.*: Spiriva; *Irl.*: Spiriva; *Israel*: Spiriva; *Ital.*: Spiriva; *Jpn*: Spiriva; *Malaysia*: Spiriva; *Mex.*: Spiriva; *Neth.*: Spiriva; *Norw.*: Spiriva; *NZ*: Spiriva; *Philipp.*: Spiriva; *Pol.*: Spiriva; *Port.*: Spiriva; *Rus.*: Spiriva (Спирива); *S.Afr.*: Forvent; Spiriva; *Singapore*: Spiriva; *Spain*: Spiriva; *Swed.*: Spiriva; *Switz.*: Spiriva; *Thai.*: Spiriva; *Turk.*: Spiriva; *UK*: Spiriva; *Ukr.*: Spiriva (Спирива); *USA*: Spiriva; *Venez.*: Spiriva.

Multi-ingredient Preparations. *India*: Duova.

Tipelukast *(USAN, rINN)*

KCA-757; MN-001; Tipélukast; Tipelukastum; Типелукаст.
4-(6-Acetyl-3-{3-[(4-acetyl-3-hydroxy-2-propylphenyl)sulfanyl]propoxy}-2-propylphenoxy)butanoic acid.
$C_{29}H_{38}O_7S$=530.7
CAS — 125961-82-2.
UNII — 08379P260O.

Profile

Tipelukast is a leukotriene receptor antagonist (p. 1195.2), a phosphodiesterase inhibitor, and 5-lipoxygenase inhibitor that is under investigation for the treatment of asthma.

Tranilast *(USAN, rINN)*

MK-341; N-5'; Tranilastum; Траниласт.
N-(3,4-Dimethoxycinnamoyl)anthranilic acid.
$C_{18}H_{17}NO_5$=327.3
CAS — 53902-12-8.
UNII — HVF50SMY6E.

Uses and Administration

Tranilast has a stabilising action on mast cells resembling that of sodium cromoglicate (p. 1226.1). It is also stated to inhibit collagen synthesis in fibroblasts. It is used in the prophylactic management of asthma (p. 1195.2) and in allergic rhinitis (p. 612.1), conjunctivitis (p. 611.1), and eczema (p. 1684.1). It is also used in the management of keloids and hypertrophic scarring. The usual oral adult dose is 100 mg three times daily. For details of doses in children, see below. Eye drops containing tranilast 0.5% are used four times daily for allergic conjunctivitis.

Tranilast has been investigated for the prevention of restenosis after coronary artery revascularisation procedures but was found to be ineffective. A topical gel containing tranilast is also under investigation to prevent adhesion formation after surgery.

Administration in children. Tranilast is given to children for the prophylactic management of asthma, in allergic rhinitis and eczema, and in the management of keloids and hypertrophic scars. An oral daily dose of 5 mg/kg, given in 3 divided doses, may be used.

Sarcoidosis. For a mention of possible benefit from tranilast in cutaneous sarcoidosis, see p. 1612.2.

Adverse Effects and Precautions

Adverse effects reported with tranilast have included gastrointestinal disturbances, headache, drowsiness or insomnia, dizziness, malaise, and skin rashes and generalised pruritus. Rarely, liver function disturbance or jaundice, renal dysfunction, cystitis-like symptoms, anaemia, leucopenia, thrombocytopenia, palpitations, oedema, facial flushing, and stomatitis may occur. Tranilast should be used with caution in patients with impaired hepatic or renal function. Haematological monitoring is recommended.

Irritation and blepharitis have been reported after topical application to the eye.

Licensed product information advises against the use of tranilast in pregnancy because of teratogenicity in *animal* studies.

Tranilast should not be used for the treatment of acute asthma attacks. The general cautions described under sodium cromoglicate (p. 1227.2) also apply.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ao Te Min (奥特敏); *Jpn*: Rizaben.

Multi-ingredient Preparations. *China*: Shun Qi (顺奇).

Tretoquinol Hydrochloride *(pINNM)* ⊗

AQ-110; (tretoquinol); Hidrocloruro de tretoquinol; Ro-07-5965; Tretoquinol, Chlorhydrate de; Tretoquinol, hidrocloruro de; Tretoquinoli Hydrochloridum; Trimethoquinol Hydrochloride; Trimetoquinol Hydrochloride; Третохинола Гидрохлорид.
(-)-1,2,3,4-Tetrahydro-1-(3,4,5-trimethoxybenzyl)isoquinoline-6,7-diol hydrochloride monohydrate.
$C_{19}H_{23}NO_5.HCl.H_2O$=399.9
CAS — 30418-38-3 (tretoquinol); 18559-59-6 (anhydrous tretoquinol hydrochloride).
ATC — R03AC09; R03CC09.
ATC Vet — QR03AC09; QR03CC09.
UNII — 5S28YGI1ZQ.

Pharmacopoeias. In *Jpn*.

Profile

Tretoquinol is a direct-acting sympathomimetic reported to have a selective action on beta$_2$ receptors (a beta$_2$ agonist). It has properties similar to those of salbutamol (p. 1220.2). It is given as the hydrochloride for its bronchodilating properties in the management of reversible airways obstruction, as in asthma (p. 1195.2) or in some patients with chronic obstructive pulmonary disease (p. 1199.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hong Kong*: Inolin†; *Indon.*: Inolin: *Jpn*: Inolin.

Tulobuterol Hydrochloride *(BANM, rINNM)* ⊗

C-78; Hidrocloruro de tulobuterol; HN-078 (tulobuterol); Tulobutérol, Chlorhydrate de; Tulobuterol, hidrocloruro de; Tulobuterolhydroklorid; Tulobuterolli Hydrochloridum; Tulobuterolihydrokloridi; Тулобутерола Гидрохлорид.
2-*tert*-Butylamino-1-(2-chlorophenyl)ethanol hydrochloride.
$C_{12}H_{18}ClNO.HCl$=264.2
CAS — 41570-61-0 (tulobuterol); 56776-01-3 (tulobuterol hydrochloride).
ATC — R03AC11; R03CC11.
ATC Vet — QR03AC11; QR03CC11.
UNII — VNC1218170.

NOTE. The names Berachin, Senikarin-DS, Tulobunist, and Tulobuten have been used as trade marks for tulobuterol or tulobuterol hydrochloride.

Pharmacopoeias. In *Jpn*.

Profile

Tulobuterol is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on beta$_2$ receptors (a beta$_2$ agonist). It has properties similar to those of salbutamol (p. 1220.2).

Tulobuterol is used as a bronchodilator in the management of reversible airways obstruction, as in asthma (p. 1195.2) and in some patients with chronic obstructive pulmonary disease (p. 1199.1). It is given orally in a usual dose of tulobuterol hydrochloride 2 mg twice daily. An increased need for, or decreased duration of effect of, tulobuterol indicates deterioration of asthma control and the need for review of therapy. Tulobuterol has also been given as the base by inhalation from a metered-dose inhaler. A transdermal formulation of tulobuterol base is also available; a dose of 2 mg daily is used with anti-inflammatory therapy.

For doses of tulobuterol used in children aged 14 years and under, see Administration in Children, below.

References to the transdermal formulation of tulobuterol.

1. Uematsu T, *et al.* The pharmacokinetics of the β$_2$-adrenoceptor agonist, tulobuterol, given transdermally and by inhalation. *Eur J Clin Pharmacol.* 1993; **44:** 361–4.
2. Iikura Y, *et al.* Pharmacokinetics and pharmacodynamics of the tulobuterol patch. HN-078, in childhood asthma. *Ann Allergy* 1995; **74:** 147–51.
3. Fukuchi Y, *et al.* Clinical efficacy and safety of transdermal tulobuterol in the treatment of stable COPD: an open-label comparison with inhaled salmeterol. *Treat Respir Med* 2005; **4:** 447–55.
4. Yoshihara S, *et al.* The use of patch formulation of tulobuterol, a long-acting beta2-adrenoceptor agonist, in the treatment of severe pediatric asthma. *Ann Allergy Asthma Immunol* 2006; **96:** 879–80.
5. Fujimoto K, *et al.* Comparison of the clinical efficacy of salmeterol and sustained-release tulobuterol (patch) on inadequately controlled asthma patients on inhaled corticosteroids. *J Asthma* 2006; **43:** 501–7.
6. Nishiyama O, *et al.* Comparison of the effects of tulobuterol patch and salmeterol in moderate to severe asthma. *Clin Exp Pharmacol Physiol* 2006; **33:** 1016–21.
7. Kobayashi Y, *et al.* Addition of transdermal or inhaled long-acting β$_2$-agonists in adult asthmatic patients treated with inhaled corticosteroids: switchover study from tulobuterol patch to salmeterol dry powder inhaler. *J Asthma* 2007; **44:** 77–81.
8. Yamagata T, *et al.* Comparison of bronchodilatory properties of transdermal and inhaled long-acting β$_2$-agonists. *Pulm Pharmacol Ther* 2008; **21:** 160–5.

Administration in children. Tulobuterol hydrochloride has been used to treat bronchospasm in children in the following *oral* doses:

- 1 to 6 years of age: 250 to 500 micrograms twice daily
- 6 to 10 years of age: 0.5 to 1 mg twice daily
- 10 to 14 years of age: 1 to 1.5 mg twice daily

Children 14 years of age and over may be given the adult dose of tulobuterol, see above.

Transdermal delivery of tulobuterol is also used in children, in the following doses:

- 6 months to 3 years of age: 500 micrograms once daily
- 3 to 9 years of age: 1 mg once daily
- 9 years of age and older: as for adults (see above)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Amiald (阿米迪); *Ger.*: Brelomax†; *Jpn*: Hokunalin; *Mex.*: Bremax†; *Philipp.*: Bremax†; *Venez.*: Bretol.

Vilanterol Trifenatate *(USAN, rINNM)* ⊗

GW-642444M; GW-642444X; (vilanterol); Trifenatato de vilanterol; Vilantérol, Trifenatate de; Vilanterol Trifenatas; Вилантерола Трифенатат.
4-{(1*R*)-2-[(6-{2-[(2,6-Dichlorophenyl)methoxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol triphenylacetate.
$C_{24}H_{33}Cl_2NO_5.C_{20}H_{16}O_2$=774.8
CAS — 503068-34-6 (vilanterol); 503070-58-4 (vilanterol trifenatate).
UNII — 028LZY775B (vilanterol); 40AHO2C6DG (vilanterol trifenatate).

Uses and Administration

Vilanterol is a direct-acting sympathomimetic with mainly beta-adrenoceptor stimulant activity specific to beta$_2$ receptors (a beta$_2$ agonist). It has properties similar to those of salbutamol (p. 1220.2), but like salmeterol (p. 1224.1) it has a prolonged duration of action and is therefore not considered suitable for the symptomatic relief of acute attacks of bronchospasm. It is used with regular inhaled corticosteroid when a regular long-acting beta$_2$ agonist is needed for management of asthma (p. 1195.2) and chronic obstructive pulmonary disease (p. 1199.1).

Vilanterol is given as the trifenatate but doses are expressed in terms of the base; 40 micrograms of vilanterol trifenatate is equivalent to about 25 micrograms of vilanterol. It is available in dry powder inhalers, with fluticasone furoate. The dose of vilanterol may be expressed as the amount in each available dose (25 micrograms) or as the delivered dose leaving the mouthpiece (22 micrograms). In both asthma and chronic obstructive pulmonary disease, one dose is inhaled daily.

References.

1. Martinez FJ, *et al.* Fluticasone furoate/vilanterol (100/25; 200/25 micrograms) improves lung function in COPD: a randomised trial. *Respir Med* 2013; **107:** 550–9.
2. Woodcock A, *et al.* Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. *Chest* 2013; **144:** 1222–9.

Adverse Effects and Precautions

As for Salbutamol, p. 1221.3, and Salmeterol Xinafoate, p. 1224.3. Inhalation of vilanterol may be associated with paradoxical bronchospasm. Patients should also be receiving an inhaled corticosteroid.

Long-acting beta$_2$ agonists such as vilanterol are not appropriate for the treatment of acute bronchospasm.

Interactions

As for Salbutamol, p. 1223.1.

Vilanterol is metabolised by the cytochrome P450 isoenzyme CYP3A4, and use with ketoconazole, a CYP3A4 inhibitor, can increase systemic exposure to inhaled vilanterol. Patients should be monitored if treated with both vilanterol and a strong CYP3A4 inhibitor.

Pharmacokinetics

Vilanterol is rapidly absorbed after inhalation and an absolute bioavailability of about 27% has been reported. It is mainly metabolised via the cytochrome P450 isoenzyme CYP3A4, and metabolites are excreted in the urine and faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: Relvar Ellipta; *USA*: Breo Ellipta.

Zafirlukast *(BAN, USAN, rINN)*

ICI-204219; Tsafirlukasti; Zafirlukastum; ZD-204219; Зафирлукаст.
Cyclopentyl 3-[2-methoxy-4-[(*o*-tolylsulfonyl)carbamoyl]benzyl]-1-methylindole-5-carbamate.
$C_{31}H_{33}N_3O_6S$=575.7
CAS — 107753-78-6.
ATC — R03DC01.
ATC Vet — QR03DC01.
UNII — XZ629S5L50.

Uses and Administration

Zafirlukast is a selective and competitive antagonist of the leukotriene C_4, D_4, and E_4 receptors (p. 1195.2), stimulation of which by circulating leukotrienes is thought to play a role in the pathogenesis of asthma. The drug suppresses both early and late bronchoconstrictor responses to inhaled antigens or irritants, but is not suitable for the management of acute attacks of asthma.

Zafirlukast is used in the management of chronic asthma (see below). It is given orally in doses of 20 mg twice daily, taken at least 1 hour before or 2 hours after meals. For details of doses in children, see below.

General references.

1. García-Marcos L, *et al.* Benefit-risk assessment of antileukotrienes in the management of asthma. *Drug Safety* 2003; 26: 483–518.
2. Anonymous. Leukotriene receptor antagonists—an update. *Drug Ther Bull* 2005; 43: 85–8.
3. Currie GP, McLaughlin K. The expanding role of leukotriene receptor antagonists in chronic asthma. *Ann Allergy Asthma Immunol* 2006; 97: 731–41.
4. Riccioni G, *et al.* Antileukotriene drugs: clinical application, effectiveness and safety. *Curr Med Chem* 2007; 14: 1966–77.

Administration in children. In the management of chronic asthma, US licensed product information recommends a zafirlukast dose of 10 mg twice daily orally in children aged from 5 to 11 years. Children 12 years of age and over may be given the adult dose, see above. In the UK, zafirlukast is unlicensed in children under 12 years of age.

Asthma. Zafirlukast produces modest improvement in mild-to-moderate asthma (p. 1195.2),[1,2] which was of a similar order to that seen with inhaled sodium cromoglicate in one study,[3] but less than that of inhaled salmeterol in another.[4] It has also been found to be less effective than inhaled fluticasone in persistent asthma.[5-7] In a study in patients presenting to the emergency room with acute severe asthma, adding zafirlukast to standard therapy in hospital and for 28 days after discharge was associated with a reduced rate of relapse, and a reduction in the need for extended care.[8]

1. Suissa S, *et al.* Effectiveness of the leukotriene receptor antagonist zafirlukast for mild-to-moderate asthma: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1997; 126: 177–83.
2. Fish JE, *et al.* Zafirlukast for symptomatic mild-to-moderate asthma: a 13-week multicenter study. *Clin Ther* 1997; 19: 675–90.
3. Nathan RA, *et al.* Two first-line therapies in the treatment of mild asthma: use of peak flow variability as a predictor of effectiveness. *Ann Allergy Asthma Immunol* 1999; 82: 497–503.
4. Busse W, *et al.* Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma. *J Allergy Clin Immunol* 1999; 103: 1075–80.
5. Busse W, *et al.* Fluticasone propionate compared with zafirlukast in controlling persistent asthma: a randomized double-blind, placebo-controlled trial. *J Fam Pract* 2001; 50: 595–602.
6. Nathan RA, *et al.* A comparison of short-term treatment with inhaled fluticasone propionate and zafirlukast for patients with persistent asthma. *Am J Med* 2001; 111: 195–202.
7. Brabson JH, *et al.* Efficacy and safety of low-dose fluticasone propionate compared with zafirlukast in patients with persistent asthma. *Am J Med* 2002; 113: 15–21.
8. Silverman RA, *et al.* Zafirlukast treatment for acute asthma: evaluation in a randomized, double-blind, multicenter trial. *Chest* 2004; 126: 1480–9.

Rhinitis. Although it was reported to improve symptoms of seasonal allergic rhinitis (p. 612.1) in one study,[1] zafirlukast 20 mg twice daily was not effective when compared with placebo and intranasal beclometasone in another.[2] Some benefits have been reported in perennial allergic rhinitis, in particular an improvement in nasal obstruction.[3,4] A review of the role of leukotrienes in allergic rhinitis concluded that leukotriene receptor antagonists have modest efficacy given alone but can be usefully added to other treatments.[5]

1. Donnelly AL, *et al.* The leukotriene D_4-receptor antagonist, ICI 204,219, relieves symptoms of acute seasonal allergic rhinitis. *Am J Respir Crit Care Med* 1995; 151: 1734–9.
2. Pullerits T, *et al.* Randomized placebo-controlled study comparing a leukotriene receptor antagonist and a nasal glucocorticoid in seasonal allergic rhinitis. *Am J Respir Crit Care Med* 1999; 159: 1814–18.
3. Jiang R-S. Efficacy of a leukotriene receptor antagonist in the treatment of perennial allergic rhinitis. *J Otolaryngol* 2006; 35: 117–21.
4. Ho C-Y, Tan C-T. Comparison of antileukotrienes and antihistamines in the treatment of allergic rhinitis. *Am J Rhinol* 2007; 21: 439–43.
5. Peters-Golden M, Henderson WR. The role of leukotrienes in allergic rhinitis. *Ann Allergy Asthma Immunol* 2005; 94: 609–18.

Urticaria. Leukotriene antagonists, such as zafirlukast, are reported to have some benefit in the management of chronic urticaria (p. 1689.2).

Adverse Effects and Precautions

Headache, an increased incidence of respiratory-tract infection (in the elderly), and gastrointestinal disturbances have been reported with zafirlukast and other leukotriene antagonists. Other adverse effects have included generalised and abdominal pain, arthralgia, myalgia, fever, malaise, insomnia, and dizziness. Elevations in liver enzyme values and severe hepatotoxicity have been reported (see also below); fatalities have occurred. Hypersensitivity reactions, including rashes, pruritus, urticaria, and angioedema, have been reported. There have also been rare reports of agranulocytosis, bleeding, bruising and oedema. There have been a few reports of systemic eosinophilla consistent with Churg-Strauss syndrome in patients receiving leukotriene antagonists (see below); treatment should be withdrawn in these patients.

Zafirlukast and other leukotriene antagonists should not be used for the treatment of acute asthma attacks. Zafirlukast is contra-indicated in patients with hepatic impairment or cirrhosis.

Incidence of adverse effects. An observational study[1] of 7976 patients prescribed zafirlukast found it to be generally well tolerated. Similarly to UK licensed product information, the most frequently reported adverse effects (1 to 2% of patients) were headache, rash, abdominal pain, malaise, and gastrointestinal disturbances such as nausea, diarrhoea, and dyspepsia. Dizziness and palpitations were more common in the first month of treatment. An increased incidence of depression was also noted.

1. Twaites BR, *et al.* Safety of zafirlukast: results of a postmarketing surveillance study on 7976 patients in England. *Drug Safety* 2007; 30: 419–29.

Churg-Strauss syndrome. Several case series and reports suggest a link between treatment with a leukotriene receptor antagonist and the development of Churg-Strauss syndrome (p. 1603.1). A systematic review[1] of 62 cases found montelukast implicated in 29, pranlukast in 16, and zafirlukast in 17. The lung was the most common site affected followed by nerves and skin; 16 patients had cardiac involvement. It was suggested that patients who developed Churg-Strauss syndrome but had evidence of pre-existing disease were either in the final phase of developing the syndrome when a leukotriene antagonist was started, or the syndrome was unmasked when corticosteroids were reduced or withdrawn; this pattern was identified in 11 patients. However, a significant number of cases did not have any evidence of dormant or existing disease and there was a clear temporal relationship between starting treatment with a leukotriene antagonist and the onset of symptoms within 6 to 12 months. Also, development of Churg-Strauss syndrome was reported in patients with no change in inhaled or oral corticosteroids before or after starting a leukotriene antagonist, and 7 cases were not taking any inhaled or oral corticosteroids when treatment was started.

A retrospective case-control study[2] found montelukast treatment to be associated with an increased risk of developing Churg-Strauss syndrome within 3 months. As oral corticosteroid use also increased the risk, the authors of the study suggested that the onset of Churg-Strauss syndrome may be linked to an escalation in asthma therapy for gradually worsening asthma. It has been suggested that patients should be carefully monitored for signs of Churg-Strauss syndrome when taking leukotriene antagonists and when corticosteroid dosage is reduced.[3]

1. Nathani N, *et al.* Churg-Strauss syndrome and leukotriene antagonist use: a respiratory perspective. *Thorax* 2008; 63: 883–8.
2. Hauser T, *et al.* The leucotriene receptor antagonist montelukast and the risk of Churg-Strauss syndrome: a case-crossover study. *Thorax* 2008; 63: 677–82.
3. Keogh KA. Leukotriene receptor antagonists and Churg-Strauss syndrome: cause, trigger or merely an association? *Drug Safety* 2007; 30: 837–43.

Effects on the CNS. Neuropsychiatric events have been reported postmarketing in some patients taking the anti-leukotrienes montelukast, zafirlukast, and zileuton. Events reported include agitation, aggression, anxiety, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, tremor, suicidal ideation, and suicide.[1,2] A review[3] of 3 studies in which 536 patients received montelukast found no change in emotional well-being compared with placebo or any other treatment drugs and no reports of suicide, depression, or psychiatric disturbances. The authors concluded that although they did not find evidence for general concern about psychiatric adverse effects, they could not exclude the possibility of idiosyncratic reactions to montelukast.

1. FDA. Updated information on leukotriene inhibitors: montelukast (marketed as Singulair), zafirlukast (marketed as Accolate), and zileuton (marketed as Zyflo and Zyflo CR) (issued 12th June 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm165489.htm (accessed 14/08/09)
2. Health Canada. Montelukast (Singulair): suicidality and other psychiatric adverse reactions. *Can Adverse React News* 2009; 19 (3): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v19n3-eng.php#a1 (accessed 14/08/09)
3. Holbrook JT, Harik-Khan R. Montelukast and emotional well-being as a marker for depression: results from 3 randomized, double-masked clinical trials. *J Allergy Clin Immunol* 2008; 122: 828–9.

Effects on the liver. Severe hepatotoxicity has been associated with zafirlukast.[1-4] The Canadian manufacturer reported[4] in April 2004 that from worldwide postmarketing surveillance of zafirlukast there had been 46 reports of hepatitis, 14 of hepatic failure, 3 of which progressed to fulminant hepatitis, and 59 reports of other clinically significant hepatic dysfunction; 7 fatalities had occurred. In most, but not all, cases symptoms had abated and liver enzymes had returned to normal after stopping zafirlukast. It was important that prescribers, patients and/or their carers were alert to the signs and symptoms of hepatotoxicity. UK licensed product information for zafirlukast describes rare cases of hepatic dysfunction without raised liver enzyme values; zafirlukast treatment should be stopped if hepatotoxicity is suspected.

1. Grieco AJ, Burstein-Stein J. Oral montelukast versus inhaled salmeterol to prevent exercise-induced bronchoconstriction. *Ann Intern Med* 2000; 133: 392.
2. Reinus JF, *et al.* Severe liver injury after treatment with the leukotriene receptor antagonist zafirlukast. *Ann Intern Med* 2000; 133: 964–8.
3. Danese S, *et al.* Severe liver injury associated with zafirlukast. *Ann Intern Med* 2001; 135: 930.
4. AstraZeneca Canada. Important safety information regarding reports of serious hepatic events in patients receiving Accolate (zafirlukast) (issued 14th April 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/accolate_2_hpc-cps-eng.pdf (accessed 09/07/08)

Lupus. Zafirlukast was thought to be responsible for the development of lupus in a 9-year-old girl.[1]

1. Finkel TH, *et al.* Drug-induced lupus in a child after treatment with zafirlukast (Accolate). *J Allergy Clin Immunol* 1999; 103: 533–4.

Renal impairment. The UK licensed product information states that zafirlukast should be used with caution in patients with moderate or severe renal impairment because of limited experience in this group. However, the US product information mentions no such caution, and states that the pharmacokinetics of zafirlukast in patients with renal impairment do not appear to differ from those in patients with normal renal function. Only about 10% of a dose is reported to be excreted in the urine.

Tolerance. Tolerance to the beneficial effects of zafirlukast, and rebound exacerbation of asthma symptoms on withdrawal, has been described[1] in patients with persistent asthma.

1. Reid DW, *et al.* Tolerance and rebound with zafirlukast in patients with persistent asthma. *J Negat Results Biomed* 2008; 7: 3.

Interactions

Zafirlukast is metabolised by hepatic cytochrome P450, specifically the CYP2C9 isoenzyme, and has been shown to inhibit the activity of isoenzymes CYP2C9 and CYP3A4. Therefore, use with other drugs that are metabolised by these hepatic enzymes may result in increases in plasma concentrations, and possibly, adverse effects. Patients receiving warfarin may develop prolongation of the prothrombin time and anticoagulant dosage should be adjusted accordingly. Erythromycin, terfenadine, and theophylline may reduce plasma concentrations of zafirlukast; zafirlukast has rarely been reported to increase plasma-theophylline concentrations. Increased plasma concentrations of zafirlukast have been seen when given with high doses of aspirin.

Pharmacokinetics

Peak plasma concentrations of zafirlukast occur about 3 hours after oral doses. The absolute bioavailability is uncertain, but taking it with food reduces both the rate and extent of absorption, decreasing bioavailability by about 40%. Zafirlukast is about 99% bound to plasma proteins. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP2C9, and excreted principally in faeces, as unchanged drug and metabolites. About 10% of a dose is excreted in urine as metabolites. The terminal elimination half-life of zafirlukast is about 10 hours. Studies in *animals* suggest that small amounts cross the placenta; it is also distributed into breast milk.

Reviews.

1. Dekhuijzen PNR, Koopmans PP. Pharmacokinetic profile of zafirlukast. *Clin Pharmacokinet* 2002; 41: 105–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Accolate; *Austral.*: Accolate†; *Belg.*: Accolate; Resma; *Braz.*: Accolate; *Canad.*: Accolate; *Chile*: Accolate†; *China*: Accolate (安可来); *Cz.*: Accolate; *Fin.*: Accolate; *Hong Kong*: Accolate; *Hung.*: Accolate; *India*: Zuvair; *Indon.*: Accolate; *Irl.*: Accolate; *Ital.*: Accoleit; Zafirst; *Mex.*: Accolate; *Philipp.*: Accolate; *Pol.*: Accolate; *Port.*: Accolate; *Rus.*: Accolate (Аколат); *S.Afr.*: Accolate; *Singapore*: Accolate†; *Spain*: Accolate; Aeronix; Olmoran; *Switz.*: Accolate; *Thai.*: Accolate; *Turk.*: Accolate; Carrox; *UK*: Accolate; *USA*: Accolate; *Venez.*: Accolate.

Zileuton (BAN, USAN, rINN)

A-64077; Abbott-64077; Zileutón; Zileutonum; Зилеутон.

(±)-1-(1-Benzo[*b*]thien-2-ylethyl)-*N*-hydroxyurea.

$C_{11}H_{12}N_2O_2S$=236.3
CAS — 111406-87-2.
UNII — V1L22WVE2S.

Pharmacopoeias. In *US*.

USP 36: (Zileuton). A white to off-white powder. Store in airtight containers. Protect from light.

Uses and Administration

Zileuton is an orally active 5-lipoxygenase inhibitor and therefore inhibits leukotriene formation (p. 1195.2). It is used in the management of chronic asthma (see below) but has no bronchodilator properties and is not suitable for the management of acute attacks. Zileuton is given in oral doses of 600 mg 4 times daily as an immediate-release preparation. A controlled-release formulation of zileuton is also available; the usual oral dose is 1.2 g twice daily.

It has also been tried in other disorders including acne, arthritis, allergic rhinitis, and inflammatory bowel disease.

Acne. Zileuton has been investigated for its potential benefits in the treatment of acne (p. 1682.2);[1] oral doses of 600 mg 4 times daily for 3 months have produced reductions in inflammation and sebum lipid secretion in small preliminary studies.

1. Zouboulis CC. Zileuton, a new efficient and safe systemic anti-acne drug. *Dermatoendocrinol* 2009; 1: 188–92.

Asthma. Zileuton has been found to be of some benefit in asthma (p. 1195.2), including that provoked by cold air, exercise, and NSAIDs. Due to a lack of data on efficacy and the need for liver function monitoring, zileuton is considered a less desirable treatment option for addition to inhaled corticosteroids than the leukotriene receptor antagonists.

An intravenous form of zileuton has been investigated for use in asthma.

References.
1. Israel E, *et al.* The effects of a 5-lipoxygenase inhibitor on asthma induced by cold, dry air. *N Engl J Med* 1990; 323: 1740–4.
2. Israel E, *et al.* The effect of inhibition of 5-lipoxygenase by zileuton in mild-to-moderate asthma. *Ann Intern Med* 1993; 119: 1059–66.
3. McGill KA, Busse WW. Zileuton. *Lancet* 1996; 348: 519–24.
4. Israel E, *et al.* Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma: a randomized controlled trial. *JAMA* 1996; 275: 931–6.
5. O'Connor BJ, *et al.* Zileuton added to low-dose inhaled beclomethasone for the treatment of moderate to severe persistent asthma. *Respir Med* 2007; 101: 1088–96.
6. Berger W, *et al.* Zileuton: clinical implications of 5-lipoxygenase inhibition in severe airway disease. *Int J Clin Pract* 2007; 61: 663–76.

Inflammatory bowel disease. Despite initial hopes that inhibition of lipoxygenase might prove of benefit in patients with ulcerative colitis,[1] a study in those with mild or moderately active relapsing disease found that the symptomatic benefits of zileuton were confined to those not already receiving sulfasalazine.[2] A subsequent study showed zileuton was not significantly better than placebo in maintaining remission.[3] For a discussion of inflammatory bowel disease and its management, see p. 1811.3.

1. Laursen LS, *et al.* Selective 5-lipoxygenase inhibition in ulcerative colitis. *Lancet* 1990; 339: 683–5.
2. Laursen LS, *et al.* Selective 5-lipoxygenase inhibition by zileuton in the treatment of relapsing ulcerative colitis: a randomized double-blind placebo-controlled multicentre trial. *Eur J Gastroenterol Hepatol* 1994; 6: 209–15.
3. Hawkey CJ, *et al.* A trial of zileuton versus mesalazine or placebo in the maintenance of remission of ulcerative colitis. *Gastroenterology* 1997; 112: 718–24.

Rhinitis. A study in 8 patients with allergic rhinitis (p. 612.1) found that a single dose of zileuton 800 mg reduced the response to a nasal antigen challenge 3 hours later,[1] including reduced sneezing and nasal congestion.

1. Knapp HR. Reduced allergen-induced nasal congestion and leukotriene synthesis with an orally active 5-lipoxygenase inhibitor. *N Engl J Med* 1990; 323: 1745–8.

Adverse Effects and Precautions

The most commonly reported adverse effects associated with zileuton treatment are headache, pain including pharyngolaryngeal pain, gastrointestinal disturbances, myalgia, and sinusitis. Hypersensitivity, urticaria, rash, and leucopenia have been reported in a few patients. Zileuton has also been associated with raised liver enzyme values and severe hepatic injury.

Zileuton is not suitable for the treatment of acute asthma attacks.

Effects on the CNS. For information on the CNS adverse effects associated with use of anti-leukotrienes, see under Zafirlukast, p. 1240.2.

Effects on the liver. Cases of severe hepatotoxicity including fatalities, jaundice, hyperbilirubinaemia, and raised liver enzymes have been reported in patients taking zileuton. US licensed product information therefore contra-indicates the use of zileuton in patients with active liver disease or liver transaminase elevations greater than or equal to three times the upper limit of normal. Caution is required in patients with a history of liver disease or who consume substantial quantities of alcohol. Alanine aminotransferase (ALT) is considered the most sensitive indicator of liver injury due to zileuton. Most rises in ALT concentrations occurred in the first 3 months of zileuton therapy,[1] and monitoring is therefore recommended before starting zileuton therapy, once a month for the first 3 months of therapy, every 2 to 3 months for the remainder of the first year of therapy, and periodically thereafter.

1. Watkins PB, *et al.* Clinical pattern of zileuton-associated liver injury: results of a 12-month study in patients with chronic asthma. *Drug Safety* 2007; 30: 805–15.

Interactions

Zileuton has been reported to impair the metabolism of some drugs metabolised via hepatic cytochrome P450 enzymes, including propranolol, terfenadine, theophylline, and warfarin.

Pharmacokinetics

Zileuton is reported to be well absorbed from the gastrointestinal tract after oral dosage, with peak plasma concentrations of immediate-release preparations occurring within about 2 hours of a dose. It is about 93% bound to plasma proteins. It is extensively metabolised in the liver by the cytochrome P450 isoenzymes CYP1A2, CYP2C9, and CYP3A4, and excreted in the urine, largely as glucuronide metabolites. The elimination half-life is reported to be about 2.5 hours for the immediate-release preparation and about 3 hours for the controlled-release preparation.

References.
1. Wong SL, *et al.* The pharmacokinetics of single oral doses of zileuton 200 to 800 mg, its enantiomers, and its metabolites, in normal healthy volunteers. *Clin Pharmacokinet* 1995; 29 (suppl 2): 9–21.
2. Awni WM, *et al.* Pharmacokinetics and pharmacodynamics of zileuton after oral administration of single and multiple dose regimens of zileuton 600 mg in healthy volunteers. *Clin Pharmacokinet* 1995; 29 (suppl 2): 22–33.
3. Braeckman RA, *et al.* The pharmacokinetics of zileuton in healthy young and elderly volunteers. *Clin Pharmacokinet* 1995; 29 (suppl 2): 42–8.
4. Awni WM, *et al.* Population pharmacokinetics of zileuton, a selective 5-lipoxygenase inhibitor, in patients with rheumatoid arthritis. *Eur J Clin Pharmacol* 1995; 48: 155–60.
5. Awni WM, *et al.* The effect of mild or moderate hepatic impairment (cirrhosis) on the pharmacokinetics of zileuton. *Clin Pharmacokinet* 1995; 29 (suppl 2): 49–61.
6. Awni WM, *et al.* Pharmacokinetics of zileuton and its metabolites in patients with renal impairment. *J Clin Pharmacol* 1997; 37: 395–404.
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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Zyflo.

Cardiovascular Drugs

This chapter describes drugs used principally in the management of cardiovascular disorders, as well as the choice of treatment for a particular disorder. Blood products, plasma expanders, and haemostatics, which also have a role in cardiovascular disease, are described elsewhere (p. 1121.1).

The Circulatory System

The cardiovascular system consists of the heart and two vascular systems, the pulmonary and systemic circulations. The **heart** (below) pumps blood from the right ventricle through the **pulmonary circulation**, in which gas exchange occurs, and the oxygenated blood then returns to the left side of the heart, where the left ventricle pumps it to the **systemic circulation** which delivers blood to individual organs. Arteries supply blood at high pressure whereas arterioles are smaller vessels with muscular walls which allow direct control of flow through the capillary beds. Capillaries have thin walls, comprising a single layer of endothelial cells, which allow exchange of substances such as nutrients, hormones, and waste products between blood and tissues. Veins return blood from the capillary beds to the heart, and contain about 70% of the circulating blood volume.

Cardiac output is the product of heart rate and stroke volume; typically, in a 70-kg adult, these might be around 70 beats per minute, and 70 mL respectively, giving an output of around 5 litres/minute. Stroke volume in turn is dependent on **preload** (the ventricular volume at the end of diastole, when the ventricle relaxes and fills), **afterload** (the resistance to ventricular ejection, or systemic vascular resistance, determined mainly by the diameter of the arterioles), and **contractility**, or the strength of contraction of the heart muscle, which is influenced by the sympathetic nervous system but also by many other factors, including drugs, acid-base balance, and myocardial oxygen supply. In a healthy individual, cardiac output should adjust to match metabolic demand.

Blood pressure and flow is controlled by complex neurohormonal systems, involving the autonomic nervous system and peptides and regulators released by the kidneys and the circulatory system itself, such as the renin-angiotensin system and the natriuretic peptides. Substances such as nitric oxide and prostacyclin, produced by the endothelium of the vascular system, play an important role in controlling local blood flow.

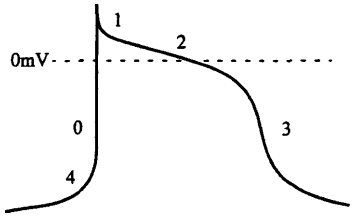
All these systems can be manipulated by pharmacological therapy with the various drug groups (see below) used in the treatment of cardiovascular disorders (p. 1246.1).

The Heart

The heart acts as a pump, maintaining circulation of blood around the body. It does this by coordinated contraction and relaxation of the cardiac muscle (myocardium). In a normal cardiac cycle the atria contract first (atrial systole), forcing blood into the ventricles, which then contract (ventricular systole), pumping blood out into the blood vessels; atria and ventricles then both relax (diastole), allowing the atria to refill before the cycle begins again. Each cycle corresponds to a heart beat and in a healthy 70-kg person at rest cycles occur regularly at a rate of 70 to 75 beats/minute, although the exact rate varies more widely than this depending on circumstances.

The contraction of myocardial cells is controlled by electrical changes across the cell membrane, which can be represented by the *action potential*. The action potential in cardiac cells has 5 phases, although the exact pattern depends on the type of cell. A typical ventricular action potential is shown in Figure 1 (below).

Figure 1. The action potential.



- phase 0 is the depolarisation phase when there is rapid influx of sodium ions (lasting a few milliseconds) and the cell contracts
- in phase 1, there is a transient rapid efflux of potassium ions and the cell begins to repolarise
- a slow influx of calcium ions then occurs which balances the potassium efflux leading to a plateau stage (phase 2) and maintenance of contraction
- this is followed by an increase in potassium efflux, while calcium influx stops, and repolarisation (phase 3) occurs
- the cell then relaxes and finally returns to the resting membrane potential (phase 4), and ion pumps return the balance of sodium and potassium to the baseline state

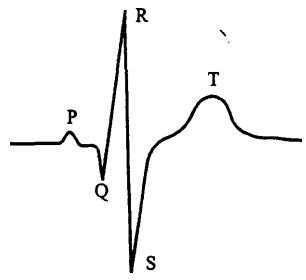
The depolarisation of one cell triggers action potentials in adjacent cells, allowing the electrical impulse to spread rapidly across the myocardium so that in a healthy heart all of the cells contract at the same time in a coordinated fashion.

Certain cells within the heart undergo spontaneous depolarisation during phase 4 and the initial depolarisation depends mainly on calcium ion influx rather than sodium ions. These *pacemaker cells* are able to initiate impulses. Although a number of cells have this property, impulses are normally generated in the *sino-atrial* (SA) or *sinus node*. They then spread across the atria, causing them to contract, but normally only pass to the ventricles through the specialised conducting cells of the atrioventricular (AV) node. From the AV node, the impulse passes through the bundle of His and down the Purkinje fibres to the ventricles, which then contract. The delay caused by this selective conduction through the AV node means that the atria contract before the ventricles and ensures the forward movement of the blood.

The heart rhythm that results from a normal cardiac cycle originating in the sinus node is known as *sinus rhythm*, and has been defined as a sinus node rate of 60 to 100 beats/minute. The rate is affected by input from the nervous system, and drugs can affect the conduction of impulses at various points in the cycle. For drugs used specifically in the management of heart rhythm disorders, see Antiarrhythmics, p. 1243.1.

The movement of electrical impulses can be recorded as an electrocardiogram (ECG). The ECG corresponds to the phases of the action potential in different parts of the heart and depends on the position of the recording leads; a typical ECG trace is shown in Figure 2, below. The P wave corresponds to atrial depolarisation, while the QRS complex corresponds to ventricular depolarisation; the PR interval corresponds to the delay between atrial and ventricular depolarisation. Phases 0 and 1 of the ventricular action potential produce the R and S waves, and phase 2 corresponds to the ST interval. The T wave represents ventricular repolarisation (phase 3).

Figure 2. A normal ECG trace.



Cardiovascular Drug Groups

Although very diverse, cardiovascular drugs can be broadly classified according to their pharmacological action. Basic details of the major groups follow, together with lists of the drugs described in this chapter.

ACE inhibitors

The main uses of ACE (angiotensin-converting enzyme) inhibitors are in the management of heart failure, hypertension, and myocardial infarction. Their actions and uses are discussed in more detail on p. 1282.2.

Described in this chapter are

Alacepril, p. 1295.3
Benazepril, p. 1314.3
Captopril, p. 1331.2
Cilazapril, p. 1336.2
Delapril, p. 1350.2
Enalapril, p. 1371.1
Enalaprilat, p. 1371.1
Fosinopril, p. 1386.2
Imidapril, p. 1409.1
Lisinopril, p. 1420.3
Moexipril, p. 1440.3
Perindopril, p. 1466.3
Quinapril, p. 1480.2
Ramipril, p. 1483.3
Spirapril, p. 1499.3
Temocapril, p. 1510.2
Trandolapril, p. 1517.2
Zofenopril, p. 1536.3

Adrenergic neurone blockers

Adrenergic neurone blockers are used in hypertension although they have largely been superseded by other drugs less likely to cause orthostatic hypotension. They have also been used in open-angle glaucoma.

Adrenergic neurone blockers act by selectively inhibiting transmission in postganglionic adrenergic nerves. They are believed to act mainly by preventing the release of noradrenaline at nerve endings; they cause the depletion of noradrenaline stores in peripheral sympathetic nerve terminals. They do not prevent the secretion of catecholamines by the adrenal medulla.

Described in this chapter are

- Debrisoquine, p. 1349.3
- Guanadrel, p. 1395.2
- Guanethidine, p. 1395.2

Alpha blockers

Alpha blockers are used mainly in the management of hypertension and to relieve urinary obstruction in benign prostatic hyperplasia.

Alpha blockers are also known as alpha-adrenergic antagonists or alpha-adrenergic receptor antagonists. Some have particular affinities for one of the subtypes of the alpha adrenoceptor. Drugs such as indoramin or prazosin are much more potent in blocking $alpha_1$ than $alpha_2$ adrenoceptors and are often termed selective $alpha_1$ blockers. Blockade of $alpha_1$ adrenoceptors inhibits the vasoconstriction induced by endogenous catecholamines. Both arteriolar and venous vasodilatation may occur resulting in a fall in blood pressure because of decreased peripheral resistance. Blockade of $alpha_2$ adrenoceptors with a selective drug such as yohimbine (p. 2372.3) can conversely lead to a rise in blood pressure. With phenoxybenzamine and phentolamine, which broadly have similar affinities for both the $alpha_1$ and $alpha_2$ subtypes of receptor, any increase in blood pressure due to $alpha_2$ blockade is prevented by the inhibition of vasoconstriction caused by $alpha_1$ blockade. Alpha blockers also act at alpha adrenoceptors in nonvascular smooth muscle, for example in the bladder where alpha blockade produces decreased resistance to urinary outflow; alpha blockers used mainly for urinary disorders are discussed under Urological Drugs, p. 2347.1. Most alpha blockers are reversible or 'competitive' inhibitors of alpha adrenoceptors; phenoxybenzamine is an irreversible or 'non-competitive' alpha blocker and is particularly useful in phaeochromocytoma.

Described in this chapter are

- Bunazosin, p. 1329.3
- Doxazosin, p. 1369.1
- Indoramin, p. 1410.2
- Phenoxybenzamine, p. 1468.1
- Phentolamine, p. 1468.3
- Prazosin, p. 1473.3
- Terazosin, p. 1511.1
- Moxisylyte, p. 1441.3
- Tolazoline, p. 1516.2
- Urapidil, p. 1520.2

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Angiotensin II receptor antagonists

Angiotensin II receptor antagonists (angiotensin II receptor blockers) are used in the management of hypertension; they may have a particular role in patients who develop cough with ACE inhibitors. Some are also used in diabetic nephropathy and in the management of heart failure. They act mainly by selective blockade of AT_1 receptors thus reducing the pressor effects of angiotensin II.

Described in this chapter are

- Candesartan, p. 1330.2
- Eprosartan, p. 1376.2
- Irbesartan, p. 1411.1
- Losartan, p. 1422.2
- Olmesartan, p. 1459.2
- Telmisartan, p. 1509.3
- Valsartan, p. 1521.2

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Antiarrhythmics

Antiarrhythmics (formerly described as cardiac depressants) are a diverse group of drugs that affect the conduction of electrical impulses within the heart (see p. 1242.1). Many of them, such as beta blockers (p. 1316.3), digoxin (p. 1353.3), lidocaine (p. 1992.1), magnesium (p. 1789.1), and phenytoin (p. 538.2) have important actions in addition to their antiarrhythmic properties and thus, have a wide range of other clinical applications.

The most widely used **classification** of antiarrhythmics is that proposed by Vaughan Williams (later modified by Harrison) and is based largely on their *in-vitro* electrophysiological effects. There are 4 main classes:

Class I includes drugs that block the fast inward sodium channels and therefore interfere with depolarisation (phase 0 of the action potential); these drugs have been called membrane-stabilising drugs and have both antiarrhythmic and local anaesthetic properties. They have different properties depending on their affinity for different states of the sodium channel (open, closed, or inactivated) and can be further subdivided depending on additional characteristics.

Class Ia drugs slow the rate of change of the depolarisation phase of the action potential, although less so than class Ic drugs. They also prolong the repolarisation phase (phase 3), possibly by an effect on potassium channels. They prolong the PR, QRS, and QT intervals on the ECG.

Described in this chapter are

- Ajmaline, p. 1295.2
- Disopyramide, p. 1363.2
- Hydroquinidine, p. 1407.1
- Pirmenol, p. 1471.1
- Procainamide, p. 1475.3
- Quinidine, p. 1481.1

Class Ib drugs have little effect on the rate of change of the depolarisation phase of the action potential in normal cells, but have a more selective effect in ischaemic or diseased tissue; they are also more effective if external potassium concentrations are high. They shorten the repolarisation phase, shorten the QT interval, and elevate the fibrillation threshold. The local anaesthetic lidocaine has class Ib properties.

Described in this chapter are

- Aprindine, p. 1306.3
- Mexiletine, p. 1436.2
- Tocainide, p. 1515.3

Class Ic drugs markedly slow the rate of change of the depolarisation phase of the action potential, but have little effect on the repolarisation phase. They prolong the PR and QRS intervals.

Described in this chapter are

- Ethacizine, p. 1379.1
- Flecainide, p. 1382.3
- Pilsicainide, p. 1470.1
- Propafenone, p. 1477.3

Class II drugs are characterised by beta-blocking activity; they reduce both heart rate and myocardial contractility, and also slow conduction of impulses through the myocardial conducting system. They reduce the rate of spontaneous depolarisation in cells with pacemaker activity but have little effect on the action potential in most myocardial cells.

Described in this chapter are

- Beta blockers (but sotalol has mainly class III activity), p. 1316.3
- Bretylium, p. 1328.2

Class III drugs slow the repolarisation phase (phase 3) and prolong the action potential duration and the QT interval. Various mechanisms may be involved, but most class III drugs act by potassium channel blockade.

Described in this chapter are

- Amiodarone, p. 1300.1
- Azimilide, p. 1313.3
- Bretylium, p. 1328.2
- Cibenzoline, p. 1336.1
- Dofetilide, p. 1367.1
- Ibutilide, p. 1407.2
- Nifekalant, p. 1455.1
- Sotalol, p. 1498.2

Class IV drugs are calcium-channel blockers (p. 1244.2) that act by blocking the slow inward calcium current and particularly affect the pacemaker cells where calcium influx is relatively more important. However, differences in tissue specificity mean that not all calcium-channel blockers have antiarrhythmic properties.

Described in this chapter are

- Cibenzoline, p. 1336.1
- Diltiazem, p. 1359.2
- Verapamil, p. 1522.1

A major limitation of the Vaughan Williams classification is that many antiarrhythmics have multiple actions, and may not fit neatly into a single class. Some are assigned to several classes, while others are included in one class although they also have characteristics of another. Bretylium is included in both class II and class III, whereas propafenone is usually considered a class Ic drug despite possessing beta-blocking properties. Beta blockers are traditionally described as class II, although some also have class I actions, while sotalol, despite sharing the properties of beta blockers, has mainly class III activity and is usually described as a class III drug. Drugs such as adenosine and digoxin do not fit into the Vaughan Williams classification at all.

Another problem with the Vaughan Williams classification is that the electrophysiological effects of antiarrhythmics are not clearly related to their effectiveness in treating a particular arrhythmia in an individual patient. Alternative classification systems have therefore been suggested, for example based on the cardiac tissue that the drug affects. Thus drugs that act on the sino-atrial node include beta blockers, class IV antiarrhythmics, and cardiac glycosides such as digoxin; class I and class III antiarrhythmics act on the ventricles; and drugs acting on atrial arrhythmias include class Ia, Ic, and III antiarrhythmics and beta blockers. Class Ia and III antiarrhythmics act on accessory pathways and drugs acting on the AV node include class Ic and IV antiarrhythmics, beta blockers, and cardiac glycosides. A simplification of this scheme is to classify drugs into those that act on both ventricular and supraventricular arrhythmias such as amiodarone, beta blockers, disopyramide, procainamide, and quinidine, those that act mainly on ventricular arrhythmias such as lidocaine, mexiletine, and phenytoin, and those that act mainly on supraventricular arrhythmias such as verapamil. The Sicilian Gambit is another approach based on the mechanisms by which arrhythmias are generated and the ways that drugs could influence them.

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Anticoagulants

Anticoagulants are used in the treatment and prophylaxis of thromboembolic disorders. They may be divided into direct anticoagulants such as the heparins, low-molecular-weight heparins, heparinoids, and direct thrombin inhibitors, and indirect anticoagulants such as the coumarin and indanedione derivatives.

Direct anticoagulants

Heparin inhibits clotting of blood *in vitro* and *in vivo* by enhancing the action of antithrombin III. Antithrombin III, which is present in plasma, inhibits the activity of activated clotting factors including thrombin (factor IIa) and activated factor X (factor Xa). With normal therapeutic doses heparin has an inhibitory effect on both thrombin and factor Xa (see Haemostasis, p. 1124.3). The low doses that are given subcutaneously for the prophylaxis of thromboembolism have a selective effect on antithrombin III's inhibition of factor Xa. Very high doses are reported to reduce the activity of antithrombin III. Heparin also has some effect on platelet function, inhibits the formation of a stable fibrin clot, and has an antilipidaemic effect.

Low-molecular-weight heparins are salts of fragments of heparin produced by chemical or enzymatic depolymerisation of the heparin molecule. Commercially available low-molecular-weight heparins differ in their method of production, molecular-weight range, and degree of sulfation. Like heparin, these compounds enhance the action of antithrombin III but they are characterised by a higher ratio of anti-factor Xa to anti-factor IIa (antithrombin activity) than heparin. Although the possibility that such selective factor-Xa inhibition would result in antithrombotic activity without anticoagulant, and hence haemorrhagic, effects has not been confirmed by clinical experience, they have more predictable effects and require less monitoring than heparin. Low-molecular-weight heparins also have less effect on platelet aggregation than heparin.

Fondaparinux and idraparinux are synthetic polysaccharides that act as direct inhibitors of factor Xa. Rivaroxaban, apixaban, and edoxaban are orally active factor Xa inhibitors.

Argatroban, bivalirudin, dabigatran, desirudin, and lepirudin are examples of direct thrombin inhibitors.

Described in this chapter are

- Apixaban, p. 1306.2
- Ardeparin, p. 1307.1
- Argatroban, p. 1307.2
- Bemiparin, p. 1314.2
- Bivalirudin, p. 1326.2
- Certoparin, p. 1334.2
- Dabigatran, p. 1347.2
- Dalteparin, p. 1348.3
- Desirudin, p. 1351.1
- Enoxaparin, p. 1372.3
- Fondaparinux, p. 1385.3
- Heparin, p. 1396.3
- Idraparinux, p. 1408.1
- Lepirudin, p. 1418.2
- Low-molecular-weight Heparins, p. 1426.1
- Nadroparin, p. 1443.2
- Parnaparin, p. 1464.2
- Reviparin, p. 1486.3
- Rivaroxaban, p. 1487.2
- Semuloparin, p. 1489.2
- Tinzaparin, p. 1514.2

The *direct thrombin inhibitors* bind to the active thrombin site and inhibit both free and clot-bound thrombin. Most are recombinant forms or synthetic analogues of hirudin and need to be given parenterally, but oral thrombin inhibitors have been developed. Dabigatran, given orally as the prodrug dabigatran etexilate, is used in the prophylaxis of venous thromboembolism.

Described in this chapter are

- Argatroban, p. 1307.2
- Bivalirudin, p. 1326.2
- Dabigatran, p. 1347.2
- Desirudin, p. 1351.1
- Hirudin, p. 1401.2
- Lepirudin, p. 1418.2

References.

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The term *heparinoid* includes heparin derivatives and has also been used more loosely to include naturally occurring and synthetic highly sulfated polysaccharides of similar structure, such as danaparoid and dermatan sulfate. Some compounds have been described in many ways; some of the terms used include sulfated glucosaminoglycans, glycosaminoglycan polysulfate compounds, or sulfated mucopolysaccharides.

Described in this chapter are

- Danaparoid, p. 1349.2
- Dermatan Sulfate, p. 1350.3
- Pentosan Polysulfate Sodium, p. 1465.1

Sodium Apolate, p. 1497.1
Suleparoid, p. 1507.2
Sulodexide, p. 1507.3

Indirect anticoagulants

Indirect anticoagulants act by depressing the hepatic vitamin K-dependent synthesis of coagulation factors II (prothrombin), VII, IX, and X, and of the anticoagulant protein C and its cofactor protein S. Warfarin, a coumarin, is the main drug used; other coumarins (although not all coumarins have anticoagulant activity) and indanediones such as phenindione are also available. Since they act indirectly, they have no effect on existing clots. Also as the coagulation factors involved have half-lives ranging from 6 to 60 hours, several hours are required before an effect is observed. A therapeutic effect is usually apparent by 24 hours, but the peak effect may not be achieved until 2 or 3 days after a dose; the overall effect may last for 5 days.

Described in this chapter are

Dicoumarol, p. 1352.2
Fluindione, p. 1385.1
Acenocoumarol, p. 1290.1
Phenindione, p. 1467.3
Phenprocoumon, p. 1468.3
Warfarin, p. 1526.3

Antiplatelet drugs

Platelet aggregation is important in haemostasis (p. 1124.3) and is also involved in thrombus formation, particularly in the arterial circulation. Antiplatelet drugs reduce platelet aggregation and are used to prevent further thromboembolic events in patients who have suffered myocardial infarction, ischaemic stroke or transient ischaemic attacks, or unstable angina, and for primary prevention of a thromboembolic event in patients at risk. Some are also used for the prevention of reocclusion or restenosis following angioplasty and bypass procedures.

Antiplatelet drugs act through a wide range of mechanisms. Aspirin (p. 22.2) is the most widely used and studied; it acts by irreversibly inhibiting platelet cyclo-oxygenase and thus preventing synthesis of thromboxane A_2. Reversible cyclo-oxygenase inhibitors such as indobufen are also available, and thromboxane synthase inhibitors and thromboxane receptor antagonists have also been used.

Drugs that interfere with adenosine metabolism have an antiplatelet effect and those used include some prostaglandins, which act by increasing platelet cyclic adenosine monophosphate levels; ticagrelor and the thienopyridines clopidogrel, prasugrel, and ticlopidine, which interfere with adenosine diphosphate mediated platelet activation; and the adenosine reuptake inhibitor dipyridamole.

Thrombin inhibitors such as heparin and the hirudins have antiplatelet and anticoagulant effects. Glycoprotein IIb/IIIa-receptor antagonists, such as abciximab, eptifibatide, and tirofiban, interfere with the final step in platelet aggregation and are used in unstable angina and as adjuncts in reperfusion and revascularisation procedures. Oral glycoprotein IIb/IIIa-receptor antagonists such as orbofiban, sibrafiban, and xemilofiban have also been investigated but results have been disappointing.

Described in this chapter are

Abciximab, p. 1281.1
Cangrelor, p. 1331.1
Cilostazol, p. 1337.1
Clopidogrel, p. 1342.3
Cloricromen, p. 1345.1
Dipyridamole, p. 1362.2
Ditazole, p. 1365.3
Eptifibatide, p. 1376.3
Heparin, p. 1396.3
Indobufen, p. 1410.1
Orbofiban, p. 1463.1
Picotamide, p. 1469.3
Prasugrel, p. 1472.3
Sarpogrelate, p. 1489.1
Ticagrelor, p. 1511.3
Ticlopidine, p. 1512.1
Tirofiban, p. 1515.1
Trapidil, p. 1517.3
Triflusal, p. 1519.3
Xemilofiban, p. 1536.1

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Beta blockers

Beta blockers are competitive antagonists at beta-adrenergic receptor sites and are used in the management of cardiovascular disorders such as hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, and heart failure. They are also given to control symptoms of sympathetic overactivity in alcohol withdrawal, anxiety states, hyperthyroidism, and tremor and in the prophylaxis of migraine and of bleeding associated with portal hypertension. Their actions and uses are discussed in more detail on p. 1316.3.

Beta blockers used mainly as eye drops to reduce raised intra-ocular pressure in glaucoma and ocular hypertension are discussed under Miotics, Mydriatics, and Antiglaucoma Drugs, p. 1999.1.

Described in this chapter are

Acebutolol, p. 1289.1
Alprenolol, p. 1296.3
Amosulalol, p. 1305.1
Arotinolol, p. 1308.1
Atenolol, p. 1308.2
Betaxolol, p. 1322.3
Bevantolol, p. 1323.2
Bisoprolol, p. 1325.3
Bopindolol, p. 1326.3
Bucindolol, p. 1328.2
Bupranolol, p. 1329.3
Carazolol, p. 1332.3
Carteolol, p. 1332.3
Carvedilol, p. 1333.1
Celiprolol, p. 1334.2
Esatenolol, p. 1377.2
Esmolol, p. 1377.3
Indenolol, p. 1410.1
Labetalol, p. 1416.2
Landiolol, p. 1418.1
Metoprolol, p. 1434.3
Nadolol, p. 1442.3
Nebivolol, p. 1444.2
Oxprenolol, p. 1463.2
Penbutolol, p. 1464.3
Pindolol, p. 1470.1
Propranolol, p. 1479.1
Sotalol, p. 1498.2
Talinolol, p. 1509.2
Tertatolol, p. 1511.2
Tilisolol, p. 1513.2
Timolol, p. 1513.2

Calcium-channel blockers

Calcium-channel blockers are used mainly in the management of angina pectoris, hypertension, and cardiac arrhythmias.

Calcium-channel blockers, (calcium antagonists, calcium-entry blockers, or slow-channel blockers) inhibit the cellular influx of calcium that is responsible for maintenance of the plateau phase of the action potential. Thus calcium-channel blockers mainly affect tissues in which depolarisation is dependent upon calcium rather than sodium influx, such as vascular smooth muscle, myocardial cells, and cells within the sino-atrial (SA) and atrioventricular (AV) nodes. The main actions of the calcium-channel blockers include dilatation of coronary and peripheral arteries and arterioles with little or no effect on venous tone, a negative inotropic action, reduction of heart rate, and slowing of AV conduction. However, the effects of individual drugs, and therefore their uses, are modified by their selectivity of action at different tissue sites and by baroreceptor reflexes.

Traditionally, calcium-channel blockers have been classified according to their chemical structure; other methods of classification relate to the subtypes of calcium channels which they block, and their effects on heart rate. There are three major groups that are highly specific blockers of calcium channels.

Dihydropyridine calcium-channel blockers (such as nifedipine) act on slow, L-type (long) channels. They have a greater selectivity for vascular smooth muscle than for myocardium and therefore their main effect is vasodilatation. They are non-rate-limiting, with little or no action at the SA or AV nodes, and negative inotropic activity is rarely seen at therapeutic doses. They are used for their antihypertensive and anti-anginal properties. Some dihydropyridine derivatives, for example nimodipine, cross the blood-brain barrier and are used in cerebral ischaemia.

Benzothiazepine calcium-channel blockers (such as diltiazem) and **phenylalkylamine** calcium-channel blockers (such as verapamil) also act on L-type channels, but they have less selective vasodilator activity than dihydropyridine derivatives. They are classed as rate-limiting and have a direct effect on myocardium, causing depression of SA and AV nodal conduction. They are used for supraventricular arrhythmias as well as angina and hypertension.

Drugs selective for fast T-type (transient) calcium channels have also been investigated. Mibefradil, a benzimidazolyl-substituted tetraline derivative, is an example of this class. It is rate-limiting and causes coronary and peripheral vasodilatation, but is no longer used clinically due to serious drug interactions.

Some drugs with calcium-channel blocking properties, including certain antihistamines such as cinnarizine, and the N-type (neuronal) calcium-channel blocker ziconotide, have non-cardiovascular indications and are described elsewhere.

For further discussion of the actions and uses of the three main groups of calcium-channel blockers, see Nifedipine, p. 1447.2, Diltiazem, p. 1359.2, and Verapamil, p. 1522.1, respectively.

Described in this chapter are

Amlodipine, p. 1304.1
Aranidipine, p. 1307.1
Azelnidipine, p. 1313.2
Barnidipine, p. 1314.1
Benidipine, p. 1316.1
Bepridil, p. 1316.2
Cilnidipine, p. 1337.1
Clevidipine, p. 1338.2
Diltiazem, p. 1359.2
Efonidipine, p. 1370.3
Felodipine, p. 1380.3
Gallopamil, p. 1390.3
Isradipine, p. 1414.2
Lacidipine, p. 1417.3
Lercanidipine, p. 1419.3
Lidoflazine, p. 1420.2
Manidipine, p. 1427.2
Nicardipine, p. 1445.2
Nifedipine, p. 1447.2
Nilvadipine, p. 1455.2
Nimodipine, p. 1455.2
Nisoldipine, p. 1456.2
Nitrendipine, p. 1456.3
Verapamil, p. 1522.1

References.

1. Sica DA. Pharmacotherapy review: calcium channel blockers. *J Clin Hypertens (Greenwich)* 2006; **8**: 53–6.
2. Liebson PR. Calcium channel blockers in the spectrum of antihypertensive agents. *Expert Opin Pharmacother* 2006; **7**: 2385–2401.
3. Frishman WH. Calcium channel blockers: differences between subclasses. *Am J Cardiovasc Drugs* 2007; **7** (suppl 1): 17–23.
4. Triggle DJ. Calcium channel antagonists: clinical uses—past, present and future. *Biochem Pharmacol* 2007; **74**: 1–9.

Cardiac inotropes

Positive cardiac inotropes increase the force of contraction of the myocardium and are therefore used in the management of acute and chronic heart failure. Some inotropes also increase or decrease the heart rate (positive or negative chronotropes), provide vasodilatation (inodilators), or improve myocardial relaxation (positive lusitropes), and these additional properties influence the choice of drug in specific situations. Drugs that are used mainly for their inotropic effects include the cardiac glycosides and phosphodiesterase inhibitors; sympathomimetics have a role as inotropes but also have other important uses.

References.

1. Feldman AM. Classification of positive inotropic agents. *J Am Coll Cardiol* 1993; **22**: 1223–7.
2. Cuthbertson BH, *et al.* Inotropic agents in the critically ill. *Br J Hosp Med* 1996; **56**: 386–91.
3. Lehtonen LA, *et al.* Pharmacokinetics and pharmacodynamics of intravenous inotropic agents. *Clin Pharmacokinet* 2004; **43**: 187–203.

Cardiac glycosides, such as digoxin, possess positive inotropic activity, which is mediated by inhibition of sodium-potassium adenosine triphosphatase (Na/K-ATPase). They also reduce conductivity in the heart, particularly through the atrioventricular node, and therefore have a negative chronotropic effect. The cardiac glycosides have very similar pharmacological effects but differ considerably in their speed of onset and duration of action. They are used to slow the heart rate in supraventricular arrhythmias, especially atrial fibrillation, and are also given in chronic heart failure.

Described in this chapter are

Acetyldigoxin, p. 1290.2
Deslanoside, p. 1351.2
Digitalis Leaf, p. 1352.3
Digitalis Lanata Leaf, p. 1352.3
Digitoxin, p. 1353.1
Digoxin, p. 1353.3
Lanatoside C, p. 1417.3
Metildigoxin, p. 1433.1
Ouabain, p. 1463.1
Proscillaridin, p. 1480.2
Strophanthin-K, p. 1507.2

Type 3 **phosphodiesterase inhibitors** are potent inotropes; they also have vasodilator effects. They are used in the short-term treatment of severe heart failure; long-term oral therapy with some phosphodiesterase inhibitors has been associated with increased mortality.

Described in this chapter are

Amrinone, p. 1305.1
Enoximone, p. 1373.3
Milrinone, p. 1438.1
Olprinone, p. 1460.1
Pimobendan, p. 1470.1

Centrally acting antihypertensives

Centrally acting antihypertensives include alpha$_2$-adrenoceptor agonists such as clonidine and methyldopa. Stimulation of alpha$_2$ adrenoceptors in the CNS results in a reduction in sympathetic tone and a fall in blood pressure. Heart rate is also reduced. They are used in the management of hypertension, although other drugs with fewer adverse effects are generally preferred. Apraclonidine (p. 2003.3) and brimonidine (p. 2004.3) are alpha$_2$-adrenoceptor agonists that are used in the management of glaucoma.

Described in this chapter are

Clonidine, p. 1339.1
Guanabenz, p. 1395.1
Guanfacine, p. 1396.1
Methyldopa, p. 1431.1
Moxonidine, p. 1442.1
Rilmenidine, p. 1487.1

Diuretics

Diuretics promote the excretion of water and electrolytes by the kidneys. They are used in the treatment of heart failure or in hepatic, renal, or pulmonary disease when salt and water retention has resulted in oedema or ascites. Diuretics are also used, either alone or with other drugs, in the treatment of hypertension, although the mechanism for their antihypertensive effect is poorly understood.

References.

1. van der Vorst MMJ, *et al.* Diuretics in pediatrics: current knowledge and future prospects. *Paediatr Drugs* 2006; **8**: 245–64.
2. Ernst ME, Moser M. Use of diuretics in patients with hypertension. *N Engl J Med* 2009; **361**: 2153–64.
3. Fuchs FD. Diuretics: still essential drugs for the management of hypertension. *Expert Rev Cardiovasc Ther* 2009; **7**: 591–8.
4. Szady AD, Hill JA. Diuretics in heart failure: a critical appraisal of efficacy and tolerability. *Drugs* 2009; **69**: 2451–61.

Carbonic anhydrase inhibitors such as acetazolamide (p. 2001.1) are weak diuretics and are used mainly to reduce intra-ocular pressure in glaucoma. They are described under Miotics, Mydriatics, and Antiglaucoma Drugs, p. 1999.1.

'Loop' or 'high-ceiling' diuretics produce an intense, dose-dependent diuresis of relatively short duration.

Described in this chapter are

Azosemide, p. 1314.1
Bumetanide, p. 1329.1
Etacrynic Acid, p. 1378.2
Furosemide, p. 1387.1
Piretanide, p. 1470.3
Torasemide, p. 1516.3

Osmotic diuretics raise the osmolality of plasma and renal tubular fluid. They are used to reduce or prevent cerebral oedema, to reduce raised intra-ocular pressure, and in acute renal failure.

Described in this chapter are

Isosorbide, p. 1412.2
Mannitol, p. 1427.3

Potassium-sparing diuretics have a relatively weak diuretic effect and are normally used with thiazide or loop diuretics. Canrenone, eplerenone, potassium canrenoate, and spironolactone are aldosterone antagonists and are particularly used in conditions where aldosterone contributes to the pathophysiology.

Described in this chapter are

Amiloride, p. 1299.1
Canrenone, p. 1331.1
Eplerenone, p. 1374.2
Potassium Canrenoate, p. 1472.2
Spironolactone, p. 1499.3
Triamterene, p. 1518.3

Thiazides (benzothiadiazines), such as bendroflumethiazide and hydrochlorothiazide, and certain other compounds, such as metolazone, with structural similarities to the thiazides, inhibit sodium and chloride reabsorption in the kidney tubules and produce a corresponding increase in potassium excretion.

Described in this chapter are

Altizide, p. 1298.2
Bemetizide, p. 1314.2
Bendroflumethiazide, p. 1315.2
Benzthiazide, p. 1316.1
Benzylhydrochlorothiazide, p. 1316.2
Butizide, p. 1329.3
Chlorothiazide, p. 1334.3
Chlortalidone, p. 1335.2
Clopamide, p. 1342.3
Cyclopenthiazide, p. 1347.2
Epitizide, p. 1374.2
Hydrochlorothiazide, p. 1403.2
Hydroflumethiazide, p. 1406.3
Indapamide, p. 1409.2
Mefruside, p. 1429.3
Methyclothiazide, p. 1430.3
Meticrane, p. 1433.1
Metipamide, p. 1433.3
Metolazone, p. 1434.1
Polythiazide, p. 1472.1
Teclothiazide, p. 1509.2
Trichlormethiazide, p. 1519.3
Tripamide, p. 1520.2
Xipamide, p. 1536.1

Endothelin receptor antagonists

Endothelin receptor antagonists act by blocking the effects of endothelin, a potent vasoconstrictor. Bosentan blocks both the endothelin ET_A and ET_B receptors, whereas ambrisentan is selective for ET_A. They are used in the management of pulmonary hypertension. Sitaxentan is another selective ET_A antagonist that was used for pulmonary hypertension, but it has been withdrawn. Tezosentan, which blocks both ET_A and ET_B, has been investigated in heart failure.

Described in this chapter are

Ambrisentan, p. 1298.2
Bosentan, p. 1327.1
Sitaxentan, p. 1496.2
Tezosentan, p. 1511.2

References.

1. Attina T, *et al.* Endothelin antagonism in pulmonary hypertension, heart failure, and beyond. *Heart* 2005; 91: 825–31.

Ganglion blockers

Ganglion blockers are nicotinic antagonists that inhibit the transmission of nerve impulses in both sympathetic and parasympathetic ganglia. Their antihypertensive action is due to sympathetic blockade, which produces peripheral vasodilatation; there is also a direct vasodilator effect on peripheral blood vessels.

Described in this chapter are

Azamethonium, p. 1313.1
Mecamylamine, p. 1429.1

Lipid regulating drugs

Lipid regulating drugs are used to modify blood lipid concentrations in the management of hyperlipidaemias and for the reduction of cardiovascular risk. The principal groups of lipid regulating drugs are the statins, fibrates, bile-acid binding resins, nicotinates, and omega-3 triglycerides; ezetimibe, an inhibitor of intestinal cholesterol absorption, is also used.

The **statins** are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-determining enzyme for cholesterol synthesis. They reduce cholesterol by stimulating an increase in low-density-lipoprotein (LDL)-receptors on hepatocyte membranes, thereby increasing the clearance of LDL from the circulation. Their main effect is to reduce LDL-cholesterol, but they may also reduce triglycerides to a modest extent and increase high-density-lipoprotein (HDL)-cholesterol. They are generally considered to be the most effective lipid lowering drugs.

Described in this chapter are

Atorvastatin, p. 1309.2
Fluvastatin, p. 1385.1
Lovastatin, p. 1425.2
Pitavastatin, p. 1471.1
Pravastatin, p. 1473.1
Rosuvastatin, p. 1488.2
Simvastatin, p. 1489.2

The **fibrates** include derivatives of fibric acid and related compounds. They are activators of peroxisome proliferator-activated receptor (PPAR)-α and inhibit the synthesis of cholesterol and bile acids, and enhance the secretion of cholesterol in bile. Their main effect is to reduce triglycerides by reducing the concentration of very-low-density lipoproteins (VLDL); they also increase HDL-cholesterol and have variable effects on LDL-cholesterol. They are used mainly in patients with hypertriglyceridaemia.

Described in this chapter are

Bezafibrate, p. 1323.2
Ciprofibrate, p. 1338.1
Clinofibrate, p. 1338.3
Clofibrate, p. 1338.3
Etofylline Clofibrate, p. 1379.2
Fenofibrate, p. 1381.1
Gemfibrozil, p. 1390.3

Bile-acid binding resins (bile-acid sequestrants) lower cholesterol by combining with bile acids in the gastrointestinal tract and preventing their reabsorption. This leads to an increased oxidation of cholesterol to replace the lost bile acids, and an increase in LDL-receptor synthesis on hepatocytes, resulting primarily in a reduction of LDL-cholesterol.

Described in this chapter are

Colesevelam, p. 1345.1
Colestilan, p. 1345.2
Colestipol, p. 1345.3
Colestyramine, p. 1346.1
Colextran, p. 1347.1

Nicotinates include nicotinic acid (p. 2083.1) and its derivatives. Nicotinic acid is a member of the vitamin B group and, in high doses, has beneficial effects on blood lipids: it reduces triglycerides and increases HDL-cholesterol, and may also modestly reduce LDL-cholesterol. Nicotinates are mainly used in hypertriglyceridaemia. Compounds derived from both nicotinic acid and clofibrate (nicotinate-fibrate derivatives) are also used.

Described in this chapter are

Acipimox, p. 1290.2
Etofibrate, p. 1379.2
Inositol Nicotinate, p. 1410.3
Nicceritrol, p. 1446.1
Nicotinyl Alcohol, p. 1447.1
Tocoferil Nicotinate, p. 1516.1
Xantinol Nicotinate, p. 1535.3

Omega-3 fatty acids are long-chain polyunsaturated fatty acids that primarily reduce triglycerides.

Described in this chapter are

Omega-3 Fatty Acids, p. 1460.1

Nitrates

Nitrates are peripheral and coronary vasodilators used in the management of angina pectoris, heart failure, and myocardial infarction. Some of them may also be used to control blood pressure during surgery. Nitrates are believed to exert their vasodilator effect through release of nitric oxide (p. 1457.1), which causes stimulation of guanylate cyclase in the vascular smooth muscle cells; this results in an increase in cyclic guanosine monophosphate. This nucleotide induces relaxation, probably by lowering the free calcium concentration in the cytosol. Nitrates are thus termed nitrovasodilators. In their action on vascular muscle, venous dilatation predominates over dilatation of the arterioles. Venous dilatation decreases venous return as a result of venous pooling, and lowers left ventricular diastolic volume and pressure (termed a reduction in preload). The smaller or less important dilatation of arterioles reduces both peripheral vascular resistance and left ventricular pressure at systole (termed a reduction in afterload). The consequent effect is a reduction in the primary determinants of myocardial oxygen demand. The effect on preload is not shared by beta blockers or calcium-channel blockers. Nitrates also have a coronary vasodilator effect which improves regional coronary blood flow to ischaemic areas resulting in improved oxygen supply to the myocardium.

Described in this chapter are

Glyceryl Trinitrate, p. 1391.2
Isosorbide Dinitrate, p. 1412.2
Isosorbide Mononitrate, p. 1413.3
Linsidomine, p. 1420.3
Molsidomine, p. 1441.1
Pentaerithrityl Tetranitrate, p. 1465.1
Propatylnitrate, p. 1478.3
Sodium Nitroprusside, p. 1497.1

Potassium-channel openers

Potassium-channel openers (potassium-channel activators) have been used in the management of hypertension; nicorandil is used in angina pectoris. They have a direct relaxant effect on smooth muscle. They act at potassium channels to allow cellular efflux of potassium which hyperpolarises the cell membrane and leads to a reduction in intracellular calcium. The reduction in intracellular calcium produces relaxation of smooth muscle. Activation of potassium channels in blood vessels produces vasodilatation. Potassium-channel openers may also have potential use in other conditions caused by smooth muscle contraction, for example asthma and urinary incontinence.

Described in this chapter are

Nicorandil, p. 1446.2

Prostaglandins

Prostaglandins (p. 2598.1) are endogenous substances with a wide range of actions. Epoprostenol (the synthetic form of prostacyclin or prostaglandin I_2) and its analogues have vasodilator and antiplatelet properties and are used in pulmonary hypertension and peripheral vascular disease, and to prevent clotting of blood in extracorporeal circuits. Limaprost, an analogue of alprostadil (prostaglandin E_1), has similar properties and is used in peripheral vascular disease.

Described in this chapter are

Beraprost, p. 1316.2
Epoprostenol, p. 1374.3
Iloprost, p. 1408.1
Limaprost, p. 1420.3
Treprostinil, p. 1518.1

Sympathomimetics

Sympathomimetics produce either direct or indirect stimulation of adrenergic receptors and have various effects depending on the specific receptors involved. Their actions and uses are described in more detail on p. 1507.3. In cardiovascular disorders, they are mainly used for their $alpha_1$ and $beta_1$ properties to provide haemodynamic support in the management of acute heart failure and shock.

Sympathomimetics with primarily non-cardiovascular uses include alpha agonists, such as phenylephrine (p. 1672.2), pseudoephedrine (p. 1676.1), and naphazoline (p. 1669.3), which are used to produce vasoconstriction of the nasal mucosa for the symptomatic relief of nasal congestion. Apraclonidine (p. 2003.3) and brimonidine (p. 2004.3) are examples of sympathomimetics with $alpha_2$-agonist properties that are used to lower intra-ocular pressure and treat glaucoma. $Beta_2$ agonists are used as bronchodilators and in premature labour and are described under Bronchodilators and Anti-asthma Drugs, p. 1195.1.

Described in this chapter are

Adrenaline, p. 1292.1
Amezinium, p. 1298.3
Denopamine, p. 1350.3
Dimetofrine, p. 1362.2
Dobutamine, p. 1365.3
Docarpamine, p. 1367.1
Dopamine, p. 1367.2
Dopexamine, p. 1368.3
Etilefrine, p. 1379.1
Ibopamine, p. 1407.1
Isoprenaline, p. 1411.3
Mephentermine, p. 1429.3
Metaraminol, p. 1430.1
Methoxamine, p. 1430.2
Midodrine, p. 1437.3
Noradrenaline, p. 1458.2
Norfenefrine, p. 1459.1
Oxedrine, p. 1463.1
Oxilofrine, p. 1463.2
Pholedrine, p. 1469.3

Thrombolytics

Thrombolytics are used in the treatment of thromboembolic disorders such as myocardial infarction, peripheral arterial thromboembolism, and venous thromboembolism (deep-vein thrombosis and pulmonary embolism), and some may be used in ischaemic stroke. They are also used to clear blocked cannulas and shunts.

Thrombolytics activate plasminogen to form plasmin, a proteolytic enzyme that degrades fibrin and thus produces dissolution of clots. Some thrombolytics, such as alteplase, act only on fibrin-bound plasminogen and have little effect on circulating, unbound plasminogen; these thrombolytics are termed fibrin-specific agents. Thrombolytics, such as streptokinase, that affect circulating, unbound as well as fibrin-bound plasminogen are termed fibrin-nonspecific agents. Although it has been suggested that the degree of fibrin specificity should influence the risk of haemorrhage, the clinical significance of this has not been established (see Haemorrhage under Adverse Effects of Streptokinase, p. 1505.3).

Described in this chapter are

Alteplase, p. 1296.3
Anistreplase, p. 1306.1
Defibrotide, p. 1350.1
Desmoteplase, p. 1351.2
Fibrinolysin, p. 1382.3
Monteplase, p. 1441.1
Pamiteplase, p. 1464.2
Plasminogen, p. 1471.3
Reteplase, p. 1486.2
Saruplase, p. 1489.2
Staphylokinase, p. 1502.3
Streptokinase, p. 1503.1
Tenecteplase, p. 1510.2
Urokinase, p. 1520.3

References.

1. Ross AM. New plasminogen activators: a clinical review. *Clin Cardiol* 1999; 22: 165–71.
2. Verstraete M. Third-generation thrombolytic drugs. *Am J Med* 2000; 109: 52–8.

Vasodilators

Vasodilator is a broad term applied to drugs that produce dilatation of blood vessels. The main groups of drugs producing vasodilatation are ACE inhibitors (p. 1282.2), nitrates (above), and direct-acting vasodilators.

Direct-acting vasodilators act predominantly on the arterioles reducing peripheral resistance and producing a fall in blood pressure. Their main use is in hypertension, although other drugs are generally preferred. Some of them are used in hypertensive crises.

Described in this chapter are

Cadralazine, p. 1330.1
Diazoxide, p. 1351.3
Dihydralazine, p. 1358.3
Hydralazine, p. 1401.2
Minoxidil, p. 1438.3
Todralazine, p. 1516.1
Tolazoline, p. 1516.2

Other vasodilators may be used for ischaemic heart disease.

Described in this chapter are

Dilazep, p. 1359.1
Fendilline, p. 1381.1
Hexobendine, p. 1401.1
Oxyfedrine, p. 1464.1
Ranolazine, p. 1484.3
Trapidil, p. 1517.3
Trimetazidine, p. 1520.1

Vasodilators are also used for cerebral and peripheral vascular disorders. Some of these are now thought to improve microcirculatory flow disturbances by altering the rheological properties of blood or tissue metabolism, and this may be more important than their vasodilator effects. Described in this chapter are

Management of Cardiovascular Disorders

Management of the main cardiovascular disorders is discussed in the following sections. These overviews focus on pharmacological therapy, but other options are also mentioned where they form an important part of treatment.

In the **heart**, disorders of the vessels, valves, myocardium, or rhythm may inhibit its efficiency as a pump, and such disorders are described under Ischaemic Heart Disease (p. 1254.2), Structural Heart Diseases (p. 1261.3), and Disorders of Heart Rhythm (p. 1266.1). In the **circulation**, disorders of arteries, veins, and capillaries may inhibit the delivery of blood to the periphery or its return to the lungs and heart and are discussed in the section named Peripheral Vascular Diseases (p. 1272.3), while disorders that primarily affect delivery of blood to the brain are discussed in the section named Cerebrovascular Diseases (p. 1269.2). The risk of developing cardiovascular disease, and current approaches to reducing this risk, are discussed in the first section, Raised Cardiovascular Risk (below). The final section (p. 1276.2) addresses the management of miscellaneous cardiovascular disorders.

Raised Cardiovascular Risk

The risk of developing cardiovascular disease depends on many factors, and these are described and discussed below along with general approaches to reducing risk. Hyperlipidaemias, atherosclerosis, and hypertension, while not in themselves usually life-threatening or even symptomatic, greatly increase the risk of developing symptomatic cardiovascular disease, and specific approaches to their management are also described in this section.

Cardiovascular risk reduction

Atherosclerotic cardiovascular disease includes ischaemic or coronary heart disease (myocardial infarction and angina pectoris), ischaemic stroke, and peripheral vascular disease. Ischaemic heart disease, in particular, is a major cause of mortality in developed countries, and cardiovascular disease overall is associated with considerable morbidity. The benefits of intervention are well established in patients at high risk of cardiovascular disease, and identification and treatment of such people is therefore an important healthcare strategy.[1-9]

The risk of having a cardiovascular event varies between individuals and epidemiological studies have established several factors, both fixed and modifiable, that are associated with increased risk. Risk factors tend to have cumulative effects, but not all are of equal weight and various algorithms have been developed that allow risk to be calculated at an individual level.[3,4,10,11]

The presence of overt atherosclerosis confers the highest risk. This is particularly so where a cardiovascular event such as myocardial infarction or ischaemic stroke has already occurred but also applies to patients with symptoms of angina or peripheral vascular disease. Patients with diabetes (type 1 or type 2) have a similar level of risk to those with atherosclerosis, even when treated. The presence of left ventricular hypertrophy also indicates high risk. Other fixed factors that add to the risk include age, sex, and family history, and these are also important in the population as a whole.

The established **modifiable risk factors** are tobacco smoking, raised blood pressure, and raised blood-lipid concentrations.[12,13] Other risk factors that have been associated with cardiovascular disease but whose relevance is less clear[14] include lack of exercise, abnormal blood clotting profile, hyperhomocysteinaemia, hyperuricaemia, and raised high-sensitivity C-reactive protein concentrations. Obesity is an established risk factor,[15] but paradoxically appears to be protective in patients with overt cardiovascular disease.[16,17] Psychosocial factors such as stress may also be involved.[18,19] Patients with abdominal obesity, hypertension, dyslipidaemia, and glucose intolerance are considered to have the **metabolic syndrome**, and are at increased risk of both cardiovascular disease and diabetes mellitus.[20-24]

The aim of cardiovascular risk reduction is to prevent clinical events occurring in people without manifestations of atherosclerosis (**primary prevention**) and to prevent further events in those with established atherosclerotic disease (**secondary prevention**). In both cases, the general approach is to abolish or reduce any modifiable risk factors that are present; for secondary prevention specific interventions may be appropriate depending on the existing disease (see individual disease reviews for details). Guidelines[1,3-6] have been published for identification and management at the individual level, including specific guidelines for women,[25] the elderly,[26] diabetics,[27,28] and those with metabolic syndrome.[24] There are also specific guidelines for reduction of cardiovascular risk perioperatively.[29] Since atheroma development may begin in childhood, and the prevalence of risk factors is increasing in young people,[30] approaches to risk reduction should also be considered from an early age,[31] especially in those at high risk.[32]

Lifestyle and dietary modifications are the mainstay of risk reduction, and should be the first step for both primary and secondary prevention. They include advice not to smoke, avoidance of obesity, increased exercise, moderation of alcohol intake, and a diet that is low in saturated fat and high in fruit, vegetables, and fish.[1,3-6,8,33-36] Similar advice is also important at a population level, as part of general health promotion and education, although this may produce only modest changes in the overall levels of risk factors.[37] While the incidence of ischaemic heart disease is falling in many parts of the world, the association between changes in classic risk factors and changes in clinical-event rates is weak, suggesting that further approaches are also needed.[38]

For secondary prevention and for patients with established risk factors, lifestyle modifications are rarely adequate alone and drug therapy is often also needed. Patients at high risk, such as those with manifestations of atherosclerosis, should begin lifestyle measures and drug treatment at the same time, but most other patients should have formal risk assessment before starting drug therapy. Specific strategies to aid smoking cessation may be required, and these are discussed on p. 2570.2. Similarly, while both blood pressure and lipid concentrations may be improved by lifestyle changes, drug therapy is often required for established hypertension (see p. 1251.1) or hyperlipidaemias (p. 1248.1). Drug therapy may also be required for the management of obesity (see p. 2315.1); rimonabant, which showed that endocannabinoid receptor antagonists could improve metabolic risk factors as well as body-weight, was withdrawn from the market due to adverse psychiatric effects, but similar approaches are under investigation.[39] Tight control of blood glucose is important in diabetic patients, although the benefit in terms of cardiovascular outcomes is not established (see Prevention of Diabetic Complications, p. 462.3). Influenza vaccination is also recommended;[40] observational studies suggest the risk of cardiovascular events is reduced in vaccinated patients, although there is a lack of evidence from controlled studies.[41] Antithrombotic therapy has an important role, and is discussed further below, along with the use of lipid regulating drugs, antihypertensives, and other drugs in patients with and without overt disease.

Antithrombotic therapy has been widely used in patients with atherosclerotic cardiovascular disease since most acute events result from thrombosis at the site of an atherosclerotic plaque. *Antiplatelet drugs* have been investigated for primary and secondary prevention of various cardiovascular disorders. Numerous studies[42,43] have established that antiplatelet therapy reduces the risk of subsequent cardiovascular events but that the risk of bleeding is increased, and absolute benefit therefore depends on the individual level of risk. In patients with a previous vascular event, the use of antiplatelet drugs for secondary prevention is well established.[3-6,44] Aspirin, started in the acute phase and continued long-term, reduces the risk of re-infarction and death after myocardial infarction and should be given indefinitely.[42] Long-term prophylaxis with aspirin also reduces the risk of future serious vascular events, including stroke, in patients who have suffered an ischaemic stroke or transient ischaemic attack,[42,45,46] regardless of age.[47] Studies also support the benefits of antiplatelet drugs for primary prevention in individuals with established cardiovascular risk factors. For example, aspirin appears to reduce the risk of myocardial infarction in patients with chronic stable angina,[48] males with risk factors for occlusive vascular disease,[49] and hypertensive patients,[50] but has little effect on the overall incidence of stroke.[43,49,50] In patients with peripheral vascular disease, benefit has been reported with various antiplatelet drugs.[51,52] The Primary Prevention Project,[53] a study in patients with at least one major risk factor, showed a reduction in cardiovascular mortality and in a composite of cardiovascular events including death, myocardial infarction, and stroke. Aspirin is also widely used for primary prevention in diabetics, although specific evidence of benefit is limited.[54-57]

Primary prevention using aspirin in healthy individuals is more controversial; studies have produced conflicting results, and there may be differences between males and females. A study in healthy male physicians in the UK[58] found no reduction in the incidence of fatal and non-fatal myocardial infarction in those who had taken aspirin, while a similar study in the US[59] showed a reduction in subjects 50 years of age or older; both showed a slight non-significant increase in the number of disabling strokes which, in the US study, were attributed to cerebral haemorrhage. In women, a large observational study in healthy US nurses[60] indicated that aspirin might reduce the risk of first myocardial infarction, but a randomised study[61] found no effect on either myocardial infarction or death, although the incidence of stroke was reduced. Meta-analyses[43,62,63] have generally concluded that, while there may be benefit for some outcomes (myocardial infarction in men and stroke in women), the effect on overall cardiovascular events may not outweigh the increased risk of bleeding and routine use of aspirin is not recommended.

Aspirin has been the most widely studied antiplatelet drug and appears to be effective over a range of doses (see p. 22.3). However, some patients have events while taking aspirin and it has been suggested that they may have aspirin resistance, although the clinical significance and implications for management are not clear.[64,65] Alternative antiplatelet drugs may be used in patients who are intolerant of aspirin (although aspirin with a proton pump inhibitor is preferred if intolerance is due to gastrointestinal effects[66]), and combination therapy may also be considered. In the CAPRIE study,[67] clopidogrel was shown to be at least as effective as aspirin in reducing cardiovascular events, including myocardial infarction and stroke, in individuals at high risk. In patients with ischaemic stroke, dipyridamole, given alone or with aspirin, is effective for secondary prevention,[68] but use of clopidogrel with aspirin increases the risk of bleeding without reducing the risk of ischaemic events.[69] Clopidogrel with aspirin is of benefit in patients with acute coronary syndromes, but in patients with high cardiovascular risk who do not present acutely the increased bleeding risk appears to outweigh any benefit.[70]

Oral anticoagulants have been used as an alternative to antiplatelet drugs or as additional therapy. Oral anticoagulants alone may be more effective than antiplatelet therapy but the risk of bleeding is increased,[49,71] and they are generally only recommended in patients unable to take antiplatelet drugs or in whom they are ineffective. The relative risks and benefits of combination therapy are more controversial,[72,73] and there is limited evidence on which to base decisions, particularly in patients with accepted indications for both anticoagulants and antiplatelet drugs. In general, for patients taking anticoagulants for other indications, antiplatelet drugs appear to add little further benefit in terms of cardiovascular risk reduction except in some patients with mechanical heart valves.[72] However, in patients with acute coronary syndromes or coronary stenting, the indication for antiplatelet drugs may be stronger, and decisions are more complex.[73]

Lipid lowering therapy has an established role in cardiovascular risk reduction, and the benefits of statins, in particular, have been shown in a wide range of patients. Meta-analyses[74-79] of randomised studies have found that statins improve outcomes when used for primary or secondary prevention, and a large epidemiological study[80] confirmed these findings. Benefit occurs across a wide range of patients, including those with raised or average cholesterol concentrations, women, and older individuals. The absolute benefit depends on the patient's initial cardiovascular risk and the degree of cholesterol reduction achieved,[77] and increased benefit has been reported[81,82] with the use of intensive lipid lowering regimens. Other lipid lowering drugs that have shown benefit include fibrates[83] and derivatives such as gemfibrozil, which was effective for secondary prevention in a study in men with low HDL-cholesterol.[84] A reduction in cardiovascular mortality has also been found with omega-3 fatty acids in some populations,[85] but their overall effect remains unclear.[86] Ezetimibe, which adds to the LDL-lowering effects of statins, has not yet been shown to have a clinical benefit.[87]

LDL-cholesterol appears to be the most important target, but other mechanisms may be involved. Low HDL-cholesterol is an established risk factor for cardiovascular disease, but the benefits of drugs specifically targeting this are controversial,[88,89] and none of the approaches to increasing HDL-cholesterol yet has an established role.[90]

There has been concern that there might be an association between low cholesterol concentrations and increased morbidity and mortality from non-cardiac causes including haemorrhagic stroke, cancer, accidents and suicide, and chronic respiratory, liver, and bowel disease.[91-96] Although controlled studies suggest that the

risk of haemorrhagic stroke may be increased,[97] meta-analyses have shown that statin therapy reduces both cardiovascular and all-cause mortality,[76,77] and that there is no significant increase in non-illness mortality.[98]

Antihypertensive drugs have an established role for cardiovascular risk reduction in patients with hypertension, and benefit may extend to patients with normal blood pressures, although this is less clear. There is also debate about which types of antihypertensive drugs are most effective; some studies have suggested that certain drug classes have additional benefits, but others dispute these claims. A meta-analysis[99] concluded that, given a similar reduction in blood pressure, the five main classes of antihypertensives had equivalent effects overall, irrespective of the presence or absence of vascular disease and the pretreatment blood pressure, and the authors suggested that combinations of low-dose antihypertensives might have a particular role.

ACE inhibitors are one of the drug groups for which a particular role has been suggested, as they have been shown to reduce cardiovascular events in a wide range of patients. Studies in patients with heart failure,[100,101] and the HOPE study[102] in patients with high cardiovascular risk, suggested benefits beyond lowering of blood pressure, possibly associated with blockade of the renin-angiotensin system.[103] *Angiotensin II receptor antagonists* appear to have similar effects.[104,105]

Several other ***general approaches*** to reducing cardiovascular risk have been tried, mostly targeted against potential risk factors or the atherosclerotic process itself, but none has an established role. Approaches tried include: use of *folic acid and vitamin B supplements* to reduce homocysteine concentrations; dietary *antoxidants* to reduce the progression of atherosclerosis; and *HRT* in women, based on the lower incidence of cardiovascular disease in premenopausal women than in men of a comparable age. These interventions are discussed further under Atherosclerosis (p. 1250.2).

The multifactorial nature of cardiovascular risk, the presence of risk factors in a wide section of the population, and the difficulty in applying lifestyle and dietary changes has led to the suggestion that routine use of a combination of drugs with established effects on cardiovascular risk might be beneficial.[106] It was estimated that a combination preparation (the polypill) containing a statin, aspirin, folic acid, and drugs from three classes of antihypertensive given to all individuals aged over 55 years could prevent about 80% of cardiovascular disease in a western society. Observational studies suggest that combinations of cardiovascular drugs are effective,[107] and formulation of such a combination (without folic acid) appears to be feasible,[108] but clinical evidence of benefit is not yet available and the role of such combinations remains to be confirmed.

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Hyperlipidaemias

Hyperlipidaemia results from a disorder in the synthesis and degradation of plasma lipoproteins. Although the main concern has generally been the overall elevation of plasma lipids (hyperlipidaemia), it is now increasingly recognised that the balance of lipids in the plasma is also important, and the term dyslipidaemia is often used. Dyslipidaemias have genetic and other causes, and are often associated with a high-fat diet. Although patients with hyperlipidaemia may have symptoms that require treatment, the major concern is their increased risk of ischaemic heart disease.

Table 1. Principal lipoproteins and associated lipids.

Lipoprotein	Lipid
Chylomicron	Triglyceride
VLDL	Triglyceride
IDL	Cholesterol and triglyceride
LDL	Cholesterol
HDL	Cholesterol

The **lipids** that are of relevance in hyperlipidaemias are cholesterol, an essential component of cell membranes and a precursor of steroid hormone synthesis, and triglyceride, an important energy source. They are transported in the blood as lipoproteins.

Lipoproteins are complex particles[1,2] comprising a hydrophilic coat of phospholipids, free cholesterol, and specific polypeptides termed apolipoproteins (apoproteins) around a core of varying proportions of triglyceride and cholesterol (present as cholesteryl ester). The lipoproteins are characterised by their density, which in general increases as they are metabolised and the proportion of cholesteryl ester to triglyceride increases. Table 1, below, lists the principal lipoproteins and their associated lipids. The lowest density lipoproteins are the **chylomicrons** which transport triglyceride derived from dietary fat, and the **VLDL** (very low-density lipoproteins; pre-β lipoproteins) which transport endogenous triglyceride mainly synthesised in the liver, to peripheral tissues. The triglyceride is hydrolysed in the peripheral tissues by lipoprotein lipase, which is activated by apolipoprotein CII present in the lipoproteins. Both chylomicrons and VLDL are progressively depleted of triglyceride, yielding increasingly dense lipoprotein particles termed 'remnant' particles. Chylomicron remnants are cleared rapidly from plasma by the liver where they are metabolised, releasing free cholesterol. VLDL remnants, which include **IDL** (intermediate-density lipoproteins; broad β-lipoproteins), may also be cleared by the liver or converted to **LDL** (low-density lipoprotein; β-lipoprotein). **HDL** (high-density lipoproteins; α-lipoproteins) are synthesised in the liver and small intestine and have a role in the transport of cholesterol from the peripheral tissues back to the liver, where it is either utilised or excreted in the bile as bile acids and unesterified cholesterol. The majority is reabsorbed from the intestines and a small proportion is excreted in the faeces.

Defining hyperlipidaemia is difficult due to the marked variation in lipid concentrations between different populations. Apparently 'normal' lipid concentrations may still be associated with a significant risk of cardiovascular disease, and this may depend on which lipids are affected. Epidemiological data show a progressive and continuous relationship between plasma-cholesterol concentrations and mortality from ischaemic heart disease. The Framingham Study[3] found a 9% increase in death from cardiovascular disease for each 10 mg/dL (0.26 mmol/litre) rise in total plasma-cholesterol concentration. Plasma-cholesterol concentrations of 5.2 mmol/litre (200 mg/dL) or less are associated with a low risk of ischaemic heart disease. The increased risk is due mainly to raised LDL-cholesterol. In contrast, HDL-cholesterol is inversely associated with ischaemic heart disease. Low plasma concentrations of HDL-cholesterol (below 1 mmol/litre or 40 mg/dL) are generally associated with increased risk of ischaemic heart disease, whereas high concentrations are protective.[4] There also appears to be an association between plasma-triglyceride concentrations and risk of ischaemic heart disease.[5] Some triglyceride-rich lipoproteins such as chylomicron remnant particles and IDL are atherogenic and the risk of heart disease increases as triglyceride concentrations increase in patients who also have high total cholesterol and low HDL-cholesterol concentrations. Hypertriglyceridaemia alone (greater than 2.3 mmol/litre or 200 mg/dL) may be an independent risk factor for ischaemic heart disease, but any clinical benefit from intervention to lower triglyceride levels is yet to be established.[6] However, the absolute risk for any individual also depends on other cardiovascular risk factors, including smoking and hypertension, and treatment decisions should in general be based on assessment of overall risk (see Cardiovascular Risk Reduction, p. 1246.1).

Hyperlipidaemias may result from several underlying defects and various methods have been used for classification.[7] A simple system is to divide them on the basis of whether raised serum cholesterol (hypercholesterolaemia), triglyceride (hypertriglyceridaemia), or both (mixed or combined hyperlipidaemia) is the predominant abnormality. Alternatively, the Fredrickson/WHO method (see Table 2, below) describes them in terms of the lipoprotein abnormality (hyperlipoproteinaemia), although this is less useful clinically. Within these systems, primary hyperlipidaemias are those with an underlying genetic defect, whereas secondary hyperlipidaemias are caused by another disease state or by drug therapy. Primary and secondary causes of hyperlipidaemia may co-exist.

Primary hyperlipidaemias (see Table 3, p. 1249) may be monogenic, relating to a single genetic defect, but much more commonly they are due to the interaction of several genes with dietary and other factors (polygenic). Individuals with common, polygenic (multifactorial) hypercholesterolaemia tend to have only mild or moderate elevations of plasma-cholesterol, whereas those with monogenic hyperlipidaemias tend to have much higher plasma-lipid concentrations.

Secondary hyperlipidaemias may have various causes. Diseases producing hypertriglyceridaemia include diabetes mellitus, chronic renal failure, and bulimia. Hypercholesterolaemia can occur in hypothyroidism, nephrotic syndrome, biliary obstruction, and anorexia nervosa. Drugs that may produce hypertriglyceridaemia and/or hypercholesterolaemia include thiazide diuretics (in high doses), beta blockers, corticosteroids, and antivirals in patients with HIV infection. Excessive alcohol intake may produce elevated plasma-triglyceride concentrations.

The degree of hyperlipidaemia seen in patients with either primary or secondary hyperlipidaemia is influenced by various factors, including, importantly, diet. A diet rich in saturated fat and cholesterol and poor in fibre can produce hypercholesterolaemia. Obesity further predisposes to hyperlipidaemia. Other factors that may influence lipid concentrations include pregnancy, lack of exercise, and smoking. After myocardial infarction cholesterol levels may be temporarily reduced for several weeks; therefore, to measure the patient's usual level of cholesterol, blood samples should be taken within a few hours of the infarction.

The majority of people with hyperlipidaemia have plasma-lipid concentrations that are only mildly or moderately elevated, and they show **no clinical symptoms**. At the other end of the spectrum, severe hypercholesterolaemia can cause tendon, tuberous, or planar xanthomas, xanthelasma, and arcus corneae; it is also associated with an increased risk of ischaemic stroke. Severe hypertriglyceridaemia can cause acute severe abdominal pain due to pancreatitis; hepatic and splenic enlargement, eruptive xanthomas, and lipaemia retinalis may also occur. However, the main concern in patients with hyperlipidaemias is the increased risk of ischaemic heart disease. In patients with very severe hypercholesterolaemia, such as familial hypercholesterolaemia, this may occur at a very young age; in those with the heterozygous form onset of heart disease during their 20s or 30s is not unusual, and in the rarer homozygous form ischaemic heart disease may develop by the age of 10.

Treatment of hyperlipidaemias. In patients with clinical symptoms, treatment is indicated to promote the regression or non-progression of disfiguring xanthomas, or to prevent attacks of acute pancreatitis in those with severe hypertriglyceridaemia. The main aim of treatment, however, particularly in patients with only mildly elevated lipids, is to reduce the risk of ischaemic heart disease.[1,8-15] Although most clinically apparent atherosclerotic disease occurs in adults, it is increasingly recognised that children and adolescents should also be considered for treatment.[16-19]

Table 2. Classification of hyperlipoproteinaemias.

WHO classification	Lipoproteins elevated	Plasma lipids affected	
		Cholesterol	Triglyceride
I	Chylomicrons	Normal or elevated	Elevated
IIa	LDL	Elevated	Normal
IIb	LDL and VLDL	Elevated	Elevated
III	VLDL with abnormally high cholesterol content	Elevated	Elevated
IV	VLDL	Normal or elevated	Elevated
V	Chylomicrons and VLDL	Elevated	Elevated

Table 3. Primary hyperlipidaemias.

	Lipoprotein Abnormality (WHO type)	Prevalence	Typical lipid concentrations (mmol/L) Cholesterol	Triglyceride	Risk of IHD	Pancreatitis
Common (polygenic) hypercholesterolaemia	IIa or IIb	Very common	6.5 to 9.0	< 2.3	+	–
Familial hypercholesterolaemia	IIa or IIb	Moderately common	7.5 to 16.0	< 2.3	+++	–
Familial hypertriglyceridaemia	IV or V	Common	6.5 to 12.0	10 to 30	?	++
Familial combined hyperlipidaemia	IIa, IIb, IV, or V	Common	6.5 to 10.0	2.3 to 12.0	++	–
Familial dysbetalipoproteinaemia or remnant hyperlipoproteinaemia	III	Uncommon	9.0 to 14.0	9.0 to 14.0	++	+
Abnormal lipoprotein lipase function	I	Rare	< 6.5	10.0 to 30.0	–	+++

+ = elevated risk; – = no risk; ? = uncertain risk; IHD = ischaemic heart disease

Since the relationship between plasma-cholesterol concentrations and ischaemic heart disease is continuous, the value of the former at which treatment with lipid regulating drugs should be started has been widely debated. Guidelines recommend that the decision to treat should be based on the overall risk profile of the patient and that other risk factors should also be treated (see Cardiovascular Risk Reduction, p. 1246.1).

- Specifically, British guidelines[20] advise that all high-risk patients should have drug therapy, including patients with established cardiovascular disease, most diabetics, patients with a ratio of total plasma cholesterol to HDL-cholesterol 6.0 or higher, and those with familial dyslipidaemias. In all cases, the target for therapy is total cholesterol below 4.0 mmol/litre and LDL-cholesterol below 2.0 mmol/litre; alternatively, a 25% reduction in total cholesterol and a 30% reduction in LDL-cholesterol should be the target if this results in a lower concentration.
- European guidelines[21] suggest that diabetics and patients with established cardiovascular disease should have a target of total cholesterol below 4.5 mmol/litre (and below 4.0 mmol/litre if feasible) and LDL-cholesterol below 2.5 mmol/litre (and below 2.0 mmol/litre if feasible); patients with total cholesterol above 8 mmol/-litre or LDL-cholesterol above 6 mmol/litre should be treated irrespective of their other risk factors.
- US guidelines[2,22] suggest that drug treatment should be considered if the LDL-cholesterol level is 190 mg/dL or higher. For patients with 2 or more risk factors, drug therapy should be considered if the LDL-cholesterol is 160 mg/dL or higher, and for those with existing cardiovascular disease, diabetes mellitus, or particularly high risk, drug therapy should be considered if LDL-cholesterol is 130 mg/dL or higher. The US guidelines also give target LDL-cholesterol levels of less than 160 mg/dL, less than 130 mg/dL, and less than 100 mg/dL, respectively, for the three risk groups. However, it has been suggested[23] that treatment may be appropriate in some very high risk patients at LDL-cholesterol concentrations below 100 mg/dL and that a goal of below 70 mg/dL may be reasonable; others consider that there is little good clinical evidence to support such targets.[24] Although low HDL-cholesterol is an additional risk factor, the benefits of raising HDL-cholesterol are not established and no target is therefore specified in the current guidelines.

The main methods of treating hyperlipidaemias are dietary and lifestyle changes and the use of lipid regulating drugs.[2,20-22] Some surgical and other procedures may also be used in familial hypercholesterolaemia (see below).

Dietary therapy should be started in all patients with hyperlipidaemia with the aim of weight reduction in the obese and a reduction in total fat intake. Dietary recommendations[20,22] include a reduction in saturated fatty acids, restriction of *trans* fatty acids, increased consumption of fish or other sources of long-chain n-3 polyunsaturated fatty acids, and increased intake of fruit and vegetables; the intake of cholesterol and n-6 polyunsaturated fatty acids should be restricted. Increased physical exercise is also recommended. Moderation of alcohol intake is advised, particularly in patients with hypertriglyceridaemia, in whom alcohol may precipitate pancreatitis. However, more rigorous diet than that often recommended may be necessary for diet alone to be of much value,[25] and most patients will require drug therapy to achieve target lipid concentrations. Patients at low cardiovascular risk should have a trial of dietary therapy before drugs are started, but in those with established cardiovascular disease or major risk factors drug therapy and dietary changes may be started at the same time.

The principal groups of **lipid regulating drugs** (hypolipidaemic drugs) are the statins, fibric acid derivatives and related compounds, bile-acid binding resins, nicotinic acid and its derivatives, the omega-3 marine triglycerides, and ezetimibe.[1,10-12,26,27]

- *Statins* (HMG-CoA reductase inhibitors) reduce cholesterol by stimulating an increase in LDL-receptors on hepatocyte membranes, thereby increasing the clearance of LDL from the circulation. Their main effect is to reduce LDL-cholesterol, but they may also reduce triglycerides to a modest extent and increase HDL-cholesterol. They are generally considered to be the most effective lipid lowering drugs.
- *Fibrates* inhibit the synthesis of cholesterol and bile acids, and enhance the secretion of cholesterol in bile. Their main effect is to reduce triglycerides by reducing the concentration of VLDL; they also increase HDL-cholesterol and have variable effects on LDL-cholesterol. They are used mainly in patients with hypertriglyceridaemia.
- *Bile-acid binding resins* lower cholesterol by combining with bile acids in the gastrointestinal tract and preventing their reabsorption. This leads to an increased oxidation of cholesterol to replace the lost bile acids, and an increase in LDL-receptor synthesis on hepatocytes, resulting mainly in a reduction of LDL-cholesterol.
- *Nicotinic acid* inhibits production of VLDL in the liver; it lowers LDL-cholesterol and triglycerides and increases HDL-cholesterol, but adverse effects may limit its use.
- *Omega-3 fatty acids* mainly reduce triglycerides.
- *Ezetimibe* is a cholesterol absorption inhibitor and reduces intestinal absorption of both dietary and biliary cholesterol.[28]
- *Dietary supplements* containing soluble fibre, such as guar gum or ispaghula, or plant stanols or sterols, may also be used to reduce cholesterol absorption; garlic preparations and other supplements have also been used, although their role is not established.[29]
- *Other drugs* that have been tried include cholesteryl ester transfer protein inhibitors, which increase HDL; however, they have not yet been shown to have clinical benefits,[30] and development of torcetrapib was stopped as it was found to increase mortality. In postmenopausal women, oestrogen therapy reduces lipid concentrations, but the adverse effects may outweigh any benefit (see Effects on the Cardiovascular System, p. 2248.2); soya protein may have a similar effect.

Choice of therapy ideally depends upon the lipid profile of the individual patient since the drug groups differ in their effects on the different lipid components.

In practice, most patients have common, polygenic *hypercholesterolaemia*, and can be treated effectively with statins as first-line therapy. Bile-acid binding resins or nicotinic acid may be alternatives, but are generally less well tolerated. Ezetimibe or fibrates may also be used, but are generally only recommended when patients are unable to take statins.[31,32] Combination therapy may be required in some patients to reach target lipid concentrations, although there is limited evidence that combination therapy has any benefit over high-dose statins.[33] The increased risk of adverse effects in patients taking statins and fibrates together should also be considered (see Effects on Skeletal Muscle under Adverse Effects of Simvastatin, p. 1493.2). Ezetimibe adds to the LDL-lowering effect of statins and appears to be safe, but there is no evidence that this improves clinical outcomes.[34]

In patients with *hypertriglyceridaemia*, statins or fibrates may be used, although fibrates should only be given first-line in severe, isolated hypertriglyceridaemia;[32] resins should not be used alone since they may increase triglyceride concentrations.

Patients with the less common *familial dyslipidaemias*[35] generally have higher lipid concentrations and require more intensive therapy. Specific treatment strategies are as follows:

- *FAMILIAL HYPERCHOLESTEROLAEMIA.* Patients with familial hypercholesterolaemia usually have very high plasma-cholesterol concentrations, which rarely respond adequately to diet alone and drug therapy is therefore often necessary in this high-risk group. For children with familial hypercholesterolaemia, drug treatment should be started by the age of 10 years; earlier or more intensive treatment may be considered in those at high risk of early coronary heart disease.[36] Aggressive therapy may lead to regression of atherosclerotic lesions.[37] The first-line drugs are the statins; high-intensity treatment is recommended, with the aim of reducing LDL-cholesterol by more than 50%,[36] but even moderate doses have been shown to reduce the risk of ischaemic heart disease.[38] Ezetimibe has been recommended as an alternative, and may also be given in addition to a statin if a further reduction in LDL-cholesterol is required.[34] Alternatives such as bile-acid binding resins, nicotinic acid, or fibrates, may be required, alone or with statins, in some patients. In some forms of familial hypercholesterolaemia, and where plasma-cholesterol concentrations are very high, plasma-triglyceride concentrations may also be raised. In these cases a fibric acid derivative or nicotinic acid may be effective, and in more severe cases the combination of a bile-acid binding resin together with a fibric acid derivative or a statin may be used.
  In the homozygous form of familial hypercholesterolaemia there may be a complete lack of functional LDL-receptors and drugs that act by increasing LDL-receptors, such as statins and bile-acid binding resins, may be less effective. However, statins may be useful as adjunctive therapy in those patients who have some LDL-receptor function. Mipomersen, an antisense oligonucleotide that inhibits apolipoprotein B synthesis, may also be used as an adjunct to other lipid regulating drugs in homozygous patients.[39] However, concerns about cardiovascular safety and hepatotoxicity may limit its use.
  In patients with the homozygous form liver transplantation is the most definitive treatment. Plasma exchange (weekly or fortnightly) or more selective procedures such as LDL apheresis, including the use of heparin to precipitate LDL (the HELP system—Heparin Extracorporeal LDL Precipitation) may also be used in combination with lipid regulating drugs. Gene therapy is under investigation as a treatment for familial hypercholesterolaemia.
- *FAMILIAL HYPERTRIGLYCERIDAEMIA.* In patients with familial hypertriglyceridaemia dietary therapy is generally adequate, but drugs may be required if there is a high risk of acute pancreatitis, such as in patients with chylomicronaemia,[40] or if there is a family history of atherosclerosis. The risk of acute pancreatitis is high when plasma-triglyceride concentrations are above 20 mmol/litre. Nicotinic acid or the fibric acid derivatives, particularly gemfibrozil, are generally recommended and may be used in combination in severe cases. Omega-3 marine triglycerides may also be of value. In severe intractable hypertriglyceridaemia, particularly type V hyperlipoproteinaemia, norethisterone has been suggested for women or oxandrolone for men.
- *FAMILIAL COMBINED HYPERLIPIDAEMIA.* Drug therapy may be used in patients who do not respond to dietary therapy alone. The choice will depend on the predominant lipid abnormality. A statin is the first choice, particularly in cases where hypercholesterolaemia is predominant. A fibric acid derivative may be used when hypertriglyceridaemia predominates, and nicotinic acid is useful where plasma concentrations of triglyceride and cholesterol are raised to a similar degree. Bile-acid binding resins should not be used alone since they can aggravate hypertriglyceridaemia, but they may be useful with a triglyceride-lowering drug in some patients.

Treatment with a combination of drugs that lowers both cholesterol and triglyceride concentrations may be required in some patients especially in those with markedly raised plasma concentrations of triglyceride or cholesterol, as treatment of these patients with drugs effective against only the predominant lipid may produce a rise in the plasma-concentrations of the other lipid. The choice of treatment in these cases is largely empirical as responses are not always predictable in individual patients.

- *FAMILIAL DYSBETALIPOPROTEINAEMIA* (remnant hyperlipoproteinaemia; remnant particle disease). In this lipid disorder the degree of hyperlipidaemia is usually severe and, although it may respond remarkably to dietary therapy, drug treatment is usually necessary. Fibric acid derivatives, statins, or nicotinic acid may be used.
- *ABNORMAL LIPOPROTEIN LIPASE FUNCTION* (chylomicronaemia). Drug therapy is largely ineffective, although fibrates and nicotinic acid may have modest effects. The condition is treated with severe restriction of dietary fat; the diet may be supplemented by medium-chain triglycerides to improve tolerability, but their value is controversial.[8]

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Atherosclerosis

Atherosclerosis is a pathological condition affecting medium and large arteries in which lipid-rich lesions (atheromas) develop in the intimal lining, leading to arterial dysfunction, obstruction of blood flow, and ischaemia. **Ischaemic heart disease** (coronary heart or coronary artery disease; p. 1254.2), which includes angina pectoris (p. 1254.3) and myocardial infarction (p. 1257.1), is the most common manifestation of atherosclerosis and in most industrialised countries ischaemic heart disease is a leading cause of death. Atherosclerosis of peripheral or cerebral arteries leads to peripheral arterial occlusive disease (under Chronic Occlusive Peripheral Arterial Disease, p. 1272.3) or ischaemic stroke (p. 1269.2). Atherosclerotic diseases are thus a major cause of mortality and morbidity and the prevention and treatment of atherosclerosis has an important role in the management of these diseases.

Atherosclerosis is a progressive condition and various stages of atheroma development are recognised.[1-3] Early lesions include fatty streaks, which develop from infancy and are composed of lipid-filled macrophages (foam cells). These progress to fibrous plaques, which consist of a core of lipid and lipid-rich macrophages surrounded by a connective-tissue matrix. Plaques may undergo calcification and may become sufficiently large to obstruct the lumen of the artery. However, acute occlusion more commonly occurs as a result of thrombosis at the site of a plaque, due to endothelial denudation or disruption of the plaque (plaque rupture or fissuring) with exposure of the thrombogenic core. Endothelial dysfunction is an important underlying factor, promoting both the development of atheromas (atherogenesis) and subsequent thrombosis.[4,5] Although symptoms depend on the site of obstruction, atherosclerosis is essentially a systemic condition, and symptoms in one vascular system suggest the presence of more extensive disease. For example, patients with peripheral or cerebrovascular disease are also likely to develop, or to have evidence of, ischaemic heart disease.

The management of atherosclerotic diseases involves treatment of the clinical manifestations (as discussed under the specific diseases) and measures to reduce the risk of cardiovascular events occurring (see Cardiovascular Risk Reduction, p. 1246.1). Approaches targeted more directly at the atherosclerotic process have also been tried, and some of these are discussed below.

Dyslipidaemia is one of the major factors underlying the development of atherosclerosis and lipid lowering has an established role in patients with atherosclerotic disease, reducing the incidence of cardiovascular events and also slowing or even reversing the progression of atherosclerosis. Although low-density lipoprotein (LDL)-cholesterol has been the main target for therapy, it is not entirely clear which lipid fractions are most important or whether some lipid lowering drugs have additional effects. For statins, there appears to be a clear correlation between their effects on LDL and their effects on atherosclerosis, with more intensive therapy leading to lower rates of progression or even to regression of atherosclerotic plaques.[5-7] However, use of adjunctive lipid regulating drugs with statins to further modify the lipid profile is less established. Studies combining statins with ezetimibe[8,9] have failed to show any additional reduction in atherosclerosis, despite further lowering LDL, whereas studies using statins with nicotinic acid,[9,10] which raises high-density lipoprotein (HDL)-cholesterol, have suggested benefit.

Oxidation of LDL is thought to be a crucial step in atherogenesis[11-13] and a number of studies have investigated the use of dietary antoxidants such as vitamins E and C and betacarotene (see Prophylaxis of Ischaemic Heart Disease, p. 2047.1). Although some studies have found a reduction in the progression of atherosclerosis, others have not confirmed this finding, and several large studies have failed to find any effect on the risk of clinical events. Polyphenol compounds found in various foods, including red wine, have also received much attention for their possible role in the prevention of atherosclerosis.

Hyperhomocysteinaemia has been suggested as a risk factor for atherosclerosis, although its importance is not clear.[4] Interventions to reduce homocysteine, such as the use of folic acid or vitamin B supplements (see Cardiovascular Disease, p. 2063.3), have been tried. Some effects on endothelial function have been noted, but there is as yet no evidence that clinical events are reduced. *Hyperuricaem a* may also be a risk factor, although again the benefits of treatment are not yet clear.[15]

Inflammation appears to have an important role in the development and progression of atherosclerosis, and in acute events due to plaque instability.[16,17] Various studies have shown an association between C-reactive protein, a marker of inflammation, and cardiovascular events, although its precise role is unclear.[14] As well as lowering lipids, statins are known to reduce concentrations of C-reactive protein, and this has been shown to correlate with their efficacy.[18] Other non-lipid effects such as improvement of endothelial dysfunction, or an effect on thrombosis, have also been suggested.

Infection is another possible cause of inflammation that has been investigated,[19] and serological and pathological studies have found an association with several organisms. The evidence appears to be strongest for *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*), although its precise role in the development or progression of atherosclerosis is unclear.[20] Treatment with antibacterials has been tried in patients with atherosclerotic disorders but any benefit has not yet been confirmed;[19,20] meta-analyses[21,22] of studies using antichlamydial drugs in patients with ischaemic heart disease have found no evidence that they reduced either mortality or further cardiovascular events. There may also be an association between periodontal infection and atherosclerosis, but further study is needed to assess the benefits of treatment.[23]

Coronary artery calcification is associated with the presence of atherosclerosis and measures to reduce calcium deposition have therefore been tried. Raised lipid concentrations appear to be involved in calcification and there is some evidence that statins may reduce progression,[24] although this has not been confirmed in all studies.[25-27] Results with calcium-channel blockers have been mixed (see under Nifedipine, p. 1448.1). Chelation therapy with disodium edetate has also been tried but again, any benefit remains to be established (see Atherosclerosis under Sodium Edetate, p. 1551.1).

Hormonal factors may also play a role in the development of atherosclerosis; women have a lower risk of atherosclerotic disease than men of a comparable age, although the difference narrows with increasing age postmenopausally. HRT lowers lipid concentrations and some angiographic or ultrasound studies have shown beneficial effects on the progression of atherosclerosis, although others have failed to confirm these findings. However, controlled studies do not support a role for HRT in the prevention of cardiovascular disease in postmenopausal women (see Effects on the Cardiovascular System, p. 2248.2).

Therapeutic angiogenesis (the development and growth of blood vessels) is also under investigation to improve perfusion in atherosclerotic diseases. Preliminary studies of growth factor proteins, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), and gene therapy to stimulate VEGF production, have shown promise.[28,29] The use of stem cells is also being investigated.[30] However, since neovascularisation of the vessel wall and plaque angiogenesis may play a role in atherosclerosis, anti-angiogenic therapy may also have potential.[31]

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Hypertension

Hypertension, particularly essential or primary hypertension, is widespread. Although it is usually asymptomatic, hypertension is a major risk factor for cardiovascular morbidity and mortality, especially that associated with stroke, and control of hypertension is therefore a major aspect of cardiovascular risk reduction. National[1-3] and international[4,5] guidelines on management have been published, but several areas of controversy remain,[6,7] and in many patients hypertension continues to be difficult to treat.[8,9]

Definitions. The term ***blood pressure*** generally means arterial blood pressure, that is, the pressure of the blood on artery walls. It is usually measured indirectly in the brachial artery just above the elbow using an appropriately calibrated sphygmomanometer[10] and is expressed in mmHg. Two measurements are made:

- *systolic* or maximum blood pressure (achieved during ventricular contraction of the heart)
- *diastolic* or minimum blood pressure (achieved during ventricular dilatation)

Hypertension means a higher than 'normal' blood pressure; it has been defined as the level of blood pressure above which intervention has been shown to reduce the associated cardiovascular risk. Many factors influence blood pressure, resulting in a bell-shaped distribution curve in the general population, and in consequence it is difficult to define an absolute norm.

Classification and subsequent treatment decisions should be based on blood pressure measurements taken on several occasions over a period that varies according to the severity of hypertension. Ambulatory blood pressure monitoring may have advantages in some situations[1,2,5,10,11] and automated devices for home monitoring may also have a role.[1,5,10] However, home and ambulatory blood pressures tend to be lower than those measured in healthcare settings, and different thresholds for normal and abnormal values apply.[1,5,10,11] Guidelines generally use conventional blood pressure measurements to determine treatment decisions since this is the basis of most outcome studies.

Normal adult blood pressure has been arbitrarily defined as a systolic pressure below 130 mmHg together with a diastolic pressure below 85 mmHg (i.e. below 130/85 mmHg), but more recent studies have suggested that optimal blood pressure, in terms of cardiovascular risk, may be lower than this. US guidelines[2] now define normal blood pressure as below 120/80 mmHg, while European[5] and British[1] guidelines classify this as optimal. Blood pressures of 130–139/85–89 mmHg are regarded as high normal[1,5] or are included in the classification of *prehypertension*.[2] Although hypertension was formerly defined in terms of diastolic blood pressure alone, it is now recognised that systolic pressure is also important in determining risk, and current guidelines give equal emphasis to both.

Blood pressure above 140 mmHg systolic, and/or 90 mmHg diastolic is generally considered to represent hypertension. Although classifications of *mild*, *moderate*, and *severe hypertension* have been widely used, these terms may be misleading since absolute cardiovascular risk is more important in determining the need for treatment and depends on other factors in addition to blood pressure. Most guidelines[1,4,5] therefore use a grading system to classify hypertension, as follows:

grade 1: 140–159/90–99 mmHg;
grade 2: 160–179/100–109 mmHg;
grade 3: ≥ 180/≥ 110 mmHg.

In the US guidelines,[2] stage 1 hypertension corresponds to grade 1, whereas stage 2 includes both grades 2 and 3.

When systolic and diastolic pressure fall into different categories the higher value is used for classification purposes.

The term *malignant* or *accelerated hypertension* has been used for rapidly progressing severe hypertension associated with retinopathy and often renal impairment, but this is now generally considered part of the spectrum of hypertensive crises (see below).

Isolated systolic hypertension occurs mainly in the elderly and has been defined[1,3] as systolic pressure of 140 mmHg or more and diastolic pressure under 90 mmHg.

Origins. In the majority of cases of hypertension the cause is unknown, and such *primary* or *essential* hypertension is probably multifactorial in origin, with genotype, as well as external factors such as diet and body-weight, playing a role.[12,13] Hypertension may also be associated with surgery or pregnancy and is prevalent in diabetics. In a limited number of cases hypertension is *secondary* to some other condition, such as renal disease, Cushing's syndrome, phaeochromocytoma, or the adverse effects of drugs such as oestrogens, and such causes may be suspected particularly in resistant or malignant hypertension.[14] Although treatment of the underlying condition will generally be desirable, the resultant hypertension will not necessarily be abolished by this.

Management of hypertension. Most of what follows relates to primary or essential hypertension in adults. Hypertensive crises, hypertension in children, and hypertension associated with surgery, diabetes, renal disease, or pregnancy are also discussed below under separate headings.

Hypertension may be discovered because of adverse vascular events, especially in the eyes, brain, kidneys, or heart, but is more often asymptomatic and only discovered on routine measurement of blood pressure. Once diagnosed, decisions have to be made about the need for treatment. It is well-established that hypertension is a risk factor for the development of stroke, heart failure, and renal damage, and to a lesser extent ischaemic heart disease, and a reduction in blood pressure is generally beneficial, although mortality remains higher than in non-hypertensives.[15] However, it is important to assess hypertension in the context of overall cardiovascular risk, including the presence of target-organ disease, such as left ventricular hypertrophy or renal disease, associated conditions such as atherosclerosis or diabetes, and other risk factors such as hyperlipidaemia or smoking. Treatment of hypertension may involve both non-pharmacological and pharmacological interventions to reduce blood pressure, as well as assessment and treatment of any other cardiovascular risk factors (see Cardiovascular Risk Reduction, p. 1246.1); any co-existing diseases should also be treated. Differences in the detail of guidelines on the management of hypertension reflect varying judgements on the justification for intervention and the relative risks and benefits of different treatments.

Non-pharmacological treatment. Adopting a healthy lifestyle is beneficial for all individuals, and any patient with raised blood pressure should be encouraged to make lifestyle changes that will reduce their cardiovascular risk. Some of these changes may also reduce blood pressure,[12,16,17] and in those who are at low overall risk no other treatment may be needed; a trial of non-pharmacological treatment is recommended in most patients before starting drug therapy,[1,2,4,5] but should not unnecessarily delay treatment, especially if the patient is at high risk.[1,5] Interventions that have been shown to reduce blood pressure include:

- reduction in excess weight
- reduction in excess alcohol consumption
- reduction in sodium intake
- adequate exercise
- reduced fat intake
- increased fruit and vegetable consumption

Other interventions that have been tried, but with less evidence of benefit, include:

- increased intake of potassium, magnesium, and calcium
- increased polyunsaturated fat intake with reduced saturated fat intake
- relaxation therapies for stress reduction.

These lifestyle changes may also be promoted in the population as a whole, or in individuals most likely to develop hypertension, in strategies for the *primary prevention* of high blood pressure.[18]

Pharmacological treatment. The main decisions in drug treatment relate to the blood pressure at which therapy should be begun, the target blood pressure, and the most appropriate drug regimen to use. Controversies exist in all these areas.

When to intervene with antihypertensive drugs depends on factors including both the measured blood pressure and the overall cardiovascular risk.

- Patients with grade 3 hypertension (180/110 mmHg or higher) should receive prompt drug treatment.[1,2,5]
- In grade 2 hypertension, drug therapy is indicated if blood pressure remains at 160/100 mmHg or higher after a period of lifestyle modification, which varies depending on the overall level of risk;[1,2,5] prompt drug therapy is advised for those at high or very high risk.[5]
- For patients with grade 1 hypertension, the need for treatment is less well established; those with associated risk factors should be given drug therapy if lifestyle modification is inadequate, but some guidelines suggest that antihypertensives are not indicated in those at lower risk,[1] or state that priority should be given to those at highest risk.[4]
- Lower thresholds may apply in patients with renal disease or diabetes (see below), but whether there is any benefit in treating uncomplicated patients with prehypertension is controversial.[19]

For *elderly patients* (over 60 years) there is evidence[20,21] to support the benefit of treating hypertension, including isolated systolic hypertension,[22] and this applies up to at least 80 years of age, suggesting a strict age limit to drug therapy is inappropriate. Guidelines therefore generally recommend that treatment decisions should not be based on age, although slower titration of drugs has been suggested[5] in older patients since they may be more susceptible to adverse effects. In the very old (those over 80 years) the benefit of starting therapy is less clear,[21-23] although a study[24] in patients aged 80 years and over found a reduction in mortality; those already being treated should continue.[1,5]

Target blood pressures are also controversial. There has been concern that over-aggressive reduction of diastolic pressure might increase the risk of ischaemic heart disease,[25,26] although a meta-analysis[27] suggested that any increased mortality at low blood pressures was not linked to antihypertensive therapy but may have been due to poor health as a cause of low blood pressure. The HOT study[28] found that effective control to maintain the diastolic pressure below 90 mmHg (at about 85 mmHg) reduced the rate of cardiovascular events, but lower pressures (of around 70 mmHg) did not provide any further benefit, while a meta-analysis[29] found no evidence of a threshold for treatment benefit down to a blood pressure of at least 115/75 mmHg. Targets for systolic blood pressure are also unclear, although a study[30] in non-diabetics found that tight control (target systolic pressure below 130 mmHg) was better than usual control (target below 140 mmHg). Target blood pressures of below 140/90 mmHg[2,5] or below 140/85 mmHg[1] are now recommended; lower targets may be considered if tolerated by the patient, particularly in patients at high risk.[5] A lower target of below 130/80 mmHg has also been suggested for patients with established ischaemic heart disease,[31] and lower targets may also be appropriate in diabetics and patients with renal disease (see below).

The drug regimen may include drugs with differing pharmacological actions; the antihypertensive mechanism is not fully understood in all cases. Historically, thiazide diuretics and beta blockers have been the mainstay of drug therapy for hypertension, but calcium-channel blockers, ACE inhibitors, angiotensin II receptor antagonists, and alpha blockers are now also widely used.

Choice of initial therapy depends on antihypertensive efficacy, safety, and long term effects on morbidity and mortality.[32,33] Studies such as the TOMHS[34] (comparing chlortalidone, acebutolol, amlodipine, enalapril, and doxazosin), and a similar study[35] (comparing hydrochlorothiazide, atenolol, diltiazem, captopril, prazosin, and clonidine), have shown that the main types of antihypertensive drug reduce blood pressure to a similar extent and in a similar proportion of patients, although the response may also depend on individual factors such as age[36] and race.[37,38] Angiotensin II receptor antagonists also effectively reduce blood pressure. However, it is now generally acknowledged that a single drug is unlikely to control blood pressure adequately and most patients will require more than one

drug to reach their treatment target. Tolerance of the drug groups is also similar, although there has been concern about the metabolic effects of thiazides and beta blockers. Alpha blockers (specifically doxazosin[39]) have been associated with an increased risk of heart failure, which may limit their use. The safety of short-acting dihydropyridine calcium-channel blockers has also been questioned, and they are no longer generally recommended for hypertension (see Effects on Mortality under Adverse Effects of Nifedipine, p. 1450.2); long-acting dihydropyridines, however, are of established benefit.[40]

All of the main drug groups are therefore established as effective antihypertensives, but their effects on long-term mortality and morbidity have been less clear. The different drug groups have differing effects on several surrogate outcomes, such as left ventricular hypertrophy[41] and endothelial dysfunction,[42] but the clinical significance of this has not been established, although there is some evidence[43] that regression of left ventricular hypertrophy is associated with a reduction in clinical events. Diuretics (particularly thiazides) and beta blockers were the first drugs to show an effect on mortality in long-term outcome studies and have therefore been preferred for initial therapy. However, long-term studies with other drug groups have now been performed, and have generally shown comparable effects on mortality and morbidity. A meta-analysis[44] concluded that there was little difference in overall cardiovascular outcomes for regimens based on ACE inhibitors, angiotensin II receptor antagonists, calcium-channel blockers, beta blockers, or diuretics, suggesting the major benefit of treatment related to reduction of blood pressure rather than to specific properties of the individual drugs. However, cause-specific outcomes did differ between the drug groups, and some large studies have also questioned the benefit of certain regimens. A study[45] (ALLHAT) comparing treatment based on a diuretic (chlortalidone), an ACE inhibitor (lisinopril), or a calcium-channel blocker (amlodipine), found no differences in all-cause mortality, but another arm of the study based on an alpha blocker (doxazosin) was stopped early due to an excess of heart failure in this group.[39] Another study[46] (ASCOT-BPLA) was also stopped early when results suggested that a regimen of amlodipine with addition of perindopril if required, prevented major cardiovascular events more effectively than a regimen of atenolol with addition of a thiazide if required. However, blood pressure reductions were greater in patients receiving the amlodipine-based regimen, making the significance of the results unclear. Subsequent meta-analyses[38,47,48] have, however, found that beta blockers may be less effective than the other major groups of antihypertensives, particularly in older patients,[38] and their role in initial therapy has therefore been questioned.

In general, guidelines acknowledge that lowering blood pressure appears to be more important than which drug is chosen for initial therapy, and that most patients will require a combination of drugs, making the initial choice less important. Thiazide diuretics, ACE inhibitors, angiotensin II receptor antagonists, or calcium-channel blockers may all be used, and choice should take into account individual patient characteristics, including age, ethnicity, contra-indications or compelling indications for specific drugs, adverse effects, and relative cost-effectiveness.[1,2,4,5] Strict guidance is therefore not generally given, although for uncomplicated patients US[2] and international[4] guidelines recommend *thiazide diuretics* as first-line, whereas in the UK[3] diuretics or *calcium-channel blockers* are recommended for older patients (55 years or over) and black patients, while in younger, non-black patients *ACE inhibitors* or *angiotensin II receptor antagonists* are preferred. Compelling indications in all the guidelines include the use of ACE inhibitors or angiotensin II receptor blockers in patients with nephropathy, diuretics or calcium-channel blockers in elderly patients, and beta blockers in patients who have had a myocardial infarction. The use of *beta blockers* as initial therapy in patients who have not had a myocardial infarction remains controversial; UK guidelines[3] issued since the publication of ASCOT-BPLA suggest that they should be avoided except in younger patients who are unable to take ACE inhibitors or angiotensin II receptor antagonists and in women of child-bearing potential, whereas more recent European guidelines[5] allow their use in all patients other than those at risk of metabolic effects.

Having decided what drug to use, treatment is started at the lowest recommended dose. If this is ineffective or only partially effective the dose may be increased (except in the case of thiazide diuretics where there is generally no additional benefit, but more adverse effects); alternatively another first-line drug may either be substituted (*sequential therapy*) or added (*combination therapy*). Two-drug combinations will control blood pressure in a higher proportion of patients and may be necessary in most patients to achieve optimal levels. Combination therapy also allows lower doses of the individual drugs to be used with a consequent reduction in adverse effects. For the four main drug groups, the effect of combining two drugs from different groups is roughly additive, and is greater than the effect of increasing the dose of a single drug.[49] Initial treatment with a low-dose combination may be considered in some patients,[2,5,50] and use of a stepped-care treatment algorithm based on this approach has been reported[51] to improve hypertension control.

The most effective combinations involve drugs that act on different physiological systems. Appropriate combinations therefore include:

- diuretic plus beta blocker
- diuretic plus ACE inhibitor
- diuretic plus angiotensin II receptor antagonist
- calcium-channel blocker plus ACE inhibitor
- calcium-channel blocker plus angiotensin II receptor antagonist
- calcium-channel blocker (except verapamil) plus beta blocker

Alpha blockers may be used with any of the other classes but are usually reserved for third-line therapy unless specifically indicated for another reason. A three-drug combination is often required, especially in severe hypertension. In patients who maintain an elevated diastolic blood pressure despite triple therapy the possibility of secondary hypertension should be considered, although factors such as non-compliance, NSAID use, or alcohol abuse may contribute to resistance.[7,8,52]

Other classes of antihypertensive drugs that are sometimes used include: centrally acting drugs such as clonidine, methyldopa, and the less sedating moxonidine; direct-acting vasodilators such as hydralazine and minoxidil; the aldosterone antagonist, eplerenone; and the renin inhibitor, aliskiren. Older drugs like the adrenergic neurone blocker guanethidine and the rauwolfia alkaloid reserpine are rarely recommended now. Endopeptidase inhibitors and endothelin antagonists are among various drug groups that are under investigation. Hypertension vaccines against angiotensin II are also being developed.

Withdrawal of drug treatment. It has been standard teaching that drug treatment for hypertension is continued indefinitely, but there have been some reports of successful withdrawal in selected patients.[53-55] If this is attempted, blood pressure must be closely monitored and lifestyle measures should be continued indefinitely.[3,5]

Hypertension in children. Hypertension is less common in children than in adults but the incidence may be increasing in parallel with an increase in childhood obesity,[56] and guidelines for diagnosis and management have been published.[57] Lifestyle measures are the mainstay of treatment, particularly in children with less severe hypertension and no evidence of target organ damage, since the benefits of treatment and the risks of long-term drug therapy are not established. However, drug treatment may be required in some cases and should generally be based on individual patient characteristics.

Hypertensive crises. Patients with severe hypertension may be divided into those in whom there is evidence of rapid or progressive CNS, cardiovascular, or renal deterioration (hypertensive *emergencies*) and those with no evidence of target-organ damage (urgent hypertensive crises or hypertensive *urgencies*).[2,58-62] In the former case the goal is a reduction in mean arterial blood pressure by 25%, or a fall in diastolic blood pressure to 100 to 110 mmHg, over a period of several minutes to several hours depending on the clinical situation; intravenous therapy is often required although oral therapy may be adequate. In the latter case a drastic reduction in blood pressure is inappropriate and oral therapy is preferred, with the aim of a reduction in blood pressure over several hours to days. In both situations too rapid a reduction of blood pressure may be detrimental and may lead to cerebral infarction and blindness, to deterioration in renal function, and to myocardial ischaemia.

If *oral treatment* can be given and there is no evidence of ongoing target-organ damage, beginning standard antihypertensive therapy is appropriate, although the patient should be closely monitored. Short-acting drugs with a rapid effect are often used, although caution is required since they may lower blood pressure abruptly. Drugs that have been recommended[2,60,61] include the beta blocker labetalol, the centrally acting drug clonidine, the ACE inhibitor captopril, and the alpha blocker prazosin, (especially when there are increased circulating catecholamines); calcium-channel blockers such as amlodipine, felodipine, and isradipine may also be suitable.[61] Diuretics may have a role in volume overload but many patients with hypertensive crises are volume depleted and diuretics may therefore be less appropriate in the initial stages. Nifedipine and captopril have been given sublingually for a faster onset, but there appears to be no clearly defined clinical advantage for this route and it is generally considered that nifedipine should not be used.[2,59,61,63]

In the emergency situation, when *parenteral therapy* is required, choice of therapy depends on concomitant clinical conditions.[58,59,61,64,65] Sodium nitroprusside given by intravenous infusion has most often been the drug of choice, but close monitoring is required as toxicity may be a problem.[2,58,60,61] Intravenous labetalol, nicardipine, or fenoldopam are suitable alternatives in most situations, and intravenous clevidipine may also be used. Other drugs that are used in specific indications include glyceryl trinitrate (in patients with coronary ischaemia), phentolamine (in phaeochromocytoma and other states associated with catecholamine excess such as the MAOI-tyramine interaction), enalaprilat (in acute heart failure), esmolol (particularly in aortic dissection or perioperatively), and hydralazine (in eclampsia, but see Hypertension in Pregnancy, below). Trimetaphan[59] and urapidil[61] have also been used.

Hypertensive emergencies in children are managed similarly to those in adults.[57,66,67]

Hypertension during surgery. Containing antihypertensive drugs in patients about to undergo surgery is not only safe but probably best up to and including the morning of surgery.[2,68]

Perioperative hypertension may occur as a result of surgery and often needs to be controlled with parenteral antihypertensives since the oral route may not be available. The parenteral drug of choice is often sodium nitroprusside; others include glyceryl trinitrate (especially after coronary artery bypass), labetalol, enalaprilat, esmolol, fenoldopam, nicardipine, and clevidipine; diazoxide, hydralazine, and methyldopa have also been used.[68-70]

Hypertension in diabetic patients. Hypertension is twice as common in diabetic as in nondiabetic subjects, and up to 50% of patients with type 2 diabetes mellitus become hypertensive.[71,72] The reasons proposed for this increased prevalence are controversial, but insulin resistance has been implicated.[73] In addition to being a major risk factor for atherosclerosis in large blood vessels, hypertension in diabetes appears to contribute to small vessel disease and is a risk factor for diabetic nephropathy and possibly for diabetic retinopathy. The UK Prospective Diabetes Study (UKPDS) Group has reported[74] that tight control of blood pressure (with a target of below 150/85 mmHg) reduces the risk of diabetes-related death and diabetic complications, including diabetic retinopathy, in type 2 diabetics.

The threshold for intervention with drug treatment may be lower in diabetic than in non-diabetic hypertensive patients and treatment targets are also lower. An initial target of 140/80 mmHg has been suggested,[1] while a target below 130/80 mmHg may be optimal and is recommended in many guidelines;[1,2,4,5,14,75] the lower target is particularly advised in type 1 diabetics with nephropathy.

All the main groups of antihypertensive drugs can be used in diabetics,[76] and most patients will require at least two drugs to achieve target blood pressure. ACE inhibitors (with angiotensin II receptor antagonists as an alternative) have been particularly recommended, as there is evidence of benefit in preserving renal function in patients with nephropathy. However, a systematic review[77] found limited evidence to support a specific renoprotective action in diabetics, independent of their effect on blood pressure. Diuretics and beta blockers have often been avoided because of their potential adverse effects on glucose and lipid metabolism, but may be used where indicated. In the UKPDS treatment with an ACE inhibitor (captopril) or a beta blocker (atenolol) was equally effective in reducing the risk of diabetic complications, although the ACE inhibitor appeared to be better tolerated.[78] Although there has been concern regarding the safety of calcium-channel blockers long-acting calcium-channel blockers have been shown to be a suitable choice.[79]

Hypertension and renal disease. Hypertension is closely linked with the kidney—the kidney may have a role in the pathogenesis of hypertension and it may also be a prime target of damage caused by hypertension. Both renal parenchymal disorders and renovascular disorders may be associated with hypertension. In the former, hypertension is often resistant to treatment and a combination of drugs including vasodilators, may be required. Antihypertensive therapy is also important in these patients since it may slow the decline in renal function in patients with nephropathy.[80] There is some evidence that ACE inhibitors may have a greater protective effect than other antihypertensives,[81,82] although this is not certain,[77] and they have been recommended as the basis of therapy (with angiotensin II receptor antagonists as an alternative), usually with a diuretic.[1,2,5] The effect of blood pressure reduction appears to be related to the degree of proteinuria, and studies have shown that patients with proteinuria higher than 1 g/day benefit from lower blood pressures.[82] Current guidelines[1,2,5] recommend a target blood pressure of below 130/80 mmHg in patients with nephropathy, with a lower target[1] of 125/75 mmHg in those with proteinuria of 1 g/day or over.

Renovascular hypertension has been defined as arterial hypertension resulting from obliteration or compression of one or both renal arteries, the commonest cause being stenosis due to atherosclerosis.[83] Underperfusion of the kidney leads to increased release of renin and a consequent

rise in blood pressure. However, the relationship between renovascular hypertension and renal artery stenosis is not clear cut; the two conditions may simply co-exist or hypertension may cause the stenosis rather than the other way round.[84,85]

Renovascular hypertension may be difficult to distinguish clinically, but carries a worse prognosis than essential hypertension, may be less amenable to treatment, carries a higher risk of progression to accelerated or malignant hypertension, and may result in irreversible ischaemic failure of the affected kidney.

Diagnostic methods used to detect renovascular hypertension include imaging studies such as ultrasonography and angiography, and functional tests such as the captopril test (see under ACE inhibitors on p. 1283.3 for further details); renal scintigraphy with and without ACE inhibition is also used.

The optimum treatment for renovascular hypertension is unclear. Blood pressure in renovascular hypertension can often be controlled by antihypertensive drugs, but for patients with renal artery stenosis, angioplasty has been widely used, with the aim of preserving renal function. However, there is little evidence that angioplasty is superior to medical therapy; control of blood pressure has been improved in some studies,[85,86] especially in patients with bilateral stenosis, but this finding was not supported by a more recent study,[87] and renal outcomes are similar with either approach. Renal function may deteriorate in patients given antihypertensives since blood flow to the kidney is reduced; however, sudden restoration of blood flow by angioplasty may also have deleterious effects. Reduced blood flow is a particular concern with the use of ACE inhibitors or angiotensin II receptor antagonists, since renal perfusion may be dependent on angiotensin II in patients with renal artery stenosis, and renovascular hypertension is often considered a contra-indication to the use of these drugs, particularly in patients with bilateral stenosis or stenosis affecting the only functioning kidney. However, they may be required in patients with resistant hypertension,[88] although they must be used cautiously and in low doses, with careful monitoring of renal function (see Precautions for ACE inhibitors, p. 1287.2).

Hypertension in pregnancy. Hypertension in pregnancy may be life-threatening to both mother and fetus. It may be pre-existing or may develop for the first time during pregnancy. Definitions vary, but hypertension presenting before 20 weeks of gestation generally continues long-term and is considered chronic hypertension. After the twentieth week (gestational hypertension) it may be transient (pregnancy-induced hypertension), chronic, or represent pre-eclampsia. Gestational hypertension is usually defined as a blood pressure of 140/90 mmHg or more on at least two occasions in a previously normotensive woman; it is considered transient hypertension if the blood pressure has returned to normal limits by the twelfth week postpartum. In pre-eclampsia, increased blood pressure occurs with proteinuria; abnormal coagulation, liver dysfunction, and oedema may also be present. Pre-eclampsia may progress to eclampsia, a convulsive phase.

Recommendations about the treatment of ***gestational*** or ***pre-existing hypertension*** during pregnancy have been controversial. Most women with chronic or transient hypertension will have grade 1 or grade 2 hypertension and a low risk of cardiovascular complications during the short period of pregnancy, and the benefits of treatment in such patients are not established. It is usually agreed that blood pressures of 170/110 mmHg or above should be treated as an emergency,[5,89] but recommendations for management of lower blood pressures are less clear. Although treatment of patients with blood pressures of 140/90 mmHg or above has been suggested,[5,89,90] there is little evidence that this improves maternal or neonatal outcomes, although the incidence of severe hypertension is reduced.[91] Some guidelines allow withdrawal of antihypertensives in pregnant women with pre-existing hypertension, with treatment restarted if the blood pressure exceeds specific threshold values.[2,90,92] However, women with mild hypertension are at an increased risk of developing pre-eclampsia, regardless of whether they receive antihypertensives, and should be closely monitored.

For women with *mild to moderate hypertension* in whom the decision is made to give antihypertensives, optimum choice of drug therapy is unclear. Women with pre-existing hypertension usually continue their existing treatment, although ACE inhibitors and angiotensin II receptor antagonists are contra-indicated in pregnancy and should be changed to an alternative. For gestational hypertension, methyldopa or beta blockers have generally been preferred, although there is little evidence that outcomes differ for any of the main drug groups.[91] A systematic review[93] found no evidence of substantive benefits with beta blockers, but another review[91] found that they reduced the risk of severe hypertension more effectively than methyldopa. Methyldopa has the advantage of reassuring long-term safety results in the infant, whereas there have been concerns about fetal growth retardation with beta blockers, particularly with atenolol.[94-96] Nifedipine[90,97] or hydralazine[90] may also be used. Diuretics are not generally recommended for controlling hypertension in pregnancy because of the theoretical risk of exacerbating the volume depletion of pre-eclampsia; however, they appear to be safe in practice and may be used if necessary.[1,92]

For patients with ***pre-eclampsia***[90,98-102] the definitive *treatment* is delivery (although pre-eclampsia may also develop post partum[101]), but where the maternal condition allows this is usually delayed to allow fetal maturation. Antihypertensive therapy is therefore given to reduce the risk of maternal complications, and prophylactic anticonvulsants, particularly magnesium sulfate, may also be given in those at high risk for eclampsia (see p. 511.1). Evidence to guide choice of antihypertensive in severe hypertension is limited.[103] Oral therapy may be appropriate, in which case methyldopa or beta blockers (preferably labetalol[5,101,104]) are usually first-line; calcium-channel blockers such as nifedipine are an alternative. However, in acute pre-eclampsia or if delivery is imminent, parenteral antihypertensives are required. Intravenous hydralazine is widely used,[2,101,104] although there is some evidence that it may be less effective and have more adverse effects than other drugs,[105] and some guidelines recommend that it should be avoided.[5] Oral or intravenous labetalol, intravenous nicardipine, and oral nifedipine are also used, and sodium nitroprusside may be required in some patients.[2,5,102,104] Glyceryl trinitrate may be used if there is pulmonary oedema.[5] Other drugs that have been given include diazoxide and clonidine.

Prevention of pre-eclampsia. Several interventions have been studied for the prevention of pre-eclampsia,[106] of which low-dose aspirin has the most evidence of benefit. Although the results of individual studies with aspirin have been mixed, meta-analyses[107,108] have concluded that it produces modest reductions in the risk of developing pre-eclampsia and its complications (such as fetal death and premature delivery), with the greatest benefits seen in those deemed at highest risk. In the UK, NICE[104] recommends that pregnant women with 2 or more moderate risk factors (first pregnancy, age of 40 years or over, pregnancy interval greater than 10 years, BMI 35 kg/m^2 or over, family history of pre-eclampsia, or multiple pregnancy) or 1 or more high risk factor (hypertension in previous pregnancy, chronic kidney disease, auto-immune disease including antiphospholipid syndrome, diabetes, or chronic hypertension) should take oral aspirin 75 mg daily from week 12 of pregnancy until birth.

Other drugs that have been tried in the prevention of pre-eclampsia include nitric oxide donors, progesterone, diuretics, and low-molecular-weight heparins, but evidence for each is lacking and NICE[104] does not recommend them for this purpose. Calcium supplementation has also been shown[109] to reduce the risks of pregnancy-induced hypertension and pre-eclampsia, although its role is not yet established. Preliminary evidence suggesting that supplementation with antoxidants such as vitamins C and E might be beneficial has not been confirmed.[110,111]

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Ischaemic Heart Disease

Ischaemic heart disease (coronary heart disease; coronary artery disease) covers a spectrum of disorders caused by an inadequate myocardial blood supply, ranging from stable angina pectoris to acute myocardial infarction. It is usually associated with atherosclerosis (p. 1250.2) of the coronary arteries.

In *stable angina pectoris* (below), atherosclerotic plaques cause a chronic restriction to blood flow. Myocardial blood supply is adequate at rest, but ischaemia and pain occur during exercise or in other situations where myocardial oxygen demand increases; however, there is no permanent damage to the heart muscle.

In *acute coronary syndromes* (below), rupture of a plaque leads to thrombosis and acute obstruction of the artery, and ischaemia and pain occur at rest. If the blockage is transient there is no permanent damage to the heart (unstable angina); prolonged blockage may lead to myocardial necrosis, ranging from non-ST elevation to acute ST-elevation myocardial infarction. Acute coronary syndromes in which there is no ST elevation (unstable angina and non-ST elevation myocardial infarction) are treated similarly and are described under angina pectoris (below); acute ST-elevation myocardial infarction is described separately (see p. 1257.1).

Acute coronary syndromes

Acute coronary syndromes are part of the spectrum of ischaemic heart disease above and include unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and acute ST-elevation myocardial infarction (STEMI). They are usually caused by rupture of an atherosclerotic plaque in one of the coronary arteries. Exposure of the plaque core leads to release of tissue factor and subsequent thrombosis, which obstructs the artery, restricting or preventing blood flow and leading to ischaemia. In unstable angina, blockage of the artery is transient and there is no permanent damage to the heart, whereas more prolonged obstruction causes myocardial necrosis (myocardial infarction). In each case, rapid resolution of thrombosis is necessary to minimise myocardial damage and all forms of acute coronary syndrome are emergency situations. Treatment strategies are the same for unstable angina and NSTEMI, and these are discussed under Angina Pectoris (below); acute STEMI is managed similarly, but additional therapies are also indicated and these are discussed under Myocardial Infarction (p. 1257.1).

Angina pectoris

Angina pectoris is a syndrome that arises from an inadequate myocardial oxygen supply (myocardial ischaemia) and is part of the spectrum of coronary or ischaemic heart disease. Myocardial oxygen supply depends upon coronary blood flow, which normally increases to meet increased oxygen demands. Ischaemia occurs when blood flow either cannot be increased, or is reduced; this may be due to a fixed obstruction in the coronary arteries, vasoconstriction, thrombus formation, or platelet aggregation. The main symptom is transient precordial discomfort ranging from a mild ache to severe pain. Some patients may also have dyspnoea, nausea, sweating, and left arm discomfort.

Three main types of angina have been described: stable angina; unstable angina; and Prinzmetal's angina. Although these are discrete groups, stable angina may become unstable, and Prinzmetal's angina may co-exist with stable or unstable angina.

Stable angina (effort angina) is usually brought on by exertion and relieved by rest. It is often called chronic stable angina and as the name implies the frequency, intensity, and duration of the attacks are stable. The main underlying disorder is coronary atherosclerosis causing a fixed obstruction in one or more coronary arteries. While the restricted coronary blood flow is still adequate for oxygenation of the unstressed heart, it is not capable of being increased to meet the increase in myocardial oxygen demand that may occur during exercise, cold exposure, emotional stress, or after eating.

Unstable angina and the related condition **non-ST elevation myocardial infarction** are acute coronary syndromes intermediate between stable angina pectoris and acute myocardial infarction. There are 3 main presentations:

- angina that presents from the beginning as severe and frequent attacks
- an increase in the frequency, intensity, and/or duration of previously stable angina, often with diminishing responsiveness to sublingual nitrates (crescendo angina)
- recurring or prolonged angina at rest

As in stable angina, the underlying disorder is usually coronary atherosclerosis, but the decreased coronary artery blood flow is usually caused by disruption of an atherosclerotic plaque, which leads to platelet adhesion and aggregation, thrombus formation, and vasoconstriction. This may result in partial occlusion of one or more coronary arteries, and the coronary blood flow can be so restricted that it does not meet the oxygenation demands of the unstressed heart. However, in unstable angina the ischaemia is not severe enough to cause myocardial damage, whereas in non-ST elevation myocardial infarction some degree of myocardial necrosis occurs, although to a lesser extent than in acute myocardial infarction. Patients with the different acute coronary syndromes may present similarly and definitive diagnosis is only possible retrospectively once the results of biochemical measurements such as cardiac troponins or cardiac enzymes are available or the ECG shows evidence of new Q waves. However, patients without ST-elevation on the presenting ECG rarely develop Q waves and are managed as for unstable angina; those with ST-elevation should be treated as for acute myocardial infarction (p. 1257.1). Patients with unstable angina are at an increased risk of sudden death or progression to myocardial infarction, and those with rest pain are at the greatest risk.

Prinzmetal's angina (variant angina) is a rare form of angina caused by coronary vasospasm, although it is often associated with atherosclerosis. It occurs spontaneously at rest and with greater frequency during the night or early hours of the morning. It is associated with transient ST-segment elevation and carries a risk of progression to myocardial infarction. Prolonged vasospasm may also lead to ventricular arrhythmias, heart block, or death.

Patients who have **angina with normal coronary arteries** as shown by angiography may have microvascular dysfunction or altered cardiac pain perception. Prognosis is generally better than in other forms of angina although quality of life may be significantly impaired.[1,2]

In addition to the types of angina described above periods of **silent myocardial ischaemia** (asymptomatic transient myocardial ischaemia) in which there is no anginal pain have been identified during ECG monitoring. In some patients all ischaemic episodes are asymptomatic. However, asymptomatic ischaemic episodes also occur in patients with angina and seem to be more common than symptomatic episodes. It is not clear why some episodes of ischaemia are symptomatic while others are not.

Treatment depends on the type of angina and involves symptomatic management of acute anginal pain, antithrombotic therapy to prevent progression to myocardial infarction, and long-term management both to prevent angina attacks and to reduce the risk of other cardiovascular events. Anti-anginal treatment is used in both stable and

unstable angina and is described in more detail below; it includes drug therapy (nitrates, beta blockers, calcium-channel blockers, and potassium-channel openers), and non-pharmacological interventions. Antithrombotics are used in unstable angina and include anticoagulants and antiplatelet drugs (see Treatment of Unstable Angina, below). Long-term measures to reduce cardiovascular risk are important in all patients, even when symptoms are controlled, and include antiplatelet therapy (which should be given to all patients unless contra-indicated), lipid lowering therapy, and lifestyle changes; these interventions are discussed in more detail under Cardiovascular Risk Reduction, p. 1246.1. Patients with ischaemic heart disease who undergo non-cardiac surgery are at risk of complications resulting from perioperative myocardial ischaemia. Perioperative use of beta blockers is controversial but may be considered in high-risk patients (see Cardiovascular Risk Reduction under Uses of Beta Blockers, p. 1317.2); and use of alpha$_2$ agonists such as mivazerol or clonidine may be considered.[3,4] There is also some evidence that statins are of benefit,[3] and perioperative use has been recommended in high-risk patients.[4]

Anti-anginal drugs act in a variety of ways. Glyceryl trinitrate and other organic *nitrates* have a vasodilator effect with venodilatation predominating over dilatation of the arterioles. Dilatation of veins decreases venous return as a result of venous pooling and lowers left ventricular diastolic volume and pressure (together termed a reduction in preload). The smaller or less important dilatation of arterioles reduces both peripheral vascular resistance and left ventricular pressure at systole (termed a reduction in afterload). The consequence of these effects is a reduction in myocardial oxygen demand. Also the vasodilator effect improves regional coronary blood flow to ischaemic areas, and alleviates coronary spasm. *Beta blockers* cause a slowing of the heart rate and reduction in contractility and therefore reduce myocardial oxygen demand. *Calcium-channel blockers* reduce the work of the heart by dilating peripheral arteries, and diltiazem and verapamil also slow the heart rate. Calcium-channel blockers also act on the coronary circulation preventing spasm. *Potassium-channel openers* act as coronary vasodilators, while nicorandil also has a nitrate component that may contribute to its effect. Newer drugs include ivabradine, a selective *sinus node I_f inhibitor*, which acts similarly to beta blockers by lowering heart rate, and ranolazine, the action of which is unclear but may depend on its effects as a *late sodium channel inhibitor*. The *xanthine oxidase inhibitor* allopurinol has been investigated for its apparent anti-ischaemic effects.[5]

The main ***non-pharmacological treatments*** used are *percutaneous coronary interventions* (PCI), such as balloon angioplasty and stenting, and bypass surgery. Balloon angioplasty is a catheter-based technique that mechanically dilates the occluded artery; coronary stents are used to prevent recoil and to reduce the incidence of restenosis. Nitrates and calcium-channel blockers may be given to alleviate coronary spasm due to the procedure. Coronary artery *bypass surgery* uses a vein or artery graft to bypass the occlusion. Both PCI and bypass surgery abolish or reduce episodes of angina in most patients but symptoms commonly recur over a period of time due to restenosis. Adjunctive therapy is therefore needed both to prevent short-term thromboembolic complications and long-term reocclusion (see Reperfusion and Revascularisation Procedures, p. 1259.2). Other non-pharmacological methods that have been tried in refractory angina include enhanced external counterpulsation, transmyocardial revascularisation, and spinal cord stimulation;[6-8] gene- and stem cell-based therapies are also under investigation.[7]

Treatment of stable angina. Management of the patient with stable angina[7,9-15] mainly involves the use of anti-anginal drugs, antiplatelet therapy, and measures to reduce cardiovascular risk. Non-pharmacological measures may also be considered. Any contributory conditions, such as anaemia, should be identified and treated.

Treatment of *infrequent* angina episodes (less than about 2 attacks per week) usually consists of glyceryl trinitrate given when required, generally sublingually; alternatively, a buccal tablet or spray formulation may be used. Isosorbide dinitrate, in the form of sublingual tablets or spray, may be used, although it has a slower onset of action than glyceryl trinitrate. Glyceryl trinitrate in sublingual or buccal forms may also be used before an activity or circumstance that might precipitate an attack.

When episodes occur *more frequently*, sublingual glyceryl trinitrate, at least on its own, may no longer be appropriate, and regular symptomatic treatment has to be considered. Choice depends upon patient characteristics and any concurrent medical conditions.

- Beta blockers are the mainstay of therapy. They are generally considered to be first-line treatment if sublingual glyceryl trinitrate is not adequate since they provide effective symptom control and have also been shown to reduce mortality in certain patients with high cardiovascular risk.[9,10,13] The different beta blockers have similar efficacy in terms of symptom control, but those with beta$_1$-selectivity may be preferred;[13] beta blockers with intrinsic sympathomimetic activity may be less effective for secondary prevention after myocardial infarction and are not recommended.[16]
- Calcium-channel blockers appear to have similar efficacy to beta blockers in terms of symptom control and cardiovascular outcomes[17] and long-acting calcium-channel blockers may be used as alternative first-line therapy,[9,13] particularly in patients unable to tolerate beta blockers. Both dihydropyridines (such as nifedipine) and rate-limiting calcium-channel blockers (diltiazem and verapamil) may be used, with choice depending on individual patient characteristics and adverse effects. Short-acting preparations of nifedipine have been associated with increased mortality and are not recommended (see Effects on Mortality under Adverse Effects of Nifedipine, p. 1450.2).
- Regular nitrate therapy is a further alternative, and includes modified-release forms of glyceryl trinitrate, for example transdermal patches, and the long-acting nitrates such as isosorbide dinitrate or isosorbide mononitrate; it may be particularly suitable in patients with left ventricular dysfunction. Reduced efficacy or tolerance occurs, particularly with nitrate preparations that produce sustained plasma concentrations, and dosage regimens including a nitrate-free period should be used (see Nitrate Tolerance, p. 1394.1).
- Nicorandil, a potassium-channel opener and nitrate, is another alternative that can be used for monotherapy.[10,13] Ivabradine may be used in patients with normal sinus rhythm and a contra-indication or intolerance for beta blockers. Ranolazine is generally used as an adjunct to other anti-anginals but may also be used first-line. Other drugs that are sometimes used include trimetazidine, which has anti-ischaemic effects through a metabolic action and may be of benefit in refractory angina, and the nitrovasodilator molsidomine. Several other vasodilators have also been used (see p. 1245.3) but no longer have an established role.

Where optimal therapy with a single drug fails to control symptoms, *combination therapy* may be used. There is additional benefit from nitrates with beta blockers, since nitrates can moderate the excessive effects that beta blockers may have in increasing left ventricular diastolic volume and pressure and in inducing bradycardia. Calcium-channel blockers may also be used with nitrates; the use of verapamil or diltiazem with a nitrate may be preferrable to nifedipine (or other dihydropyridine derivative) with nitrates as both nifedipine and nitrates cause reflex tachycardia, hypotension, and headaches. Use of beta blockers with calcium-channel blockers may also be of benefit,[18] although adverse effects can be a problem. Combined therapy with beta blockers and dihydropyridines or diltiazem improves exercise tolerance, but caution is needed with dihydropyridines in patients with heart failure (although amlodipine and felodipine appear to be safe) and with diltiazem in patients with conduction disorders. Verapamil should generally be avoided with beta blockers as the risk of conduction disorders is particularly high (see p. 1525.2). Nicorandil and ranolazine are both suitable for use with other anti-anginals, and ivabradine may be used with beta blockers if additional therapy is required.

Triple therapy using a nitrate, a beta blocker, and a calcium-channel blocker may sometimes be used although it is likely to be associated with more adverse effects.

Revascularisation procedures are the main non-pharmacological treatment used in stable angina, and have generally been reserved for patients who are not controlled by medical therapy.[13,19] Both PCI and coronary artery bypass surgery are suitable, and the choice between them is not entirely clear; a systematic review[20] and a meta-analysis[21] found that both procedures had similar effects on mortality, but the need for further revascularisation procedures was lower with bypass surgery. In general, PCI is preferred in patients with single-vessel disease, whereas bypass surgery is usual in patients with triple-vessel disease, disease of the left main coronary artery, or impaired left ventricular function.[22,23] Routine revascularisation of all patients has been investigated, but has no clear advantage over optimal medical therapy. Symptom control and quality of life may be higher with revascularisation,[24,25] but the benefit diminishes with time,[26] and recurrent angina after revascularisation may be challenging to treat.[8] Similarly, there appears to be little difference in terms of mortality or major cardiovascular events, although meta-analyses[27,28] have come to conflicting conclusions.

Treatment of unstable angina. Unstable angina and non-ST segment elevation myocardial infarction are managed similarly,[29-37] and are generally regarded as an emergency. Patients with a change in the pattern of previously stable angina or with recurring or prolonged angina at rest should therefore be hospitalised and rapidly assessed. Presenting symptoms are similar for all the acute coronary syndromes and a resting ECG should be obtained as a priority. This allows identification of patients with ST elevation, who require treatment for acute myocardial infarction (p.. 1257.1), and also allows initial risk stratification. In patients without ST elevation, the immediate priority is to control symptoms and reduce ischaemia; at the same time, the risk of progression to acute myocardial infarction should be assessed, and subsequent treatment planned as appropriate. *Initial treatment* involves antiplatelet drugs, anticoagulants, nitrates, beta blockers, and possibly calcium-channel blockers; additional antiplatelet therapy and urgent revascularisation may then be considered. Once the patient has been stabilised, underlying risk factors should be identified and treated, and long-term anti-anginal therapy may be given.

- Aspirin is routinely included in the initial treatment. It inhibits platelet aggregation and substantially reduces the incidence of myocardial infarction and death, although it has not been shown to reduce the number of ischaemic episodes or to relieve pain during the acute phase.
- The thienopyridines may be alternatives if aspirin is not tolerated; clopidogrel has fewer adverse effects than ticlopidine and is generally preferred. Dual antiplatelet therapy with clopidogrel and aspirin, both started immediately, may provide additional benefit[38] and has been recommended.[29,31,36,37] Further oral antiplatelet drugs that may be given include prasugrel (which may be used in patients undergoing planned PCI) and ticagrelor.[39]
- Anticoagulants are generally given in addition to aspirin to reduce thrombin generation and fibrin formation, although the optimum choice is unclear.[29]
  Both unfractionated heparin[40,41] and low-molecular-weight heparin[41] reduce the number of ischaemic episodes and major cardiovascular events during the acute phase, and also longer term. There is some evidence that low-molecular-weight heparins may be more effective than unfractionated heparin.[42-44] They may also be easier to use since low-molecular-weight heparins are given subcutaneously, whereas unfractionated heparin is generally given by continuous infusion for at least 48 hours,[30] although it may also be effective subcutaneously.[45] Reactivation of unstable angina may occur when treatment with either unfractionated[46] or low-molecular-weight heparin[47] is stopped; it is less likely in patients who are also taking aspirin,[46] and the risk may be reduced if treatment is stopped gradually. Guidelines[29,31,36] therefore allow the use of either unfractionated or low-molecular-weight heparin; unfractionated heparin may be preferred in patients undergoing bypass surgery[29] but either is suitable for PCI.[48]
  The pentasaccharide fondaparinux may be an alternative; it is at least as effective as enoxaparin[49] and may be the preferred option in patients for whom urgent PCI is not planned;[31,37] however, the incidence of catheter thrombosis was increased with fondaparinux in patients undergoing PCI[50] and unfractionated heparin should be given at the time of the procedure if PCI is performed.[29,31,37] For patients in whom early PCI is planned, the direct thrombin inhibitor bivalirudin is another alternative;[37] a study[51,52] in patients scheduled for PCI found that bivalirudin was as effective as heparin (unfractionated or low-molecular-weight) and the risk of bleeding was reduced.
- Nitrates are widely used although evidence from controlled studies is limited.[29,31] The initial treatment may be given intravenously to produce a fast response and to provide better dose control than can be achieved with other routes. Glyceryl trinitrate or isosorbide dinitrate are used. Generally, the intravenous route is only used during the acute phase, and once the patient is stabilised the infusion is withdrawn, usually within about 48 hours. Sublingual glyceryl trinitrate may be tried initially in patients with less severe symptoms.
- Treatment with a beta blocker is started during the acute phase to reduce myocardial oxygen demand. Oral treatment is usually preferred,[29,31] although the intravenous route may be used initially if required. Beta blockers with intrinsic sympathomimetic activity do not reduce resting heart rate and are not recommended.[16,29,30]
- Calcium-channel blockers may be added to therapy although they are generally reserved for patients with angina refractory to treatment with the above drugs, or in whom beta blockers are contra-indicated. However, calcium-channel blockers are the drugs of choice if the angina has a vasospastic aetiology, for example in Prinzmetal's angina. The choice of calcium-channel blocker is described under the treatment of stable angina above.
- Thrombolytics have been tried in unstable angina but do not improve outcome and are associated with an excess of bleeding complications; thrombolytic therapy is

therefore not recommended in patients with unstable angina.[29,30]

Once the initial therapy has been started patients at high or intermediate risk of progression to acute myocardial infarction, including those with recurrent ischaemia and those with raised cardiac troponins, should be assessed for *additional treatment*. Patients may be assigned to either an invasive or a conservative strategy. For those in whom an invasive strategy is chosen, early angiography is performed, with urgent revascularisation if appropriate. For those assigned to a conservative strategy and in patients at lower risk, angiography and revascularisation are only performed if medical therapy fails to control symptoms or if indicated by stress testing. Choice between the two remains controversial. Meta-analyses[53-55] have suggested that an invasive strategy is associated with a reduction in recurrent angina; there may also be a reduction in myocardial infarction and mortality in the longer term, although a later review[56] was unable to confirm this. Benefit appears greater in men and high-risk women,[57] and a conservative strategy may be appropriate in those at lower risk. Bleeding risk should also be considered.[58]

- Additional antiplatelet therapy with glycoprotein IIb/IIIa inhibitors may have a role in patients treated invasively or conservatively.[59] Benefit has been established in patients undergoing PCI (see Reperfusion and Revascularisation Procedures, p. 1259.2), but results in patients treated medically have been less consistent. A meta-analysis[60] of studies of glycoprotein IIb/IIIa inhibitors in unstable angina or non-ST elevation myocardial infarction found that they reduced the risk of death or myocardial infarction in patients who were not scheduled for early revascularisation, particularly in those at high risk of progression, such as those with raised troponins. However, many of the patients included in the analysis did receive revascularisation and the use of glycoprotein IIb/IIIa inhibitors in patients not undergoing intervention remains questionable.[29] Whether all the glycoprotein IIb/IIIa inhibitors are effective is also unclear. For patients not undergoing PCI, individual studies have reported beneficial results with: tirofiban and aspirin, alone[61] or with heparin;[62] with eptifibatide[63] in addition to standard therapy; but not with abciximab[64] in addition to aspirin and heparin. The benefit of treatment with glycoprotein IIb/IIIa inhibitors in patients already taking aspirin and clopidogrel is also unproven.[65,66]
- The use of statins early after admission for acute coronary syndromes has been recommended,[31] although meta-analyses have come to differing conclusions regarding their benefit. One analysis[67] found early use of statins had no effect on outcomes at 1 or 4 months after the initial event, but another[68] reported a reduction in cardiovascular events with statin therapy for 6 months or longer; benefit may be increased with high-dose regimens.[69]

After discharge, patients should take aspirin and a beta blocker indefinitely; clopidogrel should also be continued with aspirin for up to 12 months.[29,31,37] Statins should be continued, and other measures to reduce cardiovascular risk should be adopted. Anti-ischaemic drugs should be given as required; some patients are given a long-acting nitrate for long-term prophylaxis, although nitrates have not been shown to protect against subsequent cardiovascular events. Long-term oral anticoagulation has been used but is not routine therapy, and studies of warfarin with aspirin have given mixed results.[70,71] Prolonged use of low-molecular-weight heparins has been investigated,[72,73] but benefit has not been confirmed.

Treatment of Prinzmetal's angina. This should be treated like unstable angina with the addition of a calcium-channel blocker;[74] the selection of an appropriate calcium-channel blocker is described above under the treatment of stable angina. Beta blockers may increase the number of attacks of chest pain in patients with Prinzmetal's angina; this occurs especially with non-cardioselective beta blockers, which should be avoided. Once stabilised, maintenance should include a nitrate, or calcium-channel blocker, or both to protect against further spasm. Surgery may be considered in some patients.

Treatment of angina with normal coronary arteries. Symptomatic treatment with standard anti-anginal drugs is the mainstay in patients with angina but no evidence of coronary artery disease, although response varies. Beta blockers appear to be the most effective treatment and are usually considered first-line.[1,2]

Treatment of silent myocardial ischaemia. Silent myocardial ischaemia has been recognised as a potential risk factor for future cardiovascular morbidity and mortality and research has been undertaken to assess whether suppressing such episodes can improve long-term outcome. Although many of the therapies used in angina reduce the incidence of silent ischaemia it is not yet clear whether complete suppression of ischaemia affects prognosis.[75,76] Other studies have suggested that periods of ischaemia may protect the heart during subsequent myocardial infarction, although the clinical significance of this is unclear.[77,78]

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Myocardial infarction

Myocardial infarction is an acute coronary syndrome (p. 1254.2) in which necrosis of the heart muscle occurs as a result of acute ischaemia. In the initial stages, clinical symptoms are similar to those of unstable angina, but necrosis results in irreversible damage to the myocardium and long-term complications. The definition of myocardial infarction has changed considerably as the accuracy of detecting myocardial necrosis has improved. It is now considered that any degree of necrosis associated with clinical ischaemia should be defined as myocardial infarction,[1] since it is associated with a worse prognosis, although this definition includes many cases that would formerly have been classified as unstable angina. However, most evidence for treatment is based on earlier classifications, and in practice the diagnosis of acute myocardial infarction is generally made on clinical grounds, determined by characteristic symptoms, ECG changes (ST-segment elevation or bundle branch block), and changes in biochemical markers. The following discussion relates to the management of acute ST-elevation myocardial infarction (STEMI); the management of non ST-elevation myocardial infarction (NSTEMI) is discussed under Angina Pectoris (p. 1254.3).

Although the incidence may be declining, myocardial infarction remains a leading cause of mortality in western societies. The introduction of aspirin and reperfusion techniques has transformed the management of acute STEMI, but a significant number of sudden deaths occur within the first hour and therefore before treatment can be begun. While new therapies for the management of acute STEMI may further reduce in-hospital mortality, earlier recognition and presentation for treatment is important if survival is to be improved further, and primary prophylaxis in patients at risk or at a population level may also have a role (see Cardiovascular Risk Reduction, p. 1246.1). Patients who survive a myocardial infarction are at high risk for further cardiovascular events and often develop complications such as arrhythmias, left ventricular failure, persistent angina, and venous thromboembolism. Management of acute STEMI therefore involves both early treatment of the acute condition, and long-term therapy in survivors to reduce risk and to treat and prevent complications.

Myocardial ischaemia generally occurs as a result of coronary artery occlusion, usually due to thrombosis at the site of a recently ruptured atheromatous plaque; in a few patients coronary embolism or spasm, arteritis, spontaneous thrombosis, or a sudden severe rise in blood pressure, as in phaeochromocytoma, is responsible. The immediate consequence of coronary occlusion is myocardial ischaemia, which leads to impaired contractility, arrhythmias, and eventually myocardial cell death. The lay term 'heart attack' describes both sudden cardiac death and myocardial infarction. Sudden death is usually due to ventricular fibrillation and most patients who are resuscitated from ventricular fibrillation develop features of myocardial infarction or have coronary artery disease. In many cases myocardial infarction is asymptomatic or 'silent' and is only diagnosed due to characteristic changes on the ECG.[2]

Early management. Guidelines,[3-7] recommendations,[8] and reviews[9-14] emphasise the importance of rapid recognition and treatment of patients with acute STEMI. The initial symptoms are usually chest pain, breathlessness, and sweating. The chest pain is typically severe and resembles that of angina pectoris, being precordial with radiation to the neck, lower jaw, and left arm; chest pain lasting more than 20 minutes is generally considered to indicate myocardial infarction, although this is absent in many patients. Other signs and symptoms include nausea and vomiting, bradycardia, hypotension, and apprehension. The characteristic ECG changes confirm the clinical diagnosis and guide initial treatment; elevation of biochemical markers such as troponins and cardiac enzymes develops later and is useful for confirming the diagnosis and determining prognosis.

Those patients with myocardial infarction who develop ventricular fibrillation very quickly have a high mortality and require rapid provision of life support measures. Ventricular fibrillation is treated by defibrillation followed by adrenaline and possibly antiarrhythmics if defibrillation alone is unsuccessful (see Cardiac Arrest, p. 1268.3, for further details). Paramedic ambulance teams experienced in defibrillation and programmes aimed at educating the public in the basic techniques of cardiopulmonary resuscitation have an important role. Patients with suspected myocardial infarction should be admitted to hospital and where possible managed in a coronary care unit.

The immediate priority in patients with suspected acute STEMI is to give aspirin (as discussed below), to relieve symptoms such as pain and anxiety, and to confirm the diagnosis so that reperfusion can be achieved as rapidly as possible.

Symptom control. *Pain* should be relieved with an opioid analgesic, usually diamorphine or morphine given intravenously (see Myocardial Infarction Pain, p. 10.1); an antiemetic such as metoclopramide intravenously may also be necessary. Supplemental oxygen is also recommended, although this has been questioned (see under Precautions for Oxygen, p. 1805.2). An inhaled mixture of nitrous oxide and oxygen (Entonox) has sometimes been used to provide pain relief before arrival in hospital; sublingual glyceryl trinitrate or an alternative fast-acting nitrate may also be given. A benzodiazepine may be useful for *anxiety*.

Reperfusion. In patients with confirmed STEMI, the value of rapid reperfusion is well established. The extent of myocardial necrosis or recovery depends on the speed and completeness with which coronary blood flow can be restored,[15] and reperfusion should therefore be achieved as rapidly as possible. Two methods are commonly used: pharmacological reperfusion with intravenous thrombolytics, or mechanical reperfusion with percutaneous coronary intervention (PCI).

Thrombolytics are given intravenously to break up the thrombus or clot and restore the patency of the coronary artery, thereby limiting infarct size and irreversible damage to the myocardium.[16] Several large studies have established that thrombolytics can preserve left ventricular function and improve short-term and long-term mortality in patients with ECG evidence of ST elevation or new left bundle branch block (for more details see Ischaemic Heart Disease under Uses of Streptokinase, p. 1503.3). The greatest benefit is seen in those given thrombolytics early;[17] mortality is significantly reduced in those receiving treatment within 6 hours of symptom onset, and there is also benefit up to 12 hours. In those presenting later than 12 hours, the benefits are less well established; there has been some evidence of early excess mortality due to cardiac rupture in some patients given late thrombolytics. Although thrombolytics are often withheld in older patients, there is evidence of a benefit in those aged up to 85 years;[18] the possible increase in short-term mortality may be outweighed by improved longer-term outcomes.[19]

Streptokinase has been the most widely used thrombolytic, although fibrin-specific thrombolytics such as alteplase are increasingly preferred.[6,7,20] Overall efficacy appears to be similar for all the drugs available and factors such as cost, method of use, and contra-indications help to determine the choice. If streptokinase or anistreplase, so-called antigenic thrombolytics, have been used recently, non-antigenic drugs such as alteplase or urokinase should be given. However, choice of thrombolytic is probably less important than ensuring that one is given as soon as possible; recommendations are for a delay of no more than 30 minutes between first contact with the medical system (ambulance arrival or admission to hospital) and thrombolytic therapy,[3-5,7,20] and this should be given before admission where possible. Studies have found that prehospital thrombolysis is feasible and safe in various settings,[21] and it has also been shown to improve short-term[22] and long-term mortality.[23] However, there is some evidence that re-infarction rates are higher after prehospital thrombolysis,[24] and the optimum protocol remains unclear.

Percutaneous coronary interventions include balloon angioplasty, coronary stenting, and similar procedures. They are effective methods for reopening occluded coronary arteries,[25] including in elderly patients,[19] and can be used in acute coronary syndromes (primary PCI) and in stable coronary heart disease. PCI is also safe and effective in patients in whom thrombolytics have failed to achieve adequate reperfusion (rescue PCI)[26] and appears to have benefits over repeated thrombolytics or conservative therapy.[27] Early PCI after successful thrombolysis appears to be of benefit,[28,29] but routine use of thrombolytics or combined thrombolytics and glycoprotein IIb/IIIa receptor antagonists before PCI appears to provide no additional benefit and may be detrimental, particularly if a full dose of thrombolytic has been given.[30,31]

Choice of reperfusion strategy is controversial and depends on patient factors and availability.[15,16,25] PCI is more effective at opening occluded arteries than thrombolysis. Studies have shown that it is associated with lower mortality and re-infarction rates both early and late after STEMI,[32] with benefit maintained up to 5 years,[33] including in patients with cardiogenic shock.[34] However, the advantage of PCI over thrombolysis appears to diminish as the delay to reperfusion increases; although some analyses[35] have found that PCI is superior to thrombolysis irrespective of the time delay, others have suggested[36] that thrombolysis may be preferred if the delay to PCI is 90 minutes or more, although this depends on patient characteristics.[37] Guidelines[3,6,7] therefore recommend that all patients with STEMI presenting within 12 hours should be reperfused, and that primary PCI should be the treatment of choice where it can be performed within 90 minutes, even if this means transferring the patient to another hospital. Where the delay will be longer than 90 minutes, the patient has had symptoms for less than 2 hours, and thrombolysis is available, this should be the preferred strategy, but angiography and rescue PCI should be performed as soon as possible. Patients with cardiogenic shock, heart failure, or contra-indications to thrombolysis should receive primary PCI. PCI is also preferred in patients presenting later than 3 hours after symptom onset, but for those with a delay of more than 12 hours reperfusion (PCI or thrombolysis) should only be performed if there is evidence of ongoing ischaemia.

The overall efficacy of reperfusion is limited by persistent coronary occlusion, re-occlusion, and infrequent but serious bleeding complications (including intracranial haemorrhage with thrombolytics), and long-term restenosis after PCI. Antiplatelet and antithrombin drugs are given as **adjuncts to thrombolytics** to improve reperfusion and limit re-occlusion,[38] and have been given in the ambulance as an adjunct to prehospital thrombolysis.[39] Adjunctive therapy is also necessary with PCI to prevent re-occlusion and restenosis; for a discussion see under Reperfusion and Revascularisation Procedures (p. 1259.2).

Antiplatelet drugs. The value of giving oral aspirin as an antiplatelet drug was shown by the ISIS-2 study,[40] in which aspirin started during the first 24 hours after myocardial infarction reduced mortality and also reduced the incidence of re-infarction and stroke. Use with streptokinase proved to be more effective than either streptokinase or aspirin alone. Aspirin should therefore be taken as soon as possible when myocardial infarction is suspected and the tablet chewed so that some buccal absorption occurs;[3,20]

Additional antiplatelet therapy has been investigated in an attempt to further improve outcomes. There is some evidence that early use of clopidogrel in addition to aspirin and other standard therapies (including thrombolytics) improves outcomes,[41,42] and immediate dual antiplatelet therapy with aspirin and clopidogrel is now recommended.[5-7,20] Glycoprotein IIb/IIIa inhibitors may also add to the effects of aspirin in some patients, although most benefit is in patients undergoing primary PCI. In those given thrombolytics, no mortality benefit has been shown with abciximab,[43,44] although early patency rates may be improved.[45] Similarly disappointing results have been reported with eptifibatide[46] and tirofiban.[47]

Anticoagulants. Heparin was widely used in acute myocardial infarction before thrombolytics were available and anticoagulants have an established role in patients undergoing PCI,[3,7,20] but the necessity for adjuvant anticoagulants in addition to aspirin in patients treated with thrombolytics is not certain. Heparin may provide benefit by preventing re-occlusion of the artery after thrombolysis, a particular problem with fibrin-specific thrombolytics such as alteplase, and many of the studies supporting the use of thrombolytics included unfractionated heparin. An overview of randomised studies[48] found that in patients receiving aspirin, addition of heparin (intravenously or subcutaneously) produced a small reduction in mortality but was associated with an excess of major bleeds,

while a later meta-analysis[49] found no conclusive benefit with intravenous unfractionated heparin, although most of the studies included were underpowered to show an effect on mortality. Low-molecular-weight heparins have also been tried. They appear to be more effective than unfractionated heparin,[49-51] but studies have generally compared short-term unfractionated heparin (up to 48 hours) with longer-term low-molecular-weight heparin (4 to 8 days), and any benefit may reflect the longer duration of treatment. Guidelines[5,7,20] recommend that all patients receiving thrombolytics should be given an anticoagulant, and either unfractionated or low-molecular-weight heparin may be used. Fondaparinux, a direct factor Xa inhibitor, is also effective,[52] and may be used as an alternative,[5-7,20] although it is not suitable in patients undergoing PCI.[20] Direct thrombin inhibitors have generally proved disappointing as adjuncts to thrombolytics (see Ischaemic Heart Disease under Lepirudin, p. 1418.3), although they may have a role in patients with heparin-induced thrombocytopenia.[3] Longer-term use of heparin to prevent systemic embolisation may be considered in patients at risk of developing left ventricular mural thrombosis or in those with complications likely to result in immobility.

Standard early therapy for STEMI therefore consists of antiplatelet drugs, anticoagulants, and immediate pharmacological or mechanical reperfusion. **Other early treatments** that have been tried include beta blockers, nitrates, ACE inhibitors, magnesium, and metabolic support.

Beta blockers. In studies performed before the routine use of thrombolytics, intravenous beta blockers, such as atenolol and metoprolol, given in the early period after myocardial infarction were associated with a reduction in mortality. Contributory mechanisms were considered to be a reduction in size of infarction or number of re-infarctions and an antiarrhythmic effect, although the ISIS-1 study[53] suggested that beta blockers improved early survival by reducing the incidence of cardiac rupture. The role of intravenous beta blockers in the reperfusion era is less clear. A systematic review[54] of randomised studies found that early use of beta blockers provided, at most, a small mortality benefit; most of the studies preceded routine use of reperfusion, although some thrombolytic studies were included. A later randomised study,[55] in which about half of the patients received thrombolytics, found that early intravenous metoprolol followed by oral dosage did not reduce mortality at 28 days; there was a reduction in re-infarction and ventricular fibrillation but this was offset by an increase in deaths due to cardiogenic shock, particularly during the first few days. Current recommendations[5-7] are that intravenous beta blockers should not be used in patients with cardiogenic shock or other contra-indications, and it has been suggested[5] that early use should be reserved for patients with hypertension.

Nitrates. Intravenous nitrates are widely used in acute myocardial infarction, although evidence to support their use in patients undergoing reperfusion is limited. An overview[56] of studies carried out before reperfusion (thrombolysis or PCI) became routine found that the use of intravenous nitrates (glyceryl trinitrate or sodium nitroprusside) within 24 hours of the onset of pain was associated with a reduction in mortality, but whether they are of benefit in addition to reperfusion is not clear. However, they appear to be safe[57] and may therefore be given where clinically indicated for ongoing ischaemic pain.[3,6] Nicorandil, which is both a potassium-channel opener and a nitrate, has also been tried in the early stages of myocardial infarction, but results have been mixed.[58,59]

ACE inhibitors. ACE inhibitors have an established role in the long-term management of patients after myocardial infarction, but their use in the early stages is more controversial (see p. 1284.3). A systematic review[60] of studies of ACE inhibitors started within the first 1 to 2 days after acute myocardial infarction found that 30-day mortality and the incidence of heart failure were reduced in those given ACE inhibitors, although the greatest absolute benefit was seen in high-risk patients such as those who had already developed heart failure. Guidelines[3,7] therefore agree that patients with evidence of heart failure should be given early treatment with ACE inhibitors; routine use in all patients may be considered[3,6] but is less well-established. Angiotensin II receptor antagonists may be used if ACE inhibitors are not tolerated.[7]

Magnesium. Magnesium has an important physiological role in maintaining the ion balance in muscle including the myocardium and it has been suggested that use of magnesium in acute myocardial infarction might protect against both arrhythmias and reperfusion injury. Although early studies reported some benefit, larger studies found no effect on mortality, and a systematic review[61] concluded that it was unlikely that magnesium reduced mortality; ventricular arrhythmias were less frequent, but profound hypotension and bradycardia were increased. Routine use of magnesium is therefore not currently recommended.

Metabolic support. Infusions containing glucose, insulin, and potassium have been used in small numbers of patients with the aim of providing metabolic support in the acute phase of myocardial infarction. A meta-analysis of randomised controlled studies that were performed before the widespread use of thrombolytics found that mortality was reduced in recipients of glucose-insulin-potassium,[62] but large randomised studies[63] in patients undergoing reperfusion have found no overall effect on mortality, and routine use is not recommended.[7] Intensive glucose control, including insulin-glucose infusions, is however of benefit in diabetics with acute myocardial infarction (see Myocardial Infarction under Insulin, p. 482.3) and short-term outcomes may also be improved in non-diabetics with hyperglycaemia treated with insulin.[64]

Other early treatments that have been investigated[65] include hypothermia, hyperbaric oxygen, calcium modulation, and complement inhibitors such as pexelizumab. Early use of stem cell infusions[66,67] or colony-stimulating factors[68,69] to promote myocardial repair has also been tried, but the optimum approach remains unclear.[70]

Long-term management. Patients who survive the immediate post-infarction period remain at high risk for cardiovascular mortality. The main predictors of poor outcome are the extent of left ventricular dysfunction, residual myocardial ischaemia, and ventricular arrhythmias. Follow-up should include cardiac rehabilitation and the identification and modification of risk factors for ischaemic heart disease (see Cardiovascular Risk Reduction, p. 1246.1). Angiography should be considered in all patients not treated with primary PCI,[5,7] and echocardiography may be useful for assessing left ventricular function. Exercise testing, myocardial imaging techniques, and pharmacological stress testing (see Myocardial Imaging under Dipyridamole, p. 1362.3) may have a role,[3] particularly in patients where concern about ischaemia continues after angiography.[7]

Drug therapy is important in the long-term management of patients after myocardial infarction, both for symptom control and for secondary prevention,[3,7,71,72] and there is some evidence that increased use of established therapies has reduced overall mortality.[73]

- *Aspirin*, given during the acute phase and then continued for one to two years, has been shown to reduce mortality and re-infarction rates. A meta-analysis[74] confirmed the benefit of prolonged antiplatelet treatment in the secondary prevention of myocardial infarction and patients should receive antiplatelet therapy indefinitely. Clopidogrel appears to be as effective as aspirin[75] and may be used in patients intolerant of, or with contra-indications to, aspirin. Dual antiplatelet therapy with both aspirin and clopidogrel for 2 to 4 weeks may also be considered after acute STEMI,[5,71] and it may be reasonable to continue long-term.[5,7]
- *Oral anticoagulation* is only recommended after acute myocardial infarction if patients have some other indication, although warfarin may be used in patients unable to take antiplatelet drugs.[7,71] There is some evidence that medium-intensity warfarin anticoagulation (INR 2.0 to 2.5) given with aspirin may be more effective than aspirin alone,[76] but bleeding is increased and the combination is only generally recommended as an alternative in patients requiring dual antiplatelet therapy who are unable to take clopidogrel.[71]
- Long-term prophylactic treatment with oral *beta blockers* (most studies have used propranolol, metoprolol, or timolol) has reduced mortality and the rate of re-infarction.[54] In patients with no contra-indications to beta-blocker therapy (see Precautions, p. 1320.3) they are usually started before hospital discharge and continued for a minimum of one year; indefinite use has been recommended.[3,5,7,71] A survey of 201 752 patients who had a myocardial infarction found that low-risk patients and those with conditions often considered to be contra-indications also benefited from a beta blocker.[77] There is also clear evidence of benefit in the elderly,[78,79] although beta blockers have often been underused in such patients.
- *Calcium-channel blockers* are not routinely used in the long-term management of myocardial infarction, although in selected patients without heart failure verapamil or diltiazem may be of some benefit if beta blockers are contra-indicated.
- *ACE inhibitors* reduce left ventricular remodelling, a process which sometimes follows myocardial infarction and is a recognised precursor of symptomatic heart failure. Myocardial infarction patients with left ventricular dysfunction benefit from long-term oral ACE inhibitors started early after infarction and continued for at least 4 to 6 weeks.[80,81] Long-term use of ACE inhibitors in patients without left ventricular dysfunction is less established, since less benefit has been found in this group. However, the HOPE study[82] found that treatment with ramipril significantly improved outcome in patients at high risk for cardiovascular disease, including patients with previous myocardial infarction but preserved left ventricular function, and some guidelines[5,71] therefore consider that long-term use of ACE inhibitors is reasonable in all patients after myocardial infarction although it is not mandatory.[7]
- *Angiotensin II receptor antagonists* may be an alternative; a study[83] comparing valsartan with captopril found that both were equally effective, although another study[84] comparing losartan with captopril suggested that ACE inhibitors should remain first-line.
- *Aldosterone receptor blockade* with a drug such as eplerenone improves mortality in patients with left ventricular dysfunction[85] and is recommended in patients with evidence of heart failure.[5-7,71]
- *Statins* are effective in the primary and secondary prevention of myocardial infarction in patients with both high and average cholesterol concentrations and their use has been advocated in all patients who have suffered a myocardial infarction (see Cardiovascular Risk Reduction, p. 1246.1).
- *Omega-3 acid ethyl esters* improve outcomes when added to standard therapy[86] and may be considered if dietary intake is inadequate.[71]
- Some patients, for example those with myocardial ischaemia or poor left ventricular function, may require long-term *nitrates*, but there is no evidence to support their routine use in all patients.[7]

Post-infarction problems such as heart failure (left ventricular dysfunction), angina pectoris, and arrhythmias are discussed on p. 1262.3, p. 1254.3, and p. 1266.1 respectively.

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Reperfusion and revascularisation procedures

Ischaemia due to impaired blood flow is a major factor in cardiovascular disorders such as angina pectoris (p. 1254.3), myocardial infarction (p. 1257.1), peripheral vascular disease (p. 1272.3) and ischaemic stroke (p. 1269.2). The underlying cause is usually atherosclerosis (p. 1250.2); this leads to narrowing of arteries with a consequent reduction in blood flow, while rupture of the atherosclerotic plaque may lead to thrombosis and acute occlusion of the artery. Restoration of blood flow is therefore one of the main aims of treatment for atherosclerotic disorders, and may be achieved by pharmacological and non-pharmacological methods. The choice of method depends on the condition being treated and is discussed under the individual diseases. Pharmacological methods such as thrombolysis are usually only used in acute occlusion to break down the blood clot and restore flow. Non-pharmacological methods may be used in acute occlusion or electively in situations where stenosis of the blood vessel restricts but does not totally obstruct flow. The methods used in the coronary circulation include percutaneous coronary interventions (PCI) such as balloon angioplasty and stenting,[1-3] and surgical procedures such as coronary artery bypass grafting (CABG); similar techniques are used for peripheral vascular and cerebrovascular disease. Where non-pharmacological methods are used, adjunctive drug therapy is required to prevent and treat acute and long-term complications, and this is the focus of the following discussion.

Patients undergoing surgery or PCI are at risk of **thrombosis** during and immediately after the procedure due to damage to the arteries at the site of intervention and the use of angioplasty catheters or extracorporeal circulation. Antithrombotic therapy with anticoagulants and antiplatelet drugs therefore has an important role[2-5] at the time of the procedure and may also be needed long-term (see below). However, use of antithrombotics inevitably increases the risk of bleeding, and it is important to consider the relative risks of thrombosis and bleeding in the individual patient when selecting an antithrombotic strategy.[6]

Anticoagulants are used in both surgery and PCI.

Surgery

- For surgery involving cardiopulmonary bypass, high doses of unfractionated heparin are given by intravenous infusion. The dose is usually adjusted according to the activated clotting time (ACT), although monitoring blood-heparin concentrations may be an alternative. A target ACT of 400 to 480 seconds has been suggested,[7] with reversal of anticoagulation at the end of surgery. Lower doses may be adequate in patients undergoing 'off-pump' or 'beating-heart' surgery (target ACT 250 seconds[7]) and in peripheral bypass surgery, although the optimum degree of anticoagulation is not established.
- Alternatives to heparin have been tried and positive results have been reported with hirudins (bivalirudin[8] and lepirudin[9]) and with the direct thrombin inhibitor argatroban,[10] although they are usually reserved for patients with heparin-induced thrombocytopenia.[7]
- Antifibrinolytics have been given to reduce bleeding complications after surgery, although there is some evidence that use of aprotinin may be detrimental (see Haemorrhagic Disorders under Uses and Administration of Aprotinin, p. 1133.3).

PCI

- In PCI, unfractionated heparin is generally used since it can be rapidly reversed if emergency surgery is required, but the high doses needed to achieve a target ACT of 250 to 350 seconds[2,3] make bleeding a problem. Lower doses of heparin may be effective and safer, particularly if glycoprotein IIb/IIIa-receptor antagonists are also used, and a target ACT of 200 to 250 seconds has been suggested;[2,3] however, an analysis[11] found no clear relation between heparin dose and outcome.
- Low-molecular-weight heparins have been used, although evidence for their efficacy is limited;[2,3,12,13] a meta-analysis[14] that included mostly non-blinded studies found that low-molecular-weight heparin was as safe and effective as unfractionated heparin, and further studies[15,16] have come to similar conclusions. A subsequent meta-analysis concluded that bleeding events were less common with low-molecular-weight heparins in PCI without reduction in efficacy.[17]
- Direct thrombin inhibitors may be another alternative;[2,3,13] bivalirudin appears to be as effective as heparin,[18-20] and may be safer than heparin in PCI for acute myocardial infarction,[21] while a study with desirudin[22] found fewer early ischaemic events but no long term benefit compared with heparin.
- Fondaparinux has also been tried,[23] but the risk of catheter thrombosis may be increased and additional unfractionated heparin is recommended at the time of the procedure.[3,13]

Antiplatelet drugs have an important role in reducing acute thrombotic complications and in long-term treatment.

Surgery

- In patients undergoing surgical bypass, they are not usually started until after the procedure since they increase the risk of bleeding, and patients who are already taking such drugs usually have them withheld for several days before elective surgery.[24] However, the need for this has been questioned. Blood loss and use of blood products are higher in patients who continue antiplatelets pre-operatively,[25-28] but this is only in those taking higher doses (325 mg or more of aspirin daily),[28] and there is some evidence that use of aspirin pre-operatively may improve outcomes.[29]

PCI

- The use of antiplatelet drugs with anticoagulants during PCI is of established benefit. Aspirin is considered standard therapy,[2,3,13] and patients who are not already taking aspirin are usually given a loading dose at least 2 hours before the procedure; a thienopyridine (such as clopidogrel or ticlopidine) may be used in patients unable to tolerate aspirin. However, aspirin does not completely inhibit platelet function and combination therapy and more potent drugs have also been studied.
- Use of a thienopyridine with aspirin improves outcomes and is now generally recommended,[2,3,13] although the

dose and timing have been debated. Pretreatment appears to be most effective,[30] but the increased bleeding risk may be of concern if emergency surgery is required. For clopidogrel, use of a 300-mg loading dose shortly before the procedure appears to be safe, but efficacy may be reduced if it is given less than 6 hours before the intervention[2,3] and there is some evidence that it needs to be given at least 15 hours before.[31] A higher dose of 600 mg may be effective if given at least 2 hours before PCI[32,33] and has been recommended,[3] particularly in patients with non-ST elevation acute coronary syndromes.[13] However, in patients with stable angina, routine use of a 600-mg loading dose at least 6 hours before angiography was no more effective than a selective strategy in which the same dose was given immediately after angiography only to those patients proceeding to PCI.[34] Prasugrel, which has a faster onset and more consistent effect than clopidogrel, has been used as an alternative in patients with acute coronary syndromes and may be superior in terms of ischaemic outcomes, but is associated with a higher rate of bleeding.[35]

- Glycoprotein IIb/IIIa-receptor antagonists such as abciximab, eptifibatide, and tirofiban given intravenously improve outcomes in a variety of patients undergoing PCI,[36] including those with acute coronary syndromes, those undergoing elective PCI, and patients receiving intracoronary stents. However, recommendations for their use vary,[2,3,13,37] and some guidelines consider them unnecessary in low-risk patients unless complications occur. Although usually given at the time of the procedure, there is some evidence[38-40] that early use may be beneficial in patients undergoing PCI for acute myocardial infarction.

  In most studies glycoprotein IIb/IIIa-receptor antagonists have been given as adjuncts to heparin and aspirin, and their role in patients also taking clopidogrel is less clear, particularly in patients at lower risk. While some observational studies have suggested improved outcomes,[41] others have found no benefit,[42] and randomised studies have also shown mixed results. For abciximab, improved outcomes have been reported in patients pretreated with clopidogrel undergoing PCI electively[43] or for acute coronary syndromes (although only in those with raised troponins),[44] but a study[45] in patients with acute ST-elevation myocardial infarction found no benefit. For tirofiban, pre-hospital use in addition to clopidogrel improved outcomes in patients undergoing PCI for acute myocardial infarction,[39] and benefit was also seen in patients shown to be poor responders to aspirin and/or clopidogrel.[46] There is also some evidence[47] that use of glycoprotein IIb/IIIa-receptor antagonists (in this case eptifibatide) with both clopidogrel and aspirin may make the routine use of heparin unnecessary.

Other acute complications during PCI include vasospasm, reperfusion injury, and arrhythmias; lack of reflow in the target artery ('no-reflow') may result from vasospasm or distal embolisation. Vasodilators such as nitrates or calcium-channel blockers may be given at the start of the procedure to reduce vasospasm.[2] Where vasospasm causes no-reflow, *verapamil, adenosine, or sodium nitroprusside may be* used,[2] although they are not recommended for routine prophylaxis.[48] Some benefit has been reported[49] from intracoronary thrombolysis immediately after PCI, but this requires confirmation. Various drugs have been tried for cardioprotection,[50] and to protect against myocardial reperfusion injury,[51] but none yet has an established role.

Long-term treatment. Patients undergoing surgical or percutaneous revascularisation remain at risk of thrombosis after the procedure as the endothelium heals, and are also at risk of further cardiovascular events due to generalised atherosclerosis. Antithrombotic therapy should therefore be continued long-term, and patients should also be assessed for their overall cardiovascular risk and treated as appropriate (see Cardiovascular Risk Reduction, p. 1246.1).

Anticoagulants are usually only given intravenously at the time of the procedure and oral anticoagulants such as warfarin are not routinely used. They may have a role in addition to aspirin in patients at high risk of graft occlusion after peripheral artery bypass,[52] although a study[53] comparing oral anticoagulants with aspirin found no difference in reocclusion or mortality, whereas bleeding was higher in patients receiving anticoagulants. Patients undergoing PCI who are taking oral anticoagulants for other indications require careful assessment, and choice of long-term therapy again depends on the balance between bleeding and thrombotic risks.[54,55]

Antiplatelet drugs have an established role in reducing major coronary events after surgical and percutaneous revascularisation procedures,[55-57] and may also reduce reocclusion after peripheral percutaneous interventions[58] and peripheral-artery bypass grafting.[59] Aspirin is recommended indefinitely in all patients,[13,24,52] although the optimum dose after PCI is unclear.[60] Clopidogrel may be used as an alternative in patients unable to take aspirin, but may also be given as additional therapy. There is evidence that it reduces major coronary events when given with aspirin after PCI,[61] and long-term use of the combination has been recommended,[3,13,24] especially in patients with coronary stents. Prasugrel may be used instead of clopidogrel in patients with acute coronary syndromes, although any increase in efficacy may be offset by the higher incidence of bleeding.[35]

Coronary artery stents[1,62] were initially developed to treat or prevent acute occlusion of the vessel due to elastic recoil after balloon angioplasty, but are now used routinely in most PCI to reduce the risk of restenosis (see below), although their effect on mortality is unclear.[63] Thrombotic occlusion 2 to 14 days after the procedure (subacute stent thrombosis) is a major complication with stent use, and initially led to the use of intensive anticoagulant/antiplatelet regimens.[62] However, with optimal stent deployment and use of heparin during the procedure, oral antiplatelet drugs alone appear to be adequate, and a combination of aspirin with a thienopyridine is now recommended. Aspirin should be continued indefinitely, but the optimum duration for thienopyridine therapy is less clear. Most experience has been with clopidogrel, and recommendations depend on the type of stent used. For patients with bare metal stents, clopidogrel should be given for at least 2 to 4 weeks,[2] and treatment for 12 months has been recommended.[3,24] For patients with drug-eluting stents, the risk of occlusion persists for longer, and the benefit of continuing clopidogrel is better established.[64,65] Combination therapy is therefore recommended for at least 12 months,[3,24,66] and may be continued indefinitely if tolerated.[24] Cilostazol has also been used, both as an alternative to thienopyridines[67,68] (although some have suggested[69] *that aspirin plus cilostazol may carry a higher* risk of stent thrombosis after PCI than other double regimens), and as part of a triple platelet regimen.[69-71] Heparin-coated stents may also have a role.[72]

Restenosis is a specific long-term complication of percutaneous procedures.[1,73,74] Several pathological processes are believed to be responsible, including platelet aggregation and thrombus formation, elastic recoil, vascular remodelling, and neointimal hyperplasia. Symptomatic restenosis often requires a repeat revascularisation procedure and increases the risk for clinical events. Stents reduce restenosis by preventing elastic recoil and vascular remodelling, but are associated with a higher risk of neointimal hyperplasia, and in-stent restenosis is a particular problem.[75,76] This has led to the investigation of drugs to prevent restenosis, but results with systemic therapy have generally been disappointing. Greater success has been reported with drug-eluting stents, and these are now widely used, as discussed below; however, they are not without complications, and oral therapies continue to be investigated.

Although **systemic therapy** with antiplatelet drugs and anticoagulants reduces the risk of thrombus formation, there is little evidence that they reduce the degree of restenosis; studies with cilostazol have suggested that it may have some effect,[77,78] but this is not yet established. Lipid-regulating drugs are indicated in most PCI patients for cardiovascular risk reduction, but again their effects on restenosis are unclear;[73] there is weak evidence that omega-3 fatty acids[79] reduce restenosis, while mixed results have been reported with statins[80,81] and with probucol.[82,83] Folate therapy (folic acid, vitamin B_6, and vitamin B_{12}) has been tried since it reduces plasma-homocysteine concentrations, a risk factor for atherosclerosis and possibly restenosis, but again results have been mixed.[84]

Antiproliferative drugs have been tried, but early positive results have generally not been confirmed in larger studies.[73,85] Sirolimus, which is widely used in drug-eluting stents, has shown benefit[86-88] when given orally. Other drugs for which positive or mixed results have been reported include angiotensin II receptor antagonists,[89,90] calcium-channel blockers,[91,92] corticosteroids,[93] and thiazolidinediones,[94] but none has an established place in therapy.

The disappointing results with systemic drug treatment may relate to the difficulty in achieving adequate concentrations at the target site and **localised methods** of treatment, including radiotherapy and drugs, have therefore been tried. Intracoronary radiotherapy (brachytherapy) is effective but is complex to perform and not widely available, and drug-based methods are therefore preferred.

Drug-eluting stents are the most common approach. These usually consist of metal stents coated with a polymer containing the drug, which is then released over a period of time, and they allow the localised delivery of high doses of drugs to the site of vessel injury. Stents eluting antiproliferative drugs (mainly sirolimus or paclitaxel) are most widely used and have been shown to reduce neointimal proliferation and clinical events, including the need for repeat revascularisation,[95-97] although whether they have a long-term benefit over bare-metal stents in all patients is not clear.[98-101] They are also effective for the treatment of in-stent restenosis in bare-metal stents. There is some evidence that sirolimus is superior to paclitaxel,[10] but the clinical importance of this seems doubtful.[102,103] Sirolimus analogues such as everolimus, zotarolimus, and umirolimus are also used, while other drugs such as dexamethasone and lanreotide have been tried or are *available. Heparin-coated stents, which* have been used to reduce periprocedural thrombosis (above), may also have a longer-term effect on restenosis.[72] Other approaches include antibody-coated stents, bioresorbable stents, and local gene therapy. Use of paclitaxel-coated angioplasty balloons has also been tried[105,106] and may overcome some of the problems associated with the long-term presence of stents in the coronary arteries.

One of the main complications reported with the use of drug-eluting stents is late stent thrombosis.[107,108] It appears to be more common than with bare-metal stents,[109] and has been attributed to mechanisms such as delayed endothelialisation caused by the drug or hypersensitivity reactions related to the polymer coating.[110,111] However, analyses using different definitions of late thrombosis have suggested[112] that there is no significant difference between the types of stent, and the clinical relevance of any increase in the incidence of late thrombosis remains unclear. The effect of drug-eluting stents on mortality has also been debated; some analyses[113,114] have reported an increased mortality with drug-eluting stents, whereas others[109,111] have found no significant effect. There is some evidence[116,117] that outcomes with drug-eluting stents are worse in high-risk clinical situations, yet observational studies[118,119] suggest they are as safe as bare metal stents in such patients. The FDA has stated[66] that the concerns about thrombosis do not outweigh the benefits of drug-eluting stents when used for their approved indications, but that outcomes may not be the same in other patients.

Duration of antiplatelet therapy is an important factor in the development of stent thrombosis,[108] but the prolonged requirement for dual antiplatelet therapy may cause problems in patients with drug-eluting stents who require surgery for other indications.[120] There is some evidence that thienopyridines can be safely withheld for a short period if aspirin is continued,[121] but surgery should ideally be delayed for at least the 12 months recommended as a minimum for dual therapy; bare-metal stents may be preferred in patients scheduled for surgery who require PCI.

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Structural Heart Diseases

Cardiomyopathies

Cardiomyopathy is a broad term used to describe diseases of the heart muscle associated with cardiac dysfunction. It was formerly used specifically for disorders without a known cause (idiopathic cardiomyopathy), but advances in diagnostic techniques and an increased understanding of disease mechanisms and genetic factors mean that many of these disorders now have an identified cause, and the definition has broadened. Cardiomyopathies are a major cause of heart failure and the term has sometimes been used for heart failure in general.

Primary cardiomyopathies are those which affect only or mainly the heart muscle, rather than being part of a wider systemic disorder. They have traditionally been classified on the basis of anatomic and functional features into 3 main types: dilated, hypertrophic, and restrictive, of which dilated and hypertrophic are the most common. These classifications are not ideal, and some newly identified forms (such as arrhythmogenic right ventricular cardiomyopathy and ion channelopathies) do not fit into this scheme. Classification based on the origin of the disorder (such as genetic versus

acquired) may therefore be preferred.[1] However, the former definitions remain widely used, particularly in reviews of management,[2-15] and these are the classifications used in the following discussion.

Dilated cardiomyopathy (previously known as congestive cardiomyopathy) is characterised by systolic dysfunction with dilated and poorly contracting ventricles and a low cardiac output. The right, left, or both ventricles may be affected. Although there may be some ventricular hypertrophy, because of the dilatation there is no overall increase in the thickness of the ventricle walls. Genetic forms of dilated cardiomyopathy do occur, but it is usually acquired, developing as a consequence of another cardiovascular or systemic disorder. Ischaemic heart disease is one of the main cardiovascular causes; others include systemic or pulmonary hypertension, valvular disorders, and congenital heart disease. Myocarditis (infectious, or as a result of toxins or drugs),[16,17] metabolic disorders, nutritional deficiencies, pregnancy, and immunological conditions, can also lead to dilated cardiomyopathy. Patients may be asymptomatic for some time but the initial manifestations are commonly those of heart failure; chest pain, systemic and pulmonary embolism, and arrhythmias may also occur. Management of dilated cardiomyopathy is mainly symptomatic and supportive and should generally follow the conventional strategies for heart failure (see below), including ACE inhibitors, diuretics, and beta blockers. Early studies[18-20] of beta blockers in patients with dilated cardiomyopathy found significant improvements in cardiac function and symptoms, and prevention of clinical deterioration, but failed to show a significant effect on overall mortality. However, a further study evaluating carvedilol therapy in patients with heart failure, including patients with dilated cardiomyopathy, was stopped early because mortality was significantly less in the carvedilol groups[21] and the CIBIS-II study[22] using bisoprolol was also stopped early because of favourable results. A long-term study[23] using metoprolol reported better survival in those taking metoprolol for up to 7 years. Although calcium-channel blockers are not usually used in heart failure, symptomatic improvement has also been reported with the calcium-channel blocker diltiazem.[24]

Patients with dilated cardiomyopathy may be at particular risk for systemic or pulmonary thromboembolism, due to blood stasis in the poorly contracting ventricle. Chronic oral anticoagulation has therefore been suggested, although current recommendations generally limit its use to those with atrial fibrillation, previous systemic embolism, or severe left ventricular dysfunction.[2,25] Arrhythmias should be treated as appropriate (see Cardiac Arrhythmias, p. 1266.1); amiodarone may be particularly suitable as it has no negative inotropic effect. Low-dose amiodarone has been tried in patients at high risk of sudden death, but its role has not yet been confirmed.[2,8] Implantable cardioverter-defibrillators may have a role in some patients.[26]

Treatments directed at the underlying cause of the cardiomyopathy have also been tried, but results have generally been disappointing. Metabolic and nutritional supplements such as growth hormone, levothyroxine, and levocarnitine have been investigated, and some positive results have been seen with immunosuppressants or drugs with immunological effects, such as pentoxifylline, in patients with presumed myocarditis. However, none of these has an established role.

Surgical treatments that restore ventricular shape and function have been tried but cardiac transplantation remains the main method of improving survival; mechanical support of the heart may be used as a bridge to recovery or transplantation.

Hypertrophic cardiomyopathy (previously known as obstructive cardiomyopathy) is characterised by ventricular hypertrophy but the ventricles are not dilated. This leads to diastolic dysfunction since diastolic filling is impaired by the stiff hypertrophied ventricular walls. It is an inherited condition occurring as an autosomal dominant trait and can occur at any age although presentation during the second decade of life is common. Patients may be asymptomatic or may have chest pain, syncope, dyspnoea, or arrhythmias. Sudden death associated with emotional stress or exercise is not an uncommon finding and patients should avoid intense exercise. However, overall life expectancy is similar to that of the general population and many patients have little or no disability and do not require treatment.[5,11]

Patients should be investigated for the presence of any arrhythmias and treated appropriately (see Cardiac Arrhythmias, p. 1266.1) although this may not necessarily prevent sudden death. Atrial fibrillation is particularly important and is probably most effectively treated with amiodarone.[4,5,11-13] Anticoagulation should be considered in all patients with sustained atrial fibrillation.[4,5,11-13]

Beta blockers may be used for control of symptoms. They curtail emotion- or exercise-induced tachycardia. Anginal pain is also reduced and syncopal attacks may be prevented. Calcium-channel blockers (usually verapamil) also improve symptoms and exercise tolerance and may be considered in those who continue to have disabling symptoms or who are unable to tolerate beta blockers; however, verapamil may have adverse effects in patients with outflow obstruction and it should be used with caution in such patients.[9-13] In a crossover study,[27] exercise capacity was not improved by either verapamil or nadolol, although most patients preferred one or other of the drugs rather than placebo and quality of life did appear to be improved by verapamil. Other drugs that may provide symptomatic relief include disopyramide, which is used for its negative inotropic effect and is often given with beta blockers. Diuretics may be needed for congestive symptoms but may also reduce cardiac output. Surgery or septal ablation to reduce outflow obstruction may be of benefit in some patients whose symptoms are resistant to drug therapy.[4,5,9-13,28,29]

The risk of sudden death is difficult to assess, particularly in asymptomatic patients. Neither beta blockers nor verapamil, as used for possible symptomatic relief, prevent ventricular arrhythmias. However, there is some evidence[30] that high-dose therapy with beta blockers may improve survival in children with hypertrophic cardiomyopathy. Low-dose amiodarone may have a role in high risk patients, but adverse effects may limit its use;[9,31] implantable cardioverter-defibrillators are also used in some patients.[11-13,31]

In **restrictive cardiomyopathy** the filling of the ventricles is impaired, often due to endomyocardial fibrosis,[32] resulting in mostly diastolic dysfunction. Diuretics may improve congestive symptoms but should be used cautiously as they may decrease cardiac output. Arrhythmias should be treated if they are symptomatic and anticoagulation is advised, particularly in patients with atrial fibrillation, valvular disorders, or a low cardiac output.[6] Surgery may be of benefit in some patients.[32]

Management of **arrhythmogenic right ventricular cardiomyopathy** may involve implantation of a defibrillator, the use of antiarrhythmic drugs (notably sotalol), or catheter ablation.[33-37]

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Heart failure

Heart failure is a clinical diagnosis made in a patient with a known or suspected cardiac disorder who presents with dyspnoea, fatigue, and oedema (peripheral and/or pulmonary). It may be graded as mild, moderate, or severe depending upon whether symptoms such as dyspnoea and fatigue appear on ordinary physical exertion, on little exertion, or at rest, respectively. Another grading system (that of the New York Heart Association) has four grades (NYHA grades I, II, III, IV), again partly classified on appearance of symptoms in relation to exertion (with grade IV representing the most severe form). The discussion that follows focuses on the chronic form of heart failure; acute heart failure, which may result in cardiogenic shock, is covered under Shock, p. 1279.3.

Heart failure is a common condition[1] and is a consequence of abnormalities in cardiac structure or function. It may result from disorders or diseases of the heart muscle, injury, or cardiovascular stress such as hypertension or valve disorders. Myocardial infarction is one of the leading causes of heart failure, and chronic myocardial ischaemia may also be a contributing factor. Cardiomyopathies, cor pulmonale, infections causing myocardial damage, and cardiotoxicity arising from alcoholism or induced by drugs may also lead to heart failure. The increased demands put on the heart by chronic severe anaemia or hyperthyroidism can also be precipitating factors.

Traditionally, heart failure has been thought of in purely haemodynamic terms, as a condition in which the heart is unable to provide an adequate blood flow to meet the metabolic demands of the body. However, it is now appreciated that compensatory neurohormonal mechanisms play just as important a role in its development.[2,3] Echocardiography, the most useful investigative procedure in patients with heart failure, assesses haemodynamic factors; it allows assessment of ventricular function and ejection fraction, enables structural changes to be seen and rapidly identifies patients with potentially correctable abnormalities such as valvular disease. Measurement of blood concentrations of natriuretic peptides has been suggested as another useful investigation;[4-7] this relates to the neurohormonal mechanisms involved.

Echocardiography may identify dysfunction of either the right or left ventricle (right- or left-sided heart failure), although dysfunction of both ventricles is likely to be present to some extent. In most patients, the predominant finding is that of a dilated and poorly contracting left ventricle, with a reduction in both ventricular ejection fraction and cardiac output. This represents left ventricular systolic dysfunction, and is particularly common in patients with heart failure after myocardial infarction. Patients with symptoms of heart failure but a preserved left ventricular ejection fraction are often described as having diastolic dysfunction or isolated left ventricular diastolic dysfunction;[8-10] cardiac output is usually normal in such patients, but fails to increase in response to exercise. Diastolic dysfunction is more common in the elderly and also occurs in some cardiomyopathies (see p. 1261.3); many patients have both diastolic and systolic dysfunction. Asymptomatic left ventricular dysfunction has been found in some patients, especially those in the early postmyocardial infarction period, and although these patients are not strictly defined as having heart failure, treatment is recommended to prevent the development of full symptomatic disease.

Neurohormonal disturbances both result from, and contribute to, the deterioration in ventricular function.[3]

Myocardial injury or impairment leads to an inability of the ventricles to empty adequately during systole. The resulting ventricular dilatation increases wall tension and initially leads to an increase in contraction while the decrease in cardiac output and blood pressure results in activation of the sympathetic nervous system, leading to an increase in the force and frequency of contraction. Reduced renal blood flow also leads to activation of the renin-angiotensin-aldosterone system, resulting in vasoconstriction and fluid retention. At the same time, an increase in wall stress also occurs in the atria, leading to secretion of atrial natriuretic peptide; this inhibits the release of noradrenaline but also has direct vasodilator and natriuretic actions that lower the haemodynamic load on the heart. Thus, in the short term, compensation for myocardial injury can occur and cardiac output may be maintained. In the long term, these compensatory haemodynamic and neurohormonal mechanisms become ineffective. Ventricular dilatation progresses, the sympathetic nervous system and renin-angiotensin system are persistently activated, ventricular hypertrophy occurs, and ventricular function deteriorates progressively.

Management. Heart failure is a progressively disabling condition associated with considerable morbidity and mortality. Management is aimed therefore not only at providing symptomatic relief, but also at improving prognosis, in terms of both progression and mortality. Reviews[1-14] and guidelines[4-7] have been published about the management of heart failure due to left ventricular systolic dysfunction. The management of patients with preserved left ventricular ejection fraction, or diastolic dysfunction, is less clear.[3-10,15] In theory, this should differ from systolic dysfunction, but there have been few studies specifically in such patients. Many of the early studies were based on a clinical diagnosis of heart failure and may have included patients with diastolic dysfunction, and there is evidence that they might benefit from some standard treatments,[16] but therapy for such patients is not established and the following discussion is specific for patients with systolic dysfunction unless stated otherwise.

Treatment involves non-pharmacological and pharmacological interventions. Any underlying cause or exacerbating factors should be corrected, and several general measures may be beneficial. Weight reduction should be considered in the overweight and moderate salt restriction may be undertaken. In acute heart failure bed rest may become necessary, but in controlled chronic heart failure exercise should be encouraged and specific exercise programmes may be of benefit.[4-7,17,18] Immunisation with influenza and pneumococcal vaccines is advised.[4-7] Anaemia may be both a cause and a consequence of heart failure and should be treated appropriately (see p. 1121.2). Drug therapy of heart failure is based on the use of diuretics, ACE inhibitors or angiotensin II receptor antagonists, and beta blockers; aldosterone antagonists, cardiac glycosides, and vasodilators may also be used. Surgical interventions and implantable devices may have a role in selected patients.

Diuretics have been the mainstay in the treatment of heart failure, and continue to have an important role.[19] They provide very effective symptomatic control in patients with peripheral or pulmonary oedema and rapidly relieve dyspnoea. If symptoms of fluid retention are only mild, a *thiazide diuretic*, such as *bendroflumethiazide* or *hydrochlorothiazide*, may be adequate. However, in most cases, especially in moderate or severe fluid retention, a *loop diuretic* such as *furosemide* will be necessary. Combination treatment with diuretics that behave synergistically by acting at different sites (the principle of sequential nephron blockade) may be needed in some patients, especially when there is diuretic resistance.[20] A loop diuretic with either a thiazide or *metolazone* is often used,[4,6,7] but severe fluid and electrolyte disturbances may occur, particularly with metolazone. *Spironolactone* is an aldosterone antagonist and has diuretic and possibly additional effects, as discussed below.

However, diuretics are not a sufficient treatment on their own as clinical stability tends to deteriorate over time. In addition, although a meta-analysis[21] has suggested that diuretics have beneficial effects on symptoms and mortality, there have been no long-term studies assessing the effect of diuretics on prognosis, and drugs that have been shown to have a mortality benefit are also required.

At all stages of chronic heart failure, ***ACE inhibitors*** given orally produce additional clinical benefit to that seen with diuretics. They relieve symptoms such as dyspnoea and improve exercise tolerance. Since angiotensin II appears to be involved in the generation of cardiac arrhythmias, an antiarrhythmic effect has also been suggested, although this has not been established.[22] Studies have shown that ACE inhibitors improve survival and reduce the progression of mild or moderate heart failure to more severe stages.[23] ACE inhibitors may also be beneficial in asymptomatic left ventricular dysfunction.[24] The Studies of Left Ventricular Dysfunction (SOLVD)[25] studies indicated that ACE inhibitors, in this case enalapril, might protect against myocardial infarction, unstable angina, and cardiac death in patients with either symptomatic or asymptomatic disease. ACE inhibitors are recommended[4-7] in all patients with left ventricular systolic dysfunction, whether or not they have symptoms. Where tolerated, doses should be titrated to those found to be effective in randomised studies, rather than according to symptomatic response.

ACE inhibitors have also been given to patients shortly after suffering myocardial infarction (p. 1257.1) but before the development of symptomatic heart failure and appear to be beneficial. However, it is not yet clear which patients should be given such therapy or when it should be started.

Angiotensin II receptor antagonists have been investigated both as alternatives to ACE inhibitors, and also with ACE inhibitors to provide more complete blockade of the renin-angiotensin system. As alternatives to ACE inhibitors, they appear to have a similar efficacy.[26] An early study[27] suggested that *losartan* improved mortality compared with enalapril, but this was not confirmed in the larger ELITE II study,[28] although losartan was found to be better tolerated. Studies with losartan[29] and *valsartan*[30] in patients with heart failure after myocardial infarction also failed to show superiority over ACE inhibitors. However, there were generally fewer adverse effects with angiotensin II receptor antagonists, and a further study[31] found that *candesartan* was of benefit in patients who could not take ACE inhibitors. Guidelines continue to recommend ACE inhibitors as first-line therapy, but angiotensin II receptor antagonists are an acceptable alternative, particularly in those unable to tolerate ACE inhibitors.

Dual inhibition of the renin-angiotensin system using ACE inhibitors and angiotensin II receptor antagonists together may be of benefit; both candesartan[32] and valsartan[33] have been shown to reduce hospitalisation for heart failure when added to ACE inhibitors, although the effects on mortality are unclear. Although one study[33] suggested detrimental effects in patients who were also taking beta blockers, this has not been confirmed. Use of ACE inhibitors and angiotensin II receptor antagonists together may therefore be considered in patients who remain symptomatic despite standard therapy, including patients receiving beta blockers.[4-6] However, this approach has been criticised.[34]

Beta blockers can inhibit the persistent activation of the sympathetic nervous system that is associated with disease progression. This benefit far outweighs their negative inotropic effects, and the role of selected beta blockers in the long-term management of heart failure is established. Beta blockers are recommended[4-7] in all patients with clinically stable heart failure due to left ventricular systolic dysfunction and should be given with ACE inhibitors and diuretics. They must be introduced cautiously since symptoms may initially worsen, but if tolerated the doses should then be titrated to those found to be effective in randomised studies. Temporary withdrawal or dosage reduction may be necessary in patients with acute decompensation[6] (see below). It is not a class effect: only *bisoprolol, carvedilol, nebivolol,* and long-acting preparations of *metoprolol* have shown positive effects on mortality and morbidity in patients with varying degrees of heart failure and are recommended for such use.[6] It is unclear which of these provides the greatest effect, but a meta-analysis[35] in patients with mild to moderate heart failure suggested that vasodilating beta blockers such as carvedilol have a greater effect on overall mortality than those that do not produce vasodilatation. The degree of heart-rate reduction achieved appears to be more important than specific doses.[36]

Beta blockers also appear to be of value in heart failure due to idiopathic dilated cardiomyopathy (see Cardiomyopathies, p. 1261.3) and possibly in isolated diastolic dysfunction.

Aldosterone antagonists may have a role in some patients with heart failure.[37-39] Raised levels of aldosterone appear to contribute to the pathophysiology of heart failure and, while ACE inhibitors suppress aldosterone production, the effect is not complete. Aldosterone antagonists have therefore been tried as adjuncts to ACE inhibitors. In patients with severe heart failure, addition of low-dose *spironolactone* to ACE inhibitors and loop diuretics reduced the risk of death or hospitalisation.[40] Another aldosterone antagonist, *eplerenone*, has shown benefit,[41] when added to standard therapy in patients with heart failure after myocardial infarction. Guidelines[4-7] therefore recommend that aldosterone antagonists may be added to standard therapy in patients with moderate to severe heart failure, and in patients with heart failure after myocardial infarction. In patients with less severe heart failure, their adjunctive role is less clear, although a small study[42] has suggested that spironolactone may be of benefit and, in a more recent study, eplerenone[43] has been shown to reduce hospitalisation and mortality among mildly symptomatic patients. However, adverse effects may limit use, and all patients taking aldosterone antagonists with ACE inhibitors must have their plasma-potassium concentrations closely monitored. Aldosterone antagonists should not be used in patients who are taking both ACE inhibitors and angiotensin II receptor antagonists.[6]

Cardiac glycosides such as *digoxin* or *digitoxin* have an extremely long history in the management of heart failure. They are positive inotropes and increase the contractility of the heart thereby increasing cardiac output. Additional effects in heart failure appear to be due to neuroendocrine suppression such as inhibition of the sympathetic nervous system and indirect arterial vasodilatation.

The benefit of cardiac glycosides in heart failure accompanied by atrial fibrillation is not disputed although beta blockers are generally preferred. However, their role in patients with sinus rhythm has been debated. There is evidence that withdrawal of digoxin from patients taking diuretics (the PROVED study)[44] or ACE inhibitors (the RADIANCE study)[45] carries a considerable risk of clinical deterioration, and patients stable on such combinations should therefore be continued on them. However, the large DIG study[46] found that, while addition of digoxin to diuretics and ACE inhibitors improved symptoms, there was no effect on mortality, and a systematic review[47] came to a similar conclusion. The role of digoxin therefore appears to be limited, although it may be used in patients who remain symptomatic despite ACE inhibitor, diuretic, and beta-blocker therapy.[4-7] No clear benefit has been found in patients with diastolic heart failure.[48]

Various ***vasodilators*** have been studied in heart failure. There appears to be no specific role for direct-acting vasodilators, but some benefit has been reported with a combination of *isosorbide dinitrate* and *hydralazine*. The rationale for using them together has been that nitrates produce mainly venous dilatation whereas hydralazine produces arterial vasodilatation, although other mechanisms may also be involved. Used together, they alleviate peripheral vasoconstriction and produce symptomatic control, including a benefit on exercise tolerance, but are of somewhat limited efficacy in long-term control. A modest improvement in long-term survival has been noted but this effect is less than that seen with ACE inhibitors. Subgroup analysis suggested that the effect might be greater in black patients, and a later study[49] in black patients found that addition of isosorbide dinitrate and hydralazine to standard therapy improved both morbidity and mortality. Use of isosorbide dinitrate with hydralazine may be considered in patients with left ventricular dysfunction who are unable to tolerate ACE inhibitors or angiotensin II receptor antagonists,[4-7] or as an adjunct to ACE inhibitors in those unable to tolerate angiotensin II receptor antagonists or aldosterone antagonists.[6] Additional therapy with hydralazine and isosorbide dinitrate may also be considered in patients who remain symptomatic despite treatment with ACE inhibitors, beta blockers, and angiotensin II receptor blockers or aldosterone antagonists,[4-7] particularly if patients are of African-American descent.

Calcium-channel blockers, especially verapamil, diltiazem, and the short-acting dihydropyridines, are generally contra-indicated in heart failure because of their negative inotropic activity. Amlodipine has been shown not to adversely affect survival, and it may be considered if the use of a calcium-channel blocker is essential for controlling hypertension or angina.[4,6,7]

Phosphodiesterase inhibitors act as both positive inotropes and vasodilators, a combination of mechanisms that appears particularly attractive in heart failure. Short-term use improves haemodynamic variables, and intravenous *amrinone* or *milrinone* may have a role in patients with severe heart failure unresponsive to other treatment. However, studies with long-term oral phosphodiesterase inhibitors have generally been disappointing. A systematic review[50] found that treatment with oral phosphodiesterase inhibitors was associated with a significant increase in mortality in patients with heart failure, and their use is not currently recommended.

Antiarrhythmics are not routinely used in heart failure since many have a negative inotropic effect. However, sudden deaths in patients with severe heart failure have been attributed to ventricular arrhythmias,[51] and antiarrhythmics such as *amiodarone*, which is not a negative inotrope, have therefore been tried. A meta-analysis[52] of 5 studies involving 1452 patients with symptomatic compensated heart failure indicated that amiodarone reduced the rate of arrhythmic or sudden death in high-risk patients and that this resulted in an overall reduction in mortality, but a later study[53] in mild to moderate heart failure found no survival benefit. Adverse effects may also limit the use of amiodarone, and it is currently only recommended in patients who also have symptomatic arrhythmias.[7] Implantable devices may be an alternative. A reduction in mortality has been shown[53] with use of implantable cardioverter-defibrillators, while resynchronisation therapy using biventricular pacemakers improves symptoms and reduces mortality.[54] Both implantable cardioverter-defibrillators and resynchronisation therapy may therefore be

considered in selected patients,[4-7] and there is evidence that they may be used safely together.[55]

The risk of thromboembolism is increased in heart failure, but the role of routine *antithrombotic* therapy is unclear.[56-58] Anticoagulants should be given to patients who have additional indications, such as atrial fibrillation, but the role of *aspirin* in heart failure has been controversial, since there has been some suggestion that it might reduce the benefit of ACE inhibitors. However, there is limited evidence for either benefit or harm with use of the combination[6,7] (see NSAIDs, under Interactions of ACE Inhibitors, p. 1288.3), and some guidelines[4] recommend that aspirin should be given to heart failure patients with appropriate indications, such as atherosclerosis.

Miscellaneous drugs targeting various mechanisms have been tried in heart failure. *Ivabradine*, a selective sinus node I_f inhibitor that slows the heart rate, may reduce hospital admissions and deaths associated with heart failure.[59] However, for many other drugs results have been disappointing, and toxicity and increased mortality have also been seen. *Epoprostenol*, a prostaglandin that causes vasodilatation, has been associated with increased mortality. The oral sympathomimetic inotrope *ibopamine*, an oral dopamine agonist, has similarly produced negative effects. Increased mortality has also been reported with long-term intermittent *dobutamine* infusions, although a small study[60] suggested that survival might be increased if patients were also given amiodarone. *Moxonidine*, a centrally-acting antihypertensive, has also been associated with increased mortality. *Endothelin antagonists* such as *bosentan* appear to be ineffective.[61] Disappointing results have also been reported[62] with *tumour necrosis factor antagonists* such as *etanercept* and *infliximab*, and there have been reports[63] of exacerbation of heart failure in some patients.

Other approaches that have been tried include inhibition of neutral endopeptidase, the enzyme that inactivates atrial natriuretic peptide, with drugs such as *candoxatril*. *Omapatrilat*, a dual inhibitor of endopeptidase and angiotensin-converting enzyme, has shown some benefit,[64] but adverse effects may limit its use. *Vasopressin antagonists*, such as *tolvaptan*, are also used; they increase free-water clearance and improve symptoms of fluid overload, but mortality benefits have not yet been shown.[65] The direct renin inhibitor *aliskiren* is under investigation. Positive haemodynamic effects have been reported with *growth hormone*, although further studies are needed.[66] Studies with *statins* have reported mixed results,[67-69] but there may be some benefit with *omega-3 fatty acid* supplementation.[70]

Many patients with chronic heart failure have exacerbations of their condition (**decompensated heart failure**) requiring hospitalisation.[71,72] Guidelines for treatment are limited[6,7,73] although several approaches are under investigation.[74] Treatment of acute decompensation is similar to that for patients with cardiogenic shock (see Shock, p. 1279.3). Standard therapies should be continued where possible; temporary withdrawal or dosage reduction of beta blockers may be considered but is not necessary in most patients.[7,75] Patients with peripheral or pulmonary oedema due to fluid overload may need intravenous diuretics. Intravenous vasodilators reduce cardiac filling pressure and increase cardiac output and may be needed if symptoms are severe or there is an inadequate response to diuretics. Intravenous nitrates are often used; *nesiritide*, a natriuretic peptide with vasodilator properties, is an alternative, although its effects on mortality are controversial.[76] If cardiac output is low, intravenous inotropes, such as dobutamine or milrinone, may be required. *Levosimendan*, a calcium-sensitiser with both vasodilator and inotropic actions, may also be used. Patients who cannot be weaned from intravenous inotropes may require long-term continuous infusions, either as palliative therapy or as a bridge to transplantation, but regular intermittent infusions may increase mortality and are not generally recommended.[7]

Some patients with **refractory heart failure** may be suitable for ***surgical*** management. Heart transplantation is the optimum surgical therapy but availability is limited and various alternatives have been tried.[77] Left ventricular assist devices may be useful as a bridge to recovery or transplantation, but are not yet established for long-term use. Revascularisation or mitral valve repair may have a role in selected patients, but procedures to augment the heart muscle or reduce ventricular dilatation are not generally recommended[6] since there is limited evidence to support their use.

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Valvular heart disease

Valvular heart disease affects the normal function of the heart and leads to disorders of blood circulation. The principal cause of valvular disease in the developing world is rheumatic heart disease. Other causes are more common in western countries; they include congenital abnormalities, cardiovascular disorders such as ischaemic heart disease and hypertension, and degenerative disorders. Any of the heart valves may be affected but disorders of the aortic and mitral valves are most significant; more than one valve may be involved in some patients.

The symptoms of valvular heart disease depend upon the valve that is affected, and whether the problem is stenosis or regurgitation. All valve disorders place a haemodynamic burden on the heart and ultimately lead to heart failure. Other consequences include the development of pulmonary hypertension and arrhythmias. Infective endocarditis and

thromboembolic disorders, in particular stroke or systemic embolism, are important complications.

The main aims of treatment in patients with valvular heart disease are to reduce symptoms, prevent complications, and reduce mortality.[1-3] Surgical management is usually necessary once symptoms develop and may also be warranted in some patients who are asymptomatic. Medical therapy is generally reserved for pre-operative symptom control and for patients who are unsuitable for surgery.

Medical treatment for **symptomatic patients** is similar to that used in other forms of heart failure (see p. 1262.3). In acute situations sodium nitroprusside and inotropes such as dopamine or dobutamine may be indicated, but for chronic therapy diuretics, digoxin, ACE inhibitors, and beta blockers are used. The choice of drug depends on the valve affected. ACE inhibitors and other vasodilators have generally been avoided in *aortic stenosis* since any reduction in blood pressure cannot be balanced by an increase in cardiac output and there is a theoretical risk of severe hypotension. However, symptomatic improvement has been reported[4] with enalapril in patients with severe aortic stenosis and preserved left ventricular function, although it was not tolerated in those with left ventricular dysfunction, and sodium nitroprusside has been used successfully for acute symptoms.[5] Some guidelines also recommend that beta blockers should be avoided in aortic stenosis.[2] For patients with *aortic regurgitation* who require medical therapy, vasodilators may be of particular value, especially in severe forms.[6] Symptomatic benefit has also been reported[7] with ACE inhibitors in *mitral stenosis*. Arrhythmias should be treated with standard antiarrhythmics (see p. 1266.1).

Drug therapy to prevent the progression of valvular disorders has generally been disappointing. Although similarities have been suggested between aortic stenosis and atherosclerosis, an observational study[8] in asymptomatic patients taking ACE inhibitors for hypertension found no effect on the progression of stenosis, and initial indications of benefit[8] with statins in patients with calcific aortic stenosis were not confirmed in later studies.[9,10] The results of an early study[11] indicating that long-term vasodilator therapy with nifedipine improved outcome in asymptomatic patients with severe aortic regurgitation were not confirmed by a later study of long-term therapy with nifedipine or enalapril.[12] Another study[13] found no benefit with ACE inhibitors in asymptomatic patients with mitral regurgitation.

Surgery is the mainstay of treatment in valvular heart disease and generally involves valve replacement with either bioprosthetic (tissue) or mechanical valves; the latter are longer lasting, but pose a greater risk for thromboembolism. Valve repair may be suitable in some cases, particularly for mitral regurgitation, while balloon valvulotomy may have a role in some patients with stenosis.[3] Valve replacement alleviates symptoms, but patients remain at risk for complications.

In **asymptomatic patients** and in those with **prosthetic valves**, the main aim of therapy is to prevent the complications of bacterial endocarditis and of systemic embolism from thrombus formation within the heart. Antibacterial prophylaxis should be given to patients with valvular heart disease where indicated (see Endocarditis, p. 179.2). Antithrombotic therapy has an important role in patients with prosthetic valves[14] but in asymptomatic patients long-term thromboembolism prophylaxis is generally only recommended in those with another risk factor for embolisation, such as atrial fibrillation, a dilated left atrium, left ventricular dysfunction, a hypercoagulable state, or previous systemic embolism.[3,15,16]

Long-term treatment with an oral anticoagulant such as warfarin is generally regarded as essential for patients with a *mechanical prosthetic heart valve*,[2,3,16] but the optimum level of anticoagulation is unclear. The risk of thromboembolism depends upon the type and position of the valve and the presence of other risk factors, but must be balanced against bleeding risk. In the UK, specific target INRs are recommended where the valve type and position are known and vary between 2.5 and 3.5 for valves in the aortic position and between 3.0 and 3.5 for valves in the mitral position. If specific information is not available a generic target of 3.0 is recommended for valves in the aortic position and 3.5 for valves in the mitral position.[17] In the USA, the recommended INR range is 2.5 to 3.5, with a lower range of 2.0 to 3.0 suggested as being adequate for most types of valves in the aortic position when there are no other risk factors.[3,16] However, a large study[18] in patients stratified to different target INR ranges found that the risk of moderate to severe thromboembolism and of bleeding complications was comparable for INRs ranging from 2.0 to 4.5; patients had aortic or mitral valve replacement, or both, and all had one particular type of valve. There is evidence that adding an antiplatelet drug (dipyridamole or low-dose aspirin) further reduces the risk of death and thromboembolism although the risk of bleeding is increased.[19] Adjunctive antiplatelet drugs may be considered, particularly for patients with additional risk factors such as embolism while on warfarin therapy, or ischaemic heart disease.[2,3,16] Alternatively, or in addition, patients with systemic embolism despite an adequate INR may have their target INR range increased.[16]

For patients with *bioprosthetic heart valves* anticoagulants are recommended for the first 3 months after replacement,[16] although aspirin may be equally effective,[20] and it is often used instead of anticoagulants when only the aortic valve is involved. Longer term oral anticoagulant therapy is generally considered necessary only for patients with additional risk factors (as for asymptomatic patients, above).[3,16] An INR of 2.0 to 3.0 appears adequate for patients with bioprosthetic heart valves. Low-dose aspirin has been recommended[3,16] in patients with bioprosthetic valves who do not require oral anticoagulants, although other guidelines[2] state that there is no evidence to support this.

For patients on long-term anticoagulation, interruption of therapy for surgical procedures or due to bleeding complications exposes patients to the risk of thromboembolism. A study[21] in patients with haemorrhage suggested that it is safe to withhold oral anticoagulants. For patients undergoing surgery, the evidence for either withholding anticoagulants or converting to an alternative form of antithrombotic therapy perioperatively is not conclusive, although recommendations have been made.[2,3,22] The decision depends on the relative risks for bleeding and thromboembolism in the individual patient. In procedures with a low bleeding risk, anticoagulation can usually be continued. In procedures with a higher bleeding risk, anticoagulants may be withheld if the risk of thromboembolism is low, but otherwise conversion to heparin is recommended. The optimum type and dose of heparin to use is not clearly established. While some guidelines recommend low-molecular-weight heparin as first-line,[22] there have been concerns about its safety[23] and others suggest that unfractionated heparin should be preferred.[2,3]

The use of anticoagulants is also controversial in patients with infective endocarditis, partly because of the substantial increase in risk of haemorrhage in these patients, but also because of the likelihood that surgery will be required. Routine anticoagulation is not advised, and patients who are already taking oral anticoagulants should generally have their therapy changed to heparin until it is clear that surgery is not required and the patient is stable.[3,16]

If obstruction of prosthetic valves by thrombus formation occurs, surgical intervention is usually recommended.[2,3,24] Thrombolytics such as streptokinase or urokinase may be used[16] but are often ineffective and are associated with high risk. They are therefore usually reserved for patients at greatest risk from surgical intervention,[2,3] although a study[25] of patients with left-sided prosthetic valve thrombosis found thrombolytics to be more successful than surgery, especially in the critically ill. Repeated treatments[26] may increase the success rate. Heparin may have a role in non-obstructive thrombosis. Patients who have had a valve thrombosis should have their anticoagulant control optimised;[2] higher target INRs or adjunctive antiplatelet therapy may be considered.[3,16]

The haemodynamic changes that occur during **pregnancy** may complicate the management of women with valvular heart disease.[27-29] In addition, pregnancy is a known risk-factor for thromboembolism and patients with valvular heart disease who become pregnant are therefore at increased risk.[30] However, long-term prophylaxis with an oral anticoagulant such as warfarin presents a problem since warfarin is generally contra-indicated in pregnancy (see Adverse Effects under Warfarin, p. 1528.2). Women with mechanical prosthetic valves must continue anticoagulation but choice of therapy is unclear.[3,31,32] A systematic review[33] found that continued use of oral anticoagulants increased the risk to the fetus, but that thromboembolic complications were higher with heparin. Most guidelines therefore advise that the choice should be discussed with the patient, balancing the risks for each individual, but specific recommendations vary.[2,3,32] The main risk of embryopathy with warfarin is between weeks 6 and 12 of gestation and heparin therapy is often substituted during this period and also at term (to avoid an anticoagulated neonate). However, satisfactory outcomes have been reported[34] with use of warfarin throughout pregnancy, including the first trimester. The risk of embryopathy appears to be lower with daily warfarin doses of 5 mg or lower,[3] and patients with an adequate INR at this dose may continue warfarin until the 36th week, before switching to heparin.[2] If heparin is substituted for warfarin, either during the first trimester or throughout pregnancy, use of an adequate dosage is critical, and strict monitoring is required. Adjusted-dose subcutaneous heparin, with an initial dose of 17 500 to 20 000 units subcutaneously every 12 hours has been suggested;[32] intravenous heparin may be an alternative, but low-dose subcutaneous heparin should not be used as it provides inadequate protection. Low-molecular-weight heparin has also been used, although this is controversial;[2,3,23] if it is used, anti-factor Xa concentrations should be monitored carefully. Low-dose aspirin may be used as an adjunct to subcutaneous heparin or warfarin in women at high risk of thromboembolism.[3,32]

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Disorders of Heart Rhythm

Cardiac arrhythmias are disorders of the rhythm of the heart (p. 1242.1) that may affect its ability to maintain blood circulation. They can be asymptomatic and in some cases benign, but often cause symptoms and may lead to syncope and sudden death; thromboembolic disorders associated with atrial arrhythmias are a common cause of stroke. Cardiac arrest secondary to arrhythmias requires advanced cardiac life support.

Cardiac arrhythmias

A *cardiac arrhythmia* can be defined as any abnormality of rate, regularity, or site of origin of the cardiac impulse or as a disturbance in conduction that causes an abnormal sequence of activation. Arrhythmias may therefore occur due to disorders of the SA node, affecting initiation of impulses; disorders of the AV node and conducting system, affecting spread of the impulse to the ventricles; or abnormal conduction through other myocardial cells such as accessory pathways. Impulses may be generated outside the SA node (*ectopic pacemakers*), particularly in the AV node or the His-Purkinje system. The normal rate of impulse generation by these ectopic pacemakers is less than that of the SA node and therefore they do not usually trigger the heart beat, although they may become dominant in some situations. Since the action potential depends on the movement of ions across cell membranes, electrolyte disorders may be an important cause of arrhythmias; congenital disorders affecting the ion channels (channelopathies) are also increasingly being recognised as a cause.

Arrhythmias may be classified as bradyarrhythmias (slow) or tachyarrhythmias (fast), depending on the heart rate, and as supraventricular (atrial or AV junctional) or ventricular, depending on their presumed site of origin. They may also be divided on the basis of the underlying mechanism into those associated with abnormal automaticity, re-entry, or triggered activity (see Tachyarrhythmias, below). Symptoms depend on the arrhythmia but may include fatigue, dyspnoea, dizziness, and syncope; sudden death may occur. *Palpitations*, an unacceptable awareness of the beating heart, may occur normally in circumstances such as emotion, exercise, or stress but can also occur with arrhythmias.

Bradyarrhythmias are commonly caused by sinus node dysfunction (sick sinus syndrome), which either depresses impulse generation or disturbs the conduction of impulses from the sinus node to the atria.[1] In some patients periods of bradycardia and tachycardia alternate (bradycardia-tachycardia syndrome), making management difficult. *Heart block* (AV block) is another cause of bradycardia, and involves disturbance of conduction of the atrial impulse to the ventricles. First-degree block, in which the impulse is delayed, is usually asymptomatic but may progress to second- or third-degree block, with intermittent (second-degree) or complete (third-degree) failure of atrial impulses to reach the ventricles. This usually causes bradycardia since the intrinsic rate of ventricular contraction is slower than that of the atria, but in AV dissociation ventricular activity is faster than, and independent of, the atrial activity.

Tachyarrhythmias may arise in either the atria or the ventricles. The precise mechanism is often unclear, but for many of the clinically important tachyarrhythmias it involves *re-entry*. Impulses normally spread in a single direction and die out once ventricular contraction occurs, but in re-entry the impulse continues to propagate in a cyclical manner, reactivating the heart. Abnormal automaticity and triggered activity are alternative mechanisms that may be involved.

Ectopic beats, extrasystoles, or *premature contractions* can arise in either the atria or the ventricles and, although their precise meaning and definition differs, for practical purposes they can be considered equivalent. They are usually asymptomatic and of no prognostic importance, but some patients suffer palpitations or other distressing symptoms; in patients with heart disease, ventricular ectopics may be associated with more serious arrhythmias and the risk of sudden cardiac death may be increased.[2]

Diagnosis. The precise identification of an arrhythmia is not always easy, but is important for correct management since inappropriate use of antiarrhythmics may be not only ineffective but actively harmful. Clinical symptoms may be useful, but the mainstay of diagnosis is the electrocardiogram (ECG), which records the electrical rhythm of the heart. A typical normal ECG trace is shown in Figure 2, p. 1242. Many arrhythmias have distinctive ECG patterns, but this is not always the case; an arrhythmia with a narrow QRS complex is always supraventricular in origin whereas a broad QRS complex can indicate either a supraventricular or ventricular origin. Other specialised tests and features relevant to the individual arrhythmias may aid diagnosis.

Management. Treatment of arrhythmias may be indicated to relieve symptoms and/or to improve survival. Choice of therapy depends on the arrhythmia involved, the presence of structural heart disease, and other patient factors such as pregnancy.[3] For tachyarrhythmias, antiarrhythmic drugs (see p. 1243.1 for an explanation of the classification of antiarrhythmics) and external electrical cardioversion have been widely used, although ablation of arrhythmic pathways and implantable cardioverter-defibrillators have an increasing role;[4] management of various tachyarrhythmias is discussed below. For **bradyarrhythmias**, atropine or sympathomimetics are usually used for acute control,[5,6] while cardiac pacing is the treatment of choice for long-term management.[1,7,8]

Atrial fibrillation is a supraventricular tachyarrhythmia with an underlying mechanism of re-entry and is the commonest arrhythmia encountered clinically.[9] It is usually associated with disorders that predispose the atria to re-entry, although it is now recognised that the arrhythmia may start from an ectopic focus, often in the pulmonary vein. The main underlying cardiovascular disorders are ischaemic or hypertensive heart disease and heart failure, and the incidence increases markedly with age. Rheumatic heart disease is also an important cause, although this is now less common in developed countries. Other causes include hyperthyroidism and acute alcohol intoxication. Atrial fibrillation is also relatively common after cardiothoracic surgery, although this is usually self-limiting. In some patients there is no obvious cause ('lone' atrial fibrillation).

Atrial fibrillation is characterised by an irregular and very rapid atrial rate (usually more than 300 beats/minute) and, although the AV node is incapable of conducting all the impulses adequately, the increased ventricular response results in a rapid and totally irregular ventricular rate. Atrial fibrillation has been classified in several ways, but patients with 2 or more episodes are generally considered to have recurrent atrial fibrillation; this may be classed as paroxysmal (intermittent) if the arrhythmia terminates spontaneously, or persistent (chronic) if it is sustained. Persistent atrial fibrillation that does not respond to cardioversion or where cardioversion is not attempted is classed as permanent.

Atrial fibrillation can cause distressing symptoms such as severe palpitations and exercise intolerance, and occasional patients present with acute haemodynamic instability that is potentially fatal. However, for most patients atrial fibrillation is not immediately life-threatening. The increased heart rate may lead to tachycardia-induced cardiomyopathy, while left atrial dilatation and reduced cardiac output lead to stasis of blood in the left atrium, which can result in thrombus formation and subsequent systemic embolisation, notably ischaemic stroke. Thromboembolic events are relatively rare in lone atrial fibrillation but the risk is very much increased if other cardiovascular disease is present, especially rheumatic heart disease.

Management of atrial fibrillation[9-16] is focused mainly on symptom control and prevention of long-term morbidity and mortality, including thromboembolic complications. The available approaches are to restore and maintain sinus rhythm (*rhythm control*), or to control the ventricular rate while allowing atrial fibrillation to continue (*rate control*). Use of anticoagulation depends on the risk of thromboembolic events but may be required with either strategy. For patients with life-threatening haemodynamic instability, immediate therapy to restore sinus rhythm is required.[16]

- Rate control may be used for both acute management of symptoms and maintenance therapy and generally involves drugs that act on the AV node to slow conduction.[17] Digoxin has traditionally been used, but has a slow onset of action and is not effective during exercise and is no longer considered first-line in most patients. Beta blockers or rate-limiting calcium-channel blockers such as diltiazem or verapamil are usually the preferred treatment; they provide effective rate control, including during exercise, and may be given intravenously when acute control is needed. Digoxin may be used in sedentary patients, and is also useful in patients with heart failure; it is often given with beta blockers or calcium-channel blockers since many patients require more than one drug to maintain an adequate rate. Amiodarone or its analogue dronedarone, which have rate-limiting properties as well as an antifibrillatory effect, may be used if symptoms are not controlled by such combinations; catheter ablation of AV conduction pathways followed by permanent pacing may be necessary in patients intolerant or unresponsive to drug therapy.[9,15,18]
- In a rhythm control approach, restoration of sinus rhythm (cardioversion) may be achieved either by synchronised direct current or with drugs; both methods require thromboprophylaxis (which is discussed below).[9] Choice of method depends on the duration of atrial fibrillation, availability, and preference; direct current cardioversion restores sinus rhythm more rapidly and is more effective than pharmacological cardioversion if atrial fibrillation is not of recent onset but has the disadvantage that it needs to be performed under sedation or general anaesthesia. Pharmacological cardioversion is effective in atrial fibrillation of recent onset[9,14,15,19,20] but by 7 days, cardiac remodelling largely abolishes its value. Flecainide and propafenone are the drugs most widely recommended as first-line;[9,14,15] ibutilide and dofetilide are alternatives.[9,15] Amiodarone may also be used;[9,14,15] it has a slower onset but is equally effective[21] and is particularly useful in patients with structural heart disease.[9,16] Vernakalant is a newer alternative whose place in therapy is yet to be decided. Intravenous magnesium has been tried but results have been mixed.[22,23] Drugs with limited or no evidence of efficacy include digoxin, sotalol, quinidine, disopyramide, and procainamide.[9,15] *Adjunctive* pharmacological therapy may be started before electrical cardioversion to increase the success of the procedure and to reduce the risk of early recurrence;[9,14,15] drugs used include amiodarone, flecainide, ibutilide, propafenone, and sotalol.

  Once sinus rhythm has been achieved, long-term *maintenance* drug therapy needs to be considered since relapse is common. Patients with a first episode of atrial fibrillation are rarely started on maintenance therapy, particularly if a reversible cause has been identified and can be treated.[14,15] However, patients who have troublesome symptoms due to paroxysmal or recurrent atrial fibrillation are usually given long-term antiarrhythmics. The ability of these drugs to maintain sinus rhythm is modest,[24] and choice should be guided by safety considerations rather than efficacy.[9,14] Beta blockers may be tried initially,[9,14] particularly in patients with lone atrial fibrillation,[15] and they have the advantage of providing rate control if relapse occurs, but dronedarone, flecainide, propafenone, or sotalol are often required.[9,18] Amiodarone and dofetilide may also be used; amiodarone may be more effective than other antiarrhythmics[25] but its use is limited by long-term adverse effects and it is generally only recommended in resistant cases or in patients with heart failure who are unsuitable for alternative therapy. Catheter ablation procedures such as isolation of the pulmonary veins are an alternative to drugs in certain patients when drug treatment has failed.[9,18] Since ablation may in fact be more effective than drug treatment its use as first-line therapy might also sometimes be reasonable, but the balance of risks and benefits is still unclear.[9,18] Surgery or implantable defibrillators may be used in selected cases. Patients with infrequent episodes of paroxysmal atrial fibrillation and good response to drugs may be prescribed single doses of flecainide or propafenone for outpatient use ('pill-in-the-pocket') if symptoms recur.[9,14,15,26]

The choice between rate and rhythm control has been debated. Rhythm control has theoretical advantages since restoration of sinus rhythm should both alleviate symptoms and reduce thromboembolic risk. However, the adverse effects and limited efficacy of antiarrhythmic drugs in preventing relapse may limit any benefit. A review[27] and meta-analyses[28,29] of studies comparing rate control with rhythm control found little difference between the two strategies in terms of symptom control or clinical events, and choice therefore depends on patient characteristics and preference.[9,14,15] For elderly patients with minimal symptoms rate control is generally the preferred option, whereas younger patients or those who remain symptomatic despite rate control should be considered for rhythm control.

Prophylaxis of atrial fibrillation may have a role in some situations. Although atrial fibrillation after cardiothoracic surgery is usually self-limiting, it may be associated with increased morbidity and mortality, and prophylaxis should be considered. Beta blockers, amiodarone, and sotalol are effective,[6,9,14,15,30-33] and rate-limiting calcium-channel blockers such as diltiazem or verapamil have also been suggested.[6] Other classes of drug may also be effective.[33] Some benefit has been reported with magnesium,[34,35] although this was not confirmed in a more recent study.[36] Corticosteroids may also be of benefit.[37] Statins appear to reduce the incidence of atrial fibrillation after surgery,[38] and omega-3 fatty acids have also shown some benefit.[39] For non-surgical patients, several 'upstream' therapies have been investigated in an attempt to prevent or delay the cardiac remodelling associated with hypertension, heart failure, or inflammation, and so deter either new occurrences of atrial fibrillation or progression of established disease.[9,40] Results of studies with ACE inhibitors, angiotensin II receptor antagonists, and statins have been promising,[40] but there is not enough evidence to recommend them for prevention in patients without pre-existing licensed indications.[9] Other drugs under investigation include aldosterone antagonists and omega-3 fatty acids.

Prevention of thromboembolic events, particularly ischaemic stroke, is a major aspect of atrial fibrillation management.[41] Patients are at risk both during cardioversion procedures and long-term, and should be given appropriate antithrombotic therapy. If atrial fibrillation has

been present for less than 48 hours, it is safe to perform cardioversion covered only by unfractionated or low-molecular-weight heparin.[9,42] This approach is also acceptable in unstable patients who require urgent cardioversion, regardless of the duration of arrhythmia.[9,42] Atrial fibrillation of 48 hours or longer carries a much greater risk of embolisation, and oral anticoagulants are given for 3 weeks before cardioversion.[9,42] In those who cannot take oral anticoagulants or who require rapid (but not urgent) cardioversion, the presence or absence of thrombi may be revealed with transoesophageal echocardiography. If no thrombi are revealed, cardioversion may be performed under cover of unfractionated or low-molecular-weight heparin. If thrombi are revealed and elimination with a 3-week course of oral anticoagulants is impossible or unsuccessful, adopting a rate-control strategy may be safer than cardioversion.[9] The ventricular rate should be controlled in all patients who are waiting for cardioversion. After cardioversion, every patient should be given oral anticoagulants for at least 4 weeks, except where atrial fibrillation has lasted less than 48 hours in a patient with no risk factors for stroke.[9,42]

Atrial fibrillation increases risk of stroke fivefold, and whether a rate- or rhythm-control strategy has been adopted, indefinite prophylaxis with antithrombotic drugs should be offered to all patients considered at risk, including those whom cardioversion has restored to sinus rhythm. The vitamin K antagonist warfarin is most commonly used, but newer oral anticoagulants such as the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors apixaban and rivaroxaban have also been shown to be effective, and appear to cause less risk of major bleed when compared with warfarin.[43,44] In choosing a drug for prophylaxis, efficacy must always be balanced against an increased bleeding risk. For patients with 1 or more major risk factors (previous stroke, transient ischaemic attack, or thromboembolism; age over 75 years; or valvular heart disease) or 2 or more non-major risk factors (hypertension; heart failure; or diabetes) for stroke, the benefits of anticoagulation are established.[9] For everyone else, the relative risks and benefits are less clear and the decision to treat depends more on individual patient factors.

In those at lower risk of thromboembolism, alternative strategies with a reduced risk of bleeding may be more appropriate. Antiplatelet therapy is an acceptable alternative. There is good evidence that aspirin reduces the risk of stroke,[45,46] but it is less effective than warfarin for both primary[47] and secondary prevention,[48] and is usually only recommended in patients with a particularly high risk of haemorrhage or low risk of stroke, or in those who are unwilling or unable to take anticoagulants.[9] Dual antiplatelet therapy with aspirin and clopidogrel may also be considered.[18]

Further strategies to increase the efficacy of antithrombotic therapy while minimising the bleeding risks have been tried. Use of low-dose warfarin with aspirin has been shown[49,50] to be less effective than adjusted-dose warfarin and is not recommended, although a study[51] using triflusal and moderate-dose phenprocoumon reported beneficial effects. Non-pharmacological approaches such as closure of the left atrial appendage have also shown some success.[52]

Atrial flutter is an arrhythmia somewhat similar in nature to atrial fibrillation[53-55] and is likewise characterised by a rapid (about 300 beats/minute) atrial rate, although the atrial rhythm is more regular and organised, and by a corresponding increase in the ventricular rate. It is far less common than atrial fibrillation, to which it often degenerates if left untreated; it may revert to normal sinus rhythm in some cases. It carries a similar risk of thrombosis, and recommendations for anticoagulation should be followed as for atrial fibrillation.[9,14,15,42] Management strategies for atrial flutter are broadly similar to those outlined above for atrial fibrillation, namely controlling the increased ventricular response rate and cardioversion. However, in general terms drug therapy for either of these interventions is less successful in flutter than in fibrillation. Cardioversion with drug therapy has a relatively low success rate and cardiac pacing is usually used, which often results in a self-terminating atrial fibrillation. Synchronised direct current cardioversion may be used to restore sinus rhythm if pacing fails. Radiofrequency ablation is an alternative for those resistant to, or intolerant of, standard therapy;[53,55] its high success rate and low risk of complications have led some to suggest it as a first-line option for many patients.[54,55]

Other atrial arrhythmias include **atrial premature beats** and various types of **atrial tachycardia.** Premature beats are usually asymptomatic but if symptoms are severe (the awareness of a pause between normal beats) beta blockers may be used.[56] Atrial tachycardia may also be treated with beta blockers or rate-limiting calcium-channel blockers,[57,58] but if it is due to digoxin toxicity, withdrawal of digoxin may be all that is required.[57] For focal atrial tachycardia, flecainide, sotalol, and amiodarone may also be effective, but catheter ablation is generally preferred.[59]

Paroxysmal supraventricular tachycardia is a re-entry arrhythmia. The term paroxysmal atrial tachycardia was formerly used, but became obsolete when it was realised that many such arrhythmias arise in the atrioventricular junction rather than in atrial muscle. The re-entry circuit can be either due to an accessory pathway between the atria and ventricles (atrioventricular reciprocating tachycardia; AVRT) or re-entry can occur at the site of the node itself (atrioventricular nodal reciprocating tachycardia; AVNRT). It is a relatively common arrhythmia occurring in otherwise healthy individuals. It may resolve spontaneously, or reflex vagal stimulation by respiratory manoeuvres, prompt squatting, or pressure over one carotid sinus may restore normal sinus rhythm. If symptoms associated with the rapid heart rate are severe, treatment will be needed. For termination of paroxysmal supraventricular tachycardia adenosine given intravenously is often the drug of choice;[56,57,60-63] intravenous verapamil or diltiazem, or intravenous beta blockers, are alternatives. If there is no response, or in patients with a wide QRS complex and unclear diagnosis, propafenone, flecainide, procainamide, sotalol, amiodarone, or ibutilide may be used.[56,57,61] Direct current cardioversion may be necessary in some cases, particularly in those who are unstable. Long-term maintenance therapy to prevent recurrence is required in some patients, but there is limited evidence to guide choice of therapy.[57] For many patients radiofrequency catheter ablation is the preferred treatment, particularly in those with AVRT and an accessory pathway. Alternatively, pharmacological therapy may be used. Drugs that block AV conduction are first-line and include beta blockers, rate-limiting calcium-channel blockers, and digoxin. Flecainide and propafenone, class Ic drugs that act on atrial refractoriness, may be used if first-line drugs are ineffective; amiodarone is generally preferred if patients have structural heart disease. Other drugs that may be used include sotalol, quinidine, procainamide, and dofetilide.

Wolff-Parkinson-White syndrome[64,65] is a congenital abnormality characterised by an accessory atrioventricular conduction pathway known as a Kent bundle that leads to ventricular pre-excitation. Although many patients remain asymptomatic, there is an increased risk of atrial fibrillation or paroxysmal supraventricular tachycardia with a danger of degeneration into ventricular fibrillation, particularly if AV-blocking drugs are used. Antiarrhythmics should be used with great caution in such patients, and catheter ablation of the accessory pathway is the treatment of choice.[57,61]

Supraventricular tachycardia can occur rarely *in utero* and is associated with hydrops fetalis and perinatal mortality and morbidity. Treatment is with antiarrhythmic drugs such as digoxin, flecainide, sotalol, or amiodarone given to the mother (transplacental therapy).[58,66-68] In resistant cases direct intraperitoneal or intravascular dosage to the fetus may be necessary.

Ventricular tachycardia[69-73] is usually a re-entry arrhythmia and is often associated with underlying cardiovascular disease such as myocardial infarction or cardiomyopathies. It may also be caused by drugs that prolong the QT interval, or by digoxin toxicity. Congenital channelopathies such as Brugada syndrome[74] and long QT syndrome[75] may cause ventricular arrhythmias in patients with structurally normal hearts. The heart rate is about 120 to 250 beats/minute and the tachycardia, which arises in the ventricles below the AV node, can be paroxysmal, consisting of short self-terminating episodes, or can be sustained (lasting 30 seconds or longer). Ventricular tachycardia can be asymptomatic (if the episodes are non-sustained) or cause minimal symptoms such as palpitations, but is potentially a serious condition which may lead to reduced cardiac output, shock, and progression to **ventricular fibrillation** and cardiac arrest. It is one of the most common causes of sudden unexplained cardiac death.[76] The ECG trace of ventricular tachycardia may be confused with that of supraventricular tachycardia but since the treatments differ markedly, every effort should be made to obtain the correct diagnosis; if the diagnosis is unclear the patient should be treated for ventricular tachycardia.[5,57]

The *initial treatment* of ventricular tachycardia depends largely on the haemodynamic status of the patient. Unstable patients with ventricular fibrillation or pulseless ventricular tachycardia, and patients with irregular sustained ventricular tachycardia, should be given defibrillation, as outlined under Advanced Cardiac Life Support (p. 1268.3). More stable patients with regular monomorphic ventricular tachycardia may be treated with intravenous antiarrhythmics or by sedation and direct current cardioversion; pacing may be effective in some patients. Amiodarone is widely recommended;[5,6,77,78] procainamide is an alternative[5,6,77] and may be preferred if a rapid effect is required.[78] Sotalol may also be used,[5,6] and lidocaine (which was previously the drug of choice) may have a role in some patients, although it is generally less effective. Other alternatives that are available in some countries include ajmaline, flecainide, and propafenone. In some patients with non-sustained ventricular tachycardia, beta blockers may be effective; catheter ablation may have a role if termination of the arrhythmia is not urgent.[78]

After restoration of normal sinus rhythm *maintenance therapy* needs to be considered. Long-term treatment is generally not warranted in low risk patients such as those who have had asymptomatic non-sustained ventricular tachycardia, but patients with severe symptoms or those at high risk of sudden cardiac death, such as survivors of ventricular fibrillation and pulseless ventricular tachycardia, require treatment. Although antiarrhythmic drugs have been used, studies have shown that implantable cardioverter defibrillators reduce mortality more effectively, and these are now recommended for most patients,[6,8,78,79] although the adverse effects need to be considered.[80] Beta blockers are also effective and may be used,[6,78] but there is little evidence to support the use of other drugs, even when electrophysiological testing is used, and they are no longer generally recommended. Amiodarone reduces the risk of sudden cardiac death but has no effect on overall mortality.[81] Sotalol, or amiodarone with a beta blocker, may have a role if implantable cardioverter defibrillators are considered inappropriate;[6] they may also be used to prevent frequent device activation in patients with implantable cardioverter defibrillators and recurrent arrhythmias.[78,82] although the effect of drugs on energy requirements for defibrillation needs to be considered.[83] Catheter ablation may be used if drug therapy is ineffective.[73] There is also some evidence that drugs that are beneficial for cardiovascular risk reduction may reduce the risk of ventricular arrhythmias, including ACE inhibitors and omega-3 fatty acids, but their role is not yet established.[78]

Myocardial infarction is a particular risk factor for ventricular arrhythmias and prophylactic treatment has therefore been tried. Arrhythmias are particularly common early after acute myocardial infarction and lidocaine has been used prophylactically; however, there is little evidence of benefit and routine use is no longer recommended.[84,85] Implantable cardioverter defibrillators may be used for primary prevention of sudden cardiac death in patients with evidence of sustained ventricular tachycardia more than 48 hours after acute myocardial infarction, particularly in patients who also have heart failure; beta blockers,[86,87] amiodarone,[88] or sotalol, may also be considered. Patients with asymptomatic ventricular arrhythmias may also be at increased risk of sudden death but use of antiarrhythmic drugs increases mortality[86,87,89] and is not advised.

Primary prophylaxis may also have a role in other cardiac disorders that are known to cause ventricular arrhythmias and sudden cardiac death, including heart failure, cardiomyopathies, and Brugada syndrome or similar congenital disorders. Implantable cardioverter defibrillators are recommended in high risk patients; beta blockers and amiodarone may have a role in specific cases.[78,90]

QT prolongation and drug-induced arrhythmias. Antiarrhythmic drugs also have proarrhythmic properties and may exacerbate or induce arrhythmias of all kinds, and non-cardiac drugs may also have proarrhythmic effects. *Torsade de pointes* is a particularly serious ventricular arrhythmia that is often drug-induced.[91] It is associated with prolongation of the QT interval (prolongation of ventricular repolarisation), which allows afterdepolarisations to trigger a re-entry tachycardia; this is often non-sustained, but may persist for long enough to cause syncope or it may even progress to ventricular fibrillation. Drugs that cause QT prolongation include antiarrhythmics and several non-cardiac drugs[92-97] including phenothiazines, tricyclic antidepressants, antihistamines such as astemizole and terfenadine, antibacterials such as erythromycin, the antimalarial halofantrine, and the lipid lowering drug probucol. Patients with congenital channelopathies may also have QT prolongation and develop torsade de pointes, often in response to stress- or exercise-induced tachycardia;[75] other causes include electrolyte disorders and bradycardia. If torsade de pointes is drug-induced, withdrawal and subsequent avoidance of the offending drug is mandatory. Initial therapy is usually with intravenous magnesium, to correct any contributory magnesium deficiency, with temporary pacing of the atria or ventricles and correction of any other electrolyte disorders as appropriate.[91] Isoprenaline has been given cautiously to increase the heart rate and shorten the QT interval, until pacing is instituted. Congenital long QT syndromes are usually treated with beta blockers and avoidance of trigger factors, with implantable cardioverter defibrillators in selected patients;[75,78,98] pacing may increase the risk of sudden cardiac death and is no longer generally advised.[75]

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Cardiac arrest

Cardiac arrest is the cessation of effective cardiac mechanical activity and may be associated with four arrhythmias, namely **ventricular fibrillation, pulseless ventricular tachycardia, asystole,** and **pulseless electrical activity (electromechanical dissociation).** In ventricular fibrillation and pulseless ventricular tachycardia there is chaotic electrical and mechanical activity; in asystole a total absence of both activities; and in pulseless electrical activity an absence of mechanical activity, or undetectable activity, in the presence of some electrical activity. The latter two arrhythmias carry a particularly poor prognosis. In adults, ventricular fibrillation is the commonest presentation and usually results from ischaemic heart disease. In children, asystole is more common and usually results from respiratory or circulatory failure.

Cardiac arrest is an emergency and should be treated with full life support measures.

International recommendations[1] for advanced life support and the period surrounding cardiac arrest have been published by the International Liaison Committee on Resuscitation. American,[2] European,[3] and UK[4] guidelines have also been published; these are based on the international recommendations and, apart from some differences in detail, are broadly similar. **Basic life support** (cardiopulmonary resuscitation; CPR) should be started immediately in all unresponsive victims with absent or abnormal breathing, and continued throughout the resuscitation attempt.[1] The purpose of CPR is to maintain cardiorespiratory function until spontaneous circulation can be restored by defibrillation and/or advanced cardiac life support measures, and good quality CPR with a minimum of interruptions greatly increases both the likelihood of conversion to sinus rhythm and overall survival.[1,5] It usually consists of chest compressions and ventilation (mouth-to-mouth/mask or mouth-to-nose), although in witnessed primary cardiac arrest in adults, continuous chest compressions without ventilation are probably as effective as standard CPR and may be given by untrained laypersons

or those unwilling or unable to give ventilation.[1,5,6] For respiratory arrest, CPR with ventilations is preferable.[1]

Subsequent procedures will depend to some extent on the type of arrhythmia present. Rapid electrical **defibrillation** is of paramount importance in converting ventricular fibrillation or pulseless ventricular tachycardia to sinus rhythm by causing momentary asystole that allows the natural pacemakers to resume normal activity. Defibrillation is of no use in asystole or pulseless electrical activity (so-called non-shockable rhythms) and these patients should be treated directly with intravenous drugs as described below.

The first defibrillating shock must be given as quickly as possible;[1] however, prior CPR may increase the likelihood of successful defibrillation, and it is unknown whether or not a specified period of CPR before defibrillation should routinely be given in unwitnessed cardiac arrest.[1,7] After this, CPR should immediately be resumed for 2 minutes before the rhythm is assessed. A further shock should then be given if indicated,[1] followed by immediate resumption of CPR; and this cycle of CPR, assessment, and shock should be continued throughout resuscitation. In adult cases of witnessed cardiac arrest, a precordial thump may be given if a defibrillator is not immediately available; this sometimes aborts the arrhythmia if given within seconds of the loss of cardiac output.[1,8]

CPR and defibrillation alone may be insufficient to convert to or sustain normal rhythm, and **advanced cardiac life support** (ACLS) is often necessary. This includes securing the airway, providing high-flow oxygen, and giving intravenous or intraosseous drugs as indicated.

- *Adrenaline* is given to increase the efficacy of basic life support by improving coronary and cerebral blood flow via its alpha agonist effects.[9] A dose of 1 mg is given intravenously to adults, and should be started after the second[2] or third[3,4] defibrillating shock and repeated every 3 to 5 minutes (every other cycle) while resuscitation continues. For non-shockable rhythms, the same dose and frequency may be started as soon as intravenous or intraosseous access is established.[2-4]
- *Vasopressin* (as argipressin) is an alternative to adrenaline,[1,2] and US guidelines[2] permit a single intravenous dose of 40 units to replace either the first or second dose of adrenaline in patients with any type of cardiac arrest. This is not a universal recommendation, and European guidelines[3] emphasise that since the evidence for adrenaline is stronger it remains first-line.
- *Amiodarone* is the first-line antiarrhythmic for refractory ventricular tachycardia or fibrillation;[1] it is given after the third unsuccessful defibrillating shock.[2-4]
- *Lidocaine* is an alternative to amiodarone, but its performance in studies has been much less convincing and it should be used only when amiodarone is not available.[1-4]
- *Atropine* may be given for symptomatic bradycardia;[1] its routine use during asystole or pulseless electrical activity is no longer recommended.[2-4]
- *Dopamine, isoprenaline, adrenaline, aminophylline,* or *pacing* may be tried in bradycardia refractory to atropine.[2-4]
- The routine use of *sodium bicarbonate* is no longer recommended; however, it may be used if there is hyperkalaemia or after tricyclic antidepressant overdose.[2-4]
- *Other drugs* may be given to treat any reversible causes of cardiac arrest such as hypovolaemia, hypoxia, pneumothorax, pulmonary embolism, drug overdose, electrolyte or glucose imbalances, and hypothermia. Therapy should given promptly once resuscitation has been started.

The principles of cardiac arrest management in **children** are similar to those in adults. However, the cause in children is usually asphyxia and so ventilation during CPR is important; asystole is more common than ventricular fibrillation; and the defibrillating energies and doses of drugs may be different.[1-4,10]

The length of time that a resuscitation attempt should continue is a matter of judgement. In most cases, recovery is unlikely to occur after 20 or 30 minutes of unsuccessful resuscitation, although for persistent ventricular fibrillation or pulseless ventricular tachycardia, or where the cause is hypothermia or drug intoxication, a longer resuscitation attempt is reasonable.[3,11]

Post-resuscitation care should include appropriate management of those sequelae of whole-body ischaemia known as post-cardiac arrest syndrome, notably brain injury, myocardial dysfunction, reperfusion response, and any persistent pathology responsible for the original cardiac arrest.[12-14] Therapeutic hypothermia is recommended in those who remain unconscious after resuscitation, and such patients should be cooled to 32 degrees to 34 degrees for 12 to 24 hours.[1,12-15] Hyperglycaemia should be corrected (and hypoglycaemia avoided), and reperfusion strategies such as thrombolysis and PCI should be performed where indicated.[1,12-14] In survivors of ventricular fibrillation and pulseless ventricular tachycardia in whom it is considered there is a high risk of recurrence, implantable cardioverter defibrillators may be used. Drug therapy may also be used prophylactically (see Ventricular Tachycardia under Cardiac Arrhythmias, p. 1266.1).

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Cerebrovascular Disease

Cerebrovascular disease is a broad term covering any disorder of the cerebral circulation. Ischaemic and haemorrhagic stroke, including subarachnoid haemorrhage, are acute forms, and management of their vascular aspects is discussed in this section. They may also have long-term neurological consequences and are an important cause of vascular dementia (see p. 388.1). Cerebrovascular disease has also been used as a synonym for cerebrovascular insufficiency, also discussed in this section.

Cerebrovascular insufficiency

Drugs with cardiovascular effects have been promoted for the treatment of cognitive impairment attributed to the rather vague concept of 'cerebrovascular insufficiency' (chronic impairment of cerebral blood flow).

Both Alzheimer's disease and vascular dementia share risk factors with atherosclerotic vascular diseases, including coronary and peripheral vascular disease, and there is some evidence that measures for cardiovascular risk reduction (p. 1246.1), particularly antihypertensive drugs, may reduce the incidence of dementia.[1] However, the benefits of cardiovascular drugs in patients with established cognitive impairment are less clear.

Vasodilators have been the main drugs used, but there is little convincing evidence of benefit[2] and those that have been shown to improve symptoms are now thought to do so by altering the rheological properties of blood or by effects on tissue metabolism rather than by cerebral vasodilatation. Similarly, ergot derivatives with vasodilator properties, such as codergocrine mesilate and nicergoline, have been widely used, but there is little evidence to support this. Some benefit has been reported with calcium-channel blockers such as nimodipine and nicardipine, but again they do not have an established role.

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Stroke

Stroke, sometimes called a cerebrovascular accident, is the major consequence of cerebrovascular disease and has been defined as an acute neurological dysfunction of vascular origin with sudden (within seconds) or at least rapid (within hours) occurrence of symptoms and signs corresponding to the involvement of focal areas of the brain. The cause may be ischaemic or haemorrhagic,[1-4] and duration of symptoms varies. Signs and symptoms that disappear within a few minutes or hours (24 hours at most) have usually been termed transient ischaemic attacks (below). However, even transient symptoms may be associated with permanent brain damage, and it has been suggested[5] that the term transient ischaemic attack should be reserved for cases where imaging studies show that no infarction has occurred.

- **Ischaemic stroke** is by far the commonest type and generally results from occlusion of cerebral arteries. This may be caused by local thrombosis at sites of atheroma, but more commonly results from thromboemboli arising from outside the brain and lodging in the cerebral vessels; an example of the latter is cardioembolic infarction associated with atrial fibrillation or acute myocardial infarction. Arterial occlusion results in inadequate cerebral perfusion, which leads to ischaemia and subsequently to stroke. If signs and symptoms persist for more than 24 hours or lead to death, it is generally considered that infarction has taken place and the event is termed a *completed stroke*. About 20% of patients with acute ischaemic stroke have worsening of symptoms within a few days of onset. This is termed *progressing stroke, stroke-in-evolution,* or *unstable stroke,* and may be due to progression of the thrombosis; haemorrhagic conversion, with bleeding into the infarcted area, may also occur.
- **Transient ischaemic attacks** are acute episodes of focal neurological deficit or monocular visual loss (amaurosis fugax), mainly due to ischaemia associated with atherothrombosis. There is usually complete clinical recovery but a tendency for recurrence, and patients are also at an increased risk of stroke.
- **Haemorrhagic stroke** is secondary to subarachnoid or to intracerebral haemorrhage. *Subarachnoid haemorrhage* is bleeding into the fluid-filled subarachnoid space between the brain and the skull, and usually occurs after rupture of an aneurysm; other causes include arteriovenous malformations and hypertensive microaneurysms. *Intracerebral haemorrhage* is bleeding into the parenchyma of the brain, and may result from rupture of arteries damaged by chronic hypertension. Haemorrhage produces a focal haematoma causing a local increase in pressure which may lead to further bleeding and enlargement of the haematoma. The increase in pressure in the area of the haematoma may also produce local ischaemia.

Clinical **presentation** of stroke can vary enormously in severity and combination of signs and symptoms, and depends on the site and extent of infarction or haemorrhage. Haemorrhagic stroke is typically of sudden onset with severe headache, vomiting, and rapid deterioration of consciousness (all signs of raised intracranial pressure) but mild to moderate haemorrhage may be difficult to distinguish from infarction on the basis of clinical signs alone. Neurological deficits in all forms of stroke may include impairments to speech, balance, vision, touch sensation, and movement. Recovery is variable and patients have been classed as major or minor stroke (reversible ischaemic neurological deficit) victims according to their degree of recovery at a given time after the stroke.

Accurate **diagnosis** of the type of stroke is important since management is very different and interventions that are beneficial in infarction may be dangerous in patients with haemorrhage. Clinical presentation may suggest the type of stroke but this is not always reliable. Imaging is therefore usually required to distinguish between haemorrhagic and ischaemic stroke and should be performed as a matter of urgency.[6-9] Computed tomography (CT) is the most widely used technique, although magnetic resonance imaging (MRI) may be preferred where it is available; MRI is more sensitive but availability is limited and it is not suitable for all patients. Diagnosis of transient ischaemic attacks usually rests on the patient's history as these short attacks are seldom witnessed by a physician and there are no objective confirmatory tests; however, imaging has an important role in determining aetiology and guiding subsequent management.[5,8,10,11]

Management of stroke involves immediate treatment of the acute stroke, treatment and prevention of complications such as swallowing disorders or spasticity, rehabilitation, and long-term treatment for secondary prevention. Where possible, patients should be managed within a stroke unit since this has been shown to improve outcome. Patients with a transient ischaemic attack are at high risk of subsequent stroke and should be started on long-term preventative therapy as soon as possible.[12-14] Primary prevention may be considered in other individuals at risk of ischaemic stroke; this includes those with atrial fibrillation, a major risk factor for stroke (see Cardiac Arrhythmias, p. 1266.1), and those with risk factors for atherosclerosis (see Cardiovascular Risk Reduction p. 1246.1). The role of endarterectomy in individuals with carotid artery stenosis is discussed under Long-term Management, below.

Ischaemic stroke. Reviews[15-21] and guidelines[6-9,22] emphasise that, as in myocardial infarction, early recognition of symptoms and prompt evaluation and treatment of stroke are of vital importance. The aim of treatment is to limit or reverse damage to the brain. Ischaemia deprives the cells of oxygen and glucose, leading

to infarction, but this appears to be time-dependent. While some tissue may be irreversibly damaged when the patient presents, there is evidence that surrounding tissue (the 'ischaemic penumbra') may be salvageable. Restoration or improvement of blood flow is therefore a logical means to preserve this tissue; strategies to protect the cells from the consequences of ischaemia are an alternative approach.

Acute management involves general supportive measures, and specific treatments to reverse ischaemia and protect the brain tissue. General supportive measures include ensuring adequate oxygenation and fluid and electrolyte balances, avoiding hypercapnia and hyperglycaemia or hypoglycaemia, abolishing seizures, and treating fever; nutritional status should also be assessed. Control of hypertension is controversial since lowering the blood pressure may reduce cerebral perfusion and worsen ischaemia, and hypertension usually resolves spontaneously without treatment.[23] Antihypertensive therapy may be indicated in specific patients, such as those with severe hypertension or those being considered for thrombolytic therapy.

Specific therapy for ischaemic stroke is limited. As in myocardial infarction, the main cause of ischaemic stroke is thromboembolic occlusion, and use of antithrombotic drugs such as antiplatelets, heparin, and thrombolytics, therefore appears logical. However, evidence of benefit is not as clear as it is in myocardial infarction, and the risks may be greater; the presence of haemorrhage must be excluded and the risk of potentiating spontaneous secondary brain haemorrhage (haemorrhagic transformation) must be borne in mind. Other strategies to improve blood flow or to limit the effects of ischaemia using neuroprotectants have also been tried, but results to date have been disappointing.

Antiplatelet drugs. Aspirin has been evaluated in two large studies—the International Stroke Trial (IST)[24] and the Chinese Acute Stroke Trial (CAST).[25] The combined results of these studies[25] showed that aspirin 160 mg[25] or 300 mg[24] daily started within 48 hours of symptom onset produced about 9 fewer deaths or non-fatal strokes per 1000 patients in the first few weeks following ischaemic stroke. Aspirin has therefore been recommended for patients with ischaemic stroke who are not receiving thrombolytic or anticoagulant therapy, and should be started within 24 or 48 hours of stroke onset.[6-9,26] For patients treated with thrombolysis, aspirin should be started after 24 hours.[8,9,26] Other antiplatelet drugs are under investigation, but do not yet have an established role;[6,7] a study with the glycoprotein IIb/IIIa antagonist abciximab was stopped early due to an increased incidence of bleeding,[27] although studies using lower doses continue.[28]

Anticoagulants are not routinely recommended in the early management of acute ischaemic stroke,[6,8,9] although they may have a role in selected patients.[7] Anticoagulation should prevent further thrombus formation and limit the size of the cerebral infarct; however, any benefit may be offset by an increase in intracranial haemorrhage, and a systematic review[29] has suggested there is no evidence to support routine use. The IST,[24] which evaluated two dosages of heparin (5000 units or 12 500 units subcutaneously twice daily), found no benefit from either regimen and the higher dose particularly was associated with haemorrhagic stroke and bleeding. Another study,[30] comparing the low-molecular-weight heparin tinzaparin with aspirin, similarly found no benefit. It had been suggested that patients with cardioembolic stroke were likely to benefit from heparin therapy,[31] even though there is a special risk of haemorrhagic transformation in these patients, which means that early anticoagulation is often hazardous. However, the IST[24] failed to show any benefit in this group, and a study[32] of low-molecular-weight heparin in patients with acute ischaemic stroke and atrial fibrillation also showed no benefit. No improvement in outcome was reported after 3 months in a study of danaparoid given in acute ischaemic stroke.[33] A study[34] with ancrod found an improvement in outcome when given within 3 hours of stroke onset, but a further study was terminated due to lack of benefit.

The risk of venous thromboembolism (deep-vein thrombosis and pulmonary embolism) is increased after stroke, particularly in immobile patients, and prophylaxis may be considered in those at high risk.[7,8,26] Low-dose subcutaneous heparin or low-molecular-weight heparin are suitable; use of low-molecular-weight heparin has been recommended[9] based on a study[35] suggesting that enoxaparin was superior to unfractionated heparin, but this remains to be confirmed.

Thrombolytics. Intravenous thrombolytics increase the risk of cerebral haemorrhage and have therefore generally been contra-indicated in both ischaemic and haemorrhagic stroke. However, there is evidence that use of thrombolytics in ischaemic stroke may be of benefit, despite the increased risk of bleeding, and they may have a role in selected patients,[36-38] particularly if they can be given in the early stages.[39] A study[40] with alteplase given within 3 hours of the onset of stroke (NINDS—National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial) found that clinical outcome was improved, despite an increased incidence of symptomatic intracerebral haemorrhage. Patients treated with alteplase were more likely to have minimal or no disability 3 months after stroke,[40] and this benefit was maintained at 12 months.[41] However, there was no difference in mortality or rate of recurrence of stroke. On the basis of this study, most guidelines[6-8,26] now recommend alteplase for selected patients if it can be given within 3 hours of stroke onset, and this appears to be safe in practice.[42,43] Use of alteplase up to 4.5 hours after stroke onset has also been recommended.[9,44] An observational study[45] suggested that alteplase was safe within this timeframe, while a randomised study[46] found that alteplase given between 3 and 4.5 hours after stroke onset improved outcomes, although the authors stressed that treatment within 3 hours was still preferred. Other thrombolytics, such as streptokinase, have generally produced less favourable results, and none of these are currently recommended. The intra-arterial route has also been tried and may be used in selected patients.[6,7,9,26] Combined use of intravenous and intra-arterial alteplase,[47] as well as use of adjunctive therapies such as therapeutic ultrasound[48] or antithrombotics, are under investigation but do not yet have an established role.[6]

Other approaches that have been tried include various methods to improve cerebral blood flow. Haemodilution with *dextran* or *pentastarch* has generally been disappointing and is not usually recommended.[6,7,9] Drug-induced hypertension may also increase cerebral blood flow and appears to be safe,[49] but clinical benefit is unproven.[6] Hypoxia and hypocapnia may cause cerebral vasoconstriction as well as directly contributing to ischaemic injury, and there have been anecdotal reports and small studies reporting benefit with *hyperbaric oxygen therapy*, although a systematic review[50] suggested that clinical benefit was unlikely. Treatment with *corticosteroids* or hyperosmolar diuretics such as *glycerol* or *mannitol* in an attempt to reduce the cerebral oedema has also been disappointing. There may be some benefit with glycerol, but further evidence is needed.[51]

Neuroprotection. Ischaemia leads to a complex series of biochemical changes, the 'ischaemic cascade', resulting eventually in cell necrosis. The process is incompletely understood, but steps include calcium influx and release of neurotransmitters. Drugs acting at different steps in this ischaemic cascade, sometimes termed neuroprotectants, have been tried in acute ischaemic stroke in the hope of limiting the damage caused by ischaemia. Results of studies so far have been largely disappointing, and no drug has yet been found to be effective. However, research continues,[52] with early treatment and combination therapies being a particular focus.

Long-term management. Patients who have had an ischaemic stroke or transient ischaemic attack are at risk of further stroke but are also at increased risk of other cardiovascular events, including myocardial infarction and sudden death. Long-term treatment for secondary prevention therefore has an important role.[7-9,12,53-58] All patients should be assessed for standard cardiovascular risk factors, particularly hypertension, and these should be treated as appropriate (see under Raised Cardiovascular Risk, p. 1246.1). There is some evidence that reduction of blood pressure and lipids reduces the risk of stroke irrespective of the presence of hypertension or hyperlipidaemia.[55] Statins reduce the risk of stroke in patients at high risk for cardiovascular events[59,60] and atorvastatin has been shown to reduce the risk of recurrent stroke in patients with isolated cerebrovascular disease;[61] long-term treatment with statins is therefore recommended.[7-9,12] Reduction of blood pressure, whether raised or normal, has also been recommended;[7,9,56] ACE inhibitors or angiotensin II receptor antagonists have been suggested as being particularly beneficial,[62] although the evidence is not conclusive and a subsequent study[63] with the angiotensin II receptor antagonist telmisartan found no effect on the risk of recurrent stroke. Atrial fibrillation is a specific risk factor for stroke and should also be treated (see Cardiac Arrhythmias, p. 1266.1). Hypercoagulability may increase the risk of stroke and blood screening for polycythaemia, thrombocytosis, and abnormal coagulation function has been recommended. Carotid endarterectomy is of established benefit for secondary prevention in patients with clinically significant carotid stenosis,[7-9,64] but its role in primary prevention is less clear and benefits may not outweigh risks.[65,66] Antithrombotic therapy may also have a specific role.

Antiplatelet drugs. Long-term prophylaxis with antiplatelet drugs reduces the risk of future serious vascular events including stroke in patients who have already suffered an ischaemic stroke or transient ischaemic attack,[12,24,56,67] regardless of age.[68] Most evidence relates to aspirin, although the optimum dose is unclear; medium doses of 75 to 325 mg of aspirin daily have been most widely studied[67] and an analysis of studies using aspirin over a dose range of 50 to 1500 mg daily found no relationship between dose and the reduction in risk of stroke.[69] In patients undergoing carotid endarterectomy the risk of stroke, myocardial infarction, and death over 3 months may be lower for those taking medium dose aspirin compared with higher doses.[70] Additional benefit has been reported for aspirin given with dipyridamole, and this combination is now preferred over aspirin monotherapy.[8,9,12,26] Dipyridamole has been given alone but is less effective than the combination[71,72] and is not generally recommended. Clopidogrel alone has a similar efficacy to aspirin with dipyridamole[73] and may be used as an alternative;[7,9,12,26] it is the preferred option in patients unable to tolerate aspirin[8,26] but should not be given with aspirin for stroke prevention since any benefit is offset by an increased risk of bleeding.[74] Ticlopidine has also been used, but adverse effects are a problem and a study[75] in black patients found that it was less effective than aspirin.

Anticoagulants. Oral anticoagulants have an established role in patients with cardioembolic stroke, but in patients with non-cardioembolic stroke or with transient ischaemic attacks they have no clear advantage over antiplatelet drugs,[76,77] and some studies[78,79] comparing warfarin with aspirin have been stopped early due to increased bleeding risks with the anticoagulant. Anticoagulants are therefore not generally recommended for secondary prevention in non-cardioembolic stroke[7-9,12,56] although they have been used in patients with recurrent symptoms despite antiplatelet therapy and may be considered in other selected patients.[7,8,26,56]

Subarachnoid haemorrhage. Aneurysmal subarachnoid haemorrhage[80-84] is associated with high morbidity and mortality, early deaths being due to damage from initial bleeding, recurrence of bleeding, and infarction. Infarction is often a result of vasospasm which is one of the pathophysiological mechanisms that contributes to stopping the bleeding; clot formation and increasing intracranial pressure are other processes involved. Up to a quarter of patients with subarachnoid haemorrhage develop delayed cerebral ischaemia mainly between days 5 and 14 after the initial bleed, and again vasospasm may be a contributory factor.

Early medical treatment aims to prevent delayed cerebral ischaemia, to prevent rebleeding, and to stabilise the patient. Surgical or endovascular interventions to clip or embolise the aneurysm or correct the arteriovenous malformation are then performed to prevent further haemorrhage. Vasospasm and delayed cerebral ischaemia may be prevented by maintaining or slightly increasing plasma volume and blood pressure, and a fluid intake of 2 to 3 litres daily has been recommended.[80] However, there is no good evidence to support routine volume expansion[85] and the main aim should be to maintain normal plasma volume and avoid hypotension. Volume expansion may, however, be a reasonable approach for treating vasospasm if it becomes established.[84]

Oral nimodipine is of benefit[86] and should be started as soon as possible after diagnosis of aneurysmal subarachnoid haemorrhage.[8,84] Antiplatelet drugs have also been tried and may improve outcomes, but this remains to be confirmed.[87] Statin therapy has also been reported to reduce cerebral vasospasm,[88] although a meta-analysis[89] found no significant effect. Established vasospasm may be treated by angioplasty, or intra-arterial vasodilators may be given.[84] There is some evidence of benefit with intra-arterial papaverine,[90] although adverse effects have also been reported;[91] verapamil has also been used.[92] Use of antifibrinolytics such as aminocaproic acid or tranexamic acid to prevent rebleeding is of uncertain benefit. A systematic review[93] found that any benefits were offset by an increase in poor outcomes due to cerebral ischaemia, and antifibrinolytics are therefore generally no longer recommended.[80] However, there is some evidence that short-term use followed by early surgery may reduce rebleeding without increasing ischaemic complications,[94,95] and this has been suggested[84] as a reasonable approach. Paradoxically, high doses of aminocaproic acid have been associated with increased bleeding after subarachnoid haemorrhage (see Effects on the Blood, under Adverse Effects of Aminocaproic Acid, p. 1132.1); the significance of this is unclear. Headache can be managed with analgesics such as paracetamol, codeine, dihydrocodeine, or tramadol.[82,83] Localised haematomas may be amenable to surgical evacuation, and intraventricular thrombolytics have also been used.[96]

Intracerebral haemorrhage. Outcome of intracerebral haemorrhage depends on the location and size of the haematoma (determined by CT), on the level of consciousness, and on the progression of neurological signs, and development of increased intracranial pressure.[97-100] Any known cause of bleeding, such as warfarin anticoagulation, should be reversed.[8,101] Optimum management of blood pressure is uncertain; in those with 150 to 220 mmHg systolic, a rapid reduction to 140 mmHg systolic is probably safe,[101] but hypoperfusion should be avoided. Short-acting antihypertensives such as nicardipine, labeta-

lol, esmolol, or sodium nitroprusside are generally used, although theoretically nitroprusside may increase intracranial pressure and should be avoided if this is already raised.[98] Surgical drainage of the haematoma may sometimes be possible, but its role is uncertain;[9,98,101] routine early surgery for all patients has not been shown to improve outcome,[102] but has been recommended in previously fit patients with hydrocephalus.[8] Instillation of a thrombolytic to improve aspiration of the haematoma has been reported,[103] but benefit has not been established. Raised intracranial pressure should be controlled[101] (see below). Seizures should be treated with antiepileptics, but prophylaxis is not recommended.[101] Use of activated factor VII to reduce the risk of further bleeding provided some benefit,[104] but has not been shown to improve survival or functional outcome.[105] Long-term management of risk factors, particularly hypertension, should be considered for secondary prevention.

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Raised intracranial pressure

The intracranial compartment consists of brain parenchyma, vascular tissue, and cerebrospinal fluid (CSF). Since the skull is a rigid structure an increase in the volume of any one of these components without a compensatory decrease in one of the others will lead to raised intracranial pressure (intracranial hypertension). Conditions that may be associated with an increase in intracranial volume, and thus pressure, include: formation of cerebral oedema after head injury or ischaemic stroke, or around tumours; mass-lesions such as tumours or haemorrhage; CNS infections; and metabolic disorders. Increased dural sinus venous

pressure, increased resistance to CSF outflow, or an increased rate of formation of CSF may also raise intracranial pressure. In idiopathic intracranial hypertension there is no obvious cause. Raised intracranial pressure can produce irreversible damage to the CNS and is potentially fatal; herniation of brain tissue can occur and reduced cerebral blood flow can lead to cerebral ischaemia. *Symptoms of raised intracranial pressure include* headache, which is often worse in the morning and may wake the patient from sleep, vomiting, drowsiness, and visual disturbances; papilloedema reliably indicates raised intracranial pressure but may not be present in all patients.

Both pharmacological and physical methods may be used to reduce raised intracranial pressure, although evidence for a beneficial effect on outcomes is limited for most therapies.[1] Choice depends to some extent on the underlying cause,[1-11] but in acutely raised intracranial pressure the initial aim is to reduce the volume of the intracranial contents as quickly as possible to prevent brain damage. In most cases, this involves general measures and drug therapy, but for patients with haematoma, ischaemic stroke, or tumours, surgery is often the treatment of choice, although drugs and other methods may be used to control intracranial pressure before surgery.

Cerebral blood flow depends on both intracranial pressure and cerebral perfusion pressure and it is important that ***measures to reduce intracranial pressure*** do not adversely affect cerebral perfusion. Blood pressure should be monitored and intracranial pressure monitoring is also often advised since lowering the intracranial pressure too far is also deleterious. Pain and agitation increase intracranial pressure and patients should receive adequate analgesia; benzodiazepines may be given to control unnecessary movement but if this is ineffective the use of neuromuscular blockers such as pancuronium or atracurium with artificial ventilation should be considered. Raising the patient's head to promote venous drainage may be helpful, although this is controversial since cerebral perfusion pressure may be reduced; however, head elevation by 15 degrees to 30 degrees appears to be safe and is widely used, and the head should be kept in a neutral position.[1,5] Hyperventilation reduces the intracranial pressure by constricting the cerebral blood vessels and controlled hyperventilation has been used. However, cerebral blood flow may also be reduced, so routine use is not generally advised,[1-3,8] although hypoxia should be avoided.[5] Restriction of fluid intake has been advised but, again, cerebral perfusion pressure may be reduced if hypotension occurs and intravenous fluids should therefore be given as appropriate. Fever should be treated,[5] but the use of controlled hypothermia to provide neuroprotection is not established; a review[12] of its use in head injury found no evidence that it improves outcome.

Where these general measures fail to reduce intracranial pressure adequately, **removal of CSF** through a ventricular catheter may be effective, and is particularly suitable if an intraventricular pressure monitor is being used.[1,5] Alternatively, pharmacological treatment may be given.

The mainstay of ***pharmacological treatment*** for acutely raised intracranial pressure is hyperosmolar therapy.[1,3,13] Mannitol is usually the treatment of choice, although hypertonic sodium chloride is increasingly being used. Glycerol or sorbitol are further options, and urea and hypertonic glucose have also been used. Loop diuretics have been given as an alternative to osmotic diuretics or as adjuncts to them.

Osmotic diuretics act by increasing the osmolality of plasma and drawing water out of the tissues, as well as by promoting an osmotic diuresis, but care should be taken to avoid hypovolaemia and they should not be used in patients who are dehydrated. Caution is also required in patients with intracranial haemorrhage since the reduction in intracranial pressure could exacerbate bleeding.[4] Osmotic diuretics may also be used for acute intracranial hypertension associated with brain tumours. They are not routinely recommended for reducing intracranial pressure in cerebral malaria, and use in other CNS infections is controversial; however, they may have a role in patients with bacterial meningitis if intracranial pressure is raised.[9]

- *Mannitol* decreases intracranial pressure and increases cerebral blood flow both by an osmotic effect and by decreasing blood viscosity.[2,13] It is widely used to reduce intracranial pressure after severe head injury,[2,3,6] although evidence from randomised studies is limited.[14] It is also used to control intracranial pressure before surgery, as well as in patients with ischaemic stroke or hepatic failure, and in children with diabetic ketoacidosis.
- In addition to its ability to lower intracranial pressure *glycerol* is reported to be able to increase blood flow to areas of brain ischaemia; it may be given orally or intravenously. There is some evidence[15,16] that routine use of oral glycerol improves neurological outcomes in children with bacterial meningitis. However, there have been reports of severe adverse effects including haemolysis, haemoglobinuria, and renal failure in patients given glycerol.
- *Hypertonic sodium chloride* has been shown to reduce intracranial pressure in several studies and it may have a role in raised intracranial pressure associated with traumatic or non-traumatic causes.[1,2,5,17,18] It has a potential advantage over osmotic diuretics in that it also treats hypovolaemia. However, evidence that its use improves outcomes is not yet available.
- Strongly *hyperosmotic glucose* solutions (25 to 50%) have been used to reduce raised intracranial pressure and cerebral oedema caused by delirium or acute alcohol intoxication.

If control is required for more than a few hours, repeated or continuous dosage of osmotic diuretics may be necessary. Mannitol may accumulate with continuous infusion and repeated bolus doses are generally preferred. Fluid and electrolyte balance and plasma osmolality should be closely monitored.

Corticosteroids have an accepted and important role in the management of raised intracranial pressure associated with tumour-induced cerebral oedema.[1,7] They may be used intravenously in high doses to control acutely raised intracranial pressure due to a rapidly expanding tumour. Lower doses are given orally for maintenance or where the onset of cerebral oedema is more insidious. Corticosteroids have also been tried in patients with stroke, but results have been disappointing. Although corticosteroids have been widely used in traumatic head injury, a large randomised study[19] found that they increased the risk of mortality and they are no longer routinely recommended.[1,3,5,20]

The use of barbiturate-induced coma with intravenous *thiopental* or *pentobarbital* for raised intracranial pressure has been controversial but it may be of benefit in patients refractory to conventional therapies.[2,3] In addition to their effect on intracranial pressure barbiturates may be able to protect the brain from ischaemia. *Propofol* may be an alternative, but caution is required with higher doses.[1,3,11] *Trometamol* reduces raised intracranial pressure, possibly by causing metabolic acidosis leading to vasoconstriction of cerebral vessels, and it may have a role in some patients.[1,13] Use of vasoconstrictors such as *dihydroergotamine* has also been reported.[1]

Idiopathic intracranial hypertension (pseudotumor cerebri) is a rare disorder of unknown cause in which there is a raised intracranial pressure in the absence of an intracranial mass or obstruction to CSF outflow. Although it was previously known as benign intracranial hypertension, since it is not life-threatening and is usually self-limiting, symptoms may be severe or become chronic, and there is a risk of irreversible visual loss.[21,22] Patients are often obese and tend to be young and female. Drug-induced intracranial hypertension may also occur.

Management of mild symptoms usually involves diuretic treatment with furosemide, a thiazide, or acetazolamide. Analgesics, tricyclic antidepressants, or the antiepileptic topiramate may be used to control headache.[21] Corticosteroids can control acute symptoms but long-term adverse effects limit their use. Repeated lumbar puncture to remove CSF may relieve symptoms and has been used every 2 to 5 days to induce remission. In patients who cannot be controlled medically, surgical methods such as lumboperitoneal shunting may be required. There have been reports of beneficial effects with *octreotide* in a few patients.[23,24]

Chronically raised intracranial pressure after CNS infections has also been treated with acetazolamide although there is limited evidence of benefit (see p. 2002.1).

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Other Vascular Disorders

Peripheral vascular disease, in its broadest sense, covers diseases of arteries, veins, and the lymphatic system, and includes atherosclerotic, vasospastic, thromboembolic, and inflammatory disorders. Peripheral vascular disease is commonly used as a synonym for chronic occlusive peripheral arterial disease, the management of which is discussed below. Also discussed in this section are thromboembolic disorders including venous thromboembolism and peripheral arterial thromboembolism, and also vasospastic arterial disorders. For chronic venous disease see also Varicose Veins (p. 2564.1) and Wounds and Ulcers (p. 1690.1).

Various forms of *central* vascular disorder are discussed under Cerebrovascular Disease, p. 1269.2. *Coronary* vascular disease is discussed under Ischaemic Heart Disease, p. 1254.2.

Chronic occlusive peripheral arterial disease

Peripheral arterial occlusive disease is usually caused by atherosclerosis (p. 1250.2) and is therefore very often associated with other cardiovascular diseases.[1] Although often symptomless, it may progress to **intermittent claudication**,[2,3] a condition characterised by pain that develops during exercise and disappears at rest. In severe disease pain may also occur at night or when resting (**critical limb ischaemia**).[4,5] The pain is due to ischaemia (insufficient oxygen supply) resulting from obstruction or vasoconstriction of peripheral arteries. Ischaemia may also result in trophic changes in the skin, and in severe or advanced disease, ulceration of skin and tissues can occur and may progress to gangrene. Some patients develop ulceration without previous symptoms of intermittent claudication, particularly where ischaemia is precipitated by thrombosis. Vasospasm due to smoking may also be a contributory factor. **Thromboangiitis obliterans** (Buerger's disease)[6] is another occlusive arterial disease, but it is a result of inflammatory and proliferative lesions in medium and small arteries and veins of the limbs and is almost invariably caused by tobacco exposure. The lesions are mainly thrombotic in nature. It progresses more rapidly than atherosclerotic disease; severe ulceration and gangrene, necessitating amputation, may often occur.

Management. Patients with occlusive arterial disease are at high risk of other cardiovascular events such as myocardial infarction and stroke, and treatment is important both to reduce this risk and to improve symptoms.[1,7-9] Aggressive measures to reduce cardiovascular risk (see p. 1246.1) should be implemented in all patients whether or not they have symptoms, with particular attention paid to treating obesity, hypertension, dyslipidaemias, and diabetes. Antiplatelet therapy should be given to *all* patients. Cessation of smoking is essential both to reduce risk and to halt disease progression, and in the case of thromboangiitis obliterans represents the definitive treatment. These measures do not generally improve symptoms in those with intermittent claudication, although supervised exercise programmes have been shown[10] to improve walking distance and are recommended,[7,9] and there is also some evidence[11] that *lipid lowering therapy* may do the same.

Many **drugs** have been used for symptom control in occlusive arterial disease, but studies have often been unsatisfactory and their efficacy and/or overall place in management remains to be firmly established. Analgesia is important in patients with critical limb ischaemia, particularly in those unsuitable for revascularisation.[9] Drugs intended to improve ischaemia have also been widely used, although few have an established role.

Vasoactive drugs have been the most commonly used drugs in intermittent claudication, although any purported benefit is probably due to mechanisms other than vasodilatation, such as actions on blood cells or changes in

blood rheology. *Vasodilators* do not preferentially dilate the affected arteries, which may in any case be fully dilated already. Dilatation of arteries supplying non-ischaemic tissues elsewhere in the body may actually divert blood away from the affected ischaemic area—the so-called 'steal' phenomenon; this is a known risk with all vasodilators, but especially with powerful arterial vasodilators such as hydralazine and this type of drug is not suitable for use in peripheral arterial disease.

- *Naftidrofuryl* is widely used in Europe. It has been shown to increase walking distance[12] and has been recommended as a first-line treatment in the UK.[13]
- *Cilostazol*, which has antiplatelet and vasodilator effects, may also increase walking distance[14] and has also been widely used, particularly in the USA.[1,3,7,9]
- *Pentoxifylline* has shown limited efficacy in small studies, but the evidence is considered insufficient to recommend its use.[3,8,9,13]
- Similarly, *inositol nicotinate*, although licensed in some countries for symptomatic management of intermittent claudication, does not appear to have good evidence of efficacy.[8,13]
- *Prostaglandins* such as *alprostadil* (prostaglandin E_1) and *epoprostenol* (prostacyclin) act as vasodilators and may be of benefit in occlusive arterial disease,[2,4] but their role remains unclear and their use may not be practical in most patients.[7] Oral prostaglandins such as *beraprost* have also been tried but do not appear to be effective and are not recommended.[7-9,15]
- *Other drugs* that have been tried in small studies include arginine, carnitine derivatives, and ginkgo biloba,[2] but in each case the evidence of benefit is scant. Growth factors (given locally) and gene therapy are under investigation.[2,4,5]

For patients with severe intermittent claudication that fails to respond to standard medical treatment, and for those with critical limb ischaemia (pain at rest or ischaemic ulceration), **non-pharmacological therapy** is usually required; intravascular thrombolysis may be used in acute ischaemia (see Peripheral Arterial Thromboembolism, below), but its role in chronic disease is not established.[7,9] Bypass surgery, endarterectomy, and percutaneous techniques such as angioplasty, atherectomy, and stenting are used for revascularisation; amputation may be necessary where ischaemia is irreversible. For treatment to prevent thrombosis and restenosis after revascularisation, see Reperfusion and Revascularisation Procedures, p. 1259.2.

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Thromboembolic disorders

The term thromboembolic disorder has been applied loosely to cardiovascular disorders associated with thrombus and embolus formation in blood vessels. A **thrombus** is a stationary blood clot composed of fibrin and platelets and other cellular elements. **Thrombosis** is occlusion of a vein or artery by a thrombus. An **embolus** is a fragment of blood clot, atheromatous material, or other foreign matter carried along in the bloodstream. Occlusion of a blood vessel by an embolus is termed **embolism** or **thromboembolism.**

Formation of blood clots in the body is the result of a coagulation cascade (see Haemostasis and Fibrinolysis, p. 1124.3). Under normal circumstances systemic coagulation is prevented by natural antithrombotic systems that limit blood clots to sites of vascular injury. Thromboembolic disorders occur when there is an imbalance between these systems. Three factors are involved, namely damage to the endothelial lining of blood vessels, reduced blood flow, or changes in the coagulation mechanisms of the blood. A further factor that increases the risk of clotting is the presence of an artificial surface in contact with the blood, for example mechanical heart valves, intravascular catheters, or during extracorporeal circulation procedures. Thromboembolism can occur in any part of the circulation, including the heart and the capillaries, but the characteristics of the thrombi, the consequences, and the management of thromboembolism depend to a large extent upon whether the arterial or venous system is involved.

The mainstay of management for thromboembolic disorders is antithrombotic drugs. These act at different points in the coagulation cascade and include anticoagulants and antiplatelet drugs, which are used to limit the extent of thrombosis or thromboembolism and to prevent further thromboembolic events occurring, and thrombolytics, which are used to lyse the clot.

Arterial thromboembolism is usually a consequence of damage to the endothelium due to atherosclerosis (p. 1250.2); the atheroma may block the blood vessel or, more commonly, occlusion is a result of thrombus formation at a site of a recently ruptured atheromatous plaque. Arterial thrombi contain more platelets than venous thrombi and tend to remain fixed, but emboli may break off and occlude distal vessels. Arterial emboli may also result from thrombosis within the heart, for example due to arrhythmias or valvular heart disorders.

Thrombosis or thromboembolism in the arterial circulation produces ischaemia in the tissues perfused by the artery, which may lead to infarction. It may therefore result in myocardial infarction (p. 1257.1) or unstable angina (p. 1254.3) if it occurs in coronary arteries, stroke (p. 1269.2) if it occurs in cerebral arteries, or critical limb ischaemia if it occurs in peripheral arteries (below).

Venous thromboembolism (p. 1274.1) is usually a consequence of stasis of the blood, but other factors such as local trauma or coagulation activation are also required. Reduced venous blood flow occurs in many conditions, including obesity, heart failure, and during prolonged immobilisation. Abnormal clotting may occur in conditions such as malignancy, pregnancy, liver disease, and the nephrotic syndrome, or during oestrogen therapy; it may also be due to inherited or acquired clotting disorders or thrombophilias (see below). Surgical operations are particularly associated with venous thromboembolism: trauma activates clotting factors and reduced blood flow may occur during the procedure and recovery period.

Venous thrombi have a 'red tail' of fibrin and red cells that may occlude the vein but which often separates to form an embolus; this is most likely during the early stages when the thrombus is only loosely attached. Thrombosis or thromboembolism in the venous circulation produces oedema or inflammation in the tissue drained by the affected vein. The commonest type of venous thrombosis is deep-vein thrombosis, which is associated especially with immobility and the postoperative period. Pulmonary embolism is the most serious complication of deep-vein thrombosis and occurs when part of the thrombus migrates in the circulation and becomes lodged in the pulmonary artery. Hypercoagulable states may result in deep-vein thrombosis or more generalised clotting in microvessels (microvessel thrombosis), such as thrombotic thrombocytopenic purpura or purpura fulminans (see Thrombotic Microangiopathies, p. 1159.1).

Thrombophilias are acquired or inherited disorders of the clotting system in which the antithrombotic mechanisms are impaired. Inherited deficiencies of antithrombin III, protein C and protein S all predispose to thromboembolism. Resistance to activated protein C has been identified as a major cause of inherited thrombophilia and appears to be due to a mutation in the factor V gene (factor V Leiden). A mutation in the prothrombin (factor II) gene is associated with increased concentrations of prothrombin and risk of thrombosis. Acquired thrombophilias may occur secondary to disorders such as malignancy, infection, or collagen-vascular disorders; in many cases antiphospholipid antibodies (such as lupus anticoagulant) are present. Hyperhomocysteinaemia is another risk factor and may have both inherited and acquired causes.

Inherited thrombophilias generally result in venous thromboembolism; this is often recurrent and may occur in unusual sites or at a young age. They often present when some further risk factor is present, such as pregnancy, use of combined oral contraceptives, or surgery, but the value of screening asymptomatic patients remains unclear. Acquired thrombophilias may lead to arterial or venous thromboembolism.

Patients with thrombophilias who develop thromboembolism should be treated conventionally, with anticoagulants or thrombolytics as appropriate. There continues to be debate regarding the duration of therapy, with some authorities recommending life-long anticoagulant therapy after a single episode and others recommending life-long therapy only in those with recurrent thrombosis. The optimum intensity of long-term anticoagulation in patients with thrombophilia is also debated. If anticoagulation is not continued, thromboprophylaxis should be given during high risk situations. Thromboprophylaxis is probably also necessary during pregnancy, particularly in women with antiphospholipid antibodies who are at risk for recurrent fetal loss (see Systemic Lupus Erythematosus, p. 1613.3), but the risks to the fetus from anticoagulant therapy must also be considered (see Venous Thromboembolism, p. 1274.1). Replacement of antithrombotic factors may have a role in some situations.

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Peripheral arterial thromboembolism. Thromboembolism may occur in various peripheral arteries, but most commonly affects those of the lower limbs, causing reduction in blood flow to the distal portions of the limb, which may lead to critical limb ischaemia. Sudden or acute occlusion (acute limb ischaemia) requires emergency treatment to restore blood flow and preserve the limb; similar approaches may also be necessary in chronic obstruction if the viability of the limb is threatened.

Peripheral arterial thromboembolism produces pain, pallor, and coldness in the affected limb. Numbness and paraesthesia may occur and if the clot is not removed, gangrene develops. Occlusion may be due to embolism or thrombosis, or to a combination of the two. It may occur in structurally normal arteries, particularly in patients with thrombophilia (see Thromboembolic Disorders, above). However, most patients have underlying chronic occlusive peripheral arterial disease (p. 1272.3), although this is often asymptomatic, and occlusion develops at the site of an underlying atherosclerotic plaque. Sudden onset is usually due to an embolus, which often arises from the heart; atrial fibrillation, cardiomyopathy, myocardial infarction, and valvular heart disease are all associated with peripheral arterial embolism. Thrombotic occlusion usually has a more gradual onset, particularly where atherosclerosis has already reduced blood flow and collateral vessels have developed, allowing some perfusion of the limb to be maintained.

Sudden arterial occlusion requires emergency evaluation and treatment so that circulation can be restored as quickly as possible, before loss of viability makes amputation necessary.[1-6] Both pharmacological and non-pharmacological methods may be used, depending on availability and factors such as the location and severity of the occlusion. Where there is imminent danger to the limb, surgical revascularisation (bypass surgery) has often been preferred, but improvements in drug therapy and percutaneous techniques have allowed their role as initial therapy to expand. Anticoagulation with heparin should be

started in all patients to prevent propagation of the clot and embolisation.[1-3,5,7,8] In all but the most urgent cases, angiography should be performed to assess the most suitable revascularisation method. The options available are intra-arterial thrombolytics, percutaneous clot removal, surgical clot removal, or surgical bypass. Studies comparing thrombolysis with surgical revascularisation have generally found outcomes to be similar,[9] although there is some evidence that thrombolysis should be preferred if the duration of occlusion is less than 14 days and surgical bypass should be preferred if the duration is more than 14 days.[8-10] Thrombolysis may also be used to reduce the clot burden before diagnostic angiography or as an adjunct to percutaneous removal or other surgical procedures.[5,6,8,11]

Although thrombolytics have been given systemically there is a high risk of bleeding and intra-arterial (catheter-directed) thrombolysis directly into the clot is now preferred.[2,6-8,10-13] Urokinase and alteplase are the most widely used thrombolytics and appear to be more effective than streptokinase;[10,12,14] reteplase and tenecteplase have also been tried.[2,7,8,10,12] Anticoagulants should be continued during and after thrombolysis to prevent rethrombosis, although the risk of bleeding is increased. Adjunctive antiplatelet therapy with glycoprotein IIb/IIIa-receptor antagonists such as abciximab has also been tried and appears to improve outcomes,[6,15,16] although this requires confirmation in large controlled studies.

Patients in whom an acute occlusion has been successfully treated should be assessed for long-term treatment. Those with underlying atherosclerotic disease should be treated as appropriate (see Chronic Occlusive Peripheral Arterial Disease, p. 1272.3), while those with occlusion due to embolism should be investigated for a possible source and long-term oral anticoagulation should be considered to prevent recurrence.[5]

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Venous thromboembolism. The term venous thromboembolism embraces both deep-vein thrombosis (DVT) and pulmonary embolism (PE). In DVT formation of a thrombus (blood clot), often in the pockets of valves, blocks the veins of the lower limbs or main pelvic veins or, less commonly, the veins of the upper extremities. PE occurs when the thrombus or part of it migrates in the circulation and blocks the pulmonary artery. DVT and PE are manifestations of the same disease process and are considered a single clinical entity; many patients presenting with DVT may also have asymptomatic PE, and vice versa. Various factors underlie the development of thrombosis and there are several conditions that predispose patients to venous thromboembolism (see Thromboembolic Disorders, p. 1273.2). Venous thromboembolism is a common but underdiagnosed condition and causes considerable morbidity and mortality, especially among hospitalised patients.

Prophylaxis of venous thromboembolism. Morbidity, immobilisation, and accidental or surgical trauma put hospitalised patients at great risk of developing venous thromboembolism. Without prophylaxis, the incidence ranges from 10% in the lowest-risk groups to 60% or more in groups undergoing high-risk surgery.[1] Since thromboprophylaxis significantly reduces rates of venous thromboembolism, all patients admitted to hospital should be regularly assessed for their risk of developing the latter, as well as their risk of bleeding, in order to determine the most appropriate prophylactic measures.[2,3]

Patients can be categorised as being at low, moderate, or high risk of thromboembolism.[1-3] For surgical patients, the type and duration of surgery are important factors: minor or day-case operations in mobile patients generally carry a low-risk; general, abdominal, and gynaecological operations carry a moderate risk; while all orthopaedic operations, and operations in cancer patients, are considered high risk. Non-surgical (medical) patients at high risk include those with major trauma or spinal cord injury. Age, immobility, a history of thrombophilia or previous thromboembolism, and conditions such as heart failure and lung disease, increase the risk in both surgical and medical patients, as does the presence of multiple risk factors. Cancer patients are at particularly high risk of venous thromboembolism due to immobility, malignancy, chemotherapy, and indwelling catheters.[4,5] Pregnancy is also a risk factor and is discussed in more detail separately below.

General prophylactic measures to reduce blood stasis, which include early and frequent ambulation and ensuring adequate hydration, as well as minimisation of risk factors (for example, by witholding hormonal contraceptives or removing redundant indwelling catheters) should be adopted in all patients where possible.[1-3,6] They may also be used as the sole method of prophylaxis in patients undergoing minor procedures who have no other risk factors.[1]

Mechanical interventions may help to maintain or improve blood flow in the lower limbs but are not as effective as pharmacological prophylaxis, and good quality evidence of their benefits is lacking; however, they have an important advantage in that they do not cause bleeding.[1,2,6,7] The most widely used method is the graduated compression stocking. These are of value,[8] but only if fitted correctly,[2] and compliance can be poor.[1] More complex mechanical approaches include intermittent pneumatic compression devices and foot pumps.[1-3] Mechanical prophylaxis may be combined with pharmacological prophylaxis; it may also be used as the sole method in patients at low risk, as well as in higher-risk patients unsuitable for anticoagulation (although pharmacological prophylaxis should be started if the bleeding risk drops to an acceptable level).[1-3,6,7] Compression techniques should not be used in patients with significant peripheral vascular disease.

Pharmacological prophylaxis is given to patients at moderate or high risk of venous thromboembolism.[1-3] It is usually based on the use of parenteral or oral anticoagulants, and choice of drug depends on patient factors such as renal impairment or hypersensitivity as well as the level of risk.

The use of ***heparins*** for thromboprophylaxis is well established, and they are the drug of choice for most patients requiring anticoagulants.[1-3,5] They are given in low (non-therapeutic) doses and therefore clotting time (APTT) monitoring is not usually required, although some patients (such as those at extremes of weight or with renal impairment) may benefit.[1,2] Low-molecular-weight heparins offer certain advantages over unfractionated heparin, including once-daily dosing and a lower risk of heparin-induced thrombocytopenia (HIT), and are preferred in most patients.[2,7] However, unfractionated heparin may be more suitable for those with renal impairment and in situations where quick reversal could become necessary.[2,3] ***Fondaparinux*** is an alternative to the heparins.[2] Unfractionated heparin, low-molecular-weight heparins, and fondaparinux have shown similar efficacy in most types of patients including medical, cancer, and general surgery patients.[2] The exception is in orthopaedic surgery, where low-molecular-weight heparins have shown superior efficacy to unfractionated heparin and thus are preferred.[1,2]

Alternatives to heparins in patients who develop, or are at risk of, heparin-induced thrombocytopenia (HIT) include the ***hirudins*** such as lepirudin, and the ***heparinoids*** such as danaparoid.[2]

Dextrans may be given, but are cumbersome to use and must be avoided peri-partum and in renal impairment.[2] (The management of HIT is described more fully in Effects on the Blood under Heparin, p. 1399.1.)

Vitamin K antagonists may be effective, but because they have a delayed onset of action, require careful monitoring, and increase the risk of bleeding after surgery, they are not usually used;[2] however, it has been suggested that those already on long-term warfarin for another indication may continue if appropriate.[2]

Novel oral anticoagulants have been developed with the aim of simplifying administration.[9] These include the direct thrombin inhibitor ***dabigatran*** and the direct factor Xa inhibitor ***rivaroxaban***. They do not require monitoring, but the lack of reversibility is a disadvantage.[2,3,9]

There has been controversy over the use of ***antiplatelet agents***, particularly aspirin, for thromboprophylaxis.[10] Evidence suggests they may provide some protection against venous thrombosis,[10] but most guidelines[1-3] recommend against aspirin as a sole prophylactic agent since anticoagulants are more effective. Those already taking low-dose aspirin for other indications may safely continue to do so, and it may confer a small additional reduction in thrombosis risk, although with an increased risk of bleeding.[2]

Statins have been reported to be protective against venous thromboembolism,[11] but there is not yet sufficient evidence to recommend their use for this purpose.[2,11]

The *duration* of prophylaxis again depends on the balance of risk factors. In medical patients, prophylaxis should continue throughout hospitalisation, or longer where the risk is ongoing.[2] In surgical patients, appropriate prophylaxis may be started either pre- or postoperatively depending on the choice of drug,[1,2] and the duration is usually at least 5 days or until the patient is ambulant.[1-3] However, at least 10 days of prophylaxis is recommended after total hip or knee replacement, and up to 35 days may be beneficial.[1] Extended prophylaxis may also be considered in patients with continued illness or immobility.[1,2] Graduated compression stockings are ideally worn until pre-morbid levels of mobility are reached.[1,2]

Prophylaxis during travel. Any mode of travel requiring immobilisation for 4 or more hours carries a small (2 to 4 fold) increased risk of venous thromboembolism, and this risk may continue for up to 8 weeks post-travel.[1,2,12] Certain prophylactic measures have been suggested for those on long journeys, although most of these lack good evidence of benefit. In healthy individuals, the only preventative measures required are frequent ambulation, wearing loose-fitting clothing, and remaining adequately hydrated; seated leg exercises may also be of benefit.[1,2,12,13] Graduated compression stockings reduce clotting as well as leg discomfort and oedema,[14] although they are probably unnecessary in low-risk patients.[13] They may be of more benefit in medium- or higher-risk patients,[12,13] but if used, it is important that they are fitted correctly.[1,2] Travellers deemed to be at especially high risk of thrombosis, such as those with active malignancy or after recent surgery, may be considered for pharmacological prophylaxis.[1,2,12] Low-molecular-weight heparin has been used for this purpose, and may be given in a single injection before travel.[1,2,12] Fondaparinux is an alternative.[12] Anti-platelet drugs such as aspirin are of little value and are not recommended.[1,12,13]

Treatment of venous thromboembolism. Prompt treatment of venous thromboembolism reduces mortality and morbidity considerably.[15] Patients presenting with signs and symptoms suggestive of venous thromboembolism (such as a painful, swollen calf, chest pain, or severe shortness of breath) should have the diagnosis confirmed or ruled out using D-dimer testing and/or imaging.[2] Symptomless DVT or PE that is discovered inadvertently should be treated as for symptomatic disease;[15] upper-extremity DVT is treated as for lower.[2,15,16] Each patient should also be assessed for their risk of bleeding before a treatment regimen is chosen.[2]

Initial treatment of DVT. The aims of initial treatment are prevention of thrombosis extension, PE development, and acute recurrence.[2,15] Therapeutic doses of parenteral anticoagulants should be started in all patients with suspected DVT if there are no contra-indications,[2,5,6,15,17] and continued until either the diagnosis is refuted, or for at least 5 days until long-term treatment can take its effect.[2,15,17] A ***heparin*** is the initial anticoagulant of choice. Low-molecular-weight heparins are generally preferred to unfractionated heparin as they have shown superior outcomes, and have the advantages of once-daily dosing, predictable pharmacokinetics, and a reduced incidence of HIT.[2,15] Among the low-molecular-weight heparins, there is little difference in efficacy.[2] Unfractionated heparin may be used in patients who have renal impairment or a high bleeding risk, or who are under consideration for thrombolysis.[2,15] In patients with suspected or proven HIT, ***danaparoid*** or a ***direct thrombin inhibitor*** such as lepirudin are given.[2,17] (The management of HIT is discussed more fully under Effects on the Blood under Adverse Effects of Heparin, p. 1399.1.) Alternatives to drug treatment exist, but their roles are less well defined. Inferior vena cava filters may be fitted in patients with absolute contra-indications to anticoagulation,[2,15,17,18] but they carry their own risks of complications, and should be removed and replaced with standard anticoagulation therapy as soon as the contra-indication ceases to apply. Catheter-directed or systemic thrombolytics are not routinely indicated, but

either may be considered in carefully selected patients.[2,15,17] Venous thrombectomy is also an option in certain patients.[15,17]

Initial treatment of PE. The principles of treatment for PE are similar to those for DVT, although additional haemodynamic and respiratory support is often also necessary.[2,17,19,20] The severity of PE has been classified in several ways to guide treatment. Terms such as 'massive', 'sub-massive', and 'non-massive' have been used with respect to the anatomical burden of clotting; however, the current recommendation is to treat patients according to their risk of early mortality, depending on the presence or absence of factors such as cardiogenic shock and severe hypotension.[2,17,19,20] ***Thrombolytics*** may be used in high risk PE;[2,15,17,19,21] they are not given routinely to those with intermediate-risk PE, but may be considered in carefully selected patients such as those with severe haemodynamic compromise and a low risk of bleeding, although the evidence of risks and benefits is incomplete. Thrombolysis is not recommended in low-risk patients.[2,15,17,19] Pulmonary embolectomy may be considered in high-risk patients unable to receive thrombolytics, or in whom they have failed.[15,17,19,20] The optimum treatment of right-heart emboli is uncertain, but anticoagulation alone is probably insufficient, and thrombolytics or embolectomy should probably be used.[19] Patients with suspected PE should be given therapeutic doses of parenteral anticoagulants until the diagnosis is confirmed or refuted.[2,15,19] Unlike for DVT, low-molecular-weight heparin has not been proven superior to unfractionated heparin,[2,19] and therefore either unfractionated heparin, low-molecular-weight heparin, or fondaparinux may be used for the initial treatment of PE.[2,15,19,20] However, low-molecular-weight heparin may be preferred in low-risk PE due to its ease of administration,[15] while intravenous unfractionated heparin is preferred in high-risk PE for its rapid effect, and also in patients with renal failure or at high risk of bleeding, if prompt reversal may be necessary, or if thrombolytics are to be given.[2,15,19,20] A weight-adjusted regimen of unfractionated heparin is preferred to fixed doses.[19,20]

Continued treatment of venous thromboembolism. The aim of long-term treatment is to complete initial treatment and prevent new occurrences of venous thromboembolism as well as reduce long-term consequences.[2,15] The main long-term recommendations do not differ between PE and DVT. The ***vitamin K antagonists*** (usually warfarin) are the long-term drug treatment of choice, and may be started as soon as diagnosis is confirmed, often on the same day as the parenteral anticoagulant. (In patients with HIT, warfarin should not be started until the platelet count has fully recovered.) Vitamin K antagonists are at least as effective as the low-molecular-weight heparins for long term treatment,[2] and are therefore used in most patients, with a target INR of 2.5 (2.0 to 3.0).[2,15,17] Exceptions include cancer patients[2,9,17,19] and pregnant women (see below) in whom low-molecular-weight heparins are the basis of therapy. ***Rivaroxaban***, ***apixaban***, and ***dabigatran*** are under investigation for the initial and long term treatment of venous thromboembolism.[19] Early ambulation is recommended after DVT,[15] and graduated compression stockings should be worn.[17] The optimum *duration* of anticoagulation must be carefully considered for each patient. Recurrence is reduced for as long as anticoagulation is continued; therefore, to prevent recurrence, treatment should ideally be continued for as long as the patient is at risk.[2,15] However, risk of recurrence must also be balanced against the risk of haemorrhage. It is generally recommended that treatment should continue for at least 3 months after a first episode of venous thromboembolism.[2,15,17] It may then be stopped if a reversible risk factor no longer applies.[17,19] One month after stopping anticoagulation, a D-dimer test may be used to identify patients who would benefit from resumption.[2,20] The benefits of longer periods of treatment (6 months or longer), or sometimes even indefinite treatment, can outweigh the risks in certain patients such as those with continuing risk factors (including cancer) and those with unprovoked or recurrent thromboembolism.[2,3,15,17,19,20,22] Guidance varies in this area, but the most important recommendation is continual reassessment of risk factors throughout an individual's treatment.[2,15] The use of a ***statin*** or ***aspirin*** has been tried after stopping vitamin K antagonists, but the evidence has been unconvincing and neither is recommended.[2]

Treatment of superficial-vein thrombosis (SVT). Although not traditionally encompassed by the term venous thromboembolism, SVT is a comparable disorder with similar causes.[23] Though long regarded as benign, patients may have concurrent DVT or are at risk of progression to it;[2,23] concurrent DVT should be excluded with imaging, and measures taken to treat symptoms and reduce risk of progression.[2,23] Oral NSAIDs may be effective at reducing extension and recurrence.[2] Graduated compression stockings may also be used,[2] and consideration of low- or intermediate-dose therapy with either unfractionated or low-molecular-weight heparin, or fondaparinux.[2,15] Patients in whom anticoagulants are contra-indicated may receive an 8 to 12-day course of an NSAID.[2]

Venous thromboembolism in children. The epidemiology of venous thromboembolism in children is different to that in adults, and it occurs more rarely. Treatment may be complicated by age-dependent factors that alter response to anticoagulants, as well as practical difficulties in administration.[24] However, few studies have been performed in children, and recommendations are largely based on those for adults.[6,24,25]

Venous thromboembolism in pregnancy. Pregnancy presents a particular risk for venous thromboembolism due to hormonal changes, haemostatic activation, immobility, and vascular trauma during delivery.[26] Some women who become pregnant may also be receiving regular thromboprophylaxis, for example for a mechanical heart valve. Therefore, all pregnant women should be assessed for risk of venous thromboembolism at each maternity contact,[2,27] and those found to be at excess risk should be considered for *prophylaxis*. Graduated compression stockings should be worn by such patients whenever hospitalised or otherwise immobilised.[2,27,28] Determining which patients may benefit from antenatal pharmacological prophylaxis is not always straightforward, but it is usually given to those deemed at high risk, and may also be considered in moderate-risk patients, depending on risk factors such as obesity, thrombophilias or previous unprovoked, recurrent, or oestrogen-related venous thromboembolism.[2,3,27,28] If given, it should be started in the first trimester.[2] In terms of choice, unfractionated heparin and low-molecular-weight heparin are equally effective, but low-molecular-weight heparin has a better safety profile and is usually preferred.[2,27,28] Those who cannot receive heparin may be offered danaparoid.[2,27] Vitamin K antagonists are contra-indicated because of their teratogenicity and, except in very unusual circumstances, those who are already taking vitamin K antagonists should switch to heparin before planned conception or else as soon as pregnancy is confirmed.[2,27,28] Caution is needed in anticoagulated patients peri-partum, especially if an epidural catheter is to be used, and the temporary cessation of anticoagulation is usually necessary. After delivery, regular assessments for risk of thromboembolism should continue. High-risk patients, including those who were receiving pharmacological prophylaxis antenatally, should receive it for a further 6 weeks after delivery.[2,27] Moderate-risk patients should be given pharmacological prophylaxis for at least 7 days after delivery.[2,27] Graduated compression stockings may also be of benefit.[2] If the mother was taking a vitamin K antagonist before pregnancy, it should be restarted no sooner than the third day post partum.[2]

If acute venous thromboembolism occurs during pregnancy, *treatment* is with unfractionated or low-molecular-weight heparin, again with a preference for the latter.[19,26,28] There is a lack of safety data with alternative anticoagulants such as fondaparinux,[19] and the vitamin K antagonists are contra-indicated.[19] Thrombolytics may be given to patients with high-risk PE.[20,26] Recommendations for duration of anticoagulant therapy differ; at least 6 weeks, and up to 6 months or more, of post-partum treatment seems reasonable, depending on additional risk factors.[19,26,28] Breast feeding may safely take place during anticoagulation with heparin or warfarin.[26,28] Although long-term use of unfractionated heparin, and to a lesser extent low-molecular-weight heparin, can cause osteoporosis, the risk in pregnant women appears to be rare and routine monitoring is not deemed necessary.[2]

Post-thrombotic syndrome. Post-thrombotic syndrome, the development of lower-limb symptoms secondary to DVT, occurs in about a third to a half of patients.[29] To prevent it, graduated compression stockings should be worn for as long as the patient tolerates them, but ideally for at least 2 years after the event.[2,15,17,29] Stockings are also the basis of treatment, as is frequent leg elevation.[29] Severe oedema may be relieved with intermittent pneumatic compression.[15,17,29] Although various drug therapies, including diuretics, NSAIDs, and horse-chestnut seed have been tried, their efficacy is uncertain.[29]

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Vasospastic arterial disorders

Vasospastic arterial disorders form part of the spectrum of peripheral vascular disease (see p. 1272.3), and represent an inappropriate response to temperature, resulting in vasoconstriction and/or vasospasm; Raynaud's syndrome, acrocyanosis, and chilblains are usually induced by cold, whereas erythromelalgia is caused by heat.

In **Raynaud's syndrome**, paroxysmal attacks of pallor and cyanosis, usually of the digits, occur in response to cold, or sometimes emotional stress.[1–4] Erythema replaces the cyanosis as the attacks resolve. The cause of primary Raynaud's syndrome (Raynaud's disease) is unknown. Features identified include intense vasoconstriction or vasospasm, disturbance of sympathetic nerve supply, changes in circulating catecholamines, enhanced platelet aggregation, red cell deformability, and fibrinolysis. It is probable that not all cases are due to the same mechanism. It has been suggested that the underlying problem may not be an overreaction to the initial cold insult but a defect in the normal ensuing adaptive response. Secondary Raynaud's syndrome (Raynaud's phenomenon) frequently co-exists with arterial occlusive disease such as thromboangiitis obliterans and connective tissue disorders, in particular scleroderma (systemic sclerosis). Trauma and certain drugs, notably beta blockers and ergotamine, may also be responsible for inducing secondary Raynaud's syndrome.

Management. In mild cases of Raynaud's syndrome, where attacks are infrequent and of limited severity, protective measures to keep warm are the mainstay of

treatment; this involves wearing appropriate clothing and the use of appliances such as heated gloves. Smoking should be avoided because of the vasoconstriction caused. Any underlying or co-existing disease or cause in secondary Raynaud's syndrome should be treated. Drug therapy is indicated in more severe cases.[1-4] It is directed towards producing vascular smooth muscle relaxation and vasodilatation in order to improve resting blood flow, thereby reducing the extent of tissue ischaemia. Some drugs may also act by modifying endothelial function, platelet aggregation, or blood rheology. Many drugs have been tried in Raynaud's syndrome, although only a few have an established role.

- *Calcium-channel blockers* are of benefit[5] and are generally used as first-line treatment for both primary and secondary disease where drug therapy is required,[1,3] although their usefulness in secondary disease may be limited.[4] Dihydropyridines are usually preferred; the most widely used and studied is *nifedipine*.
- Topical vasodilators such as *glyceryl trinitrate* are an alternative in those with primary disease, although their use is limited by adverse effects. They may be less effective in secondary disease.[3]
- In severe Raynaud's syndrome complicated by ulceration, *prostaglandins* may be given,[1] of which intravenous *iloprost* has accrued the most evidence;[2,4] *alprostadil*, *epoprostenol*, and oral iloprost have also been used.
- Endothelin receptor antagonists have shown benefit in severe disease,[1-3] and *bosentan* is licensed for the prevention of digital ulceration in patients with scleroderma, although it has not been shown to heal existing ulcers nor reduce the frequency or severity of attacks.[4]
- Phosphodiesterase type-5 inhibitors such as *sildenafil* have shown promise in studies of patients with secondary disease, and are suggested[3] as an alternative to prostaglandins or endothelin receptor antagonists. Evidence of a benefit in primary disease is lacking.[4]
- *Other drugs* have shown positive results in small studies, although none has sufficient evidence for firm recommendations. They include: angiotensin receptor antagonists; alpha blockers (although adverse effects may limit their use); statins (which may have pleiotropic effects on the endothelium); calcitonin gene-related peptide; antoxidants such as acetylcysteine; SSRIs; sarpogrelate; and botulinum toxin A.[1-3] The addition to therapy of an antithrombotic such as aspirin or heparin has been suggested by some.[1,3] The *BNF* notes that other drugs that may produce symptomatic benefit include naftidrofuryl or the nicotinic acid derivative inositol nicotinate; pentoxifylline is not of established value.

Acrocyanosis is characterised by a persistent blue discoloration of the skin. There is an abnormal constriction of arterioles, even at normal environmental conditions and this is potentiated by cold. **Chilblains** are an inflammatory condition (perniosis) affecting the extremities and symptoms include erythema, pruritus, and ulceration; they may be acute or chronic. Chilblains are more common in cold damp conditions. Acrocyanosis and chilblains do not generally require specific treatment; smoking cessation, protection from the cold, or symptomatic antipruritic treatment are often sufficient.[4,6] If drug therapy is required, a calcium-channel blocker may be of benefit in chilblains;[6] the role of drug therapy in acrocyanosis is uncertain.[4]

Erythromelalgia (sometimes also called erythermalgia) is a vasospastic condition usually provoked by heat although it may also be drug-induced or secondary to other conditions. It is characterised by painful, red extremities plus a burning sensation and increased skin temperature of the affected area. Aetiologies are numerous; thrombocythaemia (p. 695.2) is the most common underlying cause and, indeed, erythromelalgia may be the presenting feature of this disorder. In thrombocythaemia, arteriolar occlusion may occur as a result of platelet aggregation, and small doses of aspirin have produced considerable relief in some patients, presumably by preventing platelet aggregation. Beta blockers may also be of some help, and there are anecdotal reports of benefit with many other classes of drugs, but none is consistently effective.[4,7] Attacks should be prevented wherever possible by avoiding exposure to heat.

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Other Cardiovascular Disorders

Ascites

Ascites is the accumulation of fluid within the peritoneal cavity. Although it is not strictly a cardiovascular disorder, treatment depends mainly on cardiovascular drugs. Alcoholic hepatic cirrhosis is probably the commonest underlying cause in the western world; others include malignant neoplasms, heart failure, and tuberculosis. The following discussion is restricted mainly to **cirrhotic ascites**.

The mechanism of ascites formation in hepatic cirrhosis has been explained by various hypotheses. Whatever the mechanism, ascites formation is linked to renal sodium and water retention partly as a result of increased circulating renin and aldosterone concentrations. Portal hypertension and hypoalbuminaemia may be contributory factors.

Small amounts of ascitic fluid may go undetected but as it accumulates abdominal distension becomes apparent, and there is a feeling of discomfort. There may be respiratory distress and cardiac dysfunction in severe cases. Peripheral oedema may, or may not, be present, and dilutional hyponatraemia may develop. Renal dysfunction may progress to severe impairment (the hepatorenal syndrome). Patients are at risk of primary (spontaneous) bacterial peritonitis (p. 197.2).

Management[1-12] depends on the severity of ascites but the mainstays are dietary sodium restriction and diuretic treatment. In mild to moderate ascites, sodium restriction alone may sometimes be effective but most patients also require diuretics. Bed rest has been advocated but is no longer generally recommended.[10] Response is monitored by measuring the daily reduction in body-weight. The diuretic of choice is the aldosterone antagonist spironolactone, with the addition of a loop diuretic such as furosemide if necessary. Amiloride or another potassium-sparing diuretic may be used as an alternative to spironolactone if adverse effects are a problem. Spironolactone with furosemide from the outset has also been used. In diuretic-resistant ascites, some benefit has been reported with combined furosemide and albumin;[13] other drugs tried include vasopressin receptor antagonists (satavaptan), vasoconstrictors (terlipressin, octreotide, and midodrine), and clonidine.[11,12] In tense or refractory ascites, large-volume or total paracentesis (removal of ascitic fluid by drainage) is often used initially; patients may then be maintained on diuretics or repeated paracentesis may be used. Plasma volume replacement with albumin or dextrans after paracentesis is usual to reduce haemodynamic complications, particularly if large volumes are removed; alternative approaches that have been tried include use of vasoconstrictors such as terlipressin, midodrine, or noradrenaline, but none of these has an established role.[11] Where ascites remains refractory or repeated paracentesis is not tolerated various shunting procedures have been tried.[11,12] In severe cases liver transplantation may be necessary.

In **malignant ascites** (ascites due to malignant neoplasms; see Malignant Effusions, p. 700.1), paracentesis is often necessary but spironolactone may be of benefit in some patients.

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High-altitude disorders

Rapid ascent (ascent without time to acclimatise) to high altitudes may produce a spectrum of illness (altitude illness) ranging from the usually benign acute mountain sickness to life-threatening pulmonary oedema and cerebral oedema. Factors influencing the development of altitude illness include rate of ascent, altitude attained, sleeping altitude, and length of stay at altitude. Individual susceptibility is also an important factor. Symptoms of altitude sickness are common at altitudes above 2500 metres (8125 feet), although susceptible individuals may be affected at altitudes as low as 2000 metres (6500 feet).[1-6] Reported incidences at higher altitudes vary, but in general symptoms occur in about 50% of people ascending rapidly to altitudes of over 4000 metres (13 000 feet) and in about 75% of people at 4500 metres (14 625 feet); they are severe (pulmonary oedema or cerebral oedema) in about 4%.

Symptoms of acute mountain sickness include headache, which is worse in the supine position, nausea, vomiting, anorexia, lethargy, insomnia, and dizziness. These may develop during ascent, but characteristically occur 6 to 48 hours after arrival at altitude. They are usually short-lived and resolve after a few days at altitude. In a very few people symptoms persist for longer. Chronic mountain sickness, characterised by persistent severe hypoxia and polycythaemia, may develop during prolonged residence at high altitude. The discussion that follows is limited to management of the acute forms. A small proportion of people with acute mountain sickness suddenly deteriorate and develop pulmonary oedema or cerebral oedema, both of which may be life-threatening. Occasionally, pulmonary or cerebral oedema develops without symptoms of acute mountain sickness. Symptoms of **pulmonary oedema** include rapid onset of breathlessness and tachypnoea at rest, and a dry cough which may develop into haemoptysis. Symptoms of **cerebral oedema** include increasing headache, ataxia, mental disturbances, drowsiness and eventually coma. Pulmonary and cerebral oedema frequently occur together.

The **pathogenesis** of altitude illness is not fully understood, and it is not known whether the mechanisms of acute mountain sickness and pulmonary or cerebral oedema differ in nature or merely degree. Hypoxia, a result of the reduced partial pressure of oxygen at high altitudes, is considered the primary stimulus in the development of altitude illness.[1-4,6,7] When ascent to high altitudes occurs gradually, the bicarbonate concentration and the pH of extracellular fluid fall progressively. The falling pH increases the sensitivity of chemoreceptors to hypoxia and so permits greater ventilation, thus allowing acclimatisation. Rapid ascent to high altitudes does not allow time for these changes to occur and although the hypoxia stimulates hyperventilation, it produces a respiratory alkalosis which limits the ventilatory response to hypoxia. The hypoxaemia produced leads to neurohumoral and haemodynamic changes that ultimately result in the symptoms of altitude illness.[1] Symptoms are often worse at night when ventilation is reduced leading to a worsening of the hypoxaemia.

Prophylaxis. Altitude illness may be avoided by ascending to high altitudes slowly and thereby allowing time for acclimatisation. This may be achieved by spending several days at 1500 to 3000 metres and avoiding strenuous physical activity, thus allowing the body to adapt to the reduced oxygen pressure and to ascend above 3000 metres without sickness. Acclimatisation may also be achieved when going above 3000 metres by increasing the sleeping altitude by no more than 300 to 600 metres daily and by adding a rest day for every 1000 metres climbed;[1,2,6,7] slower rates of ascent than this have also been advised.

However, when time for acclimatisation is limited or when abrupt arrival at high altitude (for instance by air) cannot be avoided, drug prophylaxis may be considered. Prophylaxis should also be considered for those individuals who have developed symptoms on ascending to high altitudes on previous occasions.

Acetazolamide is the most frequently used drug[1-5,7] and has been shown[8,9] to effectively reduce the frequency of symptoms, although the optimum dose is not clear. It produces a mild metabolic acidosis which has the effect of stimulating chemoreceptors to produce an increase in the rate of respiration and tidal volume, and it therefore accelerates the process of acclimatisation. Although acetazolamide has diuretic actions it does not prevent fluid retention or prevent or protect against pulmonary or cerebral oedema. It improves sleep hypoxaemia and quality of sleep, reduces proteinuria, improves exercise performance, and reduces loss of muscle mass, probably by improving oxygen supply to the tissues.[10] Acetazolamide should be taken on the day of ascent or 1 or 2 days before ascent to altitudes above 3000 metres, and continued for several days at the higher altitudes.[1,7] However, there has been concern that the use of acetazolamide to prevent symptoms of acute mountain sickness may encourage too rapid an ascent and perhaps increase the risk of developing pulmonary or cerebral oedema.[10]

Dexamethasone has also been shown[8] to be effective in the prevention of acute mountain sickness. The rationale for its use is to control the mild cerebral oedema thought to contribute to the symptoms of acute mountain sickness, although it has also been shown to prevent the development of pulmonary oedema.[11] However, as the adverse effects associated with dexamethasone are more severe than those associated with acetazolamide, it is not

considered suitable for routine prophylaxis; it may have a role if acetazolamide is unavailable or contra-indicated.[1,2,6,7] If it is used, dexamethasone should be started a few hours before ascent;[7] adverse effects may be fewer if the dose is tapered before stopping.[6]

Nifedipine has been shown to lower pulmonary artery pressure and to protect against pulmonary oedema in people susceptible to the development of pulmonary symptoms at altitude.[12] It may be considered for prophylaxis in those with a history of high-altitude pulmonary oedema.

Other drugs that have shown some benefit in small studies include *spironolactone*,[8] *sildenafil*,[13,14] and *sumatriptan*.[15] *Ginkgo biloba* has also been used, but a randomised study[9] found no benefit. A study[16] with inhaled *salmeterol* suggested that it reduced the risk of pulmonary oedema in people considered to be at high risk, while *tadalafil* reduced the risk of pulmonary oedema but did not prevent acute mountain sickness.[11] *Aspirin* was reported[17] to reduce the incidence of headache in a small study in people with a history of headache at high altitude, and some benefit in preventing headache has also been reported with *gabapentin*.[18]

Treatment. Once symptoms of altitude illness develop the course of action should be determined by the severity and nature of the symptoms.

When symptoms are *mild* and are not suggestive of pulmonary or cerebral oedema, rest and mild analgesics for headache are usually all that is required; symptoms resolve within a few days and further ascent is possible.[1,2,4,5,7] *Acetazolamide* may have some benefit in relieving symptoms[1-3,19] although studies have been small. If mild symptoms of pulmonary oedema are present, such as dyspnoea and cough, rest with supplementary oxygen and further oxygen at night may resolve the symptoms and allow further ascent; however signs and symptoms at altitude may be confusing and it is always safest to descend. The use of hypnotics at altitude is not generally advised since there is a risk that respiratory depression may further reduce oxygen saturation, although some appear to be safe. A small study[20] using the short-acting benzodiazepine *temazepam* reported that sleep quality was improved without an alteration in mean oxygen saturation. Zolpidem or zaleplon may also be used.[21]

When symptoms are *moderate to severe*, and are progressing or suggestive of cerebral oedema, immediate descent is necessary.[1-5,7] Descending by as little as 400 to 500 metres is beneficial. Various drugs and therapies have been given to alleviate symptoms and to facilitate descent and should also be used when immediate descent is not possible. For example, *dexamethasone* can reduce the symptoms of acute mountain sickness and might be used in emergencies.[22,23] Portable hyperbaric chambers are available[24] and provide rapid but short-term improvement. They may be useful used with dexamethasone, which has a more sustained effect.[25]

If pulmonary oedema is present, oxygen, which relieves hypoxia and reduces pulmonary hypertension, should be given;[1-3,7] *nifedipine*, which suppresses the exaggerated hypoxic pulmonary vasoconstrictor response seen in people with pulmonary oedema, has provided benefit.[26] Positive-pressure expiration may also be useful;[2] it has the effect of increasing oxygen saturation and partial pressure of carbon dioxide at altitude. Inhalation of nitric oxide has also been reported to improve oxygenation but use may not be feasible at altitude.[27]

People with cerebral oedema should be given *dexamethasone* and oxygen therapy.[3]

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Hypotension

As discussed under Hypertension (p. 1251.1) many factors influence blood pressure making it difficult to define an absolute norm. The link between chronically raised blood pressure and cardiovascular risk is well established, and definitions of 'normal' blood pressure are based on estimates of this risk. For adults, a systolic pressure below 130 mmHg, with a diastolic pressure below 85 mmHg (i.e. below 130/85 mmHg) has generally been considered as normal, although recent guidelines[1,2] have suggested that a blood pressure below 120/80 mmHg may be more desirable. Exactly how far below these values blood pressure can safely be remains uncertain. Although acute hypotension leads to symptoms such as syncope (fainting) or shock, the consequences of chronically low blood pressure are much less clear. Thus, while there are national and international guidelines relating to the diagnosis and treatment of hypertension, there is no accepted definition for low blood pressure or hypotension.

Despite such shortcomings over definition, the existence of several acute and chronic hypotensive disorders is recognised.

Hypotension can occur after haemorrhage or in other forms of shock and the management of this acute and potentially dangerous form of low blood pressure is usually with volume replacement and vasopressors (see Shock, p. 1279.3); sympathomimetics with vasoconstrictor properties, such as noradrenaline and dopamine, are particularly useful when blood pressure is very low. Another situation in which acute hypotension can develop is during anaesthesia and surgery; spinal or epidural block is associated with a greater risk than many other forms of anaesthesia. Hypotension results from venodilatation and decreased cardiac output due to sympathetic block, and the usual treatment is again with sympathomimetics, particularly ephedrine or phenylephrine (see p. 1663.3).

Recurrent forms of acute hypotension may also occur. These include orthostatic (postural) hypotension and neurally mediated hypotension; both are important causes of syncope.[3-5] Orthostatic hypotension may be due to autonomic failure and loss of the reflex vasoconstriction that usually occurs on rising, or may be related to volume depletion. Drug treatment is usually with fludrocortisone (see p. 1634.3). For neurally mediated hypotension, however, choice of therapy is less clear.[4-12]

Neurally mediated hypotension (neurocardiogenic syncope, neurally mediated reflex syncope, vasodepressor syncope, or vasovagal syncope) is a common cause of recurrent lightheadedness (presyncope) and syncope in persons with structurally normal hearts. It is characterised by a paradoxical neurocardiogenic reflex; although the mechanism is not entirely clear, reduced cardiac filling appears to stimulate cardiac receptors that normally respond to hypertension, and there is an inappropriate autonomic response leading to vasodilatation, bradycardia, and hypotension. Diagnostic tests may be required to exclude structural or arrhythmic cardiac disorders as a cause of the syncope, and tilt-testing may be necessary to confirm the diagnosis.[5] Treatment mainly involves reassurance and non-pharmacological measures such as avoidance of triggering factors, an increase in dietary salt and fluid intake, and physical manoeuvres such as crossing the legs or tensing the muscles if presyncope occurs.[4,5,10-12] Tilt-training may be effective but motivating patients is difficult.[4,5] Cardiac pacing may be required in some patients, although there is limited evidence of benefit.[4,5,13]

Drug treatment for neurally mediated hypotension is more controversial and there is little evidence that any drugs are effective.[3-7,9,10,14] Fludrocortisone and beta blockers have been widely used, but controlled studies[15,16] with beta blockers have found no evidence that they are superior to placebo; beta blockers may also lead to an increase in adverse effects and should generally be avoided.[5,9] There is some evidence of benefit with vasoconstrictors such as midodrine,[17,18] an alpha agonist, and this may have a role in some patients.[4-6,10] Disopyramide has also been used, but is not considered first-line.[9] SSRIs have been effective in some cases.[6-8] Antimuscarinics, such as propantheline bromide, have also been tried.[7,9]

One contentious issue has been whether general and non-specific symptoms of ill health such as mental and physical fatigue, depression, and anxiety could be attributed to a chronically low blood pressure (for example, a systolic pressure below 110 mmHg or diastolic pressure below 60 mmHg).[19] In the UK and the USA such an association has not generally been accepted whereas in some European countries (e.g. Germany) a wide range of preparations, usually containing a sympathomimetic, has been available for treatment. There is some evidence that depression[20-22] and reduced general well-being[23] are associated with low blood pressure, and there may also be a link with cognitive impairment.[24] Studies have also suggested an association between chronic fatigue syndrome and either neurally-mediated[25,26] or orthostatic[27] hypotension. However, any implications for treatment are far from clear.

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Kawasaki disease

Cardiac effects including coronary artery abnormalities are the major complications of Kawasaki disease, also known as mucocutaneous lymph node syndrome of childhood. Normal immunoglobulin and aspirin are used in its initial management, and antiplatelet therapy, usually with aspirin, may be continued long term to prevent coronary thrombosis, particularly if there are coronary abnormalities. Further details concerning the overall management of Kawasaki disease are provided under Normal Immunoglobulins, p. 2405.2.

Patent ductus arteriosus

The ductus arteriosus is a vascular channel present in the fetal circulation that connects the pulmonary artery and the descending aorta. In some infants the ductus arteriosus fails to close, a condition known as persistent patent ductus arteriosus. Details of its management, including the use of diuretics in infants with signs of heart failure, are given on p. 72.2.

Phaeochromocytoma

Phaeochromocytoma[1-9] is a rare catecholamine-secreting tumour of the adrenal medulla. Patients with phaeochromocytoma are usually hypertensive and suffer headache, palpitations, and excessive sweating; the hypertension may be either episodic or sustained. However, if the tumour is mainly adrenaline-secreting, tachyarrhythmias may be associated with a normal or even decreased arterial pressure and if the tumour secretes mainly noradrenaline, vasoconstriction may lead to contraction of the venous pool and hypovolaemia. If the effects of the release of catecholamines are not controlled a life-threatening crisis ultimately ensues and may range from a shock-like syndrome with multiple organ failure to hypertensive crisis, depending on the predominance of the catecholamine secreted.

For a diagnosis of phaeochromocytoma, history and clinical symptoms are important, but a firm diagnosis requires further investigative techniques.[1-3,6,8,9] Although measurement of urinary or plasma concentrations of adrenaline and noradrenaline has been used, concentrations of their metabolites, metanephrine and normetanephrine, provide a more accurate diagnosis and measurement of these is now preferred. Additional tests such as the clonidine suppression test (p. 1340.2) or the glucagon stimulation test (p. 1554.2) are used infrequently.[8] Imaging procedures such as computed tomography, magnetic resonance imaging, scintigraphy with ^{123}I- or ^{131}I-iobenguane (*m*-iodobenzylguanidine; MIBG), or positron emission tomography, are used to locate the tumour before surgery.

Surgical removal of the tumour is the mainstay of treatment but must be preceded by pharmacological therapy to block the pressor and other effects of the excess catecholamines.[1-4,6-9] This is important for symptom control, but is also necessary in asymptomatic patients undergoing surgery since massive release of catecholamines may occur during induction of anaesthesia or when the tumour is handled. Choice of therapy is not entirely clear since there is a lack of evidence from controlled studies. Alpha blockers, given orally, are widely used, and have the advantage of both reducing blood pressure and allowing plasma volume to return to normal. Phenoxybenzamine is usually the drug of choice; it produces a long-acting, non-competitive alpha blockade that cannot be overridden by surges of catecholamine release, as may happen with competitive blockers. Selective alpha$_1$-adrenoceptor blockers such as prazosin, which causes less tachycardia, may be an alternative in some patients, particularly if the tumour secretes mainly adrenaline. Prazosin may also be preferable to phenoxybenzamine pre-operatively since its effects are more rapidly reversed, reducing the risk of postoperative hypotension. However, hypotension may be a problem, particularly at the start of treatment, and alpha blockers should therefore be started in a low dose, increased gradually until all signs of pressor activity are suppressed. Calcium-channel blockers may be used if alpha blockers are not tolerated, and may also be given with alpha blockers to enable lower doses to be used. They may be more suitable than alpha blockers in patients who are normotensive. Angiotensin receptor blockers have also been used. Beta blockers may be given for tachycardia, but must be used cautiously and must not be started until adequate alpha blockade has been established. A beta$_1$-selective blocker is preferred so that peripheral beta$_2$-mediated vasodilatation is unaffected. α-Methyltyrosine, which suppresses catecholamine synthesis, may have a role in some patients, such as those resistant to alpha blockade or those in whom the effects of alpha or beta blockade may be undesirable. In some centres it is given routinely pre-operatively to suppress catecholamine synthesis and reduce the amount released during surgery.[7]

Control of blood pressure during and after surgery is critical. Patients should be given intravenous fluids to optimise blood volume pre-operatively, and drugs used for premedication and anaesthesia should be chosen so as to avoid those which may cause pressor responses or tachycardia[4] and ideally should suppress the adrenergic response to surgical stimuli. Acute increases in blood pressure may still occur when the tumour is handled and potent vasodilators such as sodium nitroprusside[1,3,4,8,9] or glyceryl trinitrate[4,8] have been given intravenously to prevent dangerously high arterial pressures; the alpha blocker phentolamine has also been advocated[3,4,8] although tachycardia is invariably a problem. The short-acting cardioselective beta blocker esmolol may be used to control tachycardia during surgery.[3,4,8]

In patients who are unsuitable for surgery, or in those who have malignant phaeochromocytoma[5] or in whom not all of the tumour can be removed, therapy with alpha and beta blockers or other antihypertensives may be continued long-term. α-Methyltyrosine may be used as an alternative. In malignant phaeochromocytoma, ^{131}I-iobenguane, given in high doses sufficient to cause radionecrosis, has produced remission for limited periods. Alternatively, some benefit has been reported with antineoplastic therapy, although its role is not established; a regimen of cyclophosphamide, vincristine, and dacarbazine has been most widely used.

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Pulmonary hypertension

In pulmonary hypertension an increase in pulmonary vascular resistance leads to an increase in pulmonary arterial pressure. Mean pulmonary artery pressure in a resting individual at sea level is normally about 15 mmHg and pulmonary hypertension is usually defined as a pressure above 25 mmHg at rest; a pressure above 30 mmHg during exercise has also been considered diagnostic, although the relevance of this is less clear.[1] Pressures will be correspondingly higher at higher altitudes.

Pulmonary hypertension has been classified in several ways and the terminology used has changed as the underlying pathophysiology has become clearer. Previously, pulmonary hypertension was classified as primary or secondary, depending on the presence or absence of an underlying cause, but guidelines[1-4] no longer recommend these terms since they have little meaning in relation to pathophysiology or treatment. Pulmonary arterial hypertension is now the preferred term where the increased pressure is due to a disorder of the pulmonary arteries (precapillary); this may occur in isolation (idiopathic and familial forms; previously classified as primary pulmonary hypertension), or secondary to disorders such as connective tissue disease, congenital heart defects, portal hypertension, HIV infection, drugs and toxins, and pulmonary venous or capillary disease. Management is similar for all forms of pulmonary arterial hypertension and is the main focus of the following discussion. Pulmonary hypertension that is not due to pulmonary arterial dysfunction generally occurs in association with established cardiopulmonary disorders and is also discussed briefly below.

Pulmonary arterial hypertension[5-10] is a progressive disease with a high mortality rate, and patients appear to be prone to sudden death. Idiopathic pulmonary arterial hypertension occurs in patients of all ages and in both sexes but women in the fourth decade of life are those typically seen; it is also relatively common in children.[11,12] A functional classification system similar to the New York Heart Association grades used for heart failure (see p. 1262.3) may be used to indicate severity.[1-3] Initial complaints include dyspnoea on exertion, fatigue, and chest discomfort or pain. In advanced disease, cor pulmonale (an enlargement of the right ventricle due to either dilatation, hypertrophy, or both) occurs and may progress to right-sided heart failure; thromboembolic disease affecting the pulmonary arteries is also common.

Management of pulmonary arterial hypertension has generally been symptomatic, including use of drugs that decrease pulmonary arterial pressure, preferably with an increase in cardiac output. However, the observation that some therapies also improve survival[13,14] and reduce the need for transplantation, along with the development of therapies specifically targeted against the pathophysiological mechanisms underlying the disease, has widened the aims of treatment. Although most studies have been in patients with idiopathic disease, there is some evidence that patients with other forms of pulmonary arterial hypertension respond similarly, and guidelines for treatment are broadly the same.[1,3,4,15] Similar approaches are also used in children.[1,3,4,11,12]

General ***treatment*** for pulmonary arterial hypertension[1,3,4,15] includes measures to prevent hypoxia, since this causes pulmonary vasoconstriction, and treatment of associated right-sided heart failure. Oxygen therapy may be needed in some patients, and anaemia should be avoided. Pneumococcal and influenza vaccines are recommended to reduce the risk of pulmonary infections. *Diuretics* produce symptomatic benefit in patients with fluid retention, and should be given as appropriate. *Digoxin* has been used, although its role is less clearly established unless patients also have atrial fibrillation. *Oral anticoagulation* has been advised for most patients to reduce the risk of both thromboembolism in the pulmonary arteries and venous thromboembolism, but caution is required in those with an increased bleeding risk. Supraventricular arrhythmias have been associated with clinical deterioration and prophylactic *antiarrhythmics* may be considered.[1] Avoidance of pregnancy is also generally recommended,[3,4,16] although successful management is possible.[17]

Specific therapy has generally been based on the use of vasodilators. Vasoconstriction is believed to play an important role in the pathophysiology of pulmonary arterial hypertension, and many of the vasodilators used in systemic hypertension have therefore been tried.[13,18] While most reduce pulmonary artery pressure, they also reduce systemic blood pressure,[19] producing undesirable and sometimes intolerable adverse effects, and this limits their use. Non-specific vasodilators with an established role in pulmonary arterial hypertension include calcium-channel blockers and prostacyclin analogues. Endothelin receptor antagonists and phosphodiesterase inhibitors, which are more selective pulmonary vasodilators and may also have additional effects, are now increasingly used as alternatives or for combination therapy.

Calcium-channel blockers improve pulmonary haemodynamics, and there is some evidence of a survival benefit; an observational study[20] over a 5-year period found that survival was improved in patients given high doses. However, only a small proportion of patients respond,[21] and adverse effects may be a concern. Guidelines[1,3,4,15] therefore recommend that an acute response test should be performed in all patients before starting long-term treatment. Although oral calcium-channel blockers have been used for testing, this has been associated with severe adverse effects and it is now recommended that only short-acting vasodilators such as intravenous epoprostenol, intravenous adenosine, or inhaled nitric oxide, should be used. Those who respond may then be started on oral calcium-channel blockers, with the choice usually being a dihydropyridine (nifedipine or amlodipine) in patients with relative bradycardia, and diltiazem in those with relative tachycardia. The marked negative inotropic effects of verapamil should be avoided. The dose should be increased gradually, as tolerated, and long-term therapy should only be continued in patients with a sustained response.

Prostacyclin is a potent endogenous vasodilator and there is evidence that it may be deficient in patients with pulmonary arterial hypertension. Epoprostenol, a synthetic form of prostacyclin, was originally used in patients with end-stage pulmonary hypertension to sustain them long enough to have a heart-lung transplant. However, some studies have suggested that long-term therapy with epoprostenol may also have a role as an alternative to transplantation. Sustained clinical improvement and improved survival have been reported[22,23] in some patients given long-term intravenous therapy using portable infusion pumps, and guidelines[1,3,4,15] now recommend that epoprostenol may be used in patients with pulmonary arterial hypertension who do not respond to calcium-channel blockers and who are in functional class III or class IV. Use is limited by stability problems; more stable analogues such as continuous intravenous iloprost[24] or intravenous treprostinil[25] are also effective and may be used as an alternative.[1,4,15] Treprostinil can also be given by continuous subcutaneous infusion[26,27] although severe pain at the infusion site may be a problem. It may be useful in patients for whom intravenous treatment is not suitable;[15] small studies[28,29] have reported the safe transfer of patients from epoprostenol to treprostinil therapy. Prostaglandin analogues have also been given by inhalation. Epoprostenol has been used, but iloprost, which has a longer action, is generally preferred;[15,30] treprostinil may also be used.[31,32] Another analogue, beraprost sodium, has been given orally,[33-35] but is not widely available. Although thought to act mainly as vasodilators, epoprostenol and its analogues also affect vascular remodelling and platelet aggregation and this may contribute to their beneficial effects.

Endothelin receptor antagonists act as vasodilators by blocking the effects of endothelin-1, a potent endogenous vasoconstrictor that appears to be overproduced in pulmonary arterial hypertension and which also stimulates vascular remodelling and has pro-inflammatory effects. Oral endothelin receptor antagonists such as bosentan, and the selective endothelin ET$_A$ receptor antagonist ambrisentan are now widely used as first-line therapy in patients with functional class II or III pulmonary arterial hypertension.[1,3,4,15] They have positive effects on haemodynamics and symptoms,[36] and there is some evidence that bosentan improves survival,[37] although this is not established.[36] In

class III patients, outcomes appear to be comparable with first-line use of either bosentan or prostacyclin analogues,[38] and observational studies[16,39] have suggested that some patients started on prostacyclin analogues can be safely transferred to bosentan. However, in unstable functional class IV patients, epoprostenol is usually preferred.[1,3,4,15]

Phosphodiesterase type-5 inhibitors are pulmonary vasodilators and may also have antiproliferative effects.[40] Randomised studies with sildenafil[41,42] and tadalafil[43] have shown them to be of benefit in pulmonary arterial hypertension, and positive effects were also reported with vardenafil in an open-label study.[44] Both sildenafil[1,3,4] and tadalafil[1] have therefore been recommended as first- or second-line therapy in functional class II or III. Like the endothelin receptor antagonists, they have the benefit of oral dosing.

The *guanylate cyclase stimulator*, riociguat, acts on nitric oxide receptors to produce vasodilatation. It represents a new class of drugs used for the treatment of pulmonary arterial hypertension and persistent or recurrent chronic thromboembolic pulmonary hypertension, either after surgical treatment or in inoperable cases.

Combination therapy is increasingly used in patients who fail to respond to monotherapy, or who deteriorate. There is limited evidence to support the safety or efficacy of most combinations,[1,3,6,15] and further studies are needed to confirm their role. However, in functional class IV patients, initial therapy with a combination of drugs may be considered.[1] Alternative treatments that have shown some benefit include *imatinib*, a platelet-derived *growth factor* antagonist, but evidence is limited to case reports[45–47] and controlled studies are again needed. Surgical intervention, and ultimately lung or heart-lung *transplantation* may be needed in patients who do not respond to vasodilator therapy.[1,3,4]

Pulmonary hypertension associated with an established cardiopulmonary disorder is much more common than idiopathic pulmonary arterial hypertension and the clinical manifestations are dominated by those of the underlying condition. Chronic obstructive pulmonary disease is the commonest respiratory cause, but it may also occur in patients with respiratory distress syndromes, sarcoidosis, idiopathic pulmonary fibrosis, or chronic exposure to high altitude. Pulmonary arterial pressure may also be raised in chronic thromboembolic disease, and in patients with impaired left ventricular function, for example associated with myocardial infarction or mitral valve disease. Management generally involves appropriate treatment of the underlying disorder. Inhaled nitric oxide has been used in patients with acute pulmonary hypertension after cardiac surgery or associated with respiratory distress syndrome.[48] There have also been reports[49] of long-term use in patients with chronic lung disease. Standard therapies for pulmonary arterial hypertension may have a role in patients with inoperable chronic thromboembolic disease,[1,4,50] but are not generally recommended in other disorders.[51]

Persistent pulmonary hypertension of the newborn, sometimes also termed persistent fetal circulation, is a form of pulmonary arterial hypertension specifically affecting neonates. It can be primary in nature (that is, idiopathic, affecting infants with an anatomically normal heart and no pulmonary disease) or secondary, being associated with a number of cardiopulmonary conditions including congenital heart disease, diaphragmatic hernia, meconium aspiration, respiratory distress syndrome, or sepsis. The pulmonary hypertension and altered vasoreactivity lead to a right-to-left shunting of blood across the patent ductus arteriosus or foramen ovale and this often results in critical hypoxaemia.

Management generally involves high-frequency oscillatory ventilation (to achieve optimal lung inflation) and, if necessary, extracorporeal membrane oxygenation. Treatment to reduce pulmonary vascular resistance may also be tried. Mechanical hyperventilation has been used to induce alkalosis, since this reduces pulmonary vasoconstriction; intravenous sodium bicarbonate may be an alternative.[52] Inhaled *nitric oxide* which is a potent, selective pulmonary vasodilator, is also widely used.[53] Studies[54–58] have shown that it can cause marked improvement in oxygenation and a reduction in the need for extracorporeal membrane oxygenation, but no effect on mortality has been found. Early concerns that the use of nitric oxide might adversely affect neurodevelopmental outcomes have not been confirmed on long-term follow-up,[59–61] but there is also no evidence of a long-term benefit,[61] although an observational study[62] found a reduced incidence of cerebral palsy in premature infants given nitric oxide. Use of inhaled nitric oxide in combination with high-frequency oscillatory ventilation may have additional benefits.[63]

Nitric oxide is not effective in all patients and alternatives may be required.[64,65] Intravenous *epoprostenol* is used and it has also been given by inhalation,[66,67] which may reduce systemic effects. Intravenous vasodilators have also been used, although, as discussed above, this is generally limited by their systemic effects. *Tolazoline* may be given intravenously or by the endotracheal route. *Phosphodiesterase inhibitors* may have a role; dipyridamole has been used, and there have been reports[68,69] of benefit with sildenafil, including when used long-term.[70] Intravenous sildenafil has also been used.[71] Other vasodilators that have been tried include intravenous *adenosine*,[72,73] intravenous *magnesium sulfate*,[74–76] and inhaled *sodium nitroprusside*,[77] but none of these has an established role.

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Shock

Shock is a complex clinical syndrome in which there is a failure of the circulatory system to maintain cellular

perfusion and function. There are many aetiologies, but the underlying defect is either inadequate venous return to the heart due to an absolute or relative reduction in plasma volume, or failure of the pumping action of the heart. A traditional approach has been to place the cause of shock into one of several basic groups:

- *Hypovolaemic shock* results from fluid loss; cardiac output is reduced due to inadequate filling pressure. Haemorrhagic causes include severe gastrointestinal bleeding and traumatic injury, while non-haemorrhagic causes include severe vomiting and diarrhoea, polyuria, and burns. Hypovolaemia can also be present in other forms of shock; in septic or anaphylactic shock fluid loss from the vasculature may occur due to capillary leakage, while peripheral vasodilatation may lead to relative hypovolaemia
- *Cardiogenic shock* usually results from acute cardiac dysfunction or failure, leading to an inadequate stroke volume and reduced cardiac output. It has several causes, but is most often associated with acute myocardial infarction. Other cardiac causes include valvular heart disease, cardiomyopathies, and severe cardiac arrhythmias; episodes of acute heart failure may also occur due to decompensation in patients with chronic heart failure. Shock due to circulatory disorders such as massive pulmonary embolism is also sometimes classified as cardiogenic. Other forms of shock may also have a cardiac component
- *Septic shock* occurs as a complication of infectious disease and is described and defined in more detail under Septicaemia, p. 203.2. Hypotension occurs mainly due to peripheral vasodilatation, but fluid loss and direct effects on the heart may also be involved. Cardiac output may be reduced due to hypovolaemia; however, if circulatory volume is adequate, cardiac output is often high
- *Anaphylactic shock* (p. 1293.2) is the result of a hypersensitivity reaction and is similar haemodynamically to septic shock

In the early stages of shock, compensatory mechanisms are usually sufficient to maintain the blood pressure, but these generally become inadequate and patients in decompensated shock classically present with hypotension, tachycardia, and tachypnoea. The skin is often cold, clammy, and cyanotic, due to compensatory peripheral vasoconstriction, while impaired organ perfusion results in dulled mental alertness, which may progress to stupor or coma; oliguria or anuria, due to impaired renal perfusion, are also frequent. Pulmonary oedema may occur as a result of impaired cardiac output in cardiogenic shock. Complications of shock include disseminated intravascular coagulation due to platelet sludging and microvascular insufficiency, acute respiratory distress syndrome (previously termed 'shock lung') (p. 1599.3), and acute renal failure. The terms multiple organ failure syndrome (MOFS) and multiple organ dysfunction syndrome (MODS) are applied to the consequences of shock where several organs or body systems have become hypoperfused and are unable to maintain their normal function.

Management. The initial aim of treatment in all forms of shock is to restore tissue perfusion by correcting hypovolaemia and hypotension and restoring cardiac output.[1-6] Hypoxaemia should be avoided and supplemental oxygen or mechanical ventilation may be required. Intravenous opioid analgesics may be needed for pain, and an adequate diuresis should be maintained in order to prevent renal failure. Diuretics may also be required if there is pulmonary oedema; mechanical fluid removal by ultrafiltration may be an alternative, particularly in patients with renal impairment.[6,7] Impaired tissue perfusion often leads to lactic acidosis, but the need for specific treatment (see Metabolic Acidosis, p. 1777.2) is unclear; sodium bicarbonate may be given for severe acidosis,[1] although some[4] consider that it should not be used. Other electrolyte abnormalities should be corrected as appropriate.

Hypovolaemia. Restoration of the circulating volume is essential, both to replace lost fluids in hypovolaemia and to maintain cardiac filling pressure in other forms of shock; small volumes may be beneficial in cardiogenic shock, but should be given cautiously to prevent pulmonary oedema. Replacement fluids available include blood products and crystalloid or colloid plasma expanders,[8-10] and the choice depends on the clinical situation. Blood products are expensive and not always available, while the relative merits of crystalloids and colloids continue to be debated.

In haemorrhage, volume expansion to maintain organ perfusion is initially the most important consideration,[11] although in trauma patients the optimum timing and quantity of fluid to give is not clear.[9,10,12] Anaemia is generally better tolerated than hypovolaemia, but where blood loss is extensive (usually considered as 40% or more of the total blood volume), red cell replacement is also required.[11,13] This usually takes the form of packed red cells with plasma expanders, and other plasma components as required. Blood substitutes are also under investigation as an alternative to red cell products, but none yet has an established role.[9,10]

In non-haemorrhagic hypovolaemia, plasma expanders alone are used. Crystalloids (solutions containing solutes such as glucose or sodium chloride that can pass a semipermeable membrane) rapidly expand both the intravascular and extravascular compartments, which could be beneficial since both become depleted in hypovolaemia. However, large volumes may be required and the duration of effect is short as fluid is rapidly redistributed. Hypertonic crystalloid solutions may allow smaller volumes to be used. Colloids (solutions containing large molecules such as albumin, dextrans, gelatins, and etherified starches, which do not pass semipermeable membranes) expand the intravascular space more effectively; they have a longer duration of effect and smaller volumes are required. This may be beneficial since it causes less haemodilution, but the exact significance of this has been questioned; the risk of hypersensitivity reactions, including anaphylaxis, may also be a concern.

Studies comparing the use of crystalloids and colloids in hypovolaemia have generally been of poor quality and the results are difficult to interpret. A systematic review[14] of studies in critically ill patients concluded that there was a small increase in mortality associated with the use of colloids, and that since they were more expensive and of no proven benefit they should not be routinely used. A further review,[15] looking specifically at the use of albumin, also suggested an increased mortality with use of the colloid. Both reviews were severely criticised,[16-18] and the relative benefits of the different types of fluid continue to be debated. A large study[19] comparing the use of albumin and sodium chloride 0.9% in intensive care patients who required fluid resuscitation found no difference in mortality at 28 days. Updates to both reviews[20,21] to include this study found that there was no evidence of any benefit for colloids compared with crystalloids, and the authors continued to state that colloids should not be routinely used. However, there was no clear difference in mortality between patients given colloids or crystalloids, other than a suggestion[21] that albumin might increase mortality in patients with burns or hypoproteinaemia. In practice, a mixture of colloids and crystalloids tends to be given. Choice of the best crystalloid or colloid to give remains unclear; systematic reviews have found no evidence that one colloid is better than another,[22] or that hypertonic solutions are better than isotonic solutions if crystalloids are used.[23]

Hypotension and low cardiac output. Although correction of hypovolaemia may be sufficient to restore blood pressure, hypotension in shock may be profound (sometimes a systolic pressure of less than 70 mmHg) despite fluid replacement, and additional therapy with inotropes and vasopressors is often needed to improve cardiac output and reverse signs of impaired organ function.[1,4] Sympathomimetics are often used since they may have effects on the heart and the vasculature, but alternative vasoconstrictors and inotropes may also have a role.[24] Choice depends on individual patient characteristics and the type of shock, although this is generally based on theoretical considerations. A systematic review[25] of the use of vasopressors in shock found insufficient evidence to make any recommendations, while a study[26] comparing dopamine with noradrenaline as the first-line vasopressor found no significant difference in outcome, although dopamine was associated with more adverse effects.

In cardiogenic or hypovolaemic shock cardiac output is usually low but peripheral resistance is high and drugs that have mainly inotropic effects, such as dobutamine or dopamine, are often chosen. Dobutamine causes some peripheral vasodilatation and is useful where hypotension is not significant; dopamine similarly causes peripheral vasodilatation at low doses but at higher doses vasoconstriction occurs. Low-dose dopamine has been widely used as an adjunct to other inotropes since it was thought that the vasodilatation would lead to renal protection, but clinical benefit has not been established and such use is no longer recommended (see Surgery and Intensive Care, p. 1367.3). Phosphodiesterase inhibitors such as amrinone and milrinone can also be considered in low cardiac output states; they have positive inotropic activity and produce peripheral vasodilatation, and may be particularly useful in patients with decompensated chronic heart failure who have been taking beta blockers.[2,4,6] Levosimendan, a calcium sensitiser with inotropic and vasodilator properties, is another alternative and is also suitable for patients taking beta blockers.[6] Vasodilators such as intravenous glyceryl trinitrate or sodium nitroprusside may also be beneficial for patients in shock with a low cardiac output but adequate blood pressure, as well as in patients with pulmonary oedema.[1,2,6,7] They act by reducing cardiac afterload but must be used with care as there is a risk of precipitating hypotension. Mechanical circulatory support with an intra-aortic balloon pump or ventricular assist device may be required in some patients.[6,7]

Where cardiac output is high but peripheral resistance is low, for example in septic shock, vasoconstrictors such as noradrenaline or dopamine are usually preferred;[1,5] these may be given with more potent inotropes such as dobutamine or adrenaline. Adrenaline has also been given alone although renal artery vasoconstriction may limit its use; it has also been reported to cause lactic acidosis,[27] but a study[28] comparing noradrenaline plus dobutamine with adrenaline alone found no difference in outcomes in patients with septic shock. Vasopressin may be an alternative,[5,29,30] particularly in patients with vasodilatation that is resistant to sympathomimetics, but is not recommended for routine use. It may also be used as an adjunct to sympathomimetics, although no clear benefit has been shown compared with sympathomimetics alone.[31]

The opioid antagonist naloxone may also improve blood pressure in shock,[32] but its role is not established.

Specific therapies are indicated in some types of shock. In cardiogenic shock associated with ***myocardial infarction,***[2,7,33] specific therapy to restore myocardial perfusion is also required (see p. 1257.1).

In ***septic shock*** appropriate antibacterial therapy should be given as outlined under Septicaemia on p. 203.2. Methods of inhibiting endogenous mediators released in response to sepsis that are thought to be responsible for the haemodynamic effects are also under investigation but clinical benefits have not yet been shown.[3,34] Improved outcomes have been reported[35,36] with the use of low-dose corticosteroids. In severe sepsis recombinant activated protein C has been used,[5] but a systematic review[37] found no evidence to support a beneficial effect.

Adrenaline is the cornerstone of management in ***anaphylactic shock*** (see p. 1293.2).

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Abciximab *(BAN, USAN, rINN)*

7E3; Abciximabum; Absiksimab; Absiksimabi; Absximab; c7E3; c7E3 Fab; Абциксимаб.

Immunoglobulin G (human-mouse monoclonal c7E3 clone p7E3V_HC_γ1 Fab fragment anti-human platelet glycoprotein IIb/IIIa complex), disulphide with human-mouse monoclonal c7E3 clone p7E3V_HC_κ light chain.

$C_{2101}H_{3229}N_{551}O_{673}S_{15}$=47456.0

CAS — 143653-53-6.

ATC — B01AC13.

ATC Vet — Q01AC13.

UNII — X85G7936GV.

Uses and Administration

Abciximab is the Fab fragment of the chimeric monoclonal antibody 7E3. It binds to the glycoprotein IIb/IIIa receptor on the surface of platelets. This prevents binding of fibrinogen, von Willebrand factor, and other adhesive molecules to the receptor sites and inhibits platelet aggregation. It is used as an adjunct to heparin and aspirin therapy for the prevention of acute ischaemic complications in patients undergoing percutaneous coronary interventions such as angioplasty, atherectomy, and stenting. It is also used in patients with unstable angina who are candidates for such procedures. It has been investigated in acute ischaemic stroke, although results have been disappointing; it has also been tried in peripheral arterial occlusion.

Abciximab is given intravenously as a bolus injection over 1 minute in a dose of 250 micrograms/kg followed immediately by an infusion of 0.125 micrograms/kg per minute (to a maximum dose of 10 micrograms/minute). For stabilisation in patients with unstable angina the bolus dose followed by the infusion should be started up to 24 hours before the possible intervention and continued for 12 hours after; for other patients the bolus should be given 10 to 60 minutes before the intervention followed by the infusion for 12 hours.

General references.

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Administration. For reference to use of the intracoronary route for abciximab see Ischaemic Heart Disease, below.

Ischaemic heart disease. Antiplatelet drugs have an established role as adjuncts to medical or interventional treatment in patients with ischaemic heart disease (stable angina, unstable angina, or myocardial infarction) and abciximab has been used to provide additional antiplatelet effects during interventional procedures and in patients with acute coronary syndromes.

In patients undergoing acute or elective *percutaneous coronary intervention* (PCI; see Reperfusion and Revascularisation Procedures, p. 1259.2), use of abciximab as an adjunct to heparin and aspirin improves short-term[1-3] and long-term[4,5] outcomes in various groups of patients, including those receiving coronary stents.[6-8] Most benefit has been seen in patients given abciximab as a bolus injection immediately before intervention followed by intravenous infusion for 12 hours,[1,2] and in a study[9] in which abciximab was given for 18 to 24 hours before angioplasty and for 1 hour after, the initial benefit was not maintained at 6 months.

For patients undergoing PCI who are pretreated with both aspirin and clopidogrel, the role of abciximab is less clear. In stable patients undergoing elective PCI, no benefit was found at 30 days,[10] or at 1 year.[11] A study[12] in diabetic patients also found no effect on mortality or risk of myocardial infarction at 1 year, despite their higher risk, although restenosis was reduced. However, in patients undergoing PCI for *non-ST elevation acute coronary syndromes* (see Angina Pectoris, p. 1254.3), use of abciximab in addition to aspirin and clopidogrel pretreatment improved clinical outcomes at 30 days and at 1 year,[13] although the effect at 30 days was restricted to patients with raised troponins.[14] Positive results have also been reported[15,16] with abciximab given as a single bolus injection without subsequent infusion in patients undergoing coronary stenting.

In *acute ST-elevation myocardial infarction* (p. 1257.1), abciximab has been used as an adjunct to primary PCI, and has been shown to reduce re-infarction rates and mortality,[17] including specifically in patients receiving coronary stents,[18] with benefit persisting long-term.[19] The optimum timing and dosage regimen have not yet been established. Abciximab started as soon as possible after diagnosis rather than immediately before the procedure has shown benefit in some studies,[20,21] but not others,[22] and no advantage has been seen with use of both abciximab and a thrombolytic before the procedure.[22] In patients treated with thrombolytics instead of primary PCI, use of adjunctive abciximab has shown some benefit,[23] but this appears to be offset by an increased bleeding rate, even when reduced doses of thrombolytics are used.[24,25] In patients with *unstable angina* (p. 1254.3) receiving noninterventional treatment, a large study[26] with abciximab failed to show any benefit over placebo, although other glycoprotein IIb/IIIa inhibitors have a role in such patients.

Some promising results have been reported with *intracoronary* abciximab in patients with acute coronary syndromes,[27] and with abciximab-coated stents in patients with acute myocardial infarction.[28] A meta-analysis[27] of studies involving 2301 patients with acute coronary syndromes concluded that intracoronary abciximab was associated with reduced mortality and a trend towards fewer major adverse cardiac events; this was most marked in patients with acute ST-segment elevation myocardial infarction and on short-term (1 month) rather than longer term follow-up. However, some studies[29] have not reported additional benefit from use of the intracoronary route, and further studies are ongoing.[30-32]

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Adverse Effects

Bleeding during the first 36 hours after a dose is the most common adverse effect of abciximab. Other adverse effects include hypotension, nausea and vomiting, back pain, chest pain, headache, haematoma, bradycardia, fever, cardiac tamponade, and thrombocytopenia. Hypersensitivity reactions (see Precautions, p. 1282.1) have occurred on repeated use.

Effects on the blood. In clinical studies increased bleeding has been the most common adverse effect of abciximab, and this has also been reported[1] during clinical use. Thrombocytopenia is also a well documented adverse effect of abciximab therapy. In a review[2] of the major clinical studies of abciximab, mild thrombocytopenia was reported in 4.2% of patients and severe thrombocytopenia in 1.0%; patients also received heparin. There have also been case reports of patients developing severe thrombocytopenia.[3,4] It is recommended that platelet counts should be monitored before and 2 hours after starting abciximab, and that the drug should be withdrawn if thrombocytopenia occurs.[3] However, pseudothrombocytopenia also occurs in some patients and should be excluded before withdrawing therapy.[5,6] Although there have been case reports, the incidence of thrombocytopenia does not appear to be increased with other glycoprotein IIb/IIIa receptor inhibitors,[2] and there have been reports of the successful use of eptifibatide[7] and tirofiban[8] in patients who developed thrombocytopenia with abciximab.

1. Cote AV, *et al.* Hemorrhagic and vascular complications after percutaneous coronary intervention with adjunctive abciximab. *Mayo Clin Proc* 2001; 76: 890–6.
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Precautions

Abciximab should not be given to patients who are actively bleeding or to patients at increased risk of haemorrhage. Such patients include: those with haemorrhagic disorders, including thrombocytopenia; those with cerebrovascular disorders, including intracerebral neoplasms, aneurysms, or arteriovenous malformation, and those with a history of stroke; those with uncontrolled hypertension; or those who have recently undergone major surgery or severe trauma. Other patients in whom caution is required include those with severe renal impairment, vasculitis, haemorrhagic retinopathy, acute pericarditis, or aortic dissection. Abciximab should be stopped if serious uncontrolled bleeding occurs or emergency surgery is required. Abciximab should not be given to patients with severe renal impairment requiring haemodialysis, or to those with severe hepatic impairment, in whom coagulation may be affected. Platelet counts should be monitored before and after giving abciximab.

Antibodies may develop 2 to 4 weeks after a dose of abciximab and hypersensitivity reactions could occur when other monoclonal antibodies are used or after readministration of abciximab (see below). Hypersensitivity reactions have not been noted after a single dose but the possibility should be considered.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies abciximab as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Readministration. Antibodies to abciximab develop in about 5.8% of patients after use and could lead to hypersensitivity reactions or to reduced efficacy if use of abciximab is repeated. In a retrospective study[1] in 164 patients given a second course of therapy with abciximab, efficacy was not affected and no allergic or anaphylactic reactions occurred. However, severe thrombocytopenia was noted in 4% of patients, and the incidence was highest in those receiving abciximab within 2 weeks of the first course. Similar results were reported from a larger registry study;[2] the patients included had received abciximab at least 7 days previously without developing thrombocytopenia, suggesting that platelet counts need to be monitored in patients receiving a first or repeated course of abciximab.

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Interactions

There may be an increased risk of bleeding if abciximab is given with other drugs that affect bleeding, including anticoagulants, other antiplatelet drugs, or thrombolytics.

Pharmacokinetics

After intravenous doses of abciximab free plasma concentrations fall rapidly due to binding to platelet receptors. Platelet function recovers over about 48 hours although abciximab may remain in the circulation for 15 days or more in a platelet-bound state.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: ReoPro; *Austral.*: ReoPro; *Austria*: ReoPro; *Belg.*: ReoPro; *Braz.*: ReoPro; *Canad.*: ReoPro; *Chile*: ReoPro; *Cz.*: ReoPro; *Denm.*: ReoPro; *Fin.*: ReoPro; *Fr.*: ReoPro; *Ger.*: ReoPro; *Gr.*: ReoPro; *Hong Kong*: ReoPro; *India*: ReoPro; *Irl.*: ReoPro; *Israel*: ReoPro; *Ital.*: ReoPro; *Malaysia*: ReoPro; *Mex.*: ReoPro; *Neth.*: ReoPro; *Norw.*: ReoPro; *NZ*: ReoPro; *Pol.*: ReoPro; *Port.*: ReoPro; *Rus.*: ReoPro (Реопро); *S.Afr.*: ReoPro; *Singapore*: ReoPro; *Spain*: ReoPro; *Swed.*: ReoPro; *Switz.*: ReoPro; *Thai.*: Clotinab; ReoPro; *UK*: ReoPro; *USA*: ReoPro.

Acadesine *(BAN, USAN, rINN)*

Acadesina; Acadésine; Acadesinum; AICA Riboside; GP-1-110-0; GP-1-110; Акадезин.

5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide.

$C_9H_{14}N_4O_5$ = 258.2.

CAS — 2627-69-2.

ATC — C01EB13.

ATC Vet — QC01EB13.

UNII — 53IEF47B46.

Profile

Acadesine is a purine nucleoside analogue reported to have cardioprotective effects. It is being investigated in the management of myocardial ischaemia, particularly in patients undergoing coronary artery bypass graft surgery. Acadesine may protect against further ischaemia by influencing metabolism in ischaemic cells, enhancing the release of adenosine in preference to inosine after the breakdown of adenosine monophosphate.

Acadesine is also under investigation for chronic lymphocytic leukaemia.

References.

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3. Mangano DT. Effects of acadesine on myocardial infarction, stroke, and death following surgery: a meta-analysis of the 5 international randomized trials. *JAMA* 1997; 277: 325–32.
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ACE Inhibitors

ACE-Hemmer; Angiotensin-converting Enzyme Inhibitors; Inhibidores de la ECA; ИАПФ; Ингибитор АПФ; Ингибитор Ангиотензин-Превращающего Фермента.

There appear to be few significant differences between individual ACE inhibitors. They may be distinguished from each other by the presence or absence of a sulfhydryl group, whether they are prodrugs or not, their route of elimination, and their affinity for angiotensin-converting enzyme in vascular and other tissue, although whether these characteristics modify pharmacodynamics and therefore clinical efficacy is uncertain. Differences in these characteristics do however influence onset and duration of action of ACE inhibitors.

Uses and Administration

ACE inhibitors are antihypertensive drugs that act as vasodilators and reduce peripheral resistance. They inhibit angiotensin-converting enzyme (ACE), which is involved in the conversion of angiotensin I to angiotensin II. Angiotensin II stimulates the synthesis and secretion of aldosterone and raises blood pressure via a potent direct vasoconstrictor effect. ACE is identical to bradykininase (kininase II) and ACE inhibitors also reduce the degradation of bradykinin, which is a direct vasodilator and is also involved in the generation of prostaglandins. The pharmacological actions of ACE inhibitors are thought to be mainly due to the inhibition of the renin-angiotensin-aldosterone system, but since they also effectively reduce blood pressure in patients with low renin concentrations other mechanisms are probably also involved. ACE inhibitors produce a reduction in both preload and afterload in patients with heart failure. They also reduce left ventricular remodelling, a process that sometimes follows myocardial infarction. Normally, renal blood flow is increased without a change in glomerular filtration rate. ACE inhibitors also reduce proteinuria associated with glomerular kidney disease.

ACE inhibitors are used in the treatment of hypertension and heart failure and are given to improve survival after myocardial infarction and for the prophylaxis of cardiovascular events in patients with certain risk factors. They are also used in the treatment of diabetic nephropathy. They are generally given orally.

In some hypertensive patients there may be a precipitous fall in blood pressure when starting therapy with an ACE inhibitor and the first dose should preferably be given at bedtime; if possible, any diuretic therapy should be stopped a few days beforehand and resumed later if necessary.

In patients with heart failure taking loop diuretics, severe first-dose hypotension is common on introduction of an ACE inhibitor, but temporary withdrawal of the diuretic may cause rebound pulmonary oedema. Thus treatment should start with a low dose under close medical supervision.

Reviews.

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2. Hanif K, *et al.* Reinventing the ACE inhibitors: some old and new implications of ACE inhibition. *Hypertens Res* 2010; 33: 11–21.

Action. The renin-angiotensin system plays a major role in regulation of cardiovascular and renal function and blockade of this system has complex physiological effects. Although the main target for ACE inhibitors was initially thought to be the endocrine renin-angiotensin system in the circulation this mechanism alone cannot readily explain all the actions of ACE inhibitors.[2] Endogenous renin-angiotensin systems exist in many tissues and ACE inhibitors also have localised effects.[3] This may underlie some of the long-term effects of ACE inhibition, including improved endothelial function, increased arterial wall compliance, improved left ventricular function in heart failure, regression of vascular and left ventricular hypertrophy, and delayed progression of diabetic nephropathy. ACE inhibitors differ in their degree of binding to tissue ACE and in their tissue distribution, but the clinical significance of this is not clear. In one study[4] endothelial function improved with quinapril, which has high tissue specificity, but a similar effect was not seen with the less specific enalapril, despite an earlier study[5] showing it to be effective.

ACE inhibitors also have effects on the kinin system and there is some evidence that the cardiovascular actions of ACE inhibitors also involve localised accumulation of kinins.[6-8] It has been suggested[9] that the free radical scavenging property of captopril may contribute to some of its actions, although not all studies have confirmed this effect.[10]

1. Schmieder RE, *et al.* Renin-angiotensin system and cardiovascular risk. *Lancet* 2007; 369: 1208–19.
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4. Anderson TJ, *et al.* Comparative study of ACE-inhibition, angiotensin II antagonism, and calcium channel blockade on flow-mediated vasodilation in patients with coronary disease (BANFF study). *J Am Coll Cardiol* 2000; 35: 60–6.
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Bartter's syndrome. Captopril has been reported to produce beneficial responses in patients with Bartter's syndrome[1-5] (p. 1779.3), which is characterised by hyperaldosteronism, hypokalaemia, and hyperreninaemia, but with normal or reduced blood pressure. Captopril may also be used diagnostically with scintigraphy.[6]

1. Aurell M, Rudin A. Effects of captopril in Bartter's syndrome. *N Engl J Med* 1981; 304: 1609.
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Diabetic complications. Control of blood pressure plays a major role in the prevention of the sequelae of diabetes mellitus (p. 463.3). ACE inhibitors have been reported[1] to reduce the risk of major cardiovascular events in patients, including a broad range of diabetics, with either a history of cardiovascular disease or at least one additional cardiovascular risk factor. A study[2] of diabetics with no cardiovascular disease (but unknown risk factors) also found a reduction in mortality with use of ACE inhibitors. Some of the studies of ACE inhibitors for cardiovascular risk reduction have also suggested that ACE inhibitors may prevent the development of diabetes in non-diabetic patients,[3-7] but a randomised study[8] in subjects with moderately impaired glucose metabolism but low cardiovascular risk was unable to confirm this effect.

ACE inhibitors may also have benefits in other diabetic complications. They have an established role in the management of nephropathy in patients with type 1 and type 2 diabetes (see Kidney Disorders, p. 1284.1).

It has been reported[9,10] that ACE inhibitors may reduce the progression of retinopathy in normotensive patients with type 1 diabetes mellitus.

A preliminary report[11] has also suggested that ACE inhibitors may improve peripheral neuropathy in diabetic patients, but further studies are needed.

1. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; 355: 253–9. Correction. *ibid.*; 356: 860.
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3. Yusuf S, *et al.* Ramipril and the development of diabetes. *JAMA* 2001; 286: 1882–5.
4. Padwal R, Laupacis A. Antihypertensive therapy and incidence of type 2 diabetes: a systematic review. *Diabetes Care* 2004; 27: 247–55.
5. Gillespie EL, *et al.* The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. *Diabetes Care* 2005; 28: 2261–6.
6. Abuissa H, *et al.* Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 2005; 46: 821–6.
7. Aguilar D, Solomon SD. ACE inhibitors and angiotensin receptor antagonists and the incidence of new-onset diabetes mellitus: an emerging theme. *Drugs* 2006; 66: 1169–77.
8. Bosch J, *et al.* DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. *N Engl J Med* 2006; 355: 1551–62.
9. Chaturvedi N, *et al.* Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. *Lancet* 1998; 351: 28–31.
10. Mauer M, *et al.* Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med* 2009; 361: 40–51.
11. Malik RA, *et al.* Effect of angiotensin-converting-enzyme (ACE) inhibitor trandolapril on human diabetic neuropathy: randomised double-blind controlled trial. *Lancet* 1998; 352: 1978–81.

Erythrocytosis. Secondary erythrocytosis (secondary polycythaemia) is an absolute increase in red cell mass that may occur as a result of tissue hypoxia (as in chronic obstructive airways disease), or excessive erythropoietin production (as in some renal tumours or after renal transplantation). Treatment may be necessary for hyperviscosity symptoms and to reduce the risk of thromboembolic complications, and mainly involves removal of red blood cells by venesection and the use of drugs such as ACE inhibitors that inhibit erythropoiesis.

Post-transplantation erythrocytosis may resolve spontaneously in some patients but for the remainder the aim of therapy is to minimise the risk of thromboembolic and other complications by reducing the haematocrit to less than 45%. Originally treatment was by venesection but this led to severe iron deficiency. There is now evidence of beneficial effects using ACE inhibitors[1–4] or angiotensin II receptor antagonists such as losartan[5–9] and guidelines recommend these drugs for first-line therapy.[10,11] Theophylline may also be used but appears to be less effective than ACE inhibitors[1] and is usually reserved for patients who do not respond to first-line therapy; it may also be used with an ACE inhibitor but venesection may need to be used until the haematocrit falls to 45%.

Guidelines[11] recommend that patients who develop **erythrocytosis secondary to hypoxic pulmonary disease** should first be considered for methods to improve oxygenation, including long-term oxygen therapy. Those who have hyperviscosity or a haematocrit greater than 56% should undergo venesection. ACE inhibitors or angiotensin II receptor antagonists might be of use for patients who do not tolerate venesection;[11] beneficial responses have been reported with enalapril in altitude polycythaemia,[12] and with losartan in erythrocytosis secondary to chronic obstructive pulmonary disease.[13] Theophylline has also been reported to be of benefit.

1. Ok E, *et al.* Comparison of the effects of enalapril and theophylline on polycythemia after renal transplantation. *Transplantation* 1995; 59: 1623–45.
2. Beckingham IJ, *et al.* A randomized placebo-controlled study of enalapril in the treatment of erythrocytosis after renal transplantation. *Nephrol Dial Transplant* 1995; 10: 2316–20.
3. Hernández E, *et al.* Usefulness and safety of treatment with captopril in posttransplant erythrocytosis. *Transplant Proc* 1995; 27: 2239–41.
4. MacGregor MS, *et al.* Treatment of postrenal transplant erythrocytosis. *Nephron* 1996; 74: 517–21.
5. Klaassen RJL, *et al.* Losartan, an angiotensin-II receptor antagonist, reduces hematocrits in kidney transplant recipients with posttransplant erythrocytosis. *Transplantation* 1997; 64: 780–2.
6. Navarro JF, *et al.* Effects of losartan on the treatment of posttransplant erythrocytosis. *Clin Nephrol* 1998; 49: 370–2.
7. Julian BA, *et al.* Losartan, an angiotensin II type 1 receptor antagonist, lowers hematocrit in posttransplant erythrocytosis. *J Am Soc Nephrol* 1998; 9: 1104–8.
8. Iñigo P, *et al.* Treatment with losartan in kidney transplant recipients with posttransplant erythrocytosis. *Transplant Proc* 1999; 31: 2321.
9. Yildiz A, *et al.* Comparison of the effects of enalapril and losartan on posttransplantation erythrocytosis in renal transplant recipients: prospective randomized study. *Transplantation* 2001; 72: 542–5.
10. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.9.3. Haematological complications: erythrocytosis. *Nephrol Dial Transplant* 2002; 17 (suppl 4): 49–50. Also available at: http://ndt.oxfordjournals.org/cgi/reprint/17/suppl_4/49-a.pdf (accessed 20/11/06)
11. McMullin MF, *et al.* British Committee for Standards in Haematology. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. *Br J Haematol* 2005; 130: 174–95. Also available at: http://www.bcshguidelines.com/pdf/polycythaemia_05.pdf (accessed 20/11/06)
12. Plata R, *et al.* Angiotensin-converting-enzyme inhibition therapy in altitude polycythaemia: a prospective randomised trial. *Lancet* 2002; 359: 663–6.
13. Vlahakos DV, *et al.* Losartan reduces hematocrit in patients with chronic obstructive pulmonary disease and secondary erythrocytosis. *Ann Intern Med* 2001; 134: 426–7.

Genetic disorders. Small studies have suggested that ACE inhibitors may be of benefit in patients with cardiac disorders associated with Marfan syndrome,[1,2] as well as in Duchenne muscular dystrophy.[3,4]

1. Yetman AT, *et al.* Usefulness of enalapril versus propranolol or atenolol for prevention of aortic dilation in patients with the Marfan syndrome. *Am J Cardiol* 2005; 95: 1125–7.
2. Ahimastos AA, *et al.* Effect of perindopril on large artery stiffness and aortic root diameter in patients with Marfan syndrome: a randomized controlled trial. *JAMA* 2007; 298: 1539–47.
3. Duboc D, *et al.* Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy. *J Am Coll Cardiol* 2005; 45: 855–7.
4. Duboc D, *et al.* Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years' follow-up. *Am Heart J* 2007; 154: 596–602.

Heart failure. ACE inhibitors given orally produce clinical benefit in all stages of chronic heart failure (p. 1262.3) additional to that seen with diuretics. They relieve symptoms and improve survival and reduce the progression of mild or moderate heart failure to more severe stages. Thus, it is now recommended that all patients with heart failure due to left ventricular systolic dysfunction should receive ACE inhibitors, even if they are asymptomatic with diuretics alone.

The studies that have shown a benefit with ACE inhibitors have tended to use higher doses than those used in practice. A study[1] with lisinopril found that higher doses reduced the combined end-point of death or hospitalisation more than low doses and were equally well tolerated, suggesting that higher doses should be used. Studies with enalapril have failed to show a benefit of standard doses over lower doses,[2] or high doses over standard doses.[3] It is recommended[4,5] that doses should be titrated to those found to be effective in randomised studies, rather than according to symptomatic response, although lower doses may still be of benefit if higher doses are not tolerated.[4] Combination of ACE inhibitors with angiotensin II receptor antagonists to produce a more complete blockade of the renin-angiotensin system may also be of benefit,[6–8] and may therefore be considered[4,5] in patients who remain symptomatic despite standard therapy, including patients receiving beta blockers.

ACE inhibitors may also have a role in patients with asymptomatic left ventricular dysfunction, although this is less well established; no effect on short-term mortality was found in asymptomatic patients in the *SOLVD* study, but a significant survival benefit was found on long-term follow-up.[9] In patients with heart failure and preserved left ventricular function (diastolic dysfunction) the role of ACE inhibitors is unclear, although they may provide symptomatic benefit.[10] ACE inhibitors may be beneficial in patients with heart failure associated with valve disorders (but see under Precautions, p. 1287.3 for discussion of their use in aortic stenosis). There is also some evidence that ACE inhibitors may prevent the development of antineoplastic-induced cardiotoxicity,[11] although this remains to be confirmed.

The mechanism of action in heart failure is not established. ACE inhibitors have beneficial haemodynamic effects; they produce arterial and venous dilatation,[12] reducing both preload and afterload and thus improving cardiac output without increasing heart rate. Their neurohormonal effects also play a part,[13] as do their effects on cytokines. Further actions that may contribute include reduction of left ventricular hypertrophy, and an indirect action to prevent cardiac arrhythmias.[14–16]

Captopril and enalapril have both been used in infants with severe heart failure (see Administration in Children, p. 1331.3, and p. 1371.2, respectively).

1. Packer M, *et al.* Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation* 1999; 100: 2312–18.
2. The NETWORK investigators. Clinical outcome with enalapril in symptomatic chronic heart failure: a dose comparison. *Eur Heart J* 1998; 19: 481–9.
3. Nanas JN, *et al.* Outcome of patients with congestive heart failure treated with standard versus high doses of enalapril: a multicenter study. *J Am Coll Cardiol* 2000; 36: 2090–5.
4. Jessup M, *et al.* 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; 119: 1977–2016. Correction. *ibid.*; 121:e258. Also published in: *Am Coll Cardiol* 2009; 53: e1–e90. Correction. *ibid.*; 54: 2464. Also available at: http://circ.ahajournals.org/cgi/reprint/119/14/1977.pdf (accessed 11/10/10) and at: http://content.onlinejacc.org/cgi/reprint/53/15/e1.pdf (accessed 11/10/10)
5. Dickstein K, *et al.* Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. *Eur Heart J* 2008; 29: 2388–2442. Correction. *ibid.* 3069. [dose] Also available at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-HF-FT.pdf (accessed 14/10/08)
6. Struckman DR, Rivey MP. Combined therapy with an angiotensin II receptor blocker and an angiotensin-converting enzyme inhibitor in heart failure. *Ann Pharmacother* 2001; 35: 242–8.
7. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; 345: 1667–75.
8. McMurray JJV, *et al.* Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; 362: 767–71.
9. Jong P, *et al.* Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. *Lancet* 2003; 361: 1843–8.
10. Cleland JGF, *et al.* PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006; 27: 2338–45.
11. Cardinale D, *et al.* Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation* 2006; 114: 2474–81.
12. Capewell S, *et al.* Acute and chronic arterial and venous effects of captopril in congestive cardiac failure. *BMJ* 1989; 299: 942–5.
13. Deedwania PC. Angiotensin-converting enzyme inhibitors in congestive heart failure. *Arch Intern Med* 1990; 150: 1798–1805.
14. Wesseling H, *et al.* Cardiac arrhythmias—a new indication for angiotensin-converting enzyme inhibitors? *J Hum Hypertens* 1989; 3 (suppl 1): 89–95.
15. Campbell RWF. ACE inhibitors and arrhythmias. *Heart* 1996; 76 (suppl 3): 79–82.
16. Healey JS, *et al.* Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol* 2005; 45: 1832–9.

Hypertension. ACE inhibitors have an established role in the management of hypertension (p. 1251.1) and appear to have comparable effects to the other main groups of antihypertensives.[1] The Captopril Prevention Project (CAPPP) study,[2] which compared captopril-based therapy with beta blocker- or diuretic-based therapy, suggested that cardiovascular mortality was lower with captopril, although the risk of stroke was increased in those given captopril and overall mortality did not differ between the groups. In the large ALLHAT study,[3] which compared an ACE inhibitor with a calcium-channel blocker or a diuretic, overall mortality did not differ significantly between any of the groups, although there were slightly higher rates of stroke and heart failure in those given the ACE inhibitor compared with the diuretic group. ACE inhibitors are particularly recommended in diabetic patients with nephropathy as they may have beneficial effects on the kidney, and also in patients with heart failure. Other advantages that have been suggested include their lack of adverse effects on serum lipids, a reduction in left ventricular hypertrophy,[4] and a reduction in plasma fibrinogen concentrations,[5] but the clinical significance of these effects is not established.

The antihypertensive actions of ACE inhibitors may be potentiated by drugs that activate the renin-angiotensin system. Hence, combination therapy with diuretics or with calcium-channel blockers may be particularly useful.

1. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003; 362: 1527–35.
2. Hansson L, *et al.* Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999; 353: 611–16.
3. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2981–97. Correction. *ibid.* 2003; 289: 178.
4. Schmieder RE, *et al.* Reversal of left ventricular hypertrophy in essential hypertension: a meta-analysis of randomized double-blind studies. *JAMA* 1996; 275: 1507–13.
5. Fogari R, *et al.* Effects of different antihypertensive drugs on plasma fibrinogen in hypertensive patients. *Br J Clin Pharmacol* 1995; 39: 471–6.

DIAGNOSIS OF RENOVASCULAR HYPERTENSION. Captopril has been used to diagnose renovascular hypertension, since the increase in plasma renin activity after blockade of the conversion of angiotensin I to angiotensin II is greater in renovascular hypertension than in primary hypertension.[1] However, a meta-analysis[2] of various tests used for the diagnosis of renovascular hypertension found that the accuracy of the captopril test is low when compared with imaging methods such as computed tomography or magnetic resonance angiography. Captopril is also used to enhance the sensitivity and specificity of renal scintigraphy.[3] For reference to the use of captopril scintigraphy to diagnose Bartter's syndrome see p. 1282.3.

1. Muller FB, *et al.* The captopril test for identifying renovascular disease in hypertensive patients. *Am J Med* 1986; 80: 633–44.
2. Vasbinder GBC, *et al.* Diagnostic tests for renal artery stenosis in patients suspected of having renovascular hypertension: a meta-analysis. *Ann Intern Med* 2001; 135: 401–411.
3. Dowling RJ, *et al.* Imaging and stenting for renal artery stenosis. *Hosp Med* 1999; 60: 329–34.

Ischaemic heart disease. ACE inhibitors have clinical benefits in patients with ischaemic heart disease and other atherosclerotic conditions. They have an established role

in the treatment of patients after acute myocardial infarction (see below) and may also have a preventative effect; in the SAVE[1] and SOLVD[2] studies, use of ACE inhibitors in patients with heart failure was noted to lead to a reduction in the incidence of myocardial infarction. In the HOPE study,[3] treatment with ramipril significantly reduced the rate of death, myocardial infarction, and stroke in patients at high risk for cardiovascular disease, while in the EUROPA study[4] perindopril was found to reduce cardiovascular events in patients with stable ischaemic heart disease. In the QUO VADIS study,[5] giving quinapril for 1 year after coronary artery bypass grafting reduced the incidence of clinical ischaemic events although there was no effect on ischaemia during exercise testing or Holter monitoring.

The mechanisms by which ACE inhibitors produce benefit in these patients is less clear. Although a direct action to reduce atherosclerosis (p. 1250.2) has been suggested, studies have failed to confirm this effect. In the TREND study,[6] giving quinapril for 6 months was reported to improve endothelial dysfunction in patients with ischaemic heart disease, but apparently no effects on the progression of atherosclerosis or the incidence of cardiac events were found in the QUIET study[7] which used a lower dose of quinapril given for 3 years. In the PART-2 study,[8] ramipril had no effect on the progression of carotid atherosclerosis, while the PARIS study[9] found an increase in angiographic restenosis after use of quinapril. A review[10] based mainly on results from the EUROPA study considered that perindopril upregulated endothelial nitric oxide synthase activity, normalised the balance between angiotensin II and bradykinin, and reduced endothelial apoptosis; however, it noted that the ability to produce these effects varied between different ACE inhibitors, as did affinity for tissue ACE and penetration of atherosclerotic plaque.

A lack of acute anti-ischaemic effect has been found with short-term use of captopril and enalapril in patients with stable angina,[11] and with enalapril in Prinzmetal's angina;[12] however, a further study[13] in patients with stable angina reported an improvement in the results of maximal exercise testing after sublingual captopril dosage. Symptomatic benefit has also been reported[14] in patients with atherosclerotic peripheral arterial disease, and a case-control study[15] has suggested that patients with aortic disease may have a lower risk of ruptured aortic aneurysm if they are taking ACE inhibitors.

1. Pfeffer MA, *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992; 327: 669–77.
2. Yusuf S, *et al.* Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet* 1992; 340: 1173–8.
3. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342: 145–53.
4. EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003; 362: 782–8.
5. Oosterga M, *et al.* Effects of quinapril on clinical outcome after coronary artery bypass grafting (The QUO VADIS Study): QUinapril on Vascular Ace and Determinants of Ischemia. *Am J Cardiol* 2001; 87: 542–6.
6. Mancini GBJ, *et al.* Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease: the TREND (Trial on Reversing Endothelial Dysfunction) study. *Circulation* 1996; 94: 258–65.
7. Cashin-Hemphill L, *et al.* Angiotensin-converting enzyme inhibition as antiatherosclerotic therapy: no answer yet. *Am J Cardiol* 1999; 83: 43–7.
8. MacMahon S, *et al.* Randomized, placebo-controlled trial of the angiotensin-converting enzyme inhibitor, ramipril, in patients with coronary or other occlusive arterial disease. *J Am Coll Cardiol* 2000; 36: 438–43.
9. Meurice T, *et al.* Effect of ACE inhibitors on angiographic restenosis after coronary stenting (PARIS): a randomised, double-blind, placebo-controlled trial. *Lancet* 2001; 357: 1321–4.
10. Ferrari R, Fox K. Insight into the mode of action of ACE inhibition in coronary artery disease: the ultimate 'EUROPA' story. *Drugs* 2009; 69: 265–77.
11. Longobardi G, *et al.* Failure of protective effect of captopril and enalapril on exercise and dipyridamole-induced myocardial ischemia. *Am J Cardiol* 1995; 76: 255–8.
12. Guazzi M, *et al.* Ineffectiveness of angiotensin converting enzyme inhibition (enalapril) on overt and silent myocardial ischemia in vasospastic angina and comparison with verapamil. *Clin Pharmacol Ther* 1996; 59: 476–81.
13. Gemici K, *et al.* The effects of sublingual administration of captopril on parameters of exercise test and neurohormonal activation in patients with stable angina pectoris. *Int J Angiol* 1998; 7: 238–43.
14. Ahimastos AA, *et al.* Ramipril markedly improves walking ability in patients with peripheral arterial disease: a randomized trial. *Ann Intern Med* 2006; 144: 660–4.
15. Hackam DG, *et al.* Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case-control study. *Lancet* 2006; 368: 659–65.

Kidney disorders. The effects of ACE inhibitors on the kidney are complex. Although they may reduce renal function and should be used with caution in patients with renal impairment (see Adverse Effects and Treatment, p. 1285.2), ACE inhibitors may also have beneficial effects in diabetic and nondiabetic renal disease. Reducing blood pressure protects renal function regardless of the class of antihypertensive used,[1] since hypertension and the resultant proteinuria both cause kidney damage. Several studies have shown that ACE inhibitors and other drugs that block the renin-angiotensin-aldosterone system (RAS), such as angiotensin II receptor antagonists, are particularly effective[1] and they may therefore be preferred for blood pressure control in kidney disorders. However, whether they have a specific renoprotective effect beyond their antihypertensive effect is unclear.[2]

Most experience has been gained in patients with diabetic nephropathy (see p. 465.1), which is often associated with hypertension and may progress from microalbuminuria to the nephrotic syndrome and end-stage renal failure. In diabetic patients with marked proteinuria, treatment with ACE inhibitors has been reported to slow progression to end-stage renal disease, and to have a mortality benefit.[3] However, although it has been assumed that this could be extended to patients with earlier disease, this now seems to be less clear. Studies have reported that ACE inhibitors can slow progression of microalbuminuria,[4,5] and their use has been recommended, with tight glycaemic control, in all microalbuminuric diabetic patients.[6] However, the 5-year RASS study in type 1 diabetic patients without any proteinuria, which directly measured renal structural changes, found neither enalapril nor losartan to be of benefit for primary prevention of renal damage (although progression of retinopathy was slowed).[7] Further uncertainty about the benefits of blockade of the renin-angiotensin system has been produced by the results of the ONTARGET study. Angiotensin II receptor antagonists have also been reported to be effective in slowing the progression of proteinuria[3,4,8] (though mortality benefit has not been shown[3]), and dual therapy with these drugs and an ACE inhibitor had been thought to offer benefits over either alone,[9,10] but ONTARGET, which compared treatment with ramipril, telmisartan, or both in patients over 55 with atherosclerotic vascular disease or diabetes with end-organ damage,[11] found that combination therapy, despite reducing proteinuria more than either drug alone, was actually associated with a higher risk of renal events. Again, most of the patients in this study did not have proteinuria. Although the study was not powered to detect differences of major renal outcomes, this has thrown doubt on the value of combination therapy in such patients.

ACE inhibitors may also be of benefit in renal disease unrelated to diabetes, although their role is less established. Proteinuria is an important indicator of glomerular kidney disease (p. 1604.3) of various causes and may range from asymptomatic to severe. Several studies[12-19] have reported that ACE inhibitors reduce both proteinuria and the rate of decline of renal function in patients with various non-diabetic renal disorders. Meta-analyses[20,21] have concluded that ACE inhibitors are more effective than other antihypertensives, although others suggest this is uncertain.[2] There is less evidence for angiotensin II receptor antagonists alone in non-diabetic renal disease.[8] Again, dual therapy with one of these drugs and an ACE inhibitor has been suggested to offer additional renal benefit,[9] but the ONTARGET results[11] throw some doubt on this.

Patients with systemic sclerosis (see Scleroderma, p. 1942.3) are considered to be at high risk of adverse effects from ACE inhibitors; however there is evidence that these drugs are of benefit in the management of scleroderma-associated hypertension and renal crisis.[22]

1. Ravera M, *et al.* Importance of blood pressure control in chronic kidney disease. *J Am Soc Nephrol* 2006; 17 (4 suppl 2): S98–S103.
2. Casas JP, *et al.* Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet* 2005; 366: 2026–33.
3. Strippoli GFM, *et al.* Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 25/04/08).
4. Thomas MC, Atkins RC. Blood pressure lowering for the prevention and treatment of diabetic kidney disease. *Drugs* 2006; 66: 2213–34.
5. The ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med* 2001; 134: 370–9.
6. Mogensen CE, *et al.* Prevention of diabetic renal disease with special reference to microalbuminuria. *Lancet* 1995; 346: 1080–4.
7. Mauer M, *et al.* Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med* 2009; 361: 40–51.
8. Thurman JM, Schrier RW. Comparative effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on blood pressure and the kidney. *Am J Med* 2003; 114: 588–98.
9. MacKinnon M, *et al.* Combination therapy with an angiotensin receptor blocker and an ACE inhibitor in proteinuric renal disease: a systematic review of the efficacy and safety data. *Am J Kidney Dis* 2006; 48: 8–20.
10. Kunz R, *et al.* Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin-angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008; 148: 30–48.
11. Mann JF, *et al.* ONTARGET investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 2008; 372: 547–53.
12. Gansevoort RT, *et al.* Long-term benefits of the antiproteinuric effect of angiotensin-converting enzyme inhibition in nondiabetic renal disease. *Am J Kidney Dis* 1993; 22: 202–6.
13. Hannedouche T, *et al.* Randomised controlled trial of enalapril and β blockers in non-diabetic chronic renal failure. *BMJ* 1994; 309: 833–7.
14. Maschio G, *et al.* Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 1996; 334: 939–45.
15. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 1997; 349: 1857–63.
16. Ruggenenti P, *et al.* Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. *Lancet* 1998; 352: 1252–6.
17. Ruggenenti P, *et al.* Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 1999; 354: 359–64.
18. Agodoa LY, *et al.* Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA* 2001; 285: 2719–28.
19. Hou FF, *et al.* Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 2006; 354: 131–40.
20. Giatras I, *et al.* Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. *Ann Intern Med* 1997; 127: 337–45.
21. Jafar TH, *et al.* Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease: a meta-analysis of patient-level data. *Ann Intern Med* 2001; 135: 73–87.
22. Steen VD, *et al.* Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. *Ann Intern Med* 1990; 113: 352–7.

Malignant neoplasms. *Animal* and *in vitro* studies have suggested that ACE inhibitors may protect against the development of cancer. Regression of Kaposi's sarcoma was reported[1] in a patient treated with captopril (but see Effects on the Skin, p. 1286.3), and a retrospective cohort study[2] suggested that the incidence of cancer in hypertensive patients receiving ACE inhibitors was lower than expected. In a prospective cohort study[3] of 7983 patients, blocking the renin-angiotensin system appeared to protect against cancer in individuals with a polymorphism for high plasma-ACE concentrations; however, a case control study[4] in postmenopausal women found no evidence of a reduced risk of breast cancer associated with ACE inhibitor therapy.

1. Vogt B, Frey FJ. Inhibition of angiogenesis in Kaposi's sarcoma by captopril. *Lancet* 1997; 349: 1148.
2. Lever AF, *et al.* Do inhibitors of angiotensin-I-converting enzyme protect against risk of cancer? *Lancet* 1998; 352: 179–84.
3. van der Knaap R, *et al.* Renin-angiotensin system inhibitors, angiotensin I-converting enzyme gene insertion/deletion polymorphism, and cancer: the Rotterdam Study. *Cancer* 2008; 112: 748–57.
4. Meier CR, *et al.* Angiotensin-converting enzyme inhibitors, calcium channel blockers, and breast cancer. *Arch Intern Med* 2000; 160: 349–53.

Marfan syndrome. For mention of the use of ACE inhibitors in patients with Marfan syndrome see Genetic Disorders, p. 1283.2.

Migraine. Observations that attacks of migraine occurred less frequently in hypertensive patients treated with lisinopril, were confirmed by a small placebo-controlled study[1] in 47 non-hypertensive patients with migraine (p. 670.3); low oral doses (5 mg daily) may be adequate.[2]

1. Schrader H, *et al.* Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. *BMJ* 2001; 322: 19–22.
2. Schuh-Hofer S, *et al.* Efficacy of lisinopril in migraine prophylaxis – an open label study. *Eur J Neurol* 2007; 14: 701–3.

Muscular dystrophy. For reference to the use of ACE inhibitors in patients with Duchenne muscular dystrophy see Genetic Disorders, p. 1283.2.

Myocardial infarction. ACE inhibitors may be of benefit in both the prevention and treatment of myocardial infarction (p. 1257.1). They reduce left ventricular remodelling, a process which sometimes follows myocardial infarction and is a recognised precursor of symptomatic heart failure. Studies in patients with evidence of left ventricular dysfunction have shown benefit from long-term oral use of ACE inhibitors such as captopril (the SAVE study),[1] ramipril (the AIRE and AIRE extension (AIREX) studies),[2-4] or trandolapril (the TRACE study)[5,6] started about 3 days, or more, after infarction, and long-term ACE inhibitors are now established therapy in such patients.[7,8]

Early treatment with ACE inhibitors as an adjunct to standard thrombolytic therapy is less well established. Favourable results have been reported in the GISSI-3[9] and the ISIS-4[10] studies where lisinopril and captopril, respectively, were given orally starting within 24 hours of the onset of chest pain and in the Chinese Cardiac Study[11] (CCS-1) where captopril was given orally within 36 hours of the onset of symptoms. In the GISSI-3 study the beneficial effects were maintained at 6 months.[12] However, the CONSENSUS II study was stopped early when it was found that enalaprilat, given intravenously as enalaprilat and begun within 24 hours of the onset of chest pain, did not improve survival during the 180 days after infarction.[13] A substudy on some of the patients did however suggest that they may have benefited from early treatment since left ventricular dilatation was attenuated.[14] An interaction between aspirin and enalapril was postulated as one of the reasons for the overall lack of benefit seen, and further analysis of the CONSENSUS II results found that the beneficial effect of

enalapril was reduced in those patients already taking aspirin,[15] although a systematic overview[16] failed to support this finding. A systematic review of the CONSENSUS II, GISSI-3, ISIS-4, and CCS-1 studies found lower 30-day cumulative mortality and incidence of non-fatal heart failure among ACE inhibitor recipients.[17] However, the size of benefit in these studies of largely unselected patients is much smaller than in the studies of patients with left ventricular dysfunction, and there remains no clear consensus as to whether all patients should be given ACE inhibitors or only those who develop evidence of left ventricular dysfunction.

1. Pfeffer MA, *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992; 327: 669–77.
2. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993; 342: 821–8.
3. Hall AS, *et al.* Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE extension (AIREX) study. *Lancet* 1997; 349: 1493–7.
4. Cleland JGF, *et al.* Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure: a report from the AIRE study investigators. *Eur Heart J* 1997; 18: 41–51.
5. Kober L, *et al.* A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995; 333: 1670–6.
6. Torp-Pedersen C, Kober L. Effect of ACE inhibitor trandolapril on life expectancy of patients with reduced left-ventricular function after acute myocardial infarction. *Lancet* 1999; 354: 9–12.
7. Borghi C, Ambrosioni E. A risk-benefit assessment of ACE inhibitor therapy post-myocardial infarction. *Drug Safety* 1996; 14: 277–87.
8. Murdoch DR, McMurray JJV. ACE inhibitors in acute myocardial infarction. *Hosp Med* 1998; 59: 111–15.
9. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994; 343: 1115–22.
10. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995; 345: 669–85.
11. Chinese Cardiac Study collaborative group. Oral captopril versus placebo among 13 634 patients with suspected acute myocardial infarction: interim report from the Chinese Cardiac Study (CCS-1). *Lancet* 1995; 345: 686–7.
12. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. Six-month effects of early treatment with lisinopril and transdermal glyceryl trinitrate singly and together withdrawn six weeks after acute myocardial infarction: the GISSI-3 trial. *J Am Coll Cardiol* 1996; 27: 337–44.
13. Swedberg K, *et al.* Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction: results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *N Engl J Med* 1992; 327: 678–84.
14. Bonarjee VVS, *et al.* Attenuation of left ventricular dilatation after acute myocardial infarction by early initiation of enalapril therapy. *Am J Cardiol* 1993; 72: 1004–9.
15. Nguyen KN, *et al.* Interaction between enalapril and aspirin on mortality after acute myocardial infarction: subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *Am J Cardiol* 1997; 79: 115–19.
16. Latini R, *et al.* Clinical effects of early angiotensin-converting enzyme inhibitor treatment for acute myocardial infarction are similar in the presence and absence of aspirin: systematic overview of individual data from 96,712 randomized patients. *J Am Coll Cardiol* 2000; 35: 1801–7.
17. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100 000 patients in randomized trials. *Circulation* 1998; 97: 2202–12.

Pneumonia. Use of ACE inhibitors has been suggested to be of potential value in reducing the risk of community-acquired pneumonia in the elderly, particularly in those with neurological and cerebrovascular abnormalities (see also Stroke, below). A systematic review[1] considered that there was some evidence for this approach, but noted that it mostly came from studies in Asian patients. Given potential polymorphisms in ACE metabolism, future studies should include genetic data.

1. Rafailidis PI, *et al.* Use of ACE inhibitors and risk of community-acquired pneumonia: a review. *Eur J Clin Pharmacol* 2008; 64: 565–73.

Raynaud's syndrome. ACE inhibitors are among many drugs that have been tried in Raynaud's syndrome, a vasospastic arterial disorder (p. 1275.3). Variable effects have been reported. In a patient with Raynaud's syndrome captopril improved blood circulation in the fingers both acutely and during long-term therapy with a dose of 37.5 mg daily; the effect was apparently related to its effects on kinins rather than inhibition of angiotensin II formation.[1] However, a double-blind crossover study in 15 patients with Raynaud's phenomenon given captopril 25 mg or placebo three times daily for 6 weeks found that the drug improved blood flow but not the frequency or severity of attacks;[2] a similar study in patients given enalapril failed to find any subjective or objective benefits;[3] and use of quinapril for 3 years did not reduce vascular manifestations of systemic sclerosis or Raynaud's syndrome.[4] A review[5] concluded that ACE inhibitors provide only minor benefits in the treatment of Raynaud's syndrome.

In one patient, captopril[6] rapidly reversed ergotamine-induced peripheral ischaemia.

1. Miyazaki S, *et al.* Relief from digital vasospasm by treatment with captopril and its complete inhibition by serine proteinase inhibitors in Raynaud's phenomenon. *BMJ* 1982; 284: 310–11.
2. Rustin MHA, *et al.* The effect of captopril on cutaneous blood flow in patients with primary Raynaud's phenomenon. *Br J Dermatol* 1987; 117: 751–8.
3. Challenor VF, *et al.* Subjective and objective assessment of enalapril in primary Raynaud's phenomenon. *Br J Clin Pharmacol* 1991; 31: 477–80.
4. Gliddon AE, *et al.* Prevention of vascular damage in scleroderma and autoimmune Raynaud's phenomenon: a multicenter, randomized, double-blind, placebo-controlled trial of the angiotensin-converting enzyme inhibitor quinapril. *Arthritis Rheum* 2007; 56: 3837–46.
5. Wood HM, Ernst ME. Renin-angiotensin system mediators and Raynaud's phenomenon. *Ann Pharmacother* 2006; 40: 1998–2002.
6. Zimran A, *et al.* Treatment with captopril for peripheral ischaemia induced by ergotamine. *BMJ* 1984; 288: 364.

Stroke. Antihypertensive therapy reduces the risk of stroke (p. 1269.2) in patients with hypertension. However, in patients who have had a stroke, antihypertensive therapy has often been avoided due to the perceived risk of reducing cerebral perfusion. A study[1] of blood-pressure lowering with the ACE inhibitor perindopril, alone or with a diuretic, found that the risk of recurrent stroke was reduced in patients with a history of stroke or transient ischaemic attack, irrespective of whether they had a normal or raised blood pressure at study entry. Retrospective studies[2,3] have also suggested that stroke severity may be reduced in patients who are already taking ACE inhibitors. The beneficial effects of ACE inhibitors in stroke may not be entirely due to their antihypertensive effects; in the HOPE study,[4] ramipril reduced the incidence of stroke in patients with high cardiovascular risk despite only a small reduction in blood pressure.

There have also been reports[5,6] that ACE inhibitors may reduce the risk of pneumonia in patients with a history of stroke, possibly by an effect on symptomless dysphagia.[7] See also Pneumonia, above.

1. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; 358: 1033–41. Corrections. *ibid.*; 1536 and 2002; 359: 2120.
2. Kumar S, *et al.* Antiplatelets, ACE inhibitors, and statins combination reduces stroke severity and tissue at risk. *Neurology* 2006; 66: 1153–8.
3. Chitravas N, *et al.* Is prestroke use of angiotensin-converting enzyme inhibitors associated with better outcome? *Neurology* 2007; 68: 1687–93.
4. Bosch J, *et al.* Use of ramipril in preventing stroke: double blind randomised trial. *BMJ* 2002; 324: 699–702.
5. Sekizawa K, *et al.* ACE inhibitors and pneumonia. *Lancet* 1998; 352: 1069.
6. Arai T, *et al.* ACE inhibitors and pneumonia in elderly people. *Lancet* 1998; 352: 1937–8.
7. Arai T, *et al.* ACE inhibitors and symptomless dysphagia. *Lancet* 1998; 352: 115–6.

Adverse Effects and Treatment

Many of the adverse effects of ACE inhibitors relate to their pharmacological action and all therefore have a similar spectrum of adverse effects. Some effects, such as taste disturbances and skin reactions, were at one time attributed to the presence of a sulfhydryl group (as in captopril) but have now also been reported with other ACE inhibitors; however, they may be more common with captopril.

The most common adverse effects are due to the vascular effects of ACE inhibitors and include hypotension, dizziness, fatigue, headache, and nausea and other gastrointestinal disturbances.

Pronounced hypotension may occur at the start of therapy with ACE inhibitors, particularly in patients with heart failure and in sodium- or volume-depleted patients (for example, those given previous diuretic therapy). Myocardial infarction and stroke have been reported and may relate to severe falls in blood pressure in patients with ischaemic heart disease or cerebrovascular disease. Other cardiovascular effects that have occurred include tachycardia, palpitations, and chest pain.

Deterioration in renal function, including increasing blood concentrations of urea and creatinine, may occur, and reversible acute renal failure has been reported. Renal effects are most common in patients with existing renal or renovascular dysfunction or heart failure, in whom vasodilatation reduces renal perfusion pressure; this may be aggravated by hypovolaemia. Proteinuria has also occurred and in some patients has progressed to nephrotic syndrome. Hyperkalaemia and hyponatraemia may develop due to decreased aldosterone secretion.

Other adverse effects include persistent dry cough and other upper respiratory tract symptoms, and angioedema; these may be related to effects on bradykinin or prostaglandin metabolism. Skin rashes (including erythema multiforme and toxic epidermal necrolysis) may occur; photosensitivity, alopecia, and other hypersensitivity reactions have also been reported.

Blood disorders have been reported with ACE inhibitors and include neutropenia and agranulocytosis (especially in patients with renal failure and in those with collagen vascular disorders such as SLE and scleroderma), thrombocytopenia, and anaemias.

Other less common adverse effects reported with ACE inhibitors include stomatitis, abdominal pain, pancreatitis, hepatocellular injury or cholestatic jaundice, muscle cramps, paraesthesias, mood and sleep disturbances, and impotence.

ACE inhibitors have been associated with fetal toxicity (see Pregnancy under Precautions, p. 1288.1).

Most of the adverse effects of ACE inhibitors are reversible on withdrawing therapy. Symptomatic hypotension, including that after overdosage, generally responds to volume expansion with an intravenous infusion of sodium chloride 0.9%.

General reviews.

1. Parish RC, Miller LJ. Adverse effects of angiotensin converting enzyme (ACE) inhibitors: an update. *Drug Safety* 1992; 7: 14–31.
2. Alderman CP. Adverse effects of the angiotensin-converting enzyme inhibitors. *Ann Pharmacother* 1996; 30: 55–61.
3. Agustí A, *et al.* Adverse effects of ACE inhibitors in patients with chronic heart failure and/or ventricular dysfunction: meta-analysis of randomised clinical trials. *Drug Safety* 2003; 26: 895–908.
4. Adam A, *et al.* Physiopathologie des effets secondaires aigus des inhibiteurs de l'enzyme de conversion de l'angiotensine. *Bull Acad Natl Med* 2007; 191: 1433–43.

Angioedema. See under Hypersensitivity, p. 1287.1.

Cough. Treatment with ACE inhibitors has been associated with the development of cough in up to 20% of hypertensive patients; cough may be less troublesome in those with heart failure,[1] although the incidence may be higher.[2] The cough is reported to be persistent, paroxysmal, and non-productive; it causes irritation of the throat, may be accompanied by voice changes (hoarseness or huskiness), and is often worse when lying down.[1,3,4] It is more common in women and non-smokers, and may be delayed in onset by weeks or even months.

The majority of reports of this adverse effect concern captopril and enalapril,[3,4] but it has also occurred in patients receiving many of the other ACE inhibitors,[5] suggesting that the effect is common to all drugs of this class.

The mechanism that produces the reaction is uncertain but appears to be related to the non-specific blockade of ACE since angiotensin II receptor antagonists are associated with a much lower incidence of cough.[6] The sensitivity of the cough reflex is increased.[7] Prostaglandins released in the respiratory tract have been proposed as mediators,[3] but other mediators such as bradykinin[8] or substance P,[9] both of which are substrates for ACE, have been suggested. However, attempts to show a link between the effects of ACE inhibitors on cough, and bronchial hyperreactivity of the type found in obstructive airways disease and asthma have produced conflicting evidence, with bronchial hyperreactivity being shown in some studies[10] but not in others.[11]

Where the patient can tolerate the cough, it may be reasonable to continue treatment; in some cases reducing the dose may help. Spontaneous recovery or improvement in the cough has been reported.[12] Changing to an alternative ACE inhibitor is not advised since it is rarely effective.[7] Drugs that inhibit prostaglandin synthesis, including the NSAIDs sulindac[13] and indometacin,[14] have been reported to suppress the cough, but NSAIDs and ACE inhibitors may interact adversely (see under Interactions, p. 1288.3). The calcium-channel blocker nifedipine also reduced cough, although to a lesser extent than indometacin, possibly by a similar mechanism.[14] Inhaled bupivacaine,[15] inhaled sodium cromoglicate,[16,17] oral baclofen,[18] oral picotamide,[19] and oral ferrous sulfate,[20] have also been reported to be of help. However, in many patients there will be no alternative but to withdraw the ACE inhibitor, and this is recommended by some in all patients presenting with ACE inhibitor-induced cough.[21] Angiotensin II receptor antagonists may be a suitable alternative in patients with hypertension.[21]

1. Anonymous. Cough caused by ACE inhibitors. *Drug Ther Bull.* 1994; 32: 28 and 35–6.
2. Ravid D, *et al.* Angiotensin-converting enzyme inhibitors and cough: a prospective evaluation in hypertension and congestive heart failure. *J Clin Pharmacol* 1994; 34: 1116–20.
3. Coulter DM, Edwards IR. Cough associated with captopril and enalapril. *BMJ* 1987; 294: 1521–3.
4. Berkin KE, Ball SG. Cough and angiotensin converting enzyme inhibition. *BMJ* 1988; 296: 1279–80.
5. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. *Ann Intern Med* 1992; 117: 234–42.
6. Pylypchuk GB. ACE inhibitor- versus angiotensin II blocker-induced cough and angioedema. *Ann Pharmacother* 1998; 32: 1060–6.
7. Overlack A. ACE inhibitor-induced cough and bronchospasm. *Drug Safety* 1996; 15: 72–8.
8. Ferner RE, *et al.* Effects of intradermal bradykinin after inhibition of angiotensin converting enzyme. *BMJ* 1987; 294: 1119–20.
9. Morice AH, *et al.* Angiotensin-converting enzyme and the cough reflex. *Lancet* 1987; ii: 1116–18.
10. Bucknall CE, *et al.* Bronchial hyperreactivity in patients who cough after receiving angiotensin converting enzyme inhibitors. *BMJ* 1988; 296: 86–8.
11. Boulet L-P, *et al.* Pulmonary function and airway responsiveness during long-term therapy with captopril. *JAMA* 1989; 261: 413–16.
12. Reisin L, Schneeweiss A. Spontaneous disappearance of cough induced by angiotensin-converting enzyme inhibitors (captopril or enalapril). *Am J Cardiol* 1992; 70: 398–9.

13. Nicholls MG, Gilchrist NL. Sulindac and cough induced by converting enzyme inhibitors. *Lancet* 1987; i: 872.
14. Fogari R, *et al.* Effects of nifedipine and indomethacin on cough induced by angiotensin-converting enzyme inhibitors: a double-blind, randomized, cross-over study. *J Cardiovasc Pharmacol* 1992; 19: 670–3.
15. Brown RC, Turton CWG. Cough and angiotensin converting enzyme inhibition. *BMJ* 1988; 296: 1741.
16. Keogh A. Sodium cromoglycate prophylaxis for angiotensin-converting enzyme inhibitor cough. *Lancet* 1993; 341: 560.
17. Hargreaves MR, Benson MK. Inhaled sodium cromoglycate in angiotensin-converting enzyme inhibitor cough. *Lancet* 1995; 345: 13–16.
18. Dicpinigaitis PV. Use of baclofen to suppress cough induced by angiotensin-converting enzyme inhibitors. *Ann Pharmacother* 1996; 30: 1242–5.
19. Malini PL, *et al.* Thromboxane antagonism and cough induced by angiotensin-converting-enzyme inhibitor. *Lancet* 1997; 350: 15–18.
20. Lee S-C, *et al.* Iron supplementation inhibits cough associated with ACE inhibitors. *Hypertension* 2001; 38: 166–70.
21. Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. *Chest* 2006; 129 (suppl): 169S–173S.

Effects on the blood. Blood disorders have occurred in patients receiving ACE inhibitors, although there have been few reports in the literature. A reduction in haemoglobin concentration and haematocrit may occur but is not usually clinically significant, although an unfavourable effect on recovery from anaemia has been reported;[1] ACE inhibitors have also been used therapeutically to reduce the haematocrit (see Erythrocytosis under Uses, p. 1283.1). Cases of neutropenia and agranulocytosis (particularly in patients with renal or collagen vascular disorders), and thrombocytopenia have been noted. Aplastic anaemia has also occurred[2,3] and may be fatal.[3]

1. Ripamonti V, *et al.* Angiotensin-converting enzyme inhibitors slow recovery from anemia following cardiac surgery. *Chest* 2006; 130: 79–84.
2. Kim CR, *et al.* Captopril and aplastic anemia. *Ann Intern Med* 1989; 111: 187–8.
3. Harrison BD, *et al.* Fatal aplastic anaemia associated with lisinopril. *Lancet* 1995; 346: 247–8.

Effects on the kidneys. ACE inhibitors have complex effects on the kidney;[1,2] they have established renoprotective effects but also cause acute deterioration in renal function in some patients. These apparently contradictory effects are related to the action of ACE inhibitors on the renin-angiotensin-aldosterone system.

The renin-angiotensin-aldosterone system has an important role in maintaining normal renal blood flow and renal function. A reduction in renal perfusion, for example due to hypovolaemia, heart failure, or renal artery stenosis, leads to activation of this system and an increase in angiotensin II release. This results mainly in postglomerular renal vasoconstriction, which maintains renal glomerular pressure and thus glomerular filtration, despite the fall in renal blood flow.

In normal individuals with unrestricted sodium intake, the renin-angiotensin-aldosterone system is suppressed and ACE inhibitors have little effect on renal function. In patients with essential hypertension ACE inhibitors generally increase renal blood flow despite the reduction in arterial blood pressure, since this is exceeded by the effects of renal vasodilatation. However, filtration fraction falls since the pressure within the glomerulus is reduced, and there are only minor changes in glomerular filtration rate. The increase in renal blood flow is more pronounced during sodium restriction and in younger patients.

These effects are generally beneficial. However, in patients with reduced renal perfusion, glomerular filtration rate may be critically dependent on the renin-angiotensin-aldosterone system and the use of ACE inhibitors may provoke problems. Severe renal function loss or even anuria have been reported in patients with a single transplanted kidney with renal artery stenosis, or patients with bilateral renal artery disease. The stenotic kidney maintains its filtering capacity by preferential vasoconstriction of the efferent arterioles, a mechanism mainly mediated by the renin-angiotensin system; under ACE inhibition, vasodilatation of the efferent arterioles combined with the drop in arterial pressure can result in a critical decrease in filtration pressure. Hypovolaemia or sodium depletion, for example due to diuretics, also leads to activation of the renin-angiotensin-aldosterone system and predisposes patients to renal impairment. Most patients developing renal insufficiency have been using diuretics and sodium repletion can restore renal function despite continuing ACE inhibition.

Patients with heart failure may also be at risk of a decline in renal function on long-term ACE inhibitor therapy. This is because in chronic heart failure, angiotensin-II mediated systemic and renal vasoconstriction is again important in the maintenance of renal perfusion pressure. The decline may be alleviated by reduction of the dosage of diuretics or liberalisation of dietary salt intake, despite continuing the ACE inhibitor. An additional risk factor in elderly patients with heart failure is the high incidence of occult renovascular disease in these patients.[3]

Moderate impairment of renal function either before or during use of ACE inhibitors is not necessarily an indication to stop therapy. The effects of ACE inhibitors on renal function are generally reversible, and the reduction in filtration pressure may result in renoprotection. A review[4] of studies of the use of ACE inhibitors in patients with renal impairment found that those who initially lost renal function had the greatest long-term benefit.

In addition to pathophysiological effects ACE inhibitors may induce membranous glomerulopathy or interstitial nephritis. The former has been associated with captopril use, particularly at high doses, but is rare, and seems less likely to occur at the lower doses favoured today. The proteinuria usually clears without appreciable renal function loss irrespective of whether or not the drug is continued, although persistent proteinuria and renal function loss have been described. Proven interstitial nephritis has also been reported rarely, and may possibly be due to an allergic mechanism.

1. Navis G, *et al.* ACE inhibitors and the kidney: a risk-benefit assessment. *Drug Safety* 1996; 15: 200–11.
2. Schoolwerth AC, *et al.* Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. *Circulation* 2001; 104: 1985–91.
3. MacDowall P, *et al.* Risk of morbidity from renovascular disease in elderly patients with congestive cardiac failure. *Lancet* 1998; 352: 13–16.
4. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med* 2000; 160: 685–93.

Effects on the liver. Hepatotoxicity has been reported with ACE inhibitors, including captopril,[1,2] enalapril,[2] fosinopril,[3] lisinopril,[2] and ramipril.[4] Most reports have been associated with captopril. In a report[1] of 3 cases of liver disease apparently caused or aggravated by captopril, it was noted that jaundice due to captopril is usually mainly cholestatic in nature but acute hepatocellular injury has also been seen. Of 29 cases of liver dysfunction due to captopril and reported to the UK CSM, 9 had hepatocellular jaundice, with 2 deaths; 8 were cholestatic jaundice, with 1 fatality; and 3 patients had hepatorenal syndrome, all of whom died. Worldwide, excluding the UK, 164 cases of hepatic adverse reactions had been notified to the WHO by January 1989. The incidence of such reactions is estimated at 0.09 per 1000 patients but this is likely to be an underestimate. Resolution may take a long time and the drug should be withdrawn immediately at the earliest hint of liver sensitivity.

1. Bellary SV, *et al.* Captopril and the liver. *Lancet* 1989; ii: 514.
2. Hagley MT, *et al.* Hepatotoxicity associated with angiotensin-converting enzyme inhibitors. *Ann Pharmacother* 1993; 27: 228–31.
3. Chou J-W, *et al.* Successful treatment of fosinopril-induced severe cholestatic jaundice with plasma exchange. *Ann Pharmacother* 2008; 42: 1887–92.
4. Yeung E, *et al.* Ramipril-associated hepatotoxicity. *Arch Pathol Lab Med* 2003; 127: 1493–7.

Effects on the mouth. Aphthous and tongue ulcers may occur during treatment with ACE inhibitors. There have been a few reports of a 'scalded mouth syndrome', described as similar to being scalded by hot liquids, associated with captopril,[1] enalapril,[1] and lisinopril[2] therapy.

1. Vlasses PH, *et al.* "Scalded mouth" caused by angiotensin-converting enzyme inhibitors. *BMJ* 1982; 284: 1672–3.
2. Savino LB, Haushalter NM. Lisinopril-induced "scalded mouth syndrome." *Ann Pharmacother* 1992; 26: 1381–2.

Effects on the nervous system. Encephalopathy and focal neurological signs,[1] and peripheral neuropathy,[2,3] including Guillain-Barré neuropathy,[3] have been reported in patients receiving captopril. Some CNS effects of captopril may be attributable to alterations in cerebral blood flow. In a study in patients with severe heart failure, cerebral blood flow in patients aged under 65 was improved by a single dose of captopril 12.5 mg, but in patients aged over 70 there was a 13% reduction.[4] Two patients in whom captopril 6.25 mg produced impaired consciousness and paraesthesias, and dizziness, blurred vision, and aphasia, were found to have stenosis of the carotid arteries.[5] Agitation, panic, extreme depression, and insomnia was reported in a patient 4 weeks after starting treatment with enalapril; depressive episodes recurred on rechallenge.[6] There have been reports of mania possibly precipitated by captopril,[7] and visual hallucinations have been reported in association with captopril and enalapril therapy.[8]

1. Rapoport S, Zyman P. Captopril and central nervous system effects. *Ann Intern Med* 1983; 98: 1023.
2. Samanta A, Burden AC. Peripheral neuropathy due to captopril. *BMJ* 1985; 291: 1172.
3. Chakraborty TK, Ruddell WSJ. Guillain-Barré neuropathy during treatment with captopril. *Postgrad Med J* 1987; 63: 221–2.
4. Britton KE, *et al.* Angiotensin-converting-enzyme inhibitors and treatment of heart failure. *Lancet* 1985; ii: 1236.
5. Jensen H, *et al.* Carotid artery stenosis exposed by an adverse effect of captopril. *BMJ* 1986; 293: 1073–4.
6. Ahmad S. Enalapril-induced acute psychosis. *DICP Ann Pharmacother* 1991; 25: 558–9.
7. Peet M, Peters S. Drug-induced mania. *Drug Safety* 1995; 12: 146–53.
8. Haffner CA, *et al.* Hallucinations as an adverse effect of angiotensin converting enzyme inhibition. *Postgrad Med J* 1993; 69: 240.

Effects on the pancreas. By 1994 the UK CSM[1] noted that there had been 23 reports of pancreatitis associated with ACE inhibitors (captopril 11, enalapril 10, fosinopril 1, and quinapril 1), and since then, pancreatitis (in some cases fatal) has been reported with most of the commonly used ACE inhibitors. Causality has proved difficult to establish,[2] however, and a retrospective cohort study[3] was unable to confirm an association between ACE inhibitors and pancreatitis in elderly patients, despite the large sample size.

1. CSM/MCA. Drug-induced pancreatitis. *Current Problems* 1994; 20: 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 04/04/08)
2. Singh S. Angiotensin-converting enzyme (ACE) inhibitor-induced acute pancreatitis: in search of the evidence. *South Med J* 2006; 99: 1327–8
3. Cheng RMS, *et al.* Association between ACE inhibitors and acute pancreatitis in the elderly. *Ann Pharmacother* 2003; 37: 994–8.

Effects on the respiratory system. Cough is a recognised adverse effect of ACE inhibitors but evidence for a link with bronchial hyperreactivity or airways obstruction is conflicting (see Cough, p. 1285.3). In reports of adverse respiratory reactions to ACE inhibitors submitted to the Swedish Adverse Drug Reactions Advisory Committee and to WHO, symptoms of airway obstruction such as dyspnoea, asthma, and bronchospasm occurred rarely, usually within the first few weeks of treatment.[1] However, the evidence for a causal link between ACE inhibitors and these symptoms was questioned.[2]

Severe nasal obstruction was associated with enalapril treatment in a 45-year-old woman with a history of mild rhinorrhoea and sneezing. Symptoms cleared within 2 days of stopping enalapril and recurred on rechallenge.[3] Another woman taking enalapril developed obstructive sleep apnoea,[4] which improved when the enalapril was stopped.

There have been case reports of pneumonitis associated with treatment with captopril[5] and perindopril.[6]

1. Lunde H, *et al.* Dyspnoea, asthma, and bronchospasm in relation to treatment with angiotensin converting enzyme inhibitors. *BMJ* 1994; 308: 18–21.
2. Inman WHW, *et al.* Angiotensin converting enzyme inhibitors and asthma. *BMJ* 1994; 308: 593–4.
3. Fennerty A, *et al.* Enalapril-induced nasal blockage. *Lancet* 1986; i: 1395–6.
4. Cicolin A, *et al.* Angiotensin-converting enzyme inhibitors and obstructive sleep apnea. *Mayo Clin Proc* 2006; 81: 53–5.
5. Kidney JC, *et al.* Captopril and lymphocytic alveolitis. *BMJ* 1989; 299: 981.
6. Benard A, *et al.* Perindopril-associated pneumonitis. *Eur Respir J* 1996; 9: 1314–16.

Effects on skeletal muscle. Severe muscle pain and weakness, accompanied by morning stiffness, was reported[1] in a patient taking enalapril. Symptoms resolved within a few days of stopping the drug.

1. Leloët X, *et al.* Pseudopolymyalgia rheumatica during treatment with enalapril. *BMJ* 1989; 298: 325.

Effects on the skin. Skin rashes may occur during treatment with ACE inhibitors; they have been reported in 1 to 6% of patients receiving captopril. Angioedema is also an adverse effect of ACE inhibitors (see Hypersensitivity p. 1287.1). There have been reports of bullous pemphigoid,[1] hyperhidrosis,[2] Kaposi's sarcoma,[3] lichen planus,[4] onycholysis,[5,6] pemphigus,[7,8] exacerbation of psoriasis,[9] and cutaneous hypersensitivity vasculitis[10] associated with use of captopril. Kaposi's sarcoma has also been reported[11] with lisinopril. Onycholysis has also occurred with enalapril,[12] pemphigus with enalapril[13,14] and ramipril,[15] and bullous pemphigoid with lisinopril.[16] Lichen planus pemphigoides has been reported with ramipril.[17] A severe cutaneous reaction, resembling early mycosis fungoides, and possibly allergic in nature, has been reported after use of captopril or enalapril.[18] An interstitial granulomatous drug reaction presenting as erythroderma was reported with enalapril.[19] Vulvovaginal pruritus with dysuria[20] has also been noted in a patient receiving enalapril.

1. Mallet L, *et al.* Bullous pemphigoid associated with captopril. *DICP Ann Pharmacother* 1989; 23: 63.
2. Morse MH. Hyperhidrosis: a possible side effect of captopril treatment. *BMJ* 1984; 289: 1272.
3. Puppin D, *et al.* Kaposi's sarcoma associated with captopril. *Lancet* 1990; 336: 1251–2.
4. Cox NH, *et al.* Lichen planus associated with captopril: a further disorder demonstrating the 'tin-tack' sign. *Br J Dermatol* 1989; 120: 319–21.
5. Brueggemeyer CD, Ramirez G. Onycholysis associated with captopril. *Lancet* 1984; i: 1352–3.
6. Borders JV. Captopril and onycholysis. *Ann Intern Med* 1986; 105: 305–6.
7. Partrey PS, *et al.* Captopril-induced pemphigus. *BMJ* 1980; 281: 194.
8. Butt A, Burge SM. Pemphigus vulgaris induced by captopril. *Br J Dermatol* 1995; 132: 315–16.
9. Hamlet NW, *et al.* Does captopril exacerbate psoriasis? *BMJ* 1987; 295: 1352.
10. Miralles R, *et al.* Captopril and vasculitis. *Ann Intern Med* 1988; 109: 514.
11. Bilen N, *et al.* Possible causal role of lisinopril in a case of Kaposi's sarcoma. *Br J Dermatol* 2002; 147: 1042–4.
12. Gupta S, *et al.* Nail changes with enalapril. *BMJ* 1986; 293: 140.
13. Kuechle MK, *et al.* Angiotensin-converting enzyme inhibitor-induced pemphigus: three case reports and literature review. *Mayo Clin Proc* 1994; 69: 1166–71.
14. Frangogiannis NG, *et al.* Pemphigus of the larynx and esophagus. *Ann Intern Med* 1995; 122: 803–4.
15. Vignes S, *et al.* Ramipril-induced superficial pemphigus. *Br J Dermatol* 1996; 135: 657–8.
16. Kaliñska-Bienias A, *et al.* Can pemphigoid be provoked by lisinopril? *Br J Dermatol* 2006; 155: 854–5.

17. Ogg GS, et al. Ramipril-associated lichen planus pemphigoides. Br J Dermatol 1997; 136: 412–14.
18. Furness PN, et al. Severe cutaneous reactions to captopril and enalapril: histological study and comparison with early mycosis fungoides. J Clin Pathol 1986; 39: 902–7.
19. Chen Y-C, et al. Interstitial granulomatous drug reaction presenting as erythroderma: remission after discontinuation of enalapril maleate. Br J Dermatol 2008; 158: 1143–5.
20. Heckerling PS. Enalapril and vulvovaginal pruritus. Ann Intern Med 1990; 112: 879–80.

Gynaecomastia. Painful unilateral gynaecomastia was reported in a patient with SLE and renal impairment who was given captopril for hypertension.[1] In view of reports of breast enlargement in women given penicillamine it was suggested that the sulfhydryl structure might be responsible; however, gynaecomastia has also been reported in 2 patients receiving enalapril,[2,3] which does not contain the sulfhydryl grouping.

1. Markusse HM, Meyboom RHB. Gynaecomastia associated with captopril. BMJ 1988; 296: 1262–3.
2. Nakamura Y, et al. Gynaecomastia induced by angiotensin converting enzyme inhibitor. BMJ 1990; 300: 541.
3. Llop R, et al. Gynecomastia associated with enalapril and diazepam. Ann Pharmacother 1994; 28: 671–2.

Hypersensitivity. Some of the adverse effects of ACE inhibitors might be mediated by the immune system, but evidence of specific **hypersensitivity reactions** seems to be limited. An IgG antibody to captopril was present in the serum of 2 of 45 patients taking the drug but the clinical significance was unclear.[1] A reaction resembling serum sickness was reported in a patient given captopril, with deposition of immune complexes in the glomerular basement membrane, and symptoms of rash, arthralgia, epidermolysis, fever, and lymphadenopathy.[2] Eosinophilia has also been reported.[3] The formation of antinuclear antibodies and lupus-like reactions have been described.[4,5]

Treatment with ACE inhibitors (enalapril, captopril, or lisinopril) has been associated with **anaphylactoid reactions** in patients undergoing high-flux haemodialysis using polyacrylonitrile membrane (AN69).[6,7] The UK CSM has advised that the combined use of ACE inhibitors and such membranes should be avoided.[8] Similar anaphylactoid reactions have occurred in patients taking ACE inhibitors while being treated for severe hypercholesterolaemia by extracorporeal removal of low-density lipoproteins (LDL-apheresis) with dextran sulfate columns.[9] These reactions are thought to be bradykinin-mediated. Prolonging the interval between the last dose of ACE inhibitor and dextran sulfate apheresis has averted the reaction;[10] successful prevention has also been reported with the bradykinin receptor antagonist icatibant acetate (p. 2531.1).[11] Hypotensive reactions associated with blood transfusion through bedside leucoreduction filters in patients taking ACE inhibitors have also been attributed to bradykinin.[12] There have also been rare reports of severe allergic reactions, including anaphylaxis, occurring in patients taking ACE inhibitors who were stung by insects or during desensitisation with Hymenoptera venom (e.g. bee or wasp venom).[13]

Angioedema, a known adverse effect of ACE inhibitors,[14-18] is reported to occur in 0.1 to 0.2% of patients.[16,17] The incidence may be higher in black American[19] or Afro-Caribbean[20] patients. There is no evidence that it results from an immunological mechanism in these patients and it has been suggested that the effect is due to impaired kinin degradation. However, angioedema has been reported with lisinopril in a patient who had previously tolerated captopril.[21] The onset of angioedema has usually been within hours or at most a week of starting treatment with the ACE inhibitor,[16] but can occur after prolonged therapy for several months or years.[22-25] It may also occur episodically with long symptom-free intervals.[25] Visceral angioedema, presenting as abdominal pain with diarrhoea, nausea, and vomiting,[26,27] cerebral angioedema,[28] and penile angioedema,[29] have also been reported. If angioedema occurs the ACE inhibitor should be withdrawn and if there is swelling affecting the tongue, glottis, or larynx likely to cause airway obstruction, adrenaline should be given (see p. 1292.3). Fatalities have occurred.[30] Angiotensin II receptor antagonists have been suggested as an alternative in patients unable to tolerate ACE inhibitors, but there have also been reports of angioedema associated with their use (see under Losartan Potassium, p. 1424.1). For a report of angioedema occurring after use of alteplase for stroke in patients taking ACE inhibitors, see under Interactions of Alteplase, p. 1298.1.

1. Coleman JW, et al. Drug-specific antibodies in patients receiving captopril. Br J Clin Pharmacol 1986; 22: 161–5.
2. Hoorntje SJ, et al. Serum-sickness-like syndrome with membranous glomerulopathy in patient on captopril. Lancet 1979; ii: 1297.
3. Kayanakis JG, et al. Eosinophilia during captopril treatment. Lancet 1980; ii: 923.
4. Schwartz D, et al. Enalapril-induced antinuclear antibodies. Lancet 1990; 336: 187.
5. Pelayo M, et al. Drug-induced lupus-like reaction and captopril. Ann Pharmacother 1993; 27: 1541–2.
6. Verresen L, et al. Angiotensin-converting-enzyme inhibitors and anaphylactoid reactions to high-flux membrane dialysis. Lancet 1990; 336: 1360–2.
7. Tielmans C, et al. ACE inhibitors and anaphylactoid reactions to high-flux membrane dialysis. Lancet 1991; 337: 370–1.
8. CSM. Anaphylactoid reactions to high-flux polyacrylonitrile membranes in combination with ACE inhibitors. Current Problems 33 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024451&RevisionSelectionMethod=LatestReleased (accessed 04/04/08)
9. Olbricht CJ, et al. Anaphylactoid reactions, LDL apheresis with dextran sulphate, and ACE inhibitors. Lancet 1992; 340: 908–9.
10. Keller C, et al. LDL-apheresis with dextran sulphate and anaphylactoid reactions to ACE inhibitors. Lancet 1993; 341: 60–1.
11. Davidson DC, et al. Prevention with icatibant of anaphylactoid reactions to ACE inhibitor during LDL apheresis. Lancet 1994; 343: 1575.
12. Quillen K. Hypotensive transfusion reactions in patients taking angiotensin-converting-enzyme inhibitors. N Engl J Med 2000; 343: 1422–3.
13. Stumpf JL, et al. Safety of angiotensin-converting enzyme inhibitors in patients with insect venom allergies. Ann Pharmacother 2006; 40: 699–703.
14. Wood SM, et al. Angio-oedema and urticaria associated with angiotensin converting enzyme inhibitors. BMJ 1987; 294: 91–2.
15. Hedner T, et al. Angio-oedema in relation to treatment with angiotensin converting enzyme inhibitors. BMJ 1992; 304: 941–6.
16. Israill ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy: a review of the literature and pathophysiology. Ann Intern Med 1992; 117: 234–42.
17. Vleeming W, et al. ACE inhibitor-induced angioedema. Drug Safety 1998; 18: 171–88.
18. Bas M, et al. Das ACE-Hemmer-induzierte Angioödem. Laryngorhinootologie 2007; 86: 804–8.
19. Brown NJ, et al. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. Clin Pharmacol Ther 1996; 60: 8–13.
20. Gibbs CR, et al. Angioedema due to ACE inhibitors: increased risk in patients of African origin. Br J Clin Pharmacol 1999; 48: 861–5.
21. McElligott S, et al. Angioedema after substituting lisinopril for captopril. Ann Intern Med 1992; 116: 426–7.
22. Chin HL, Buchan DA. Severe angioedema after long-term use of an angiotensin-converting enzyme inhibitor. Ann Intern Med 1990; 112: 312–13.
23. Edwards TB. Adverse effects of ACE inhibitors. Ann Intern Med 1993; 118: 314.
24. Chu TJ, Chow N. Adverse effects of ACE inhibitors. Ann Intern Med 1993; 118: 314.
25. Adverse Drug Reactions Advisory Committee (ADRAC). Angioedema – still a problem with ACE inhibitors. Aust Adverse Drug React Bull 2005; 24: 7. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0504.htm (accessed 06/11/06)
26. Mullins RJ, et al. Visceral angioedema related to treatment with an ACE inhibitor. Med J Aust 1996; 165: 319–21.
27. Byrne TJ, et al. Isolated visceral angioedema: an underdiagnosed complication of ACE inhibitors? Mayo Clin Proc 2000; 75: 1201–4.
28. Decloedt E, et al. Cerebral angioedema associated with enalapril. Br J Clin Pharmacol 2009; 68: 271–3.
29. McCabe J, et al. Penile angioedema associated with the use of angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers. Am J Health-Syst Pharm 2008; 65: 420–1.
30. Cupido C, Rayner B. Life-threatening angio-oedema and death associated with the ACE inhibitor enalapril. S Afr Med J 2007; 97: 244–5.

Overdosage. There have been reports of overdosage with captopril,[1,2] enalapril,[3-6] and lisinopril.[7,8] The main adverse effect is hypotension which usually responds to supportive treatment and volume expansion. Activated charcoal may be given in severe overdosage if the patient presents within 1 hour of ingestion. If hypotension persists, sympathomimetics may be given, although they are not usually required. Specific therapy with angiotensinamide (p. 1306.1) may be considered if conventional therapy is ineffective,[5,6,8] but it is not widely available. There has also been a report[9] of the successful use of naloxone after captopril overdosage.

1. Augenstein WL, et al. Captopril overdose resulting in hypotension. JAMA 1988; 259: 3302–5.
2. Graham SR, et al. Captopril overdose. Med J Aust 1989; 151: 111.
3. Waeber B, et al. Self poisoning with enalapril. BMJ 1984; 288: 287–8.
4. Lau CP. Attempted suicide with enalapril. N Engl J Med 1986; 315: 197.
5. Jackson T, et al. Enalapril overdose treated with angiotensin infusion. Lancet 1993; 341: 703.
6. Newby DE, et al. Enalapril overdose and the corrective effect of intravenous angiotensin II. Br J Clin Pharmacol 1995; 40: 103–4.
7. Dawson AH, et al. Lisinopril overdose. Lancet 1990; 335: 487–8.
8. Trilli LE, Johnson KA. Lisinopril overdose and management with intravenous angiotensin II. Ann Pharmacother 1994; 28: 1165–8.
9. Varon J, Duncan SR. Naloxone reversal of hypotension due to captopril overdose. Ann Emerg Med 1991; 20: 1125–7.

Precautions

ACE inhibitors are usually contra-indicated in patients with aortic stenosis or outflow tract obstruction (but see below). They should not generally be used in patients with renovascular disease or suspected renovascular disease, but are occasionally necessary for severe resistant hypertension in such patients, when they should only be given with great caution and under close specialist supervision. The elderly, or patients with peripheral vascular diseases or generalised atherosclerosis, may be at high risk because they may have clinically silent renovascular disease. Renal function should be assessed in all patients before use of ACE inhibitors and should be monitored during therapy. Patients with existing renal disease or taking high doses should be monitored regularly for proteinuria. Regular white blood cell counts may be necessary in patients with collagen vascular disorders, such as SLE and scleroderma, or in patients also given immunosuppressive therapy, especially when they also have impaired renal function. ACE inhibitors should be used with caution in patients with a history of idiopathic or hereditary angioedema.

Patients with heart failure and patients who are likely to be sodium or water depleted (for example, those receiving treatment with diuretics or dialysis) may develop symptomatic hypotension during the initial stages of ACE inhibitor therapy. Treatment should therefore be started under close medical supervision, using a low dose and with the patient in a recumbent position to minimise this effect.

Anaphylactoid reactions have occurred in patients taking ACE inhibitors during haemodialysis using high-flux polyacrylonitrile membranes, during LDL-apheresis with dextran sulfate columns, and during desensitisation with wasp or bee venom (see Hypersensitivity under Adverse Effects, above).

ACE inhibitors have been associated with fetal toxicity and should not be used during pregnancy (see p. 1288.1).

Aortic stenosis. Vasodilators, including ACE inhibitors, are usually contra-indicated in obstructive cardiac disorders such as aortic stenosis since cardiac output cannot increase to compensate for systemic vasodilatation and there is a risk of severe hypotension. However, a study[1] in patients with symptomatic aortic stenosis found that enalapril was well-tolerated and improved symptoms, and a drug withdrawal study[2] in hypertensive patients with asymptomatic aortic stenosis suggested that ACE inhibitors had beneficial haemodynamic effects. Another study[3] in patients with heart failure and perceived contra-indications to ACE inhibitors (including 17.3% with aortic stenosis) found that survival was improved in those given ACE inhibitors. There is also some evidence that ACE inhibitors may slow the progression of calcific aortic stenosis, but this remains to be confirmed.[4]

1. Chockalingam A, et al. Safety and efficacy of angiotensin-converting enzyme inhibitors in symptomatic severe aortic stenosis: Symptomatic Cardiac Obstruction-Pilot study of Enalapril in Aortic Stenosis (SCOPE-AS). Am Heart J 2004; 147: E19.
2. Jiménez-Candil J, et al. Effects of angiotensin converting enzyme inhibitors in hypertensive patients with aortic valve stenosis: a drug withdrawal study. Heart 2005; 91: 1311–18.
3. Ahmed A, et al. A propensity score analysis of the impact of angiotensin-converting enzyme inhibitors on long-term survival of older adults with heart failure and perceived contraindications. Am Heart J 2005; 149: 737–43.
4. Newby DE, et al. Emerging medical treatments for aortic stenosis: statins, angiotensin converting enzyme inhibitors, or both? Heart 2006; 92: 729–34.

Breast feeding. In the UK the MHRA and Committee on Human Medicines advise that there is some evidence of transfer of ACE inhibitors into breast milk, and since, although the concentrations are unlikely to be clinically significant, there are insufficient data to exclude the possibility of profound neonatal hypertension (particularly in premature infants), these drugs should not be used during breast feeding.[1] Captopril, enalapril, or quinapril, for which there are the most data, should be avoided during the first few weeks after delivery, but may be considered once the infant is older; other ACE inhibitors should be avoided altogether in favour of drugs with better established safety profiles during breast feeding. Angiotensin II receptor antagonists should also be avoided in view of the lack of established safety profiles.

For the contrary view of the American Academy of Pediatrics that use of captopril is usually compatible with breast feeding see p. 1332.1.

1. MHRA/CHM. ACE inhibitors and angiotensin II receptor antagonists: recommendations on use during breastfeeding. Drug Safety Update 2009; 2 (10): 3–4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON046452&RevisionSelectionMethod=LatestReleased (accessed 19/07/10)

Diarrhoea. Several reports[1-5] have indicated that patients taking ACE inhibitors may develop life-threatening hypotension and signs of renal failure after volume depletion due to diarrhoea.

1. McMurray J, Matthews DM. Effect of diarrhoea on a patient taking captopril. Lancet 1985; i: 581.
2. Benett PR, Cairns SA. Captopril, diarrhoea, and hypotension. Lancet 1985; i: 1105.
3. McMurray J, Matthews DM. Consequences of fluid loss in patients treated with ACE inhibitors. Postgrad Med J 1987; 63: 385–7.
4. Stirling C, et al. Diarrhoea, vomiting and ACE inhibitors: an important cause of acute renal failure. J Hum Hypertens 2003; 17: 419–23.
5. McGuigan J, et al. Life threatening hyperkalaemia with diarrhoea during ACE inhibition. Emerg Med J 2005; 22: 154–5.

Ethnicity. ACE inhibitors are less effective as antihypertensives in Afro-Caribbean black patients than in white patients. A similar difference has been reported in heart failure; in a pooled analysis[1] of the Studies of Left Ventricular Dysfunction (SOLVD) treatment and prevention trials, treatment with enalapril significantly reduced the risk of hospitalisation for heart failure in white patients with left ventricular dysfunction, but not in similar black patients. However, analysis[2] of the prevention arm alone showed that enalapril reduced the relative risk of disease progression to a similar extent in black and white patients.

1. Exner DV, et al. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. N Engl J Med 2001; 344: 1351–7.

2. Dries DL, *et al.* Efficacy of angiotensin-converting enzyme inhibition in reducing progression from asymptomatic left ventricular dysfunction to symptomatic heart failure in black and white patients. *J Am Coll Cardiol* 2002; 40: 311–17. Correction. *ibid.*; 1019.

Hepatic cirrhosis. It has been suggested that in patients with cirrhosis, captopril could cause a marked reduction in arterial pressure and severely compromise renal function, since maintenance of glomerular filtration rate might be mediated by angiotensin II in these patients.[1] This theory was supported by a report of a reduction in glomerular filtration rate in response to a fall in mean arterial pressure in 4 patients with resistant ascites secondary to hepatic cirrhosis.[2] The fall in mean arterial pressure was associated with orthostatic hypotension and increasing encephalopathy. Severe confusion has also been reported in 2 patients with cirrhosis during treatment with captopril 6.25 to 12.5 mg three times daily.[3] Licensed product information for another ACE inhibitor, cilazapril, advises against use in patients with ascites.

1. Ring T. Captopril and resistant ascites: a word of caution. *Lancet* 1983; ii: 165.
2. Wood LJ, *et al.* Adverse effects of captopril in treatment of resistant ascites. a state of functional bilateral renal artery stenosis. *Lancet* 1985; ii: 1008–9.
3. Jørgensen F, *et al.* Captopril and resistant ascites. *Lancet* 1983; ii: 405.

Huntington's disease. The condition of a woman with Huntington's disease deteriorated dramatically during treatment with captopril and improved on withdrawal of the drug.[1]

1. Goldblatt J, Bryer A. Huntington's disease: deterioration in clinical state during treatment with angiotensin converting enzyme inhibitor. *BMJ* 1987; 294: 1659–60.

Peripheral vascular disease. Patients with peripheral vascular disease may have a high incidence of renal artery stenosis and are therefore at high risk of renal failure with ACE inhibitor therapy (see Effects on the Kidneys, p. 1286.1). Mild renal artery stenosis was found in 64 of 374 patients (17%) with peripheral vascular disease, and severe renal artery stenosis in 52 (14%); the stenosis was bilateral in 43 (12%).[1] Renal function should be carefully monitored in any patient with peripheral vascular disease who receives ACE inhibitors.

1. Salmon P, Brown MA. Renal artery stenosis and peripheral vascular disease: implications for ACE inhibitor therapy. *Lancet* 1990; 336: 321.

Pregnancy. ACE inhibitors are contra-indicated in pregnancy as they have been associated with fetal toxicity in both *animals* and humans. The effects on the fetus appear to result from uterine blood-flow reduction and fetal hypotension due to blockade of the renin-angiotensin system, leading to impaired fetal renal function, and limited amniotic fluid output.[1] The dangers of exposure to ACE inhibitors during the second and third trimesters are clear; reports include oligohydramnios and anuria, intrauterine growth retardation, premature labour, renal failure, bony malformations, limb contractures, patent ductus arteriosus, pulmonary hypoplasia, respiratory distress syndrome, neonatal hypotension, skull ossification defects, and fetal or neonatal death.[1-3] The association between adverse fetal outcomes and first-trimester exposures has been harder to establish, however. Although use of ACE inhibitors in the first trimester had been thought to carry a lesser risk,[4-6] a review of the available experimental and clinical data concluded that the use of ACE inhibitors should be avoided throughout pregnancy.[7] A later cohort study[8] of 29 507 infants found a significantly increased risk of major congenital malformations in 209 who had been exposed to ACE inhibitors alone in the first trimester; the FDA[9] and the MHRA[10] subsequently advised that ACE inhibitors should be avoided in those planning pregnancy, and stopped immediately upon diagnosis of pregnancy. They should only be used in pregnant women where the expected benefit clearly outweighs the risk.

1. Branch RL, Martin U. Adverse effects of angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers in pregnancy. *Adverse Drug React Bull* 2007; (Oct.): 943–6.
2. Hanssens M, *et al.* Fetal and neonatal effects of treatment with angiotensin-converting enzyme inhibitors in pregnancy. *Obstet Gynecol* 1991; 78: 128–35.
3. Piper JM, *et al.* Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors. *Obstet Gynecol* 1992; 80: 429–32.
4. CDC. Postmarketing surveillance for angiotensin-converting enzyme inhibitor use during the first trimester of pregnancy—United States, Canada, and Israel, 1987-1995. *JAMA* 1997; 277: 1193–4.
5. Lip GYH, *et al.* Angiotensin-converting-enzyme inhibitors in early pregnancy. *Lancet* 1997; 350: 1446–7.
6. Steffensen FH, *et al.* Pregnancy outcome with ACE-inhibitor use in early pregnancy. *Lancet* 1998; 351: 596.
7. Shotan A, *et al.* Risk of angiotensin-converting enzyme inhibition during pregnancy: experimental and clinical evidence, potential mechanisms, and recommendations for use. *Am J Med* 1994; 96: 451–6.
8. Cooper WO, *et al.* Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006; 354: 2443–51.
9. FDA. FDA Public Health Advisory: angiotensin-converting enzyme inhibitor (ACE inhibitor) drugs and pregnancy (issued 7th June 2006). Available at: http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm053113.htm (accessed 30/07/09)
10. MHRA/CHM. ACE inhibitors and angiotensin II receptor antagonists: not for use in pregnancy. *Drug Safety Update* 2007; 1 (5): 8–9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20332176-RevisionSelectionMethod=LatestReleased (accessed 30/07/09)

Interactions

Excessive hypotension may occur when ACE inhibitors are used with diuretics, other antihypertensives, or other agents, including alcohol, that lower blood pressure. An additive hyperkalaemic effect is possible in patients receiving ACE inhibitors with potassium-sparing diuretics, potassium supplements (including potassium-containing salt substitutes), or other drugs that can cause hyperkalaemia (such as ciclosporin or indometacin), and serum-potassium concentrations should be monitored. Potassium-sparing diuretics and potassium supplements should generally be stopped before starting ACE inhibitors in patients with heart failure. However, ACE inhibitor therapy does not obviate the possible need for potassium supplementation in patients given potassium-wasting diuretics and potassium concentrations should also be monitored in these patients. The adverse effects of ACE inhibitors on the kidneys may be potentiated by other drugs, such as NSAIDs, that can affect renal function. For advice on the use of ACE inhibitors with the angiotensin II receptor antagonist losartan, see p. 1424.3. The use of ACE inhibitors with the renin inhibitor aliskiren is generally not recommended, and should be avoided in some patients (see p. 1296.2).

General references.

1. Shionoiri H. Pharmacokinetic drug interactions with ACE inhibitors. *Clin Pharmacokinet* 1993; 25: 20–58.
2. Mignat C, Unger T. ACE inhibitors: drug interactions of clinical significance. *Drug Safety* 1995; 12: 334–7.

Allopurinol. For reports of reactions in patients taking captopril and allopurinol, see p. 603.1.

Antacids. Use of captopril with antacids reduced the bioavailability of captopril although this did not significantly alter the effects on blood pressure and heart rate.[1] The bioavailability of fosinopril, and possibly other ACE inhibitors, may also be reduced by use with antacids.

1. Mäntylä R, *et al.* Impairment of captopril bioavailability by concomitant food and antacid intake. *Int J Clin Pharmacol Ther Toxicol* 1984; 22: 626–9.

Antidiabetics. Hypoglycaemia was noted in 3 type I diabetics when captopril was added to their therapeutic regimen; it was also seen in a type 2 diabetic, in whom withdrawal of hypoglycaemic drugs became necessary.[1] Subsequent study suggested that the effect was due to enhanced insulin sensitivity.[1] Similar instances of a reduction in blood sugar in both non-diabetic[2] and diabetic[3] patients given enalapril have occurred. Two case-control studies in diabetic patients receiving insulin or oral hypoglycaemics suggested that patients treated with ACE inhibitors were at increased risk of developing severe hypoglycaemia.[4,5] However, other studies in diabetic patients given captopril or enalapril have failed to find any significant alterations in blood-glucose control,[6,7] and ACE inhibitors are widely used in the treatment of hypertension in diabetic patients (see p. 1251.1) and also have a role in the management of diabetic complications such as nephropathy (see Kidney Disorders under Uses, p. 1284.1).

1. Ferriere M, *et al.* Captopril and insulin sensitivity. *Ann Intern Med* 1985; 102: 134–5.
2. Helgeland A, *et al.* Enalapril, atenolol, and hydrochlorothiazide in mild to moderate hypertension: a comparative multicentre study in general practice in Norway. *Lancet* 1986; i: 872–5.
3. McMurray J, Fraser DM. Captopril, enalapril, and blood glucose. *Lancet* 1986; i: 1035.
4. Herings RMC, *et al.* Hypoglycaemia associated with use of inhibitors of angiotensin converting enzyme. *Lancet* 1995; 345: 1195–8.
5. Morris AD, *et al.* ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. *Diabetes Care* 1997; 20: 1363–7.
6. Passa P, *et al.* Enalapril, captopril, and blood glucose. *Lancet* 1986; i: 1447.
7. Winocour P, *et al.* Captopril and blood glucose. *Lancet* 1986; ii: 461.

Azathioprine. Leucopenia has been reported in a patient given captopril with azathioprine; the effect did not occur when either drug was given alone.[1] In a similar report, neutropenia in a patient taking a regimen including azathioprine and captopril did not recur when captopril was reintroduced after stopping azathioprine.[2]

1. Kircheriz EJ, *et al.* Successful low dose captopril rechallenge following drug-induced leucopenia. *Lancet* 1981; i: 1363.
2. Edwards CRW, *et al.* Successful reintroduction of captopril following neutropenia. *Lancet* 1981; i: 723.

Ciclosporin. An additive hyperkalaemic effect with ACE inhibitors and ciclosporin is possible. Also, acute renal failure has been reported in 2 patients on ciclosporin after renal transplantation who were given enalapril.[1] Renal function recovered when the ACE inhibitor was withdrawn.

1. Murray BM, *et al.* Enalapril-associated acute renal failure in renal transplants: possible role of cyclosporine. *Am J Kidney Dis* 1990; 16: 66–9.

Digoxin. For reports of an increase in serum-digoxin concentrations during therapy with ACE inhibitors, see p. 1356.1.

Diuretics. Excessive hypotension may occur when ACE inhibitors are used with diuretics. Deterioration in renal function has also been reported with *metolazone* (see p. 1434.2) when added to captopril therapy. Severe hyperkalaemia may occur if ACE inhibitors are used with *spironolactone* (see p. 1502.2).

Epoetins. An additive hyperkalaemic effect may occur when ACE inhibitors are given with epoetins. ACE inhibitors have also been reported to antagonise the haematopoietic effects of epoetins.

General anaesthetics. Marked hypotension may occur during general anaesthesia in patients taking ACE inhibitors. In addition corrected cerebral blood flow was significantly lower in 11 patients who took captopril before general anaesthesia induced with thiopental and maintained with nitrous oxide and enflurane, than in 9 patients pretreated with metoprolol and 9 untreated controls. Although there were no complications of anaesthesia associated with captopril pretreatment, stopping ACE inhibitor therapy before anaesthesia should be considered. However, others have suggested[2] that since there is no clear evidence for stopping them, ACE inhibitors may be continued with care.

1. Jensen K, *et al.* Cerebral blood flow during anaesthesia: influence of pretreatment with metoprolol or captopril. *Br J Anaesth* 1989; 62: 321–3.
2. Anonymous. Drugs in the peri-operative period: 4 – cardiovascular drugs. *Drug Ther Bull* 1999; 37: 89–92.

Gold salts. The nitritoid reaction (flushing, nausea, dizziness, and hypotension associated with the first weeks of injectable gold treatment) has been seen[1,2] after starting treatment with an ACE inhibitor. The patients had been given sodium aurothiomalate for at least 2 years, and the reaction occurred up to 15 months after starting the ACE inhibitor.

1. Healey LA, Backes MB. Nitritoid reactions and angiotensin-converting-enzyme inhibitors. *N Engl J Med* 1989; 321: 763.
2. Nixon J, Pande I. Gold, nitritoid reactions and angiotensin-converting enzyme inhibitors. *Rheumatology (Oxford)* 2006; 45: 118–19.

Interferons. Severe granulocytopenia has been reported[1] in 3 patients with mixed cryoglobulinaemia treated with interferon alfa-2a who also received ACE inhibitors. The effect was considered to be due to synergistic haematological toxicity. However, in a further report,[2] 2 patients developed only mild granulocytopenia that was reversible despite continued therapy, while a third patient retained a normal granulocyte count.

1. Cassato M, *et al.* Granulocytopenia after combined therapy with interferon and angiotensin-converting enzyme inhibitors: evidence for a synergistic hematologic toxicity. *Am J Med* 1995; 99: 386–91.
2. Jacquot C, *et al.* Granulocytopenia after combined therapy with interferon and angiotensin-converting enzyme inhibitors: evidence for a synergistic hematologic toxicity. *Am J Med* 1996; 101: 235–6.

Interleukin-3. Marked hypotension occurred in 3 patients[1] taking ACE inhibitors who were given interleukin-3 after chemotherapy; blood pressure returned to normal when the ACE inhibitors were stopped.

1. Dercksen MW, *et al.* Hypotension induced by interleukin-3 in patients on angiotensin-converting enzyme inhibitors. *Lancet* 1995; 345: 448.

Lithium. For reports of lithium toxicity in patients taking ACE inhibitors, see p. 431.2.

Muscle relaxants. For a report of severe hypotension in a patient taking lisinopril and tizanidine, see p. 2027.2.

NSAIDs. *Indometacin* and possibly other NSAIDs, including aspirin, have been reported to reduce or abolish the hypotensive action of ACE inhibitors. A similar effect has been reported[1] with *rofecoxib*. NSAIDs cause sodium and water retention and thus may attenuate the effects of various antihypertensives. It has also been suggested that part of the hypotensive effect of ACE inhibitors is prostaglandin-dependent, which might explain this interaction with drugs such as NSAIDs that block prostaglandin synthesis. However, in a double-blind study designed to assess the role of prostaglandins,[2] indometacin did not influence the hypotensive effect of captopril or enalapril, suggesting that the effects on prostaglandins are not significant.

The possibility of an interaction between low-dose *aspirin* and ACE inhibitors has caused concern.[3-5] Both ACE inhibitors and aspirin have well-established benefits in patients with both heart failure and ischaemic heart disease, but there is limited specific evidence to support their use together. Retrospective analysis of some studies of ACE inhibitors in patients with heart failure after myocardial infarction suggested that outcome was poorer in those who were also receiving aspirin, and some small studies have suggested that aspirin antagonises the haemodynamic effects of ACE inhibitors, although results have been

conflicting and the clinical relevance of these findings is not clear. Observational studies[6,7] in patients with both ischaemic and non-ischaemic heart failure have found no evidence for a detrimental effect in patients taking both aspirin and ACE inhibitors, and a systematic review[8] of long-term studies concluded that ACE inhibitors had clinically important benefits, irrespective of the use of aspirin.

The combination of NSAIDs and ACE inhibitors may also have variable effects on renal function since they act at different parts of the glomerulus.[9] When given to patients whose kidneys are underperfused, for example because of heart failure, liver cirrhosis, or haemorrhage, renal function may deteriorate. Use of NSAIDs in patients taking ACE inhibitors with diuretics may be particularly hazardous.[10] However, specific patient groups without reduced renal perfusion may benefit from combining an NSAID with an ACE inhibitor.

Indometacin, and possibly other NSAIDs, may have an additive hyperkalaemic effect.

1. Brown CH. Effect of rofecoxib on the antihypertensive activity of lisinopril. *Ann Pharmacother* 2000; 34: 1486.
2. Gerber JG, *et al.* The hypotensive action of captopril and enalapril is not prostacyclin dependent. *Clin Pharmacol Ther* 1993; 54: 523–32.
3. Stys T, *et al.* Does aspirin attenuate the beneficial effects of angiotensin-converting enzyme inhibition in heart failure? *Arch Intern Med* 2000; 160: 1409–13.
4. Mahé I, *et al.* Interaction between aspirin and ACE inhibitors in patients with heart failure. *Drug Safety* 2001; 24: 167–82.
5. Olson KL. Combined aspirin/ACE inhibitor treatment for CHF. *Ann Pharmacother* 2001; 35: 1653–8.
6. McAllister FA, *et al.* Aspirin use and outcomes in a community-based cohort of 7352 patients discharged after first hospitalization for heart failure. *Circulation* 2006; 113: 2572–8.
7. Masoudi FA, *et al.* Aspirin use in older patients with heart failure and coronary artery disease: national prescription patterns and relationship with outcomes. *J Am Coll Cardiol* 2005; 46: 955–62.
8. Teo KK, *et al.* Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. *Lancet* 2002; 360: 1037–43. Correction. *ibid.* 2003; 361: 90.
9. Sturrock NDC, Struthers AD. Non-steroidal anti-inflammatory drugs and angiotensin converting enzyme inhibitors: a commonly prescribed combination with variable effects on renal function. *Br J Clin Pharmacol* 1993; 35: 343–8.
10. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Beware the triple whammy! *Aust Adverse Drug React Bull* 2006; 25: 18. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0610.pdf (accessed 04/04/08)

Probenecid. Giving probenecid to 4 healthy subjects during intravenous infusion of captopril caused increases in the steady-state plasma-captopril concentration. This was thought to be because probenecid reduced the tubular secretion of captopril.[1]

1. Singhvi SM, *et al.* Renal handling of captopril: effect of probenecid. *Clin Pharmacol Ther* 1982; 32: 182–9.

Pharmacokinetics

Most ACE inhibitors are given orally. Apart from captopril and lisinopril, they are generally prodrugs and after absorption undergo rapid metabolism by ester hydrolysis to the active diacid form; for example, enalapril is converted to enalaprilat. Metabolism occurs mainly in the liver. Excretion as active drug or active metabolite is mainly in the urine; some, such as benazeprilat and fosinoprilat, are also excreted via the biliary tract. Elimination of the diacid is polyphasic and there is a prolonged terminal elimination phase, which is considered to represent binding to the angiotensin-converting enzyme at a saturable binding site. This bound fraction does not contribute to accumulation of drug after multiple doses. The terminal elimination half-life does not therefore predict the kinetics seen with multiple dosing and the effective half-life for accumulation is the value usually quoted.

Reviews.

1. Burnier M, Biollaz J. Pharmacokinetic optimisation of angiotensin converting enzyme (ACE) inhibitor therapy. *Clin Pharmacokinet* 1992; 22: 375–84.
2. Hoyer J, *et al.* Clinical pharmacokinetics of angiotensin converting enzyme (ACE) inhibitors in renal failure. *Clin Pharmacokinet* 1993; 24: 230–54.
3. Song JC, White CM. Clinical pharmacokinetics and selective pharmacodynamics of new angiotensin converting enzyme inhibitors: an update. *Clin Pharmacokinet* 2002; 41: 207–24.

Acebutolol *(BAN, USAN, rINN)* ⊗

Acébutolol; Acebutololum; Asebutolol; Asebutololi; Ацебутолол

(±)-3'-Acetyl-4'-(2-hydroxy-3-isopropylaminopropoxy)butyranilide

$C_{18}H_{28}N_2O_4$=336.4

CAS — 37517-30-9.

ATC — C07AB04.

ATC Vet — QC07AB04.

UNII — 67P356D8GH.

Acebutolol Hydrochloride *(BANM, rINNM)* ⊗

Acébutolol, Chlorhydrate d'; Acebutolol, hidrocloruro de; Acebutolol-hidroklorid; Acebutololhydrochlorid; Acebutolol-hydrochlorid; Acebutololhydroklorid; Acebutololi hydrochloridum; Acebutololio hidrochloridas; Acebutololu chlorowodorek; Asebutololhydroklorid; Hidrocloruro de acebutolol; IL-17803A; M&B-17803A; Ацебутолола гидрохлорид

$C_{18}H_{28}N_2O_4$.HCl=372.9

CAS — 34381-68-5.

ATC — C07AB04.

ATC Vet — QC07AB04.

UNII — B025Y34C54.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Acebutolol Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in alcohol; very slightly soluble in acetone and in dichloromethane. A 1% solution in water has a pH of 5.0 to 7.0. Protect from light.

USP 36: (Acebutolol Hydrochloride). A white or almost white crystalline powder. Soluble in water and in alcohol; very slightly soluble in acetone and in dichloromethane; practically insoluble in ether. pH of a 1% solution in water is between 4.5 and 7.0. Store in airtight containers.

Uses and Administration

Acebutolol is a cardioselective beta blocker (p. 1316.3). It is reported to have some intrinsic sympathomimetic activity and membrane stabilising properties.

Acebutolol is used in the management of hypertension (p. 1251.1), angina pectoris (p. 1254.3), and cardiac arrhythmias (p. 1266.1).

Acebutolol is used as the hydrochloride, but doses are usually expressed in terms of the base; 110.8 mg of acebutolol hydrochloride is equivalent to 100 mg of base. It is generally given orally although slow intravenous injection has been used for the emergency treatment of arrhythmias.

In **hypertension** the usual initial oral dose is 400 mg once daily or 200 mg twice daily, increased if necessary after 2 weeks to 400 mg twice daily. Doses up to 1.2 g daily in divided doses may be given.

The usual oral dose for **angina pectoris** is 400 mg once daily or 200 mg twice daily, but up to 300 mg three times daily may be required for severe cases and total daily doses of 1.2 g have been given.

The usual initial oral dose for **cardiac arrhythmias** is 200 mg twice daily, increased according to response; up to 1.2 g daily in divided doses has been required.

Reduced doses may be required in patients with impaired renal function (see below). Elderly patients may also require lower maintenance doses; doses greater than 800 mg daily should be avoided.

Action. Acebutolol is generally considered to be a cardioselective beta blocker but there has been considerable controversy as to the degree of its selectivity and the selectivity of its primary metabolite, diacetolol.[1-3] In a review of beta blockers,[4] acebutolol was stated to be less cardioselective than other drugs such as atenolol or metoprolol. It was proposed[5] that this may be because the metabolite accumulates during chronic dosage to reach concentrations that affect both beta$_1$ and beta$_2$ receptors since cardioselectivity is only a relative and dose-related phenomenon. This remains uncertain and there is some evidence[6] that at least after single doses, diacetolol is actually more cardioselective than acebutolol itself.

1. Whitsett TL, *et al.* Comparison of the beta$_1$ and beta$_2$ adrenoceptor blocking properties of acebutolol and propranolol. *Chest* 1982; 82: 668–73.
2. Nair S, *et al.* The effect of acebutolol, a beta adrenergic blocking agent, and placebo on pulmonary functions in asthmatics. *Int J Clin Pharmacol Ther Toxicol* 1981; 19: 519–26.
3. Leary WP, *et al.* Respiratory effects of acebutolol hydrochloride: a new selective beta-adrenergic blocking agent. *S Afr Med J* 1973; 47: 1245–8.
4. Feely J, *et al.* Beta-blockers and sympathomimetics. *BMJ* 1983; 286: 1043–7.
5. Feely J, Maclean D. New drugs: beta blockers and sympathomimetics. *BMJ* 1983; 286: 1972.
6. Thomas MS, Tattersfield AE. Comparison of beta-adrenoceptor selectivity of acebutolol and its metabolite diacetolol with metoprolol and propranolol in normal man. *Eur J Clin Pharmacol* 1986; 29: 679–83.

Administration in renal impairment. The dose of acebutolol should be reduced in patients with renal impairment. It is recommended that the dose should be reduced by 50% in patients with a creatinine clearance between 25 and 50 mL/minute and by 75% in those with a creatinine clearance of less than 25 mL/minute. The dose frequency should not exceed once daily.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Breast feeding. Concentrations of acebutolol and its active metabolite diacetolol in breast milk are higher than those in maternal plasma.[1] Pharmacological effects in the neonate, including hypotension, bradycardia, and tachypnoea, have been reported,[1] and the American Academy of Pediatrics therefore considers[2] that acebutolol should be given with caution to breast-feeding mothers.

1. Boutroy MJ, *et al.* To nurse when receiving acebutolol: is it dangerous for the neonate? *Eur J Clin Pharmacol* 1986; 30: 737–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Effects on the liver. Six cases of hepatotoxicity associated with acebutolol were reported[1] in the USA to the FDA between 1985 and 1989. The syndrome consisted of markedly elevated transaminase concentrations, moderately elevated alkaline phosphatase concentrations, and other constitutional symptoms such as fever, nausea, abdominal pain, and headache. The duration of therapy before onset of symptoms ranged from 10 to 31 days; 5 patients received a daily dose of 400 mg; the dose was unspecified in the sixth patient. The syndrome resolved when acebutolol was stopped but reappeared in 2 patients who were rechallenged.

1. Tanner LA, *et al.* Hepatic toxicity after acebutolol therapy. *Ann Intern Med* 1989; 111: 533–4.

Effects on respiratory function. Bronchospasm is a recognised adverse effect of beta blockers, but other respiratory disorders have also been reported. Pleurisy and pulmonary granulomas developed in a patient given acebutolol and a diuretic; acebutolol was considered to be responsible.[1] Hypersensitivity pneumonitis has also been reported in a patient taking acebutolol.[2]

1. Wood GM, *et al.* Pleurisy and pulmonary granulomas after treatment with acebutolol. *BMJ* 1982; 285: 936.
2. Akoun GM, *et al.* Acebutolol-induced hypersensitivity pneumonitis. *BMJ* 1983; 286: 266–7.

Hypersensitivity. See Effects on Respiratory Function, above and Lupus, below.

Lupus. An increase in antinuclear antibodies has been seen with acebutolol.[1] A report of a lupus syndrome in an elderly patient given acebutolol and clonidine described remission of symptoms when acebutolol was withdrawn, but the high antinuclear antibody titre persisted for more than 9 months.[2] Acebutolol was also reported to have caused subacute cutaneous lupus erythematosus in a 57-year-old woman. The condition had resolved completely 4 months after acebutolol was stopped.[3] The authors noted that there had been 9 previous reports of lupus in patients taking acebutolol, but only one had skin manifestations.

1. Wilson JD. Antinuclear antibodies and cardiovascular drugs. *Drugs* 1980; 19: 292–305.
2. Hourdebaigt-Larrusse P, *et al.* Une nouvelle observation de lupus induit par acébutolol. *Ann Cardiol Angeiol (Paris)* 1985; 34: 421–3.
3. Fenniche S,*et al.* Acebutolol-induced subacute cutaneous lupus erythematosus. *Skin Pharmacol Physiol* 2005; 18: 230–3.

Pregnancy. Both acebutolol and its active metabolite diacetolol cross the placenta. In a study[1] in 29 pregnant women who had received acebutolol for at least one month before delivery, there was evidence of bradycardia in 12 of the 31 offspring and tachypnoea in 6.

1. Boutroy MJ, *et al.* Infants born to hypertensive mothers treated by acebutolol. *Dev Pharmacol Ther* 1982; 4 (suppl 1): 109–15.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Acebutolol is well absorbed from the gastrointestinal tract, but undergoes extensive first-pass metabolism in the liver. Although the bioavailability of acebutolol is reported to be only about 40%, the major metabolite diacetolol is active. After oral doses, peak plasma concentrations of acebutolol and diacetolol occur in about 2 and 4 hours, respectively.

Acebutolol and diacetolol are widely distributed in the body, but they have low to moderate lipid solubility and penetration into the CSF is poor. They cross the placenta and higher concentrations occur in breast milk than in maternal plasma. Acebutolol is only about 26% bound to plasma proteins, but is about 50% bound to erythrocytes. The plasma elimination half-lives for acebutolol and diacetolol are 3 to 4 hours and 8 to 13 hours respectively. Half-life values for acebutolol and diacetolol may be increased in the elderly and the half-life for diacetolol may be prolonged up to 32 hours in patients with severe renal impairment. Acebutolol and diacetolol are excreted in the urine and in the bile and may undergo enterohepatic recycling; acebutolol is also reported to be excreted directly from the intestinal wall, and more than 50% of an oral dose

can be recovered from the faeces. Acebutolol and diacetolol are removed by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Sectral; *Canad.*: Rhotral†; Sectral; *Chile*: Beloc; Grifobutol; *Cz.*: Acecor; Apo-Acebutol; Sectral; *Denm.*: Diasectral†; *Fin.*: Diasectral; Espesil; *Fr.*: Sectral; *Ger.*: Prent†; *Hong Kong*: Sectral; *Israel*: Sectral; *Ital.*: Prent; Sectral; *Neth.*: Sectral; *NZ*: ACB†; *Pol.*: Abutol†; Sectral; *Port.*: Prent; *S.Afr.*: Butobloc; Sectral; *Singapore*: ACB; Sectral; *Turk.*: Prent; *UK*: Sectral; *USA*: Sectral.

Multi-ingredient Preparations. *Belg.*: Sectrazide; *Ger.*: Sali-Prent; Tredalat; *Indon.*: Sectrazide†.

Pharmacopoeial Preparations
BP 2014: Acebutolol Capsules; Acebutolol Tablets;
USP 36: Acebutolol Hydrochloride Capsules.

Acenocoumarol *(BAN, rINN)*

Acénocoumarol; Acenocoumarolum; Acenocumarin; Acenocumarol; Acenokumarol; Asenokumarol; G-23350; Nicoumalone; Nikumalon; Аценокумарол.

(*RS*)-4-Hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]coumarin.

$C_{19}H_{15}NO_6$=353.3

CAS — 152-72-7.

ATC — B01AA07.

ATC Vet — QB01AA07.

UNII — I6WP63U32H.

Pharmacopoeias. In *Br.* and *Pol.*

BP 2014: (Acenocoumarol). An almost white to buff-coloured odourless or almost odourless powder. It exhibits polymorphism. Practically insoluble in water and in ether; slightly soluble in alcohol and in chloroform; dissolves in aqueous solutions of alkali hydroxides.

Uses and Administration

Acenocoumarol is an oral coumarin anticoagulant with actions similar to those of warfarin (p. 1527.2). It is used in the management of thromboembolic disorders (p. 1273.2). The usual dose is 4 mg on the first day and 4 to 8 mg on the second day; subsequent maintenance doses range from 1 to 8 mg depending on the response. Acenocoumarol is given in a single dose at the same time every day.

Adverse Effects, Treatment, and Precautions

As for Warfarin Sodium, p. 1528.2.

Effects on the fetus. In a group of women given acenocoumarol for anticoagulant prophylaxis of mechanical heart valves during pregnancy,[1] fetal loss occurred in 13 of 61 pregnancies where oral anticoagulation was continued during the first trimester. Apart from 1 case of hydrocephalus no malformations were reported in the other neonates.

1. Meschengieser SS, *et al.* Anticoagulation in pregnant women with mechanical heart valve prostheses. *Heart* 1999; 82: 23–6.

Interactions

The interactions associated with oral anticoagulants are discussed in detail under warfarin (p. 1529.3). Specific references to interactions involving acenocoumarol can be found there under the headings for the following drug groups: analgesics; antiarrhythmics; antibacterials; antidepressants; antiepileptics; antifungals; antigout drugs; antihistamines; antineoplastics; antiplatelets; antivirals; diuretics; gastrointestinal drugs; immunosuppressants; lipid regulating drugs; sex hormones; and vaccines.

Pharmacokinetics

Acenocoumarol is readily absorbed from the gastrointestinal tract, with peak plasma concentrations occurring within 1 to 3 hours of a single dose. About 60% of a dose is excreted as inactive metabolites in the urine, and about 30% via the faeces. It is extensively bound to plasma proteins, and has an elimination half-life of 8 to 11 hours. Acenocoumarol crosses the placenta; only small quantities have been detected in breast milk. It is given as a racemic mixture: the S-isomer is the more potent of the two, but it has a much shorter half-life and therefore anticoagulation activity is more dependent on the R-isomer. Both isomers are metabolised via the cytochrome P450 isoenzyme CYP2C9; the R-isomer is also metabolised by CYP1A2 and CYP2C19.

References.

1. Ufer M. Comparative pharmacokinetics of vitamin K antagonists: warfarin, phenprocoumon and acenocoumarol. *Clin Pharmacokinet* 2005; 44: 1227–46.
2. Beinema M, *et al.* Pharmacogenetic differences between warfarin, acenocoumarol and phenprocoumon. *Thromb Haemost* 2008; 100: 1052–7.
3. Teichert M, *et al.* Genotypes associated with reduced activity of VKORC1 and CYP2C9 and their modification of acenocoumarol anticoagulation during the initial treatment period. *Clin Pharmacol Ther* 2009; 85: 379–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acenotromb; Antitrom; Azecar; Cumarol; Dercualon; Fortonol; Hemotran; Saxion; Sintrom; *Austria*: Sintrom; *Belg.*: Sintrom; *Canad.*: Sintrom; *Chile*: Acebron; Acenox; Coarol; Isquelium; Neo-Sintrom; *Fr.*: Mini-Sintrom; Sintrom; *Gr.*: Sintrom; *Hung.*: Syncumar; *India*: Actrom; Nistrom; *Israel*: Sintrom; *Ital.*: Sintrom; *Mex.*: Sintrom; *Pol.*: Sintrom; Syncumar; *Port.*: Sintrom; *Rus.*: Syncumar (Синкумар); *Spain*: Sintrom; *Switz.*: Sintrom; *UK*: Sinthrome; *Ukr.*: Sincumar (Синкумар).

Pharmacopoeial Preparations
BP 2014: Acenocoumarol Tablets.

Acetyldigoxin

Acetildigoxina; Acetyldigoxin-beta; β-Acetyldigoxinum; Acetyldigoxinum; Acetyldigoxinum Beta; β-Acetyldigoksyna; Asetyylidigoksiini; Desglucolanatoside C; Ацетилдигоксин.

3β-[(O-3-*O*-Acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β,14β-card-20(22)-enolide (α-acetyldigoxin); 3β-[(*O*-4-*O*-Acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β,14β-card-20(22)-enolide (β-acetyldigoxin).

$C_{43}H_{66}O_{15}$=823.0

CAS — 5511-98-8 (α-acetyldigoxin); 5355-48-6 (β-acetyldigoxin).

ATC — C01AA02.

ATC Vet — QC01AA02.

UNII — P7K44M64CW.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (β-Acetyldigoxin). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

Profile

Acetyldigoxin is a cardiac glycoside with positive inotropic activity. It has the general properties of digoxin (p. 1353.3) and has been used similarly in the management of some cardiac arrhythmias (p. 1266.1) and in heart failure (p. 1262.3). Usual oral maintenance doses for the β-isomer are 200 to 400 micrograms daily; the α-isomer has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Corotal†; Lanatilin; Novodigal†; *Ger.*: Digostada†; Digotab†; Digox†; Novodigal; *Gr.*: Cedigocine.

Acipimox *(BAN, rINN)*

Acipimoxum; Asipimoks; Asipimoksi; K-9321; Аципимокс.

5-Methylpyrazine-2-carboxylic acid 4-oxide.

$C_6H_6N_2O_3$=154.1

CAS — 51037-30-0.

ATC — C10AD06.

ATC Vet — QC10AD06.

UNII — K9AY9IR2SD.

Uses and Administration

Acipimox is a lipid regulating drug related to nicotinic acid (p. 2083.1). It is used to reduce cholesterol and triglycerides in the management of hyperlipidaemias (see Action, below), including type IIa, IIb, or IV hyperlipoproteinaemias.

Acipimox is given orally in a usual dose of 250 mg two or three times daily, taken with meals. Doses of up to 1200 mg daily have been used. The dose should be adjusted in renal impairment (see below).

Action. Acipimox is used in the management of hyperlipidaemias (p. 1248.1); it is a derivative of nicotinic acid and has similar effects on plasma lipoproteins but is better tolerated.[1] Its primary action is inhibition of lipolysis, leading to a reduction in circulating free fatty acids and consequently a reduction in very-low-density lipoprotein (VLDL) production in the liver. This results in a reduction of triglycerides, particularly in patients with hypertriglyceridaemia;[2] there may also be a decrease in low-density lipoprotein (LDL)-cholesterol and total cholesterol, and an increase in high-density lipoprotein (HDL)-cholesterol. Similar effects have been reported in patients with mixed hyperlipoproteinaemias, although the reduction of triglycerides and LDL-cholesterol was not significant.[3]

Reduction of free fatty acids by acipimox has several other physiological effects that have been utilised. Insulin secretion and sensitivity may be modified, and acipimox has been tried in type 2 diabetes mellitus; it improves plasma lipids and may also reduce blood-glucose concentrations,[4] and has been of benefit in patients with type A insulin resistance.[5] Beneficial effects have also been reported[6] in patients with HIV-associated lipodystrophy and insulin resistance. Growth hormone secretion is stimulated in obese subjects, and acipimox has been used in the investigation of growth hormone disorders.[7] There is also an increase in glucose uptake by the heart, and acipimox has been used to enhance myocardial imaging in ^{18}F-fluorodeoxyglucose positron-emission tomography.[8]

1. Tornvall P, Walldius G. A comparison between nicotinic acid and acipimox in hypertriglyceridaemia—effects on serum lipids, lipoproteins, glucose tolerance and tolerability. *J Intern Med* 1991; 230: 415–21.
2. Ball MJ, *et al.* Acipimox in the treatment of patients with hyperlipidaemia: a double blind trial. *Eur J Clin Pharmacol* 1986; 31: 201–4.
3. Otto C, *et al.* Effects of acipimox on haemorheology and plasma lipoproteins in patients with mixed hyperlipoproteinaemia. *Br J Clin Pharmacol* 1998; 46: 473–8.
4. Lavezzari M, *et al.* Results of a phase IV study carried out with acipimox in type II diabetic patients with concomitant hyperlipoproteinaemia. *J Int Med Res* 1989; 17: 373–80.
5. Kumar S, *et al.* Suppression of non-esterified fatty acids to treat type A insulin resistance syndrome. *Lancet* 1994; 343: 1073–4.
6. Hadigan C, *et al.* Inhibition of lipolysis improves insulin sensitivity in protease inhibitor-treated HIV-infected men with fat redistribution. *Am J Clin Nutr* 2003; 77: 490–4.
7. Cordido F, *et al.* Effect of acute pharmacological reduction of plasma free fatty acids on growth hormone (GH) releasing hormone-induced GH secretion in obese adults with and without hypopituitarism. *J Clin Endocrinol Metab* 1998; 83: 4350–4.
8. Knuuti MJ, *et al.* Enhancement of myocardial [fluorine-18] fluorodeoxyglucose uptake by a nicotinic acid derivative. *J Nucl Med* 1994; 35: 989–98.

Administration in renal impairment. Acipimox is contra-indicated in patients with a creatinine clearance below 30 mL/minute. In patients with creatinine clearance between 30 and 60 mL/minute, the interval between doses should be increased.

Adverse Effects and Precautions

Acipimox may cause peripheral vasodilatation resulting in flushing, itching, and a sensation of heat. Rash and erythema may occur. Gastrointestinal disturbances including heartburn, epigastric pain, nausea, and diarrhoea have been reported, as well as headache, malaise, myalgia, myositis, arthralgia, and dry eye. Urticaria, angioedema, and bronchospasm may occur rarely.

Acipimox is contra-indicated in patients with peptic ulcer disease. It should be used with caution in renal impairment.

Incidence of adverse effects. In a study involving 3009 hyperlipidaemic patients with type 2 diabetes,[1] adverse effects associated with acipimox occurred in 8.8%, resulting in withdrawal in 5.5% of patients. The most frequent adverse effects involved the skin (57.6%), gastrointestinal tract (25.8%), and CNS (9.7%). Labial oedema occurred in 3 cases and an urticarial eruption, collapse, and dyspnoea in another. The incidence of adverse effects was almost twice as high in females as in males, the difference being mainly due to a greater incidence of flushing, pruritus, and skin rashes. The incidence was not affected by age. There was a mean 15.3% reduction in fasting blood-glucose concentrations and an 8.5% reduction in glycosylated haemoglobin during treatment with acipimox.

1. Lavezzari M, *et al.* Results of a phase IV study carried out with acipimox in type II diabetic patients with concomitant hyperlipoproteinaemia. *J Int Med Res* 1989; 17: 373–80.

Pharmacokinetics

Acipimox is rapidly and completely absorbed from the gastrointestinal tract and peak plasma concentrations occur within 2 hours. It does not bind to plasma proteins and the plasma half-life is about 2 hours. It is not significantly metabolised and is excreted in the urine, largely unchanged.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Olbetam; *Belg.*: Olbetam; *Chile*: Olbetam; *China*: Olbetam (乐知苹); Si Li Meng (司里蒙); YiPing (益平); *Denm.*: Olbetam; *Gr.*: Olbetam; *Hong Kong*: Olbetam; *Hung.*: Olbetam; *Israel*: Olbetam; *Ital.*: Olbetam; *Neth.*: Nedios; Olbetam; *NZ*: Olbetam; *S.Afr.*: Olbetam; *Singapore*: Olbetam; *Switz.*: Olbetam; *Thai.*: Olbetam; *UK*: Olbetam.

Adenosine *(BAN, USAN)*

Adenocin; Adenoslini; Adenosin; Adenosina; Adénosine; Adenosinum; Adenozin; Adenozinas; Adenozyna; SR-96225; SUNY-4001; Аденозин.

6-Amino-9-β-D-ribofuranosyl-9*H*-purine.

$C_{10}H_{13}N_5O_4$=267.2

CAS — 58-61-7.

ATC — C01EB10.

ATC Vet — QC01EB10.

UNII — K72T3FS567.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Adenosine). A white, or almost white, crystalline powder. Slightly soluble in water; soluble in hot water; practically insoluble in alcohol and in dichloromethane; dissolves in dilute mineral acids.

USP 36: (Adenosine). A white, odourless crystalline powder. Slightly soluble in water; practically insoluble in alcohol. Store in airtight containers. Protect from light.

Stability. Adenosine was found to be stable[1] when mixed with glucose 5%, lactated Ringer's, sodium chloride 0.9%, or a mixture of glucose 5% and lactated Ringer's and stored in polypropylene syringes or PVC bags.

1. Ketkar VA, *et al.* Stability of undiluted and diluted adenosine at three temperatures in syringes and bags. *Am J Health-Syst Pharm* 1998; 55: 466–70.

Uses and Administration

Adenosine is an endogenous adenine nucleoside that is one of the components of nucleic acids (p. 2573.1) and many coenzymes; as such, it is involved in many biological processes. It acts as an antiarrhythmic by stimulating adenosine A_1-receptors and slowing conduction through the AV node. It does not fit into the usual classification of antiarrhythmics (p. 1243.1). It also produces peripheral and coronary vasodilatation by stimulating adenosine A_2-receptors.

Adenosine is used to restore sinus rhythm in the treatment of paroxysmal supraventricular tachycardia, including that associated with the Wolff-Parkinson-White syndrome (but see Effects on the Heart, below). It is also used for the differential diagnosis of broad or narrow complex supraventricular tachycardias and in myocardial imaging.

In the treatment of **paroxysmal supraventricular tachycardia**, adenosine may be given in an initial dose of 3 mg by rapid intravenous injection. If this dose is not effective within 1 to 2 minutes, 6 mg may be given and if necessary, 12 mg after a further 1 to 2 minutes. Alternatively, an initial dose of 6 mg followed if necessary by two further doses of 12 mg at 1 to 2 minute intervals may be used, but this higher initial dose should not be given to heart transplant patients as they have an increased sensitivity to adenosine. For differential **diagnosis of supraventricular tachycardias** a similar dosage regimen is used, beginning with a dose of 3 mg followed by 6 mg and then 12 mg at 1 to 2 minute intervals if required. Doses for children with paroxysmal supraventricular tachycardia are discussed below.

In **myocardial imaging** adenosine is given by intravenous infusion in a dose of 140 micrograms/kg per minute for 6 minutes. The radionuclide is injected after 3 minutes of the infusion.

Adenosine and its derivatives, such as adenosine phosphate (p. 2430.2) and adenosine triphosphate (p. 2430.3), have been used in various metabolic disorders because of their role in biological processes. Adenosine triphosphate, as the disodium salt, has been used as an antiarrhythmic.

General references.

1. Innes JA. Adenosine use in the emergency department. *Emerg Med Australas* 2008; 20: 209–15.
2. Eltzschig HK. Adenosine: an old drug newly discovered. *Anesthesiology* 2009; 111: 904–15.

Administration in children. Adenosine may be given by rapid intravenous injection for the management of paroxysmal supraventricular tachycardia in children. Dosage recommendations vary. Licensed product information in the USA states that children weighing less than 50 kg, including neonates and infants, may be given an initial dose of 50 to 100 micrograms/kg; if this is not effective the dose may be increased by 50 to 100 micrograms/kg increments at 1 to 2 minute intervals until the arrhythmia is controlled or a single dose of 300 micrograms/kg is reached. Paediatric advanced cardiac life support guidelines[1] in the USA recommend an initial dose of 100 micrograms/kg (maximum 6 mg) followed by a second dose of 200 micrograms/kg (maximum 12 mg) if required, and are applicable to infants and children. In the UK, the *BNFC* recommends an initial intravenous injection of 100 micrograms/kg for children aged 1 to 12 years, or 150 micrograms/kg for neonates and infants up to 1 year; the dose may be increased by increments of 50 to 100 micrograms/kg at 1 to 2 minute intervals, to a maximum single dose of 300 micrograms/kg for neonates and 500 micrograms/kg for infants and children.

1. The American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 12: pediatric advanced life support. *Circulation* 2005; 112: (suppl 1): IV167–IV187. Also available at: http://circ.ahajournals.org/cgi/reprint/112/24_suppl/IV-167 (accessed 10/07/07)

Cardiac arrhythmias. Adenosine is used for the termination of paroxysmal supraventricular tachycardia[1–4] (p. 1266.1) and may often be the drug of choice. Bolus intravenous injection of adenosine produces a rapid response and the extremely short plasma half-life (less than 10 seconds) allows dosage titration every 1 to 2 minutes so that most episodes can be controlled within 5 minutes without the danger of drug accumulation.

Adenosine has been used successfully in pregnant women with paroxysmal supraventricular tachycardia[5–8] and cardioversion of fetal supraventricular tachycardia by direct fetal therapy with adenosine has been reported.[9,10]

Adenosine can be used for the differential **diagnosis** of broad complex tachycardia where the mechanism is unknown.[1] If the cause is supraventricular, adenosine will terminate the arrhythmia or produce AV block to reveal the underlying atrial rhythm. If the cause is ventricular, adenosine will have no effect on the tachycardia, whereas if an alternative treatment such as verapamil is given to these patients severe hypotension and cardiac arrest can occur.

1. Faulds D, *et al.* Adenosine: an evaluation of its use in cardiac diagnostic procedures, and in the treatment of paroxysmal supraventricular tachycardia. *Drugs* 1991; 41: 596–624.
2. Rankin AC, *et al.* Adenosine and the treatment of supraventricular tachycardia. *Am J Med* 1992; 92: 655–64.
3. Anonymous. Adenosine for acute cardiac arrhythmias. *Drug Ther Bull* 1993; 31: 49–50.
4. Holdgate A, Foo A. Adenosine versus intravenous calcium channel antagonists for the treatment of supraventricular tachycardia in adults. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 16/02/10).
5. Mason BA, *et al.* Adenosine in the treatment of maternal paroxysmal supraventricular tachycardia. *Obstet Gynecol* 1992; 80: 478–80.
6. Afridi I, *et al.* Termination of supraventricular tachycardia with intravenous adenosine in a pregnant woman with Wolff-Parkinson-White syndrome. *Obstet Gynecol* 1992; 80: 481–3.
7. Hagley MT, Cole PL. Adenosine use in pregnant women with supraventricular tachycardia. *Ann Pharmacother* 1994; 28: 1241–2.
8. Hagley MT, *et al.* Adenosine use in a pregnant patient with supraventricular tachycardia. *Ann Pharmacother* 1995; 29: 938.
9. Blanch G, *et al.* Cardioversion of fetal tachyarrhythmia with adenosine. *Lancet* 1994; 344: 1646.
10. Kohl T, *et al.* Direct fetal administration of adenosine for the termination of incessant supraventricular tachycardia. *Obstet Gynecol* 1995; 85: 873–4.

Ischaemic heart disease. Adenosine produces coronary vasodilatation and may be used to provide a pharmacological stress in patients undergoing assessment of their ischaemic heart disease when exercise stress is inappropriate.[1] It has been used with radionuclide imaging, echocardiography, and magnetic resonance imaging.

Adenosine has also been tried as an adjunct to prevent reperfusion injury in the management of acute myocardial infarction. Improved coronary blood flow has been reported[2] with intracoronary adenosine, and both intracoronary[3] and intravenous[4] adenosine have reduced infarct size, but no improvement in clinical outcomes has been shown.[5–7] A reduction in myonecrosis has also been reported[8] with intracoronary adenosine given at the start of non-urgent percutaneous coronary interventions.

1. Ali Raza J, *et al.* Pharmacological stress agents for evaluation of ischemic heart disease. *Int J Cardiol* 2001; 81: 157–67.
2. Vijayalakshmi K, *et al.* Prospective, randomised, controlled trial to study the effect of intracoronary injection of verapamil and adenosine on coronary blood flow during percutaneous coronary intervention in patients with acute coronary syndromes. *Heart* 2006; 92: 1278–84.
3. Claeys MJ, *et al.* Effect of intracoronary adenosine infusion during coronary intervention on myocardial reperfusion injury in patients with acute myocardial infarction. *Am J Cardiol* 2004; 94: 9–13.
4. Mahaffey KW, *et al.* Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial. *J Am Coll Cardiol* 1999; 34: 1711–20.
5. Ross AM, *et al.* A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). *J Am Coll Cardiol* 2005; 45: 1775–80.
6. Quintana M, *et al.* Left ventricular function and cardiovascular events following adjuvant therapy with adenosine in acute myocardial infarction treated with thrombolysis: results of the ATTenuation by Adenosine of Cardiac Complications (ATTACC) study. *Eur J Clin Pharmacol* 2003; 59: 1–9.
7. Petronio AS, *et al.* Left ventricular remodeling after primary coronary angioplasty in patients treated with abciximab or intracoronary adenosine. *Am Heart J* 2005; 150: 1015. Full version: http://download.journals.elsevierhealth.com/pdfs/Journals/0002-8703/PIIS0002870305007313.pdf (accessed 26/06/07)
8. Lee C-H, *et al.* Pretreatment with intracoronary adenosine reduces the incidence of myonecrosis after non-urgent percutaneous coronary intervention: a prospective randomized study. *Eur Heart J* 2007; 28: 19–25.

Pain. Adenosine receptors are present in the CNS and there is some evidence[1,2] that adenosine, given intravenously or intrathecally, may have an analgesic effect.

1. Hayashida M, *et al.* Clinical application of adenosine and ATP for pain control. *J Anesth* 2005; 19: 225–35.
2. Gan TJ, Habib AS. Adenosine as a non-opioid analgesic in the perioperative setting. *Anesth Analg* 2007; 105: 487–94.

Pulmonary hypertension. Vasodilators have been tried in persistent pulmonary hypertension of the newborn (p. 1278.2), but their use is generally restricted by lack of selectivity for the pulmonary circulation. A randomised placebo-controlled study[1] in 18 term infants with persistent pulmonary hypertension indicated that intravenous infusion of adenosine improved oxygenation without causing hypotension or tachycardia; however, the study was too small to assess any effect on mortality and/or the need for extracorporeal membrane oxygenation. Another observational study[2] in neonates with an inadequate response to inhaled nitric oxide suggested that addition of adenosine infusion also improved oxygenation.

1. Konduri GG, *et al.* Adenosine infusion improves oxygenation in term infants with respiratory failure. *Pediatrics* 1996; 97: 295–300.
2. Ng C, *et al.* Adenosine infusion for the management of persistent pulmonary hypertension of the newborn. *Pediatr Crit Care Med* 2004; 5: 10–13.

Adverse Effects, Treatment, and Precautions

Adverse effects of adenosine are usually transient, lasting less than a minute, due to its very short plasma half-life. They include nausea, lightheadedness, flushing, headache, angina-like chest pain, apprehension, and dyspnoea. Bronchospasm has been reported. Like other antiarrhythmics, adenosine may worsen arrhythmias. Bradycardia and heart block have been reported. Adenosine is a vasodilator and reduces blood pressure; the larger doses given by intravenous infusion may rarely produce significant hypotension and reflex tachycardia. Infusion may also be associated with abdominal, throat, neck, and jaw discomfort. Treatment is rarely needed for adverse effects but in persistent cases aminophylline or theophylline may be given.

Adenosine is contra-indicated in patients with second- or third-degree AV block or in those with sick sinus syndrome (unless they have a pacemaker) and should be avoided or used with caution in patients with QT prolongation since torsade de pointes has occurred very rarely. It is also contra-indicated in severe hypotension, in decompensated heart failure, and asthmatic subjects and those with chronic obstructive pulmonary disease. Intravenous infusion of adenosine should be used with caution in patients who may develop hypotensive complications such as those with autonomic dysfunction, pericarditis, or stenotic valvular heart disease. Patients with recent heart transplantation may have increased sensitivity to the cardiac effects of adenosine.

Use of the *University of Wisconsin solution* [UW Solution; Belzer UW Solution (commercially available as *Viaspan*)] for the hypothermic storage of kidneys before transplantation has been associated with bradycardia, prolonged PR intervals, and heart block.[1,2] The solution contains hetastarch, allopurinol, glutathione, and adenosine. The adenosine was considered to be the arrhythmogenic factor. Some centres had used the solution to flush kidneys before implantation,[2] a use for which it was never intended.[3] When used properly the adenosine in solution is catabolised to hypoxanthine and inosine, which do not cause cardiac problems, but this takes some time in hypothermic conditions.[3]

1. Prien T, *et al.* Bradyarrhythmia with University of Wisconsin preservation solution. *Lancet* 1989; i: 1319–20.
2. Vanrenterghem Y, *et al.* University of Wisconsin preservation solute and bradyarrhythmia. *Lancet* 1989; ii: 745.
3. Belzer FO. Correct use of University of Wisconsin preservation solution. *Lancet* 1990; 335: 362.

Effects on the heart. Like most antiarrhythmics, adenosine can worsen arrhythmias, and both bradyarrhythmias and tachyarrhythmias have been reported.[1] Atrial fibrillation may develop in patients given adenosine for paroxysmal supraventricular tachycardia, and in a prospective study[2] occurred in 12% of 200 patients. Although most arrhythmias are of minor importance, ventricular arrhythmias and haemodynamic compromise have been reported[3,4] in patients given adenosine for presumed supraventricular tachycardia who were later discovered to have Wolff-Parkinson-White syndrome. Fatal cardiac arrest has also occurred[5] after the use of adenosine for arrhythmias in 2 patients with underlying cardiopulmonary disorders.

There have also been reports[6,7] of myocardial infarction in patients with ischaemic heart disease given adenosine during stress imaging.

For arrhythmias associated with the use of adenosine in organ preservation solutions see above.

1. Mallet ML. Proarrhythmic effects of adenosine: a review of the literature. *Emerg Med J* 2004; 21: 408–10.

2. Strickberger SA, *et al.* Adenosine-induced atrial arrhythmia: a prospective analysis. *Ann Intern Med* 1997; 127: 417–22.
3. Exner DV, *et al.* Proarrhythmia in patients with the Wolff-Parkinson-White syndrome after standard doses of intravenous adenosine. *Ann Intern Med* 1995; 122: 351–2.
4. Nagappan R, *et al.* Potential dangers of the Valsalva maneuver and adenosine in paroxysmal supraventricular tachycardia—beware pre-excitation. *Crit Care Resusc* 2002; 4: 107–11.
5. Haynes BE. Two deaths after prehospital use of adenosine. *J Emerg Med* 2001; 21: 151–4.
6. Poland JE, Wilson LM. Myocardial infarction during adenosine stress test. Abstract: *Heart* 2002; 87: 106. Full version: http://heart.bmj.com/cgi/reprint/87/2/e2.pdf (accessed 10/07/07)
7. Reyes E, *et al.* Acute myocardial infarction during adenosine myocardial perfusion imaging. *J Nucl Cardiol* 2004; 11: 97–9.

Effects on the respiratory system. Acute exacerbation of asthma can be provoked by inhalation of adenosine. Bronchospasm has also been reported in patients with asthma[1,2] or a history of asthma[3] given adenosine intravenously and bronchospasm followed by respiratory failure in a patient with obstructive pulmonary disease.[4] Respiratory arrest has also been reported in an asthmatic patient.[5]

1. DeGroff CG, Silka MJ. Bronchospasm after intravenous administration of adenosine in a patient with asthma. *J Pediatr* 1994; 125: 822–3.
2. Drake L, *et al.* Bronchospasm induced by intravenous adenosine. *Hum Exp Toxicol* 1994; 13: 263–5.
3. Hintringer F, *et al.* Supraventricular tachycardia. *N Engl J Med* 1995; 333: 323.
4. Burkhart KK. Respiratory failure following adenosine administration. *Am J Emerg Med* 1993; 11: 249–50.
5. Patton JW, Sharma GK. Adenosine-induced respiratory arrest in an asthmatic patient. *South Med J* 2008; 101: 328–9.

Migraine. A 35-year-old man with a history of migraine developed symptoms identical to those of his usual episodes of migraine immediately after 2 intravenous bolus doses of adenosine.[1]

1. Brown SGA, Waterer GW. Migraine precipitated by adenosine. *Med J Aust* 1995; 162: 389–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies adenosine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

Dipyridamole inhibits adenosine uptake and therefore may potentiate the action of adenosine; if use of the two drugs is essential the dosage of adenosine should be reduced. Theophylline and other xanthines are competitive antagonists of adenosine. The risk of AV block may be increased if adenosine is used with other drugs that slow AV conduction.

Pharmacokinetics

Intravenous adenosine is rapidly taken up by an active transport system into erythrocytes and vascular endothelial cells where it is metabolised to inosine and adenosine monophosphate. The plasma half-life is less than 10 seconds.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Adenocor; Adenoscan; *Belg.*: Adenocor; *Braz.*: Adenocard; *Canad.*: Adenocard; Adenoscan†; *Chile*: Tricor; *China*: Adenocor (艾吉伴); Ai Duo (艾朵); Ai Wen (艾文); Xin Yi (欣颐); *Cz.*: Adenocor; *Denm.*: Adenocor; *Fin.*: Adenocor; Adenoscan†; *Fr.*: Adenoscan; Krenosin; *Ger.*: Adenoscan; Adrekar; *Gr.*: Adenocor; Adenoscan; *Hong Kong*: Adenoscan; *Hung.*: Adenocor; *India*: Adenocor; Adenoject; Cadsine; Carnosin; *Irl.*: Adenocor; Adenoscan†; *Israel*: Adenocor; *Ital.*: Adenoscan; Krenosin; *Jpn*: Adenoscan; *Malaysia*: Adenocor; *Mex.*: Krenosin; Pisdeno; *Neth.*: Adenocor; Adenoscan; *Norw.*: Adenocor†; *NZ*: Adenocor; *Philipp.*: Cardiovert; *Pol.*: Adenocor; *Port.*: Adenocor; Adenoscan; *Rus.*: Vita-Iodurol (Вита-йодурол); *S.Afr.*: Adenocor; *Singapore*: Adenocor; Adenoscan; *Spain*: Adenocor; Adenoscan; *Switz.*: Krenosine; *Thai.*: Adenocor; *UK*: Adenocor; Adenoscan; *USA*: Adenocard; Adenoscan.

Multi-ingredient Preparations. *Austria*: Vita-Gerin; *Braz.*: Anekron; Biohepax†; Enterofigon; Epativan; Epocler; Hepatox; Necro B6; *Gr.*: Collyre Vitaphakol; Suprin; *Hong Kong*: Vitacic†; *Mon.*: Vitacic; *Philipp.*: Godex†; Mitodex; *Rus.*: Oftan Catachrom (Офтан Катахром); *Ukr.*: Hepadif (Гепадиф); Vita-Iodurol (Вита-йодурол)†.

Pharmacopoeial Preparations
USP 36: Adenosine Injection.

Adrenaline (BANM) ⊗

Adrenallini; Adrenalin; Adrenalina; Adrénaline; Adrenalinum; Epinefriini; Epinefrin; Epinefrina; Epinefryna; Epinephrin/Adrenalin; Epinephrine (rINN); Epinephrine (BAN); Épinéphrine; Epinephrinum; Epirenamine; Levorenin; Suprarenin; Эпинефрин.

(*R*)-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol.

$C_9H_{13}NO_3$=183.2

CAS — 51-43-4.

ATC — A01AD01; B02BC09; C01CA24; R01AA14; R03AA01; S01EA01.

ATC Vet — QA01AD01; QB02BC09; QC01CA24; QR01AA14; QR03AA01; QS01EA01.

UNII — YKH834O4BH.

NOTE. Endogenous adrenaline and the monograph substance are the laevo-isomer.

ADN and EPN are codes approved by the BP 2014 for use on single unit doses of eye drops containing adrenaline where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

US also includes the racemic substances Racepinephrine (Racepinefrine (*rINN*)) and Racepinephrine Hydrochloride (Racepinefrine Hydrochloride (*rINNM*)).

Ph. Eur. 8: (Adrenaline). A white or almost white crystalline powder, becoming coloured on exposure to air and light. Practically insoluble in water, in alcohol, and in dichloromethane. It dissolves in hydrochloric acid. Store under nitrogen. Protect from light.

USP 36: (Epinephrine). A white to practically white, odourless, microcrystalline powder or granules, gradually darkening on exposure to light and air. With acids, it forms salts that are readily soluble in water, and the base may be recovered by the addition of ammonia water or alkali carbonates. Very slightly soluble in water and in alcohol; insoluble in chloroform, in ether, and in fixed and volatile oils. Solutions are alkaline to litmus. Store in airtight containers. Protect from light.

Adrenaline Acid Tartrate (BANM) ⊗

Adrenaliinitartraatti; Adrenaline Bitartrate; Adrenaline Tartrate; Adrénaline, Tartrate d'; Adrenalini Bitartras; Adrenalini Tartras; Adrenalinii Tartras; Adrenalinium Hydrogentartaricum; Adrenalino tartratas; Adrenalin-tartarát; Adrenalintartrat; Bitartrato de adrenalina; Bitartrato de epinefrina; Epinefrina, bitartrato de; Epinefrin-tartarát; Epinefryny wodorowinian; Epinephrine Acid Tartrate (BANM); Epinephrine Bitartrate (rINNM); Épinéphrine, Bitartrate d'; Epinephrine Hydrogen Tartrate; Epinephrinhydrogentartrat/Adrenalinhydrogentartrat; Epinephrini Bitartras; Epinephrini Tartras; Epirenamine Bitartrate; Эпинефрина битартрат.

$C_9H_{13}NO_3.C_4H_6O_6$=333.3

CAS — 51-42-3.

ATC — A01AD01; B02BC09; C01CA24; R01AA14; R03AA01; S01EA01.

ATC Vet — QA01AD01; QB02BC09; QC01CA24; QR01AA14; QR03AA01; QS01EA01.

UNII — 30Q7K153AK.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Adrenaline Tartrate; Adrenaline Acid Tartrate BP 2014; Epinephrine Acid Tartrate BP 2014). A white to greyish-white, crystalline powder. Freely soluble in water; slightly soluble in alcohol. Store in airtight containers, or preferably in a sealed tube under vacuum or under an inert gas. Protect from light.

USP 36: (Epinephrine Bitartrate). A white, or greyish-white or light brownish-grey, odourless, crystalline powder. It slowly darkens on exposure to air and light. Soluble 1 in 3 of water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Its solutions in water are acid to litmus, having a pH of about 3.5. Store in airtight containers. Protect from light.

Stability. Studies on the stability of adrenaline injections.

1. Taylor JB, *et al.* Effect of sodium metabisulphite and anaerobic processing conditions on the oxidative degradation of adrenaline injection BP [1980]. *Pharm J* 1984; 232: 646–8.
2. Stepensky D *et al.* Long-term stability study of L-adrenaline injections: kinetics of sulfonation and racemization pathways of drug degradation. *J Pharm Sci* 2004; 93: 969–80.

Adrenaline Hydrochloride (BANM) ⊗

Adrenalin Hidroklorür; Epinefrina, hidrocloruro de; Épinéphrine, Chlorhydrate d'; Epinephrine Hydrochloride (BANM); Epinephrine Hydrochloride (rINNM); Epinephrini Hydrochloridum; Hidrocloruro de epinefrina; Эпинефрина гидрохлорид.

$C_9H_{13}NO_3.HCl$=219.7

CAS — 55-31-2.

ATC — A01AD01; B02BC09; C01CA24; R01AA14; R03AA01; S01EA01.

ATC Vet — QA01AD01; QB02BC09; QC01CA24; QR01AA14; QR03AA01; QS01EA01.

UNII — WBB0470O38.

Uses and Administration

Adrenaline is an endogenous substance that is produced in the adrenal medulla and has important physiological effects. It is also used pharmacologically as a direct-acting sympathomimetic (see p. 1507.3). It is a potent agonist at both alpha and beta adrenoceptors, although the effect on beta adrenoceptors is more marked, particularly at lower doses. These properties explain many aspects of its pharmacology, although the reflex compensating responses of the body also modulate its effects.

The major effects of adrenaline are dose-related and include:

- increased speed and force of cardiac contraction (with lower doses this causes increased systolic pressure yet reduced diastolic pressure since overall peripheral resistance is lowered, but with higher doses both systolic and diastolic pressure are increased as stimulation of peripheral alpha receptors increases peripheral resistance)
- increased blood flow to skeletal muscle (reduced with higher doses); reduced blood flow in the kidneys, mucosa, and skin; little direct effect on cerebral blood flow
- relaxation of bronchial smooth muscle
- hyperglycaemia and markedly increased oxygen consumption due to metabolic effects

Adrenaline has an important role in advanced cardiac life support and in anaphylaxis and anaphylactic shock (for details of dosing, see p. 1293.1 and p. 1293.2). Adrenaline has been used in the treatment of acute asthma but more selective drugs are available, and it has no role in the chronic management of asthma (p. 1195.2). It has been given by nebulisation in severe croup (p. 1603.3). Other uses include the control of minor bleeding from the skin and mucous membranes, the management of open-angle (simple) glaucoma (p. 1999.1), and use as an adjunct to local anaesthesia (p. 1980.1).

Adrenaline is usually given by intramuscular injection, although it may also be given subcutaneously. In extreme emergencies, where a more rapid effect is required, adrenaline may be given as a dilute solution (typically 1 in 10 000) by slow intravenous injection or by slow intravenous infusion. Alternatively, if intravenous access cannot be obtained, it may also be given by the intraosseous (usually into the marrow of the tibia) or endotracheal routes. Adrenaline has sometimes been injected directly in the heart but current guidelines for the management of cardiac emergencies recommend intravenous injection; this may be into a central vein or peripherally, but in the latter case should be followed by 20 mL of intravenous fluid. Adrenaline may also be applied topically or given by inhalation. Aqueous solutions of adrenaline are usually prepared using the acid tartrate or the hydrochloride but the dosage is generally stated in terms of the equivalent content of adrenaline. Adrenaline acid tartrate 1.8 mg or adrenaline hydrochloride 1.2 mg is equivalent to about 1 mg of adrenaline.

Adrenaline relaxes the bronchial musculature and has sometimes been injected subcutaneously or intramuscularly in the management of **acute asthmatic attacks.** However, in general, the use of adrenaline in asthma has been superseded by beta$_2$ agonists, such as salbutamol, which can alleviate bronchospasm with fewer effects on the heart. If adrenaline is to be used, the adult dose is 0.3 to 0.5 mL of a 1 in 1000 aqueous solution (300 to 500 micrograms); children have received 0.01 mL/kg (10 micrograms/kg) to a maximum of 0.5 mL (500 micrograms). Adrenaline and racepinefrine (racemic adrenaline) have also been inhaled for bronchodilatation.

Adrenaline is often added to **local anaesthetics** to retard diffusion and limit absorption, to prolong the duration of effect, and to lessen the danger of toxicity. A concentration of 1 in 200 000 (5 micrograms/mL) is usually used; adrenaline should not be added when procedures involve digits, ears, nose, penis, or scrotum because of the risk of ischaemic tissue necrosis. A concentration of up to 1 in 80 000 (12.5 micrograms/mL) may be used in dental preparations where the total dose given is small.

Adrenaline constricts arterioles and capillaries and causes blanching when applied locally to mucous membranes and exposed tissues. It is used as an aqueous solution in strengths up to a 1 in 1000 dilution to check capillary **bleeding**, epistaxis, and bleeding from superficial wounds and abrasions, but it does not stop internal haemorrhage. It is usually applied as a spray or on pledgets of cotton wool or gauze.

In ophthalmology, adrenaline solutions of 0.5%, 1%, or 2% have been used as eye drops to reduce intra-ocular pressure in open-angle **glaucoma** and ocular hypertension

but other drugs are now preferred. An adrenaline borate complex (epinephryl borate) has also been used.

Advanced cardiac life support. Adrenaline has an important role in advanced cardiac life support (see Cardiac Arrest, p. 1268.3) since, through its alpha agonist effects, it causes peripheral vasoconstriction, thus increasing myocardial and cerebral blood flow. This should improve the efficacy of cardiopulmonary resuscitation or basic life support procedures, although there is no clinical study evidence for benefit.[1] Depending on the arrhythmia that has led to cardiac arrest, treatment starts with cardiopulmonary resuscitation and defibrillation. If these measures fail to restore a conventional rhythm, the next step involves the use of adrenaline.

For **adults**, adrenaline is given in a 1-mg dose, ideally intravenously into a central vein. If such venous access is not practicable adrenaline may be given through a peripheral vein followed by a flush of 20 mL or more of sodium chloride injection; however, the response is slower than with central venous injection. This intravenous 1-mg dose may be given about every 3 to 5 minutes[2-5] in further cycles of cardiopulmonary resuscitation and, if necessary, shocks. A higher dose of 5 mg or 100 micrograms/kg has been given but there is insufficient evidence of benefit and this is no longer recommended. The length of time that a resuscitation attempt should continue is a matter of judgement, but in most cases recovery is unlikely to occur after 20 to 30 minutes, although for persistent ventricular fibrillation or tachycardia, or where the cause is hypothermia or drug intoxication, a longer attempt is reasonable.

The initial dose of 1 mg is reported to be based on the dose that was given by intracardiac injection, so it would be expected that a higher dose would be required for intravenous use. Although myocardial and cerebral perfusion are increased more with higher doses, a meta-analysis[6] of studies in adults found no evidence that this gave any survival benefit.

The intravenous dose for **children** is 10 micrograms/kg.[3-5] Higher doses of 100 or 200 micrograms/kg have been used for the second and subsequent doses; however, as with adults, the use of the higher dose is not routinely recommended and both retrospective[7] and prospective[8] studies have found no improvement in outcome.

The intraosseous route is a practicable alternative to intravenous injection for adults as well as for children; doses are identical to those given intravenously.[3-5] Alternatively, adrenaline can be given to children through the endotracheal tube that will have been inserted, but only if the intravenous or intraosseous route is unavailable. Doses of 100 micrograms/kg have been suggested.[3,4] The adrenaline solution should be diluted and administered deeply using a catheter; several rapid ventilations or inflations should follow. It is recognised that the endotracheal route is imperfect[2-4] and some workers consider it to be ineffective.[9]

Although covering a somewhat different clinical situation some guidelines also include resuscitation of newborn infants (during the first few hours after birth).[2-5] Adrenaline may be used when the heart rate remains below 60 beats/minute despite adequate ventilation and chest compression. The dose of adrenaline is 10 to 30 micrograms/kg given intravenously (generally into the umbilical vein) or by intraosseous injection. If neither of these routes are available, it may be given via the endotracheal tube; standard doses are probably ineffective[10] and doses of up to 100 micrograms/kg may be required, although there is little evidence to support this.[2-4]

1. Morley P. Vasopressin or epinephrine: which initial vasopressor for cardiac arrests? *Lancet* 2001; 358: 85–6.
2. The International Liaison Committee on Resuscitation (ILCOR). 2010 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation* 2010; 122 (suppl 2): S249–S638. Also available at: http://circ.ahajournals.org/content/vol122/16_suppl_2/ (accessed 21/01/11) Also published in: *Resuscitation* 2010; 81 (suppl 1): e1–e332. Also available at: http://www.resuscitationjournal.com/issues?issue_key=S0300-9572%2810%29X0010-7 (accessed 21/01/11)
3. The American Heart Association. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010; 122 (suppl 3): S639–S946. Also available at: http://circ.ahajournals.org/content/vol122/18_suppl_3/ (accessed 21/01/11)
4. European Resuscitation Council. European Resuscitation Council guidelines for resuscitation 2010. *Resuscitation* 2010; 81: 1219–1451. Also available at: http://www.cprguidelines.eu/2010 (accessed 07/02/11)
5. Resuscitation Council (UK). 2010 Resuscitation Guidelines. Available at: http://www.resus.org.uk/pages/GL2010.pdf (accessed 21/01/11)
6. Vandycke C, Martens P. High dose versus standard dose epinephrine in cardiac arrest — a meta-analysis. *Resuscitation* 2000; 45: 161–6.
7. Carpenter TC, Stenmark KR. High-dose epinephrine is not superior to standard-dose epinephrine in pediatric in-hospital cardiopulmonary arrest. *Pediatrics* 1997; 99: 403–8.
8. Perondi MBM, *et al.* A comparison of high-dose and standard-dose epinephrine in children with cardiac arrest. *N Engl J Med* 2004; 350: 1722–30.
9. McCrirrick A, Monk CR. Comparison of i.v. and intra-tracheal administration of adrenaline. *Br J Anaesth* 1994; 72: 529–32.
10. Barber CA, Wyckoff MH. Use and efficacy of endotracheal versus intravenous epinephrine during neonatal cardiopulmonary resuscitation in the delivery room. *Pediatrics* 2006; 118: 1028–34.

Anaphylaxis and anaphylactic shock. Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction, characterised by the rapid onset of respiratory and/or circulatory problems, and usually associated with skin and mucosal changes.[1-8] It occurs when exposure to a trigger causes either an allergic reaction, most commonly involving IgE-mediated activation of basophils and mast cells, or a non-allergic (previously termed 'anaphylactoid') reaction, where the trigger has a direct action on the basophils and mast cells. In both cases this leads to the systemic release of inflammatory mediators.[2,4-10] The two forms of resulting reaction may be equally severe, and treatment is the same regardless of pathophysiology.

Many trigger substances may cause anaphylaxis, but those most commonly implicated are foods, drugs, and insect venom.[1-4,6-8,11] In a minority of cases, the cause is idiopathic, unidentifiable, or requires a co-trigger such as exercise. The signs and symptoms of anaphylaxis may closely resemble other syndromes such as hereditary angioedema, and the history is important in aiding diagnosis: usually an attack closely follows exposure to a trigger,[1,6-8,11] although in rare cases reactions may be delayed.[2,4] Common early signs and symptoms of anaphylaxis are skin and mucosal changes such as erythema, urticaria, and angioedema (seen in about 80% of reactions), rhinitis, conjunctivitis, anxiety, confusion, and gastrointestinal disturbances such as abdominal pain, vomiting, and diarrhoea.[1-3,6,8,9,11] Stridor and hoarseness of voice indicate airway obstruction, which is caused by pharyngeal and laryngeal oedema. Bronchoconstriction may occur, and can be particularly severe and difficult to treat in asthmatics. Hypotension and shock may develop from myocardial depression, vasodilatation, and capillary leak. Ultimately, cardiovascular and respiratory collapse may lead to death, with a case fatality of about 0.65 to 2%.[8] Risk of death is increased in asthma, particularly if poorly controlled.[1,5,7,8] Other (especially cardiovascular) diseases, and certain medications such as ACE inhibitors, may also increase severity.[4,5,7]

Anaphylaxis is a medical emergency and prompt treatment is vital. *Adrenaline* is the most important drug used in anaphylaxis. It acts on alpha-receptors to reverse peripheral vasodilatation and reduce oedema, and on beta-receptors to dilate the airways, increase force of myocardial contraction, suppress leukotriene and histamine release, and inhibit mast cells.[1,2,8,12] Early use is essential.[1,2,5,9,11,12] Delay has been associated with biphasic reactions and fatality,[4-6,8,9,12] and some have suggested that if the diagnosis or severity of a reaction is in doubt, it may be preferable to err on the side of caution and inject adrenaline rather than waiting too long.[8,12] There are no absolute contra-indications to its use. Adverse effects are rare and usually associated with the intravenous route:[1,2,6,10,11] although adrenaline may rarely cause cardiac ischaemia and arrhythmias, these may also be caused by anaphylaxis itself.[1,6,13]

In early anaphylaxis, adrenaline is given by *intramuscular* injection into the mid-point of the anterolateral thigh.[1-6,8,10-12] The subcutaneous and inhaled routes have also been used, but are not generally recommended due to their unfavourable pharmacokinetics.[1,2] Novel routes of administration, such as the sublingual route, are also under investigation.[4,6,8] Absorption of adrenaline from the intramuscular route is rapid, occurring within about 8 minutes. Pre-filled auto-injectors for intramuscular use may be given to those at high risk of developing anaphylactic shock, allowing patients to self-administer initial emergency treatment; however, they should still seek medical assistance as additional treatment may be required.

The dose of adrenaline for intramuscular injection is usually 300 to 500 micrograms as 0.3 to 0.5 mL of a 1 in 1000 (1 mg/mL) solution; this may be repeated at 5 to 15 minute intervals until improvement occurs.

Various intramuscular adrenaline dosage regimens have been suggested for children. A dose of 10 micrograms/kg, or the following age-specific intramuscular doses, given as a 1 in 1000 (1 mg/mL) solution, have been used:

- under 6 months: 50 micrograms (0.05 mL)
- 6 months to 6 years: 120 micrograms (0.12 mL)
- 6 to 12 years: 250 micrograms (0.25 mL)

However, to simplify dosing, particularly where auto-injectors are used, the UK Resuscitation Council[1] now recommends an intramuscular dose of 150 micrograms (0.15 mL) for children aged 6 years and younger (including those under 6 months) and 300 micrograms (0.3 mL) for those aged over 6 years; children aged over 12 years may be given 300 or 500 micrograms depending on body size and pubertal status. This may represent a relative overdose in children aged under 6 months but this may be considered acceptable if it allows an auto-injector to be used.

As anaphylaxis progresses the intravascular volume becomes depleted, leading to shock. At this stage it is probably necessary to give adrenaline *intravenously*, since absorption from other routes will be compromised; however, this route is hazardous and should only be used in life-threatening situations, and by those experienced in its use. The general principles used in the management of hypovolaemia and hypotension in shock are outlined on p. 1279.3.

A dilute solution of 1 in 10 000 (100 microgram/mL) is used intravenously with cardiac monitoring, although this may be further diluted to 1 in 100 000 (10 micrograms/mL) to allow for greater accuracy in titrating very small doses. The UK Resuscitation Council[1] recommends a slow intravenous injection of 50 micrograms (0.5 mL of the 1 in 10 000 solution), repeated according to response. Higher doses of 100 to 200 micrograms have been used in patients under anaesthesia, for whom intensive monitoring and life support are immediately available.[3,9,14] If repeated injections are required, an infusion may be started at a rate of 1 to 4 micrograms/minute.[1,3,9,10] If intravenous access is delayed or impossible, adrenaline and fluids may be given via the intra-osseous route.[1,8,11]

In children, intravenous therapy should only be used in specialist paediatric settings. The *BNFC* recommends slow intravenous injections of the 1 in 10 000 (100 micrograms/mL) solution in single doses not exceeding 50 micrograms, although some children may require as little as 1 microgram/kg (0.01 mL/kg). Again, if multiple doses are required, an intravenous infusion should be considered.

Ancillary interventions aid management,[1-6,8,9,11] although they should not delay use of adrenaline. Where possible, the likely allergen should be removed, for example, by scraping away an embedded insect sting or stopping a drug or blood transfusion. High flow oxygen should be given as soon as available, and the airways secured if necessary. Intravenous fluids should be given rapidly to restore volume. Cardiac arrest should be managed using a standard protocol (see Cardiac Arrest, p. 1268.3), including appropriate doses of adrenaline as required.[2,3,8,9,11]

The use of *antihistamines* in the management of anaphylaxis has been a matter of some debate.[15] During acute treatment they are unlikely to be life-saving, and should never be used alone.[1,5,6,8,11,15] However, some advocate an intramuscular or slow intravenous injection of an H_1-antagonist such as chlorphenamine, given after adrenaline and repeated over the next 24 to 48 hours, to counter histamine-mediated vasodilatation and bronchoconstriction[1,11] and relieve angioedema, pruritus, and urticaria.[15] Addition of intravenous H_2-antagonists such as ranitidine has also been suggested.[2,3,15]

Intravenous *corticosteroids* have little place in the immediate management of anaphylaxis since their beneficial effects are delayed for several hours. However, in severely ill patients early use of intramuscular or slow intravenous hydrocortisone may avert late sequelae[2,5,9,11] and help prevent or shorten protracted reactions,[1,11] although it is doubtful whether it prevents biphasic attacks.[9,11] Corticosteroids may be particularly useful in patients with an asthmatic component.[1,2,5,11]

Bronchodilators such as salbutamol, ipratropium, aminophylline, and magnesium sulfate, given by nebulisation or, if necessary, intravenously, are useful in those with bronchospasm.[1,5,6,8,9]

Some patients are refractory to adrenaline, especially those taking beta blockers, and *alternative vasopressors and inotropes* such as glucagon, noradrenaline, metaraminol, salbutamol, terlipressin, and vasopressin have been used successfully, while *atropine* may be useful in those who develop bradycardia.[1-3,5,9,10,14,16,17]

Biphasic reactions occur in up to 20% of cases and it is difficult to identify those at risk, so patients should be observed for at least 4 to 6 hours after an attack.[1,2,8,11] On discharge, a 3-day course of oral antihistamine and corticosteroid therapy may be considered for suppression of urticaria and prevention of further attacks.[1,11] Measuring mast cell tryptase or histamine concentrations in plasma may help confirm the diagnosis,[1,4-9,11] although such tests have suboptimal specificity and sensitivity. The risk of recurrence is substantial,[1] and the identification and avoidance of triggers is paramount in the prevention of further attacks; other measures include allergen immunotherapy (see p. 2435.1), particularly in those who have reacted to bee or wasp venom.[4-6,8] Stopping beta blockers in those at risk of anaphylaxis should be considered.[1,6]

1. Working Group of the Resuscitation Council (UK). Emergency treatment of anaphylactic reactions: guidelines for healthcare providers (revised January 2008). Available at: http://www.resus.org.uk/pages/reaction.pdf (accessed 22/03/10)
2. Soar J, *et al.* European Resuscitation Council. European Resuscitation Council guidelines for resuscitation 2005. Section 7. Cardiac arrest in special circumstances. *Resuscitation* 2005; 67 (suppl 1): S135–S170. Also available at: https://www.erc.edu/index.php/docLibrary/en/viewDoc/down%3D8/ (accessed 22/03/10)
3. The American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 10.6: anaphylaxis. *Circulation* 2005; 112: (suppl 1):

IV143–IV145. Available at: http://circ.ahajournals.org/cgi/content/full/112/24_suppl/IV-143 (accessed 22/03/10)
4. Simons FER. Anaphylaxis: recent advances in assessment and treatment. *J Allergy Clin Immunol* 2009; 124: 625–36.
5. El-Shahawany T, *et al.* Clinical immunology review series: an approach to the patient with anaphylaxis. *Clin Exp Immunol* 2008; 153: 1–9.
6. Simons FER. Anaphylaxis. *J Allergy Clin Immunol* 2010; 125 (suppl 2): S161–S181.
7. Simons FER, *et al.* Risk assessment in anaphylaxis: current and future approaches. *J Allergy Clin Immunol* 2007; 120 (suppl): S2–S24.
8. Muraro A, *et al.* EAACI Task Force on Anaphylaxis in Children. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. *Allergy* 2007; 62: 857–71.
9. Dewachter P, *et al.* Anaphylaxis and anesthesia: controversies and new insights. *Anesthesiology* 2009; 111: 1141–50.
10. Kemp SF, *et al.* World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. *Allergy* 2008; 63: 1061–70.
11. Tse Y, Ryland G. Emergency management of anaphylaxis in children and young people: new guidance from the Resuscitation Council (UK). *Arch Dis Child Educ Pract Ed* 2009; 94: 97–101.
12. Sicherer SH, Simons FE. Section on Allergy and Immunology. American Academy of Pediatrics. Self-injectable epinephrine for first-aid management of anaphylaxis. *Pediatrics* 2007; 119: 638–46.
13. Simons FER. Emergency treatment of anaphylaxis. *BMJ* 2008; 336: 1141–2.
14. Hussain AM, *et al.* Vasopressin for the management of catecholamine-resistant anaphylactic shock. *Singapore Med J* 2008; 49: e225–e228.
15. Andreae DA, Andreae MH. Should antihistamines be used to treat anaphylaxis? *BMJ* 2009; 339: 290–1.
16. Schummer C, *et al.* The pivotal role of vasopressin in refractory anaphylactic shock. *Anesth Analg* 2008; 107: 620–4.
17. Rocq N, *et al.* Successful use of terlipressin in post-cardiac arrest resuscitation after an epinephrine-resistant anaphylactic shock to suxamethonium. *Anesthesiology* 2007; 107: 166–7.

Diagnosis and testing. Long-QT syndrome is a congenital channelopathy that can cause potentially lethal arrhythmias in individuals with otherwise structurally normal hearts. At rest, the ECGs of such individuals may be normal or equivocal, and catecholamine provocation testing has been used to unmask concealed abnormalities. A bolus infusion (Shimizu protocol) or escalating infusion (Mayo protocol) of adrenaline will paradoxically lengthen the absolute QT interval in a high proportion of individuals with long-QT syndrome, and may also permit identification of specific genetic subtypes.[1-3]

1. Shimizu W, *et al.* Diagnostic value of epinephrine test for genotyping LQT1, LQT2, and LQT3 forms of congenital long QT syndrome. *Heart Rhythm* 2004; 1: 276–83.
2. Vyas H, *et al.* Epinephrine QT stress testing in the evaluation of congenital long-QT syndrome: diagnostic accuracy of the paradoxical QT response. *Circulation* 2006; 113: 1385–92.
3. Vyas H, Ackerman MJ. Epinephrine QT stress testing in congenital long QT syndrome. *J Electrocardiol* 2006; 39 (4 suppl): S107–S113.

Haemorrhage. Adrenaline has a long history of topical use to check minor bleeding. It constricts arterioles and capillaries and causes blanching. Local injection of adrenaline under endoscopic control is highly effective in controlling bleeding peptic ulcers (p. 1816.2), and is more effective if combined with other endoscopic therapies.[1] Nebulised adrenaline has been reported[2] to successfully control oropharyngeal haemorrhage.

1. Vergara M, *et al.* Epinephrine injection versus epinephrine injection and a second endoscopic method in high risk bleeding ulcers. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 28/05/10).
2. Rowlands RG, *et al.* Novel use of nebulised adrenaline in the treatment of secondary oropharyngeal haemorrhage. *J Laryngol Otol* 2002; 116: 123–4.

Priapism. Alpha agonists such as adrenaline may be effective in the treatment of priapism (see under Metaraminol, p. 1430.2). Low doses of dilute adrenaline solution have been given by intracavernosal injection in priapism caused by alprostadil (see p. 2353.2). Aspiration of blood followed by intracavernosal irrigation with a dilute adrenaline solution was also reported to be effective treatment for priapism in a group of young patients (age range, 3.9 to 18.3 years) with sickle-cell disease.[1]

1. Mantadakis E, *et al.* Outpatient penile aspiration and epinephrine irrigation for young patients with sickle cell anemia and prolonged priapism. *Blood* 2000; 95: 78–82.

Respiratory-tract disorders. Nebulised adrenaline may be used to reverse airway obstruction in inflammatory disorders such as croup since it relieves inflammation and also causes bronchodilatation. Although some studies in acute viral bronchiolitis (see Respiratory Syncytial Virus Infection, p. 961.3) have shown improvement in clinical scores,[1,2] randomised studies have failed to find any difference in outcome between infants treated with adrenaline and either salbutamol[3] or placebo.[4] A systematic review[5] found insufficient evidence to support the use of adrenaline in inpatients, although there was a suggestion that it might be of short-term benefit in outpatients.

However, the *BNFC* states that for severe croup not effectively controlled with corticosteroids, nebulised adrenaline solution 1 in 1000 may be given with close clinical monitoring in a dose of 400 micrograms/kg (up to a maximum of 5 mg) repeated after 30 minutes if necessary. The effects of nebulised adrenaline are expected to last 2 to 3 hours.

There has also been a report[6] of the successful use of nebulised adrenaline in a 15-month-old child with airway inflammation secondary to the ingestion of sodium hypochlorite.

1. Reijonen T, *et al.* The clinical efficacy of nebulized racemic epinephrine and albuterol in acute bronchiolitis. *Arch Pediatr Adolesc Med* 1995; 149: 686–92.
2. Menon K, *et al.* A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. *J Pediatr* 1995; 126: 1004–7.
3. Patel H, *et al.* A randomized, controlled trial of the effectiveness of nebulized therapy with epinephrine compared with albuterol and saline in infants hospitalized for acute viral bronchiolitis. *J Pediatr* 2002; 141: 818–24.
4. Wainwright C, *et al.* A multicenter, randomized, double-blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis. *N Engl J Med* 2003; 349: 27–35.
5. Hartling L, *et al.* Epinephrine for bronchiolitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 07/10/05).
6. Ziegler D, Bent G. Caustic-induced upper airway obstruction responsiveness to nebulized adrenaline. *Pediatrics* 2001; 107: 807–8.

Adverse Effects

Adrenaline is a potent sympathomimetic and may show the adverse effects typical of both alpha- and beta-adrenoceptor stimulation (see p. 1508.2). Adverse effects such as anxiety, dyspnoea, hyperglycaemia, restlessness, palpitations, tachycardia (sometimes with anginal pain), tremors, sweating, hypersalivation, weakness, dizziness, headache, and coldness of extremities may occur even with low doses. Since adrenaline does not readily cross the blood-brain barrier, its central effects may be largely a somatic response to its peripheral effects. Overdosage may cause cardiac arrhythmias and a sharp rise in blood pressure (sometimes leading to cerebral haemorrhage and pulmonary oedema); these effects may occur at normal dosage in susceptible subjects.

Adrenaline is a potent vasoconstrictor and gangrene may occur if adrenaline-containing local anaesthetic solutions are infiltrated into digits. Extravasation of parenteral adrenaline also results in intense vasoconstriction, leading to tissue necrosis and sloughing. Topical application of adrenaline to mucosal surfaces similarly causes vasoconstriction, which may induce hypoxia leading to compensatory rebound congestion of the mucosa. Inhalation of adrenaline has been associated with epigastric pain, which has been attributed to ingestion of some of the inhalation; it can be minimised by rinsing the mouth and throat with water after inhaling.

Adrenaline eye drops may produce severe smarting, blurred vision, and photophobia on instillation; they may also leave melanin-like deposits in the cornea and conjunctiva, and this has led to obstruction of the nasolachrymal ducts. Repeated use may cause oedema, hyperaemia, and inflammation of the eyes.

Effects on the eyes. In addition to the possibility of pigment deposition and local pain (see above) adrenaline eye drops have been associated with maculopathy, particularly in aphakic eyes (those devoid of a lens).[1] In one report,[2] maculopathy was noted in 15 patients over a period of 4 years; the patients were using adrenaline eye drops containing the hydrochloride, acid tartrate, or adrenaline borate complex (epinephryl borate). Blurring and distortion of vision were followed by decreased visual acuity, and by the appearance of oedema and sometimes haemorrhage in the macular region. A few patients developed cysts near the fovea. These effects appeared within a few weeks of, or several months after, starting therapy and were usually reversible. All except 1 of the patients were aphakic, and retrospective studies have suggested that the incidence of this complication may be up to 30% in aphakic patients.[1,2]

1. Classé JG. Epinephrine maculopathy. *J Am Optom Assoc* 1980; 51: 1091–3.
2. Kolker AE, Becker B. Epinephrine maculopathy. *Arch Ophthalmol* 1968; 79: 552–62.

Overdosage. Solutions of racepinefrine for nebulisation have inadvertently been given intravenously, resulting in severe overdosage of adrenaline. A 13-month-old infant[1] was given the equivalent of about 327 micrograms/kg of laevo-adrenaline. Marked pallor, pulselessness, and profound bradycardia developed, but the child responded to cardiopulmonary resuscitation and was subsequently discharged with no evidence of long-term sequelae. However, a 2-year-old child[2] given the equivalent of about 1.8 mg/kg developed hypertension, tachycardia, and pulmonary oedema, followed by hypotension and subsequent renal failure, requiring transplantation. Subcutaneous overdosage with laevo-adrenaline in another child[3] led to arrhythmias and myocardial ischaemia, and there has also been a report[4] of myocardial infarction and acute renal failure in an adult after injection of the solution from an adrenaline inhaler.

1. Kurachek SC, Rockoff MA. Inadvertent intravenous administration of racemic epinephrine. *JAMA* 1985; 253: 1441–2.
2. Dybvik T, *et al.* Accidental intravenous administration of 50 mg of racemic adrenaline in a 2-year-old boy. *Eur J Anaesthesiol* 1995; 12: 181–3.
3. Davis CO, Wax PM. Prehospital epinephrine overdose in a child resulting in ventricular dysrhythmias and myocardial ischemia. *Pediatr Emerg Care* 1999; 15: 116–18.
4. Woodard ML, Brent LD. Acute renal failure, anterior myocardial infarction, and atrial fibrillation complicating epinephrine abuse. *Pharmacotherapy* 1998; 18: 656–8.

Treatment of Adverse Effects

As for Sympathomimetics, p. 1508.3. Adrenaline has a short duration of activity due to inactivation in the body and treatment of severe toxic reactions in hypersensitive patients or after overdose is mainly supportive.

Digital injection. Inadvertent digital injection of adrenaline from autoinjector devices may cause acute ischaemia. Phentolamine injection has been successfully used to reverse the vasoconstriction,[1] and there has also been a report[2] of the use of iloprost infusion followed by a stellate ganglion block.

1. Velissariou I, *et al.* Management of adrenaline (epinephrine) induced digital ischaemia in children after accidental injection from an EpiPen. *Emerg Med J* 2004; 21: 387–8.
2. Barkhordarian AR, *et al.* Accidental digital injection of adrenaline from an autoinjector device. *Br J Dermatol* 2000; 143: 1359.

Precautions

As for Sympathomimetics, p. 1508.3. Adrenaline is frequently used in emergency situations and any contra-indications are therefore relative.

Adrenaline may delay the second stage of labour and some licensed product information recommends that it should not be used during this time.

Adrenaline eye drops are contra-indicated in angle-closure glaucoma unless an iridectomy has been carried out.

Contact lenses. Adrenochrome staining of soft-contact lenses of patients using adrenaline eye drops has been reported.[1] Melanin deposits may also become locked into the lens; such deposits may be broken down by hydrogen peroxide. The prodrug, dipivefrine hydrochloride (p. 2495.1) has been used without staining soft lenses.

1. Ingram DV. Spoiled soft contact lenses. *BMJ* 1986; 292: 1619.

Infection. An open study[1] comparing adrenaline with dopamine for cardiovascular support in 23 patients critically ill with severe sepsis or malaria suggested that use of adrenaline was limited by the development of lactic acidosis. However, it has been pointed out[2] that 20 of the patients had responded to fluids, a situation in which the use of inotropic or vasopressor support was considered questionable, and that adrenaline has been widely used in the treatment of septic shock. A further controlled study[3] found that although adrenaline led to higher lactate concentrations than noradrenaline with dobutamine, the effect was transient. Nevertheless, it has been recommended[4] that adrenaline should only be used in septic shock if other treatments are ineffective.

1. Day NPJ, *et al.* The effects of dopamine and adrenaline infusions on acid-base balance and systemic haemodynamics in severe infection. *Lancet* 1996; 348: 219–23. Correction. *ibid.*; 902.
2. Barry B, Bodenham A. Effects of dopamine and adrenaline infusions in severe infection. *Lancet* 1996; 348: 1099–1100.
3. Levy B, *et al.* Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. *Intensive Care Med* 1997; 23: 282–7.
4. Hollenberg SM, *et al.* American College of Critical Care Medicine. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. *Crit Care Med* 2004; 32: 1928–48.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies adrenaline as not porphyrinogenic: it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Sympathomimetics, p. 1508.3; adrenaline has direct alpha- and beta-agonist actions and its interactions are complex and may be hazardous. Particular caution is needed if adrenaline is given to patients taking beta blockers since severe hypertension may result; patients taking beta blockers may also have an impaired response to adrenaline if it is needed for anaphylaxis.

Local anaesthetics. It is common practice to give adrenaline with a local anaesthetic to produce vasoconstriction; the lowest effective concentration of adrenaline should be used. However, use with *cocaine* may increase the risk of

cardiac arrhythmias and particular caution is required. See p. 1990.3 for a report of severe complications with use of such a combination in otolaryngology.

Pharmacokinetics

As a result of enzymatic degradation in the gut and first-pass metabolism in the liver, adrenaline is almost totally inactive when given orally. Systemic absorption can occur after topical application for example of eye drops. Adrenaline acts rapidly after intramuscular and subcutaneous injection; the latter route is, however, sometimes considered to be slower and therefore less reliable for emergency use. Although absorption is slowed by local vasoconstriction it can be hastened by massaging the injection site.

Most adrenaline that is either injected into the body or released into the circulation from the adrenal medulla, is very rapidly inactivated by processes that include uptake into adrenergic neurones, diffusion, and enzymatic degradation in the liver and body tissues. The half-life of circulating adrenaline is only about 1 minute. One of the enzymes responsible for the chemical inactivation of adrenaline is catechol-*O*-methyltransferase (COMT), the other is monoamine oxidase (MAO). In general, adrenaline is methylated to metanephrine by COMT followed by oxidative deamination by MAO and eventual conversion to 4-hydroxy-3-methoxymandelic acid (formerly termed vanillylmandelic acid; VMA), or oxidatively deaminated by MAO and converted to 3,4-dihydroxymandelic acid which, in turn, is methylated by COMT, once again to 4-hydroxy-3-methoxymandelic acid; the metabolites are excreted in the urine mainly as their glucuronide and ethereal sulfate conjugates.

The ability of COMT to effect introduction of a methyl group is an important step in the chemical inactivation of adrenaline and similar catecholamines (in particular, noradrenaline). It means that the termination of the pharmacological response of catecholamines is not simply dependent upon MAO. In its role of neurotransmitter intraneuronal catecholamine (mainly noradrenaline) is, however, enzymatically regulated by MAO.

Adrenaline crosses the placenta to enter fetal circulation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: EpiPen; *Austral.*: Anapen; EpiPen; *Austria*: Anapen; EpiPen; Suprarenin; *Belg.*: EpiPen; *Braz.*: Drenalin; Efrinalin; Epifrin; *Canad.*: Anapen; Epi EZ†; Epifrin†; EpiPen; Twinject; *Chile*: Adreject; *Cz.*: Anapen; EpiPen; Twinject; *Denm.*: EpiPen; Jext; *Fin.*: EpiPen; Jext; *Fr.*: Anahelp†; Anapen; *Ger.*: Anapen; Fastjekt; InfectoKrupp Suprarenin; *Gr.*: Anapen; Epifrin; EpiPen; *Hung.*: Anapen; EpiPen; Tonogen; *India*: Adrena; Naline; *Irl.*: Anapen; EpiPen†; Jext; *Israel*: EpiPen; *Ital.*: Fastjekt; *Malaysia*: EpiPen†; *Mex.*: Pinadrina†; *Neth.*: Anapen; EpiPen; Jext; *Norw.*: EpiPen; Jext; *NZ*: Anapen; EpiPen; *Philipp.*: Adrenin; *Pol.*: Anapen; EpiPen; Fastjekt; *Port.*: Anapen; EpiPen†; Twinject; *S.Afr.*: Adrenotone; Ana-Guard†; EpiPen; Eppy†; Simplene†; *Singapore*: Anapen; EpiPen; *Spain*: Adreject†; Altellus; Epiject†; Jext; *Swed.*: Anapen; EpiPen; Jext; *Switz.*: Anapen; EpiPen; Jext; *Thai.*: EpiPen; *UK*: Anapen; EpiPen; *USA*: Adrenaclick; AsthmaHaler Mist; AsthmaNefrin; Auvi-Q; Epinal†; EpiPen; microNefrin†; Nephron†; Primatene Mist Suspension†; Primatene Mist†; S-2.

Multi-ingredient Preparations. *Arg.*: Asmopul; Yanal; *Austral.*: Rectinol; *Canad.*: Sil Trax Plus†; *Cz.*: Avenoc†; *Fr.*: Avenoc; *Gr.*: Hemorroidal; *Hung.*: Hemorid; *India*: Brovon; *Irl.*: Ganda†; *Spain*: Colirioclina Adren Astr†; Epistaxol; *UK*: Brovon; *USA*: Ana-Kit; Emergen-E.

Used as an adjunct in:. *Arg.*: Caina G; Duracaine; Gobbicaina; Larjancaina; Lidanest; Xylocaina; *Austral.*: Bucanest; Deltazine; Marcain; Nurocain†; Septanest; Xylocaine; *Austria*: Neo-Xylestesin; Scandonest; Septanest; Sopira Citocartin; Ubistesin; Ultracain Dental; Xylanaest; Xylocain; *Belg.*: Citanest; Marcaine; Xylocaine; *Braz.*: Bupiabbott Plus; Bupstesic; Lidocabbott; Marcaina; Neocaina; Novabupi; Xylestesin; Xylocaina; *Canad.*: Astracaine†; Citanest; Marcaine; Octocaine; Scandonest; Sensorcaine; Septanest; Ultracaine D-S; Vivacaine; Xylocaine; Zorcaine; *China*: Primacaine Adrenaline (必兰); Scandonest (斯康杜尼); *Cz.*: Scandonest†; Septanest S; Supracain; Ubistesin; *Denm.*: Carbocain; Dentocaine; Marcain; Scandonest; Septanest; Septocaine; Sopira Citocartin; Ubistesin; Xylocain; Xylocitin; *Fin.*: Dentocaine; Marcain; Septocaine; Ubistesin; Ultracain D-Suprarenin; Xylocain; *Fr.*: Alphacaine; Articadent; Artinibsa; Biodicaine†; Bucanest†; Deltazine; Primacaine; Scandicaine; Septanest; Ubistesin Adrenalinee; Xylocaine; Xylonor; Xylorolland; Ziacaine; *Ger.*: Sopira Citocartin; Ubistesin; Ultracain D-S; Ultracain Suprarenin; Xylocain; Xylocitin; Xylonest; *Gr.*: Artikamine; Ecocain; Lidonet; Lignospan; Marcaine; Optocain; Septanest; Ubistesin; Xylestesin-A; Xylestesin-S Special; Xylocaine; *Hong Kong*: Lidocaton†; Marcain; Ubistesin; Xylestesin-A; Xylocaine; *Hung.*: Ubistesin; Ultracain D-S; *India*: Gesicain; Lignocad; Lignodent; Lignoloc; Lignosafe; Lignox; Lox; Xylocaine; *Indon.*: Extracaine†; Pehacain; *Irl.*: Espestesin; Lignospan; Marcain; Scandonest; Xylocaine; *Israel*: Kamacaine; Lidocadren; Lignospan; Marcaine; Octocaine; Septanest; Ubistesin; *Ital.*: Alfacaina; Bupicain; Bupiforan; Bupisen; Bupisolver; Bupixamol; Carboplyina; Carbosen; Cartidont; Citocartin; Ecocain; Lident Adrenalina; Lident Adrenor; Mepi-Mynol; Mepicain; Mepident; Mepiforan; Mepisolver; Mepivamol; Optocain; Sarticain; Scandonest; Septanest; Ubistesin; Xilo-Mynol; Xylonor; Xyloplyina; *Malaysia*: Denkan; Marcain; *Mex.*: Buvacaina†; Pisacaina†; Unicaine; Xylocaina; *Neth.*: Citocartin; Lignospan; Loncarti; Marcaine; Scandicaine†; Septanest; Ubistesin; Ultracain D-S; Xylocaine; *Norw.*: Marcain; Septocaine; Xylocain; *NZ*: Marcain; Septanest; Topicaine; Ubistesin; Xylestesin-A; Xylocaine; *Philipp.*: Dentocaine; Epicaine; *Pol.*: Marcaine; *Port.*: Alphacaine†; Artinibsa; Artinostrum; Lidonostrum; Lincaina; Meganest; Octocaine; Scandinibsa; Septanest; Ubistesin; Xilonibsa; *Rus.*: Alphacaine (Альфакаин); Artifrin (Артифрин); Brilocaine (Брилокаин); Citocartin (Цитокартин); Primacaine Adrenaline (Примакаин С Адреналином); Septanest (Септанест); Ubistesin (Убистезин); Ultracain (Ультракаин); *S.Afr.*: Macaine; Scandonest; Xylotox; *Singapore*: Ubistesin; Xylestesin-A; Xylocaine; *Spain*: Anestesia Topi Braun C/A†; Artinibsa; Inibsacain; Meganest; Octocaine; Scandinibsa; Septanest; Ubistesin; Ultracain; Xilonibsa; Xylonor Especial; *Swed.*: Carbocain; Marcain; Septocaine; Ubistesin; Xylocain; *Switz.*: Alphacaine; Carbostesin; Rapidocaine; Rudocain; Scandonest; Septanest; Ubistesin; Ultracaine D-S; Xylocain; Xylonest; *Thai.*: Drocanil-A; Lidocation; Medicaine; Xylocaine; *Turk.*: Jetokain; Jetosel; Locanest-A; Ultracain; *UAE*: Ecocain; *UK*: Septanest; Xylocaine; *Ukr.*: Artifrin (Артифрин); Ultracain D-S (Ультракаин Д-С); *USA*: Citanest; Marcaine; Octocaine; Orabloc; Sensorcaine; Septocaine; Xylocaine.

Homoeopathic Preparations. *Canad.*: Avenoc†; Breathe More; *Fr.*: Diabene; L 25; L 28; Santaherba; Tarentula Complexe No 71; Vespa Complexe No 46†; *Port.*: Avenoc†; *USA*: Estrex.

Pharmacopoeial Preparations

BP 2014: Adrenaline and Cocaine Intranasal Solution; Adrenaline Eye Drops; Adrenaline Injection; Adrenaline Solution; Bupivacaine and Adrenaline Injection; Dilute Adrenaline Injection 1 in 10,000; Lidocaine and Adrenaline Injection;

USP 36: Articaine Hydrochloride and Epinephrine Injection; Cocaine and Tetracaine Hydrochlorides and Epinephrine Topical Solution; Epinephrine Bitartrate for Ophthalmic Solution; Epinephrine Bitartrate Inhalation Aerosol; Epinephrine Bitartrate Ophthalmic Solution; Epinephrine Inhalation Aerosol; Epinephrine Inhalation Solution; Epinephrine Injection; Epinephrine Nasal Solution; Epinephrine Ophthalmic Solution; Epinephryl Borate Ophthalmic Solution; Lidocaine Hydrochloride and Epinephrine Injection; Prilocaine and Epinephrine Injection; Procaine Hydrochloride and Epinephrine Injection; Racepinephrine Inhalation Solution.

Ajmaline

Aimalline; Ajmalin; Ajmalina; Ajmalinum; Rauwolfina; Rauwolfine; Аймалин.

(17*R*,21*R*)-Ajmalan-17,21-diol.

$C_{20}H_{26}N_2O_2$=326.4.

CAS — 4360-12-7.

ATC — C01BA05.

ATC Vet — QC01BA05.

UNII — 1PON08459R.

Pharmacopoeias. In *Jpn*.

Uses and Administration

Ajmaline is an alkaloid obtained from the root of *Rauwolfia serpentina* (Apocynaceae). It is a class Ia antiarrhythmic (p. 1243.1) used in the treatment of supraventricular and ventricular arrhythmias (p. 1266.1) and for differential diagnosis of Wolff-Parkinson-White syndrome. Ajmaline is given by intravenous injection in a usual dose of 50 mg over at least 5 minutes. It may also be given by intravenous infusion, and has been given orally and by intramuscular injection.

Ajmaline has also been used as the hydrochloride, monoethanolate, and phenobarbital salts.

Brugada syndrome. Brugada syndrome is a congenital disorder affecting myocardial sodium channels and may be associated with sudden cardiac death. Class 1a antiarrhythmics such as ajmaline block the sodium channel and may have a role in the diagnosis of Brugada syndrome, although they are not suitable for treatment.

References.
1. Rolf S, *et al.* The ajmaline challenge in Brugada syndrome: diagnostic impact, safety, and recommended protocol. *Eur Heart J* 2003; **24**: 1104–12.
2. Veltmann C, *et al.* Response to intravenous ajmaline: a retrospective analysis of 677 ajmaline challenges. *Europace* 2009; **11**: 1345–52.

Adverse Effects

Ajmaline depresses the conductivity of the heart, and at high doses can cause heart block. At very high doses it may produce a negative inotropic effect. High doses may cause cardiac arrhythmias, coma, and death. Arrhythmias have also been reported after usual intravenous doses (see below). Adverse neurological effects have been reported including eye twitching, convulsions, and respiratory depression. Hepatotoxicity and agranulocytosis may occasionally occur.

Effects on the heart. Electrophysiologic study[1] in 1955 patients revealed that ajmaline 1 mg/kg given intravenously could induce arrhythmias; 63 developed a supraventricular arrhythmia and 7 an atrioventricular reentrant tachycardia. Ventricular tachycardia[2,3] and torsade de pointes[4] have been reported during diagnostic use.

1. Brembilla-Perrot B, Terrier de la Chaise A. Provocation of supraventricular tachycardias by an intravenous class I antiarrhythmic drug. *Int J Cardiol* 1992; **34**: 189–98.
2. Rolf S, *et al.* The ajmaline challenge in Brugada syndrome: diagnostic impact, safety, and recommended protocol. *Eur Heart J* 2003; **24**: 1104–12.
3. Pinar Bermúdez R, *et al.* Spontaneous sustained monomorphic ventricular tachycardia after administration of ajmaline in a patient with Brugada syndrome. *Pacing Clin Electrophysiol* 2000; **23**: 407–9.
4. Haverkamp W, *et al.* Torsade de pointes induced by ajmaline. *Z Kardiol* 2001; **90**: 586–90.

Precautions

As for Quinidine, p. 1482.3.

Interactions

Antiarrhythmics. Oral use of *quinidine* with ajmaline increased plasma concentrations of ajmaline considerably in 4 healthy subjects; the elimination half-life of ajmaline was increased about twofold.[1] The pharmacokinetics of quinidine did not seem to be affected by ajmaline.

1. Hori R, *et al.* Quinidine-induced rise in ajmaline plasma concentration. *J Pharm Pharmacol* 1984; **36**: 202–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Gilurytmal; *Ger.*: Gilurytmal; *Gr.*: Gilurytmal.

Alacepril *(rINN)*

Alacépril; Alaceprilum; DU-1219; Алацеприл.

N-[1-[(*S*)-3-Mercapto-2-methylpropionyl]-L-prolyl]-3-phenyl-L-alanine acetate.

$C_{20}H_{26}N_2O_5S$=406.5.

CAS — 74258-86-9.

UNII — X39TL7JDPF.

Pharmacopoeias. In *Jpn*.

Profile

Alacepril is an ACE inhibitor (p. 1282.2) used in the treatment of hypertension (p. 1251.1). It is converted to captopril and desacetylalacepril (DU-1227) in the body after oral doses. It is given orally in a usual dose of 25 to 75 mg daily, as a single dose or in two divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Cetapril.

Aliskiren Fumarate *(BANM, USAN, rINNM)*

Aliskiren Hemifumarate; Aliskirène, Fumarate de; Aliskireni Fumaras; CGP-60536B; Fumarato de aliskireno; SPP-100 (aliskiren or aliskiren fumarate); Алискирена Фумарат.

Bis(2*S*,4*S*,5*S*,7*S*)-5-amino-*N*-(2-carbamoyl-2-methylpropyl)-4-hydroxy-2-isopropyl-7-[4-methoxy-3-(3-methoxypropoxy) benzyl]-8-methylnonanamide fumarate (2:1).

$(C_{30}H_{53}N_3O_6)_2.C_4H_4O_4$=1219.6

CAS — 173334-57-1 (aliskiren); 173334-58-2 (aliskiren fumarate).

ATC — C09XA02.

ATC Vet — QC09XA02.

UNII — C8A0P8G029.

Uses and Administration

Aliskiren is an orally active renin inhibitor used in the management of hypertension (p. 1251.1); it prevents the conversion of angiotensinogen into angiotensin I and therefore inhibits the production of angiotensin II and aldosterone. It is given as the fumarate but doses are expressed in terms of the base; 165.8 mg of aliskiren fumarate is equivalent to about 150 mg of aliskiren. The usual initial oral dose of aliskiren is 150 mg once daily, increased to 300 mg once daily if necessary. In elderly patients, no clinically meaningful additional blood pressure reduction is seen by increasing the dose to 300 mg daily. Doses may be taken with or without food, but patients should establish a routine pattern with regard to meals.

Reviews.

1. Van Tassell BW, Munger MA. Aliskiren for renin inhibition: a new class of antihypertensives. *Ann Pharmacother* 2007; **41**: 456–64.

2. Chrysant SG. Aliskiren-hydrochlorothiazide combination for the treatment of hypertension. *Expert Rev Cardiovasc Ther* 2008; 6: 305–14.
3. Jensen C, *et al.* Aliskiren: the first renin inhibitor for clinical treatment. *Nat Rev Drug Discov* 2008; 7: 399–410.
4. Sureshkumar KK, *et al.* Aliskiren: clinical experience and future perspectives of renin inhibition. *Expert Opin Pharmacother* 2008; 9: 825–37.
5. Kappert K, *et al.* Aliskiren. *Dtsch Med Wochenschr* 2008; 133: 1308–12.
6. Musini VM, *et al.* Blood pressure lowering efficacy of renin inhibitors for primary hypertension. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 10/12/13).
7. Sanoski CA. Aliskiren: an oral direct renin inhibitor for the treatment of hypertension. *Pharmacotherapy* 2009; 29: 193–212.
8. Pimenta E, Oparil S. Role of aliskiren in cardio-renal protection and use in hypertensives with multiple risk factors. *Vasc Health Risk Manag* 2009; 5: 453–63.
9. Moutzouri E, *et al.* Aliskiren, a direct renin inhibitor, in clinical practice: a new approach in the treatment of hypertension. *Curr Vasc Pharmacol* 2010; 8: 344–62.
10. Duggan ST, *et al.* Aliskiren: a review of its use as monotherapy and as combination therapy in the management of hypertension. *Drugs* 2010; 70: 2011–49. Correction. *ibid.* 2011; 71: 1280.

Heart failure. Studies[1-3] of aliskiren in patients with heart failure (p. 1262.3).

1. McMurray JJ, *et al.* Aliskiren Observation of Heart Failure Treatment (ALOFT) Investigators. Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. *Circ Heart Fail* 2008; 1: 17–24.
2. Gheorghiade M, *et al.* Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial. *JAMA* 2013; 309: 1125–35. Correction. *ibid.*; 1461.
3. Maggioni AP, *et al.* Effect of aliskiren on post-discharge outcomes among diabetic and non-diabetic patients hospitalized for heart failure: insights from the ASTRONAUT trial. *Eur Heart J* 2013; 34: 3117–27.

Adverse Effects

Aliskiren is generally well-tolerated but may produce dose-related gastrointestinal adverse effects including diarrhoea, abdominal pain, dyspepsia, and gastro-oesophageal reflux. Other adverse effects include hypotension, headache, dizziness, fatigue, back pain, and cough; rashes, hyperuricaemia, gout, hyperkalaemia, and renal calculi may also occur. Severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis are reported uncommonly; oral mucosal reactions, pruritus, and urticaria have also been noted. Angioedema has been reported rarely, and there have also been reports of seizures. As with other inhibitors of the renin-angiotensin system, dose-related decreases in haemoglobin have been reported.

Precautions

Aliskiren is contra-indicated in patients with a history of angioedema with the drug, and in those who have hereditary or idiopathic angioedema; it should be used with caution in patients who have a history of angioedema associated with other drugs. Aliskiren should be avoided in pregnancy since drugs acting on the renin-angiotensin system have been associated with fetal and neonatal morbidity and mortality.

As with other drugs that affect the renin-angiotensin system, aliskiren may cause changes in renal function; consequently, it should be used with caution in those with conditions predisposing to kidney dysfunction (such as volume depletion, heart, liver, or kidney disease, or diabetes), and renal function should be monitored periodically. Use of aliskiren is not recommended in patients with severe renal impairment (GFR < 30 mL/minute). Due to the risk of hyperkalaemia, periodic serum-potassium monitoring is recommended; patients at particular risk include those with renal insufficiency or diabetes, or those taking other medications that inhibit the renin-angiotensin system or increase serum potassium. Patients with sodium or volume depletion (for example those receiving high-dose diuretics) may have symptomatic hypotension on starting aliskiren and treatment should begin under close medical supervision.

See also Diabetes Mellitus, below, for precautions regarding the use of aliskiren with ACE inhibitors or angiotensin II receptor antagonists in patients with renal impairment or diabetes.

Diabetes mellitus. The ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints) study investigated the role of aliskiren in reducing cardiovascular and renal events in patients with type 2 diabetes and pre-existing renal disease;[1-3] aliskiren was added to conventional care which included an ACE inhibitor or an angiotensin-receptor blocker (ARB). However, analysis of interim data showed that patients were unlikely to benefit from the addition of aliskiren and that, furthermore, the risk of adverse events related to non-fatal stroke, renal complications, hyperkalaemia, and hypotension was increased with aliskiren when compared with placebo. The study was stopped early and, as a consequence of the interim findings, licensed product information contra-indicated the use of aliskiren with an ACE inhibitor or ARB in patients with diabetes, and recommended avoidance of such combinations in those with moderate to severe renal impairment (GFR < 60 mL/minute).[2]

1. Novartis, UK. Direct healthcare professional communication on potential risks of cardiovascular and renal adverse events in patients with type 2 diabetes and renal impairment and/or cardiovascular disease treated with aliskiren (Rasilez) (issued 30th December, 2011). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con140611.pdf (accessed 17/01/11)
2. FDA. FDA drug safety communication: new warning and contra-indication for blood pressure medicines containing aliskiren (Tekturna) (issued 20th April, 2012). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm300889.htm (accessed 19/06/12)
3. Parving HH, *et al.* ALTITUDE Investigators. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012; 367: 2204–13.

Interactions

An additive effect may be noted when aliskiren is given with other antihypertensives or drugs that cause hypotension. Use of aliskiren with other drugs that increase serum potassium may increase the risk of hyperkalaemia. NSAIDs can reduce the anti-hypertensive effects of aliskiren, and combined use in patients who are elderly, volume-depleted, or have renal impairment could cause further deterioration of renal function.

The use of aliskiren with ACE inhibitors or angiotensin II receptor antagonists is generally not recommended; if such therapy is considered necessary then patients must be closely monitored. Such combinations should be avoided in renally-impaired patients with a GFR of less than 60 mL/minute, and are contra-indicated in diabetic patients due to increased adverse events (see Diabetes Mellitus, under Precautions, above).

Aliskiren is a substrate for P-glycoprotein and should not be given with strong P-glycoprotein inhibitors such as ciclosporin, itraconazole, and quinidine; caution is advised if aliskiren is to be used with moderate inhibitors such as amiodarone, clarithromycin, erythromycin, ketoconazole, telithromycin, and verapamil. Aliskiren is metabolised to a small extent by the cytochrome P450 isoenzyme CYP3A4 but few significant interactions have been reported. Plasma-aliskiren concentrations may be reduced by irbesartan and increased by atorvastatin and ketoconazole but the clinical relevance is not clear.

Aliskiren may reduce the plasma concentrations of furosemide and torasemide.

Pharmacokinetics

Aliskiren is poorly absorbed from the gastrointestinal tract with a bioavailability of about 2.5%. Peak plasma concentrations occur about 1 to 3 hours after an oral dose. Absorption is reduced when aliskiren is taken with a high-fat meal. Aliskiren is about 50% bound to plasma proteins. It is excreted mainly in the faeces, possibly via the bile; about 25% of the absorbed dose is excreted in the urine as unchanged drug. Aliskiren is a substrate for the cytochrome P450 isoenzyme CYP3A4 but metabolism appears to be minimal. The elimination half-life is about 24 to 40 hours, and steady-state concentrations are reached in about 7 to 8 days.

Reviews.

1. Vaidyanathan S, *et al.* Clinical pharmacokinetics and pharmacodynamics of aliskiren. *Clin Pharmacokinet* 2008; 47: 515–31.
2. Buczko W, Hermanowicz JM. Pharmacokinetics and pharmacodynamics of aliskiren, an oral direct renin inhibitor. *Pharmacol Rep* 2008; 60: 623–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Rasilez; *Austria*: Rasilez; *Belg.*: Rasilez; *Braz.*: Rasilez; *Canad.*: Rasilez; *Chile*: Rasilez; *China*: Rasilez (锐思力); *Cz.*: Enviage†; Rasilez; Riprazo; Sprimeo†; Tekturna†; *Denm.*: Rasilez; *Fr.*: Rasilez; *Ger.*: Rasilez; *Gr.*: Enviage†; Rasilez; Riprazo; Sprimeo†; *Hong Kong*: Rasilez; *Hung.*: Rasilez; *Indon.*: Rasilez; *Irl.*: Enviage†; Rasilez; Riprazo; Sprimeo†; *Israel*: Rasilez; *Ital.*: Rasilez; *Malaysia*: Rasilez; *Mex.*: Rasilles; *Neth.*: Enviage†; Rasilez; Riprazo; Sprimeo†; *Norw.*: Rasilez; *Philipp.*: Rasilez; *Pol.*: Rasilez HCT; Rasilez; Riprazo; Sprimeo†; *Port.*: Enviage†; Rasilez; Riprazo; Sprimeo†; Tekturna†; *Rus.*: Rasilez (Расилез); *Singapore*: Rasilez; *Spain*: Rasilez; *Swed.*: Rasilez; *Switz.*: Rasilez; *Thai.*: Rasilez; *Turk.*: Rasilez; *UK*: Rasilez; *Ukr.*: Rasilez (Расилез); *USA*: Tekturna.

Multi-ingredient Preparations. *Arg.*: Rasilez D; *Austria*: Rasilez HCT; *Belg.*: Rasilez HCT; *Braz.*: Rasilez HCT; *Canad.*: Rasilez HCT; *Chile*: Rasilez D; *Cz.*: Rasilamlo; Rasilez HCT; Riprazo HCT†; *Denm.*: Rasilez HCT†; *Fr.*: Rasilez HCT; *Ger.*: Rasilez HCT; *Gr.*: Rasilez HCT; *Irl.*: Rasilamlo; Rasilez HCT; Rasitrio; Riprazo HCT†; Sprimeo HCT†; *Neth.*: Rasilamlo; Rasilez HCT; Rasitrio; *Philipp.*: Rasilez HCT; *Port.*: Rasilez HCT; *Rus.*: Co-Rasilez (Ко-Расилез); *Singapore*: Rasilez HCT; *Spain*: Rasilez HCT; *Swed.*: Rasitrio†; *Switz.*: Rasilez HCT; *USA*: Tekamlo; Tekturna HCT.

Alprenolol *(BAN, rINN)* ⊗

Alprénolol; Alprenololi; Alprenololum; Альпренолол.

1-(2-Allylphenoxy)-3-isopropylaminopropan-2-ol.

$C_{15}H_{23}NO_2$=249.4.

CAS — 13655-52-2.

ATC — C07AA01.

ATC Vet — QC07AA01.

UNII — 877K5MQ27W.

Alprenolol Benzoate *(BANM, rINNM)* ⊗

Alprénolol, benzoate d'; Alprenolol, benzoato de; Alprenololi Benzoas; Benzoato de alprenolol; Альпренолола бензоат.

$C_{22}H_{29}NO_4$=371.5.

ATC — C07AA01.

ATC Vet — QC07AA01.

UNII — T3H696761C.

Alprenolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Alprénolol, Chlorhydrate d'; Alprenolol, hidrocloruro de; Alprenolol-hidroklorid; Alprenololhydrochlorid; Alprenolol-hydrochlorid; Alprenololhydroklorid; Alprenololi hydrochloridum; Alprenololihydrokloridi; Alprenololio hidrochloridas; H56/28; Hidrocloruro de alprenolol; Альпренолола Гидрохлорид.

$C_{15}H_{23}NO_2$,HCl=285.8.

CAS — 13707-88-5.

ATC — C07AA01.

ATC Vet — QC07AA01.

UNII — 2502C2OIRK.

NOTE. The names Atenenol and Skajilol have been used as trade marks for alprenolol hydrochloride.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Alprenolol Hydrochloride). A white, or almost white, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

Profile

Alprenolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to have intrinsic sympathomimetic activity and some membrane-stabilising properties.

Alprenolol has been given orally, as the benzoate or hydrochloride, in the management of hypertension, angina pectoris, and cardiac arrhythmias.

Alteplase *(BAN, USAN, rINN)*

Alteplaasi; Alteplas; Alteplasa; Altéplase; Alteplasum; Alteplaz; G-11021 (2-chain form); G-11035; G-11044; Recombinant Tissue-type Plasminogen Activator; rt-PA; Альтеплаза.

CAS — 105857-23-6.

ATC — B01AD02; S01XA13.

ATC Vet — QB01AD02; QS01XA13.

UNII — 1RXS4UE564.

Description. Alteplase is a glycosylated protein of 527 residues having the amino acid sequence of human tissue plasminogen activator (t-PA) and produced by recombinant DNA technology.

Pharmacopoeias. In *US. Eur.* (see p. vii) includes Alteplase for Injection.

Ph. Eur. 8: (Alteplase for Injection; Alteplasum ad Iniectabile). A sterile, freeze-dried preparation of alteplase, a tissue plasminogen activator produced by recombinant DNA technology. It has a potency of not less than 500 000 units/mg of protein. It is a white or slightly yellow powder or friable mass. The reconstituted preparation has a pH of 7.1 to 7.5. Store in colourless glass containers, under vacuum or an inert gas, at a temperature between 2 degrees and 30 degrees. Protect from light. Alteplase consists of 527 amino acids with carbohydrate moieties attached.

USP 36: (Alteplase). A highly purified glycosylated serine protease with fibrin-binding properties and plasminogen-specific proteolytic activities. It is produced by recombinant DNA synthesis in mammalian cell culture. It has a potency of 522 000 to 667 000 USP units/mg of protein. Store in airtight containers in the frozen state at a temperature of -20 degrees or below.

Incompatibility and stability. Alteplase has been reported[1] to be incompatible with dobutamine, dopamine, glyceryl trinitrate, and heparin, although a subsequent study found no incompatibility between alteplase and glyceryl trinitrate.[2] Another study[3] found that dilution of a proprietary preparation of alteplase (Activase) to 90 and 160 micrograms/mL with glucose 5% resulted in precipitation of the drug. Alteplase is formulated with arginine as a

solubilising agent, and dilution with glucose 5% to concentrations below 500 micrograms/mL of alteplase makes precipitation possible. Dilution with sodium chloride 0.9% is possible to concentrations down to 200 micrograms/mL before precipitation becomes a risk.

Studies have suggested that a 1 mg/mL solution of alteplase retains its activity when frozen at -20 degrees or below for up to 6 months,[4,5] or -80 degrees for up to 7 years.[6]

1. Lee CY, *et al.* Visual and spectrophotometric determination of compatibility of alteplase and streptokinase with other injectable drugs. *Am J Hosp Pharm* 1990; 47: 606–8.
2. Lam XM, *et al.* Stability and activity of alteplase with injectable drugs commonly used in cardiac therapy. *Am J Health-Syst Pharm* 1995; 52: 1904–9.
3. Prazin BS. Maximal dilution of Activase. *Am J Hosp Pharm* 1990; 47: 1016.
4. Calis KA, *et al.* Bioactivity of cryopreserved alteplase solutions. *Am J Health-Syst Pharm* 1999; 56: 2056–7.
5. Wiernikowski JT, *et al.* Stability and sterility of recombinant tissue plasminogen activator at -30 degreesC. *Lancet* 2000; 355: 2221–2.
6. Shaw GJ, *et al.* Long-term stability of recombinant tissue plasminogen activator at -80 C. *BMC Res Notes* 2009; 2: 117. Available at: http://www.biomedcentral.com/content/pdf/1756-0500-2-117.pdf (accessed 04/08/10)

Units

The activity of alteplase can be measured in terms of international units using the third International Standard for tissue plasminogen activator recombinant, human, established in 1999, although doses are generally expressed by weight.

Uses and Administration

Alteplase is a thrombolytic drug. It is a mainly single-chain form of the endogenous enzyme tissue plasminogen activator and is produced by recombinant DNA technology. Like endogenous tissue plasminogen activator, alteplase converts fibrin-bound plasminogen to the active form plasmin, resulting in fibrinolysis and dissolution of clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p. 1124.3. Alteplase has relatively little effect on circulating, unbound plasminogen and thus may be termed a fibrin-specific thrombolytic (see p. 1245.3).

Alteplase is used similarly to streptokinase (p. 1503.1) in the treatment of thromboembolic disorders, particularly myocardial infarction (p. 1257.1) and venous thromboembolism (p. 1274.1), and to clear occluded catheters (see below). Alteplase may also be used in patients with acute ischaemic stroke (p. 1269.2).

In the treatment of acute **myocardial infarction**, alteplase is given intravenously as soon as possible after the onset of symptoms in a total dose of 100 mg; the total dose should not exceed 1.5 mg/kg in patients weighing less than 65 kg. The total dose may be given either over 1½ hours (accelerated or 'front-loaded' alteplase) or over 3 hours. The accelerated schedule has been recommended if given within 6 hours of myocardial infarction and is as follows: 15 mg as an intravenous bolus, then 750 micrograms/kg, up to a maximum of 50 mg, by intravenous infusion over 30 minutes, followed by the remainder infused over the subsequent 60 minutes. The longer schedule recommended when used more than 6 hours after myocardial infarction is as follows: 10 mg as an intravenous bolus, then 50 mg by intravenous infusion over 1 hour, followed by the remainder infused over the subsequent 2 hours.

In the treatment of acute, massive **pulmonary embolism** a total dose of 100 mg is given; the total dose should not exceed 1.5 mg/kg in patients weighing less than 65 kg. The first 10 mg is given as an intravenous bolus and the remainder by intravenous infusion over 2 hours.

In acute **ischaemic stroke**, alteplase is given in a dose of 900 micrograms/kg up to a maximum total dose of 90 mg. The dose is given intravenously over 60 minutes with 10% of it as a bolus during the first minute. Alteplase should be given as soon as possible, and up to 3 to 4.5 hours after the onset of stroke symptoms (for further information, see p. 1269.2).

To **restore function in central venous lines**, alteplase is instilled into the catheter at a concentration of 1 mg/mL. The usual dose is 2 mg, repeated after 2 hours if necessary. A total dose of 4 mg should not be exceeded. For patients weighing less than 30 kg, the dose is 110% of the internal lumen volume of the catheter, but should not exceed 2 mg, and may be repeated after 2 hours if necessary.

General references.

1. Gillis JC, *et al.* Alteplase: a reappraisal of its pharmacological properties and therapeutic use in acute myocardial infarction. *Drugs* 1995; 50: 102–36.
2. Wagstaff AJ, *et al.* Alteplase: a reappraisal of its pharmacology and therapeutic use in vascular disorders other than acute myocardial infarction. *Drugs* 1995; 50: 289–316.
3. Semba CP, *et al.* Society of Cardiovascular and Interventional Radiology (SCVIR). Alteplase and tenecteplase: applications in the peripheral circulation. *Tech Vasc Interv Radiol* 2001; 4: 99–106.
4. Lindley RI, *et al.* Alteplase and ischaemic stroke: have new reviews of old data helped? *Lancet Neurol* 2005; 4: 249–53.
5. De Keyser J, *et al.* Intravenous alteplase for stroke: beyond the guidelines and in particular clinical situations. *Stroke* 2007; 38: 2612–8.
6. Quinn TJ, *et al.* Past, present and future of alteplase for acute ischemic stroke. *Expert Rev Neurother* 2008; 8: 181–92.
7. Hacke W, *et al.* ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; 359: 1317–29.
8. Micieli G, *et al.* Safety and efficacy of alteplase in the treatment of acute ischemic stroke. *Vasc Health Risk Manag* 2009; 5: 397–409.

Administration in children. Information on usage and doses of alteplase in children is given under the individual headings below, and also under Administration in Children under Streptokinase, p. 1503.2.

Catheters and cannulas. Alteplase has been used successfully to clear thrombi in central venous catheters.[1,2] Typical doses have been 2 mg injected as a bolus into the blocked catheter. Children have been treated similarly; in one study[3] in patients weighing from 3 kg, doses ranged from 0.1 to 2 mg (as a 1 mg/mL solution), depending on the size of the catheter. Similarly, a later study using a 1 mg/mL solution gave doses of 2 mg to children weighing 30 kg or more, and a volume equal to 110% of the calculated internal volume of the catheter (rounded to the nearest 0.1 mL and not to exceed 2 mL in total) in children weighing less than 30 kg.[4] The dwell time was up to 2 hours, and doses were repeated once in patients in whom catheter function was not restored after this period. A cohort study[5] used doses of 500 micrograms for children weighing 10 kg or under, and 1 to 2 mg above this weight, with a dwell time of 2 to 4 hours. In another report, 2 children[6] were successfully treated with intravenous alteplase in doses of 10 to 50 micrograms/kg per hour for venous thrombosis associated with indwelling intravascular catheters.

Alteplase has also been instilled into central haemodialysis lines to preserve patency between dialysis sessions.[7] In a randomised, controlled study of 225 haemodialysis patients, substituting alteplase (1 mg per lumen) for one of three post-dialysis heparin instillations (5000 units/mL) each week significantly reduced the incidence of catheter malfunction and bacteraemia compared with thrice-weekly heparin.[8] Urokinase has also been used to maintain catheter patency in children with long-term venous access devices for antineoplastic therapy.[9]

For reports covering the use of alteplase to treat intracardiac thrombosis resulting from the placement of central venous lines, see Intracardiac Thrombosis, below.

1. Paulsen D, *et al.* Use of tissue plasminogen activator for reopening of clotted dialysis catheters. *Nephron* 1993; 64: 468–9.
2. Haire WD, *et al.* Urokinase versus recombinant tissue plasminogen activator in thrombosed central venous catheters: a double-blinded, randomized trial. *Thromb Haemost* 1994; 72: 543–7.
3. Jacobs BR, *et al.* Recombinant tissue plasminogen activator in the treatment of central venous catheter occlusion in children. *J Pediatr* 2001; 139: 593–6.
4. Blaney M, *et al.* CAPS Investigators. Alteplase for the treatment of central venous catheter occlusion in children: results of a prospective, open-label, single-arm study (The Cathflo Activase Pediatric Study). *J Vasc Interv Radiol* 2006; 17: 1745–51.
5. Choi M, *et al.* The use of alteplase to restore patency of central venous lines in pediatric patients: a cohort study. *J Pediatr* 2001; 139: 152–6.
6. Doyle E, *et al.* Thrombolysis with low dose tissue plasminogen activator. *Arch Dis Child* 1992; 67: 1483–4.
7. Gittins NS, *et al.* Comparison of alteplase and heparin in maintaining the patency of paediatric central venous haemodialysis lines: a randomised controlled trial. *Arch Dis Child* 2007; 92: 499–501.
8. Hemmelgarn BR, *et al.* Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. *N Engl J Med* 2011; 364: 303–12.
9. Dillon PW, *et al.* Prophylactic urokinase in the management of long-term venous access devices in children: a Children's Oncology Group study. *J Clin Oncol* 2004; 22: 2718–23.

Intracardiac thrombosis. Alteplase has been used, in a dose of 100 mg given intravenously over 2 hours, for thrombosis of prosthetic heart valves.[1]

Alteplase has been used successfully in a neonate to treat intracardiac thrombosis associated with the use of a central venous line.[2] A dose of 500 micrograms/kg given over 10 minutes was followed by infusion of 200 micrograms/kg per hour for 3 days. In another report,[3] 4 preterm infants were treated successfully. All received 400 to 500 micrograms/kg of alteplase in a 20 to 30 minute bolus. This was followed in one case by a 3-hour infusion at 100 micrograms/kg per hour.

Although thrombolytics are usually contra-indicated in patients with infective endocarditis (see Precautions for Streptokinase, p. 1506.3), alteplase has been used successfully in children with indwelling catheters who developed infective endocarditis; coagulation was monitored and fresh frozen plasma was given to maintain fibrinogen concentrations.[4]

1. Astengo D, *et al.* Recombinant tissue plasminogen activator for prosthetic mitral-valve thrombosis. *N Engl J Med* 1995; 333: 259.
2. Van Overmeire B, *et al.* Intracardiac thrombus formation with rapidly progressive heart failure in the neonate: treatment with tissue type plasminogen activator. *Arch Dis Child* 1992; 67: 443–5.
3. Ferrari P, *et al.* Early intracardiac thrombosis in preterm infants and thrombolysis with recombinant tissue type plasminogen activator. *Arch Dis Child Fetal Neonatal Ed* 2001; 85: F66–F69.
4. Levitas A, *et al.* Successful treatment of infective endocarditis with recombinant tissue plasminogen activator. *J Pediatr* 2003; 143: 649–52.

Microvessel thrombosis. Alteplase has been used in conditions where the underlying pathology is occlusion of small blood vessels by microthrombi.

Purpura and loss of circulation in the hands of a patient recovering from **fulminant meningococcaemia**[1] responded to intra-arterial infusion of alteplase 20 to 40 micrograms/kg per hour for 22 hours in the right hand, and 20 micrograms/kg per hour for 11 hours in the left. Perfusion was successfully restored to both hands, and full function subsequently attained in them. Improvement was also achieved when alteplase was given to 2 infants with septic shock and purpura fulminans caused by meningococcal infection.[2]

Intra-arterial infusion of alteplase has also been used in the treatment of severe **frost bite**. In a small retrospective study,[3] improved tissue perfusion and a reduced incidence of amputation were seen among patients treated with alteplase (along with heparin) within 24 hours of injury. Initial intra-arterial doses of 0.5 to 1 mg/hour were infused and adjusted as required over a mean duration of 26 hours (range 8 to 42 hours). Intra-arterial heparin was given at a rate of 500 units/hour.

Six patients[4] with ulcers caused by **livedoid vasculitis** and refractory to conventional treatment were treated with alteplase 10 mg infused intravenously over 4 hours daily for 14 days. Most ulcers healed rapidly; one patient required retreatment with concomitant anticoagulation. Healing of ulcers associated with **calciphylaxis** has also been reported[5] with a similar alteplase regimen.

A 4-year-old girl[6] with **haemolytic-uraemic syndrome** (see under Thrombotic Microangiopathies, p. 1159.1) responded to treatment with an intravenous infusion of alteplase 200 micrograms/kg per hour for 5 hours, subsequently reduced to 50 micrograms/kg per hour for 14 days.

Alteplase use has been reviewed[7] and mixed results found, in patients with **veno-occlusive disease of the liver**, a serious complication of bone marrow transplantation that may be caused by diffuse thrombi in the hepatic venules. Although results in patients with established veno-occlusive disease have been disappointing,[8] one study[9] suggested that alteplase given early in the course of the disease improves response rate.

1. Keeley SR, *et al.* Tissue plasminogen activator for gangrene in fulminant meningococcaemia. *Lancet* 1991; 337: 1359.
2. Zenz W, *et al.* Recombinant tissue plasminogen activator treatment in two infants with fulminant meningococcemia. *Pediatrics* 1995; 96: 44–8.
3. Bruen KJ, *et al.* Reduction of the incidence of amputation in frostbite injury with thrombolytic therapy. *Arch Surg* 2007; 142: 546–51.
4. Klein KL, Pittelkow MR. Tissue plasminogen activator for treatment of livedoid vasculitis. *Mayo Clin Proc* 1992; 67: 923–33.
5. Sewell LD, *et al.* Low-dose tissue plasminogen activator for calciphylaxis. *Arch Dermatol* 2004; 140: 1045–8.
6. Kruez W, *et al.* Successful treatment of haemolytic uraemic syndrome with recombinant tissue-type plasminogen activator. *Lancet* 1993; 341: 1665–6.
7. Terra SG, *et al.* A review of tissue plasminogen activator in the treatment of veno-occlusive liver disease after bone marrow transplantation. *Pharmacotherapy* 1997; 17: 929–37.
8. Bearman SI, *et al.* Treatment of hepatic venoocclusive disease with recombinant human tissue plasminogen activator and heparin in 42 marrow transplant patients. *Blood* 1997; 89: 1501–6.
9. Schriber J, *et al.* Tissue plasminogen activator (tPA) as therapy for hepatotoxicity following bone marrow transplantation. *Bone Marrow Transplant* 1999; 24: 1311–14.

Ocular disorders. Intra-ocular alteplase has been used to treat postoperative fibrinous deposits that can form after procedures such as surgery for cataracts[1] or glaucoma,[2] including cataracts in children.[3] Doses ranging from 6 to 25 micrograms have been used. Intra-ocular bleeding has occurred as a complication of such use.[2,4] Alteplase has also been used prophylactically in children undergoing surgery for congenital cataracts.[5]

Intra-ocular alteplase has also been used for treatment of subhyaloid haemorrhage,[6,7] including that seen in shaken baby syndrome.[8] Successful treatment of subretinal macular haemorrhage with alteplase injected directly into the subretinal area around the clot has also been reported.[9]

1. Heiligenhaus A, *et al.* Recombinant tissue plasminogen activator in cases with fibrin formation after cataract surgery: a prospective randomised multicentre study. *Br J Ophthalmol* 1998; 82: 810–15.
2. Lundy DC, *et al.* Intracameral tissue plasminogen activator after glaucoma surgery: indications, effectiveness, and complications. *Ophthalmology* 1996; 103: 274–82.
3. Mehta JS, Adams GGW. Recombinant tissue plasminogen activator following paediatric cataract surgery. *Br J Ophthalmol* 2000; 84: 983–6.
4. Azuara-Blanco A, Wilson RP. Intraocular and extraocular bleeding after intracameral injection of tissue plasminogen activator. *Br J Ophthalmol* 1998; 82: 1345–6.
5. Siatiri H, *et al.* Intracameral tissue plasminogen activator to prevent severe fibrinous effusion after congenital cataract surgery. *Br J Ophthalmol* 2005; 89: 1458–61.
6. Schmitz K, *et al.* Therapy of subhyaloidal haemorrhage by intravitreal application of rtPA and SF_6 gas. *Br J Ophthalmol* 2000; 84: 1324–5.
7. Koh HJ, *et al.* Treatment of subhyaloid haemorrhage with intravitreal tissue plasminogen activator and C_3F_8 gas injection. *Br J Ophthalmol* 2000; 84: 1329–30.
8. Conway MD, *et al.* Intravitreal tPA and SF_6 promote clearing of premacular subhyaloid hemorrhages in shaken and battered baby syndrome. *Ophthalmic Surg Lasers* 1999; 30: 435–41.
9. Singh RP, *et al.* Management of subretinal macular haemorrhage by direct administration of tissue plasminogen activator. *Br J Ophthalmol* 2006; 90: 429–31.

Peripheral arterial thromboembolism. Although surgery has been the first-line therapy for peripheral arterial thromboembolism (p. 1273.3), thrombolytics have an increasingly important role, either alone or as an adjunct to surgery or percutaneous interventions.[1] Alteplase has been given intravenously but intra-arterial infusion directly into the clot is now preferred. Such treatment, which is usually reserved for patients who have had limb ischaemia for less than 14 days, may be limb-sparing; a small case series[2] found that successful thrombolysis was associated with a greatly reduced rate of subsequent amputation. Alteplase may also be given intra-arterially to remove distal clots during surgical and percutaneous procedures. The optimum dose is unclear.[3,4] For direct intra-arterial infusion into the clot, doses in the range of 0.2 to 1 mg/hour have been commonly used,[5] while for distal clots alteplase has been given intra-arterially as three doses of 5 mg at 10-minute intervals.[4,6]

An *intravenous* dose of 500 micrograms/kg per hour for the first hour followed by 250 micrograms/kg per hour until clot lysis occurred has been used in infants.[7] Treatment of arterial thrombosis in neonates has been reported, using doses of alteplase ranging from 100 to 500 micrograms/kg per hour *intravenously*.[8,9] The *BNFC* recommends a dose for any intravascular thrombosis in neonates and children of 100 to 500 micrograms/kg per hour by intravenous infusion over 3 to 6 hours; a second dose may be given if needed. The maximum daily dose should not exceed 100 mg. However, a retrospective study[10] of 80 infants and children with arterial or venous thrombi found that although treatment with alteplase may be effective, it is associated with a low safety margin and an unknown risk-benefit ratio.

1. Norgren L, *et al.* Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007; 45 (suppl S): S5–S67.
2. Disini L, *et al.* Successful intra-arterial alteplase infusion is a predictor of 12-month limb survival in patients with lower limb arterial occlusion. *Clin Radiol* 2008; 63: 636–41.
3. Ward AS, *et al.* Peripheral thrombolysis with tissue plasminogen activator: results of two treatment regimens. *Arch Surg* 1994; 129: 861–5.
4. Giannini D, Balbarini A. Thrombolytic therapy in peripheral arterial disease. *Curr Drug Targets Cardiovasc Haematol Disord* 2004; 4: 249–58.
5. Henke PK, Stanley JC. The treatment of acute embolic lower limb ischemia. *Adv Surg* 2004; 38: 281–91.
6. Chester JF, *et al.* Peroperative t-PA thrombolysis. *Lancet* 1991; 337: 861–2.
7. Zenz W, *et al.* Tissue plasminogen activator (alteplase) treatment for femoral artery thrombosis after cardiac catheterisation in infants and children. *Br Heart J* 1993; 70: 382–5.
8. Weiner GM, *et al.* Successful treatment of neonatal arterial thromboses with recombinant tissue plasminogen activator. *J Pediatr* 1998; 133: 133–6.
9. Farnoux C, *et al.* Recombinant tissue-type plasminogen activator therapy of thrombosis in 16 neonates. *J Pediatr* 1998; 133: 137–40.
10. Gupta AA, *et al.* Safety and outcomes of thrombolysis with tissue plasminogen activator for treatment of intravascular thrombosis in children. *J Pediatr* 2001; 139: 682–8.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p. 1505.1. Allergic reactions are less likely with alteplase than with streptokinase and repeated use may be possible.

Hypersensitivity. Alteplase is considered non-antigenic, and hypersensitivity reactions are rare; however, the risk may be increased in those taking ACE inhibitors—see ACE Inhibitors under Interactions, below. For further discussion of hypersensitivity reactions with thrombolytics, including anaphylactoid reactions in atopic patients given alteplase, see under Streptokinase, p. 1506.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alteplase as not porphyrinogenic it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Thrombin generation. Alteplase produces considerable thrombin generation which may result from direct activation of the coagulation system by plasmin or by positive feedback of the coagulation system by clot-bound thrombin. This excessive thrombin generation was considered a possible cause of myocardial infarction in a patient undergoing thrombolytic therapy with alteplase for venous thrombosis.[1] Streptokinase produced no evidence of excessive thrombin generation.

1. Baglin TP, *et al.* Thrombin generation and myocardial infarction during infusion of tissue-plasminogen activator. *Lancet* 1993; 341: 504–5.

Interactions

As for Streptokinase, p. 1507.1.

ACE inhibitors. Angioedema has been reported rarely in patients treated with alteplase, but the risk may be increased in those taking ACE inhibitors.[1-3] A prospective study[1] found that out of 176 patients treated with alteplase for acute stroke, 9 developed angioedema; the risk was strongly associated with use of an ACE inhibitor (7 of the 9). Similarly, of 312 patients treated[3] with alteplase for acute stroke, 8 developed angioedema of whom 6 were taking an ACE inhibitor.

1. Hill MD, *et al.* Hemi-orolingual angioedema and ACE inhibition after alteplase treatment of stroke. *Neurology* 2003; 60: 1525–7.
2. Hill MD, *et al.* Anaphylactoid reactions and angioedema during alteplase treatment of acute ischemic stroke. *CMAJ* 2000; 162: 1281–4.
3. Ottomeyer C, *et al.* Raising awareness of orolingual angioedema as a complication of thrombolysis in acute stroke patients. *Cerebrovasc Dis* 2009; 27: 307–8.

Glyceryl trinitrate. Although thrombolytics and nitrates are both frequently used in acute myocardial infarction a report suggested that this combination may result in impaired thrombolysis. Giving alteplase and glyceryl trinitrate intravenously to 36 patients with acute myocardial infarction produced lower plasma-antigen concentrations of tissue-plasminogen activator than alteplase given alone to 11 patients.[1] Reperfusion was sustained in only 44% of patients receiving both drugs compared with 91% of patients given alteplase alone. The authors of a subsequent study[2] suggested that these lower plasma concentrations may be due to increased hepatic metabolism of alteplase as a result of glyceryl trinitrate's effect of increasing hepatic blood flow.

1. Nicolini FA, *et al.* Concurrent nitroglycerin therapy impairs tissue-type plasminogen activator-induced thrombolysis in patients with acute myocardial infarction. *Am J Cardiol* 1994; 74: 662–6.
2. Romeo F, *et al.* Concurrent nitroglycerin administration reduces the efficacy of recombinant tissue-type plasminogen activator in patients with acute anterior wall myocardial infarction. *Am Heart J* 1995; 130: 692–7.

Pharmacokinetics

Alteplase is cleared rapidly from the plasma, mainly by metabolism in the liver. It has an initial half-life of 4 to 5 minutes and a terminal half-life of about 40 minutes.

References.

1. Krause J. Catabolism of tissue-type plasminogen activator (t-PA), its variants, mutants and hybrids. *Fibrinolysis* 1988; 2: 133–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Actilyse; *Austral.*: Actilyse; *Austria*: Actilyse; *Belg.*: Actilyse; *Braz.*: Actilyse; *Canad.*: Activase; Cathflo; *Chile*: Actilyse; *China*: Actilyse (爱通立); *Cz.*: Actilyse; *Denm.*: Actilyse; *Fin.*: Actilyse; *Fr.*: Actilyse; *Ger.*: Actilyse; *Gr.*: Actilyse; Cathflo Activase; *Hong Kong*: Actilyse; *Hung.*: Actilyse; *India*: Actilyse; *Indon.*: Actilyse; *Irl.*: Actilyse; *Israel*: Actilyse; *Ital.*: Actilyse; *Jpn*: Activacin; *Malaysia*: Actilyse; *Mex.*: Actilyse; *Neth.*: Actilyse; *Norw.*: Actilyse; *NZ*: Actilyse; *Philipp.*: Actilyse; *Pol.*: Actilyse; *Port.*: Actilyse; *Rus.*: Actilyse (Актилизе); *S.Afr.*: Actilyse; *Singapore*: Actilyse; *Spain*: Actilyse; *Swed.*: Actilyse; *Switz.*: Actilyse; *Thai.*: Actilyse; *Turk.*: Actilyse; *UK*: Actilyse; *Ukr.*: Actilyse (Актилизе); *USA*: Activase; *Venez.*: Actilyse.

Pharmacopoeial Preparations
USP 36: Alteplase for Injection.

Altizide *(BAN, rINN)* ⊗

Althiazide (USAN); Altizid; Altizida; Altizidum; P-1779; Альтизид.

3-Allylthiomethyl-6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_{11}H_{14}ClN_3O_4S_3$=383.9

CAS — 5588-16-9.

UNII — GI8CB72B0D.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Altizide). A white or almost white powder. Practically insoluble in water; soluble in methyl alcohol; practically insoluble in dichloromethane. It exhibits polymorphism.

Profile

Altizide is a thiazide diuretic (see Hydrochlorothiazide, p. 1403.2) that is used in the treatment of oedema and hypertension. It is frequently used with spironolactone.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Belg.*: Aldactazine; *Fr.*: Aldactazine; Practazin†; Spirotazine; *Gr.*: Aldactazine; *Port.*: Aldactazine; *Spain*: Aldactazine.

Ambrisentan *(BAN, rINN)*

Ambrisentân; Ambrisentanum; BSF-208075; LU-208075; Амбризентан.

(+)-(2*S*)-2-[(4,6-Dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid.

$C_{22}H_{22}N_2O_4$=378.4

CAS — 177036-94-1.

ATC — C02KX02.

ATC Vet — QC02KX02.

UNII — HW6NV07QEC.

Uses and Administration

Ambrisentan is an endothelin receptor antagonis (p. 1245.1) with similar actions to bosentan (p. 1327.1) although it has a higher selectivity for the endothelin ET_A receptor. It is used in the management of pulmonary hypertension functional class II or III (p. 1278.2). It is given orally in an initial dose of 5 mg once daily; the dose may be increased to 10 mg once daily if tolerated. When used with ciclosporin the dose should not exceed 5 mg daily (see also Interactions, below).

References.

1. Galiè N, *et al.* Ambrisentan therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2005; 46: 529–35.
2. Vatter H, Seifert V. Ambrisentan, a non-peptide endothelin receptor antagonist. *Cardiovasc Drug Rev* 2006; 24: 63–76.
3. Barst RJ. A review of pulmonary arterial hypertension: role of ambrisentan. *Vasc Health Risk Manag* 2007; 3: 11–22.
4. Galiè N, *et al.* Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation* 2008; 117: 3010–19
5. Hrometz SL, Shields KM. Role of ambrisentan in the management of pulmonary hypertension. *Ann Pharmacother* 2008; 42: 1653–9 Correction. *ibid.* 2009; 43: 794. [dose]
6. Croxtall JD, Keam SJ. Ambrisentan. *Drugs* 2008; 68: 2195–2204.
7. Kingman M, *et al.* Ambrisentan, an endothelin receptor type A-selective endothelin receptor antagonist, for the treatment of pulmonary arterial hypertension. *Expert Opin Pharmacother* 2009; 10: 1847–58.
8. Oudiz RJ, *et al.* ARIES Study Group. Long-term ambrisentan therapy for the treatment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 54: 1971–81.

Adverse Effects and Precautions

As for Bosentan, p. 1327.3.

Interactions

Ambrisentan is a substrate for several enzymes and transporters and interactions could potentially occur with inducers or inhibitors of the cytochrome P450 isoenzymes CYP3A4 and CYP2C19, P-glycoprotein, uridine diphosphate glucuronosyltransferases, and organic anion transporting polypeptide (OATP). Ciclosporin increases plasma concentrations of ambrisentan by about 50% and more than doubles the AUC; therefore doses of ambrisentan should be kept low when they are given together—see under Uses, above.

Ciclosporin. An open-label, pharmacokinetic study[1] in 28 healthy subjects indicated that exposure to ambrisentan was doubled when used with ciclosporin. Also, there was a corresponding increase in adverse effects such as headache when the 2 drugs were given together.

1. Spence R, *et al.* Potential for pharmacokinetic interactions between ambrisentan and cyclosporine. *Clin Pharmacol Ther* 2010; 88: 513–20.

Pharmacokinetics

Ambrisentan is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur about 2 hours after oral doses. It is about 99% bound to plasma proteins. Ambrisentan is excreted mainly by the liver, although the relative contribution of hepatic metabolism and biliary excretion is unknown. The terminal elimination half-life is about 15 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Volibris; *Austria*: Volibris; *Belg.*: Volibris; *Braz.*: Volibris; *Canad.*: Volibris; *China*: Volibris (凡瑞克); *Cz.*: Volibris; *Denm.*: Volibris; *Fr.*: Volibris; *Ger.*: Volibris; *Gr.*: Volibris; *Hung.*: Volibris; *Irl.*: Volibris; *Israel*: Volibris; *Ital.*: Volibris; *Malaysia*: Volibris; *Neth.*: Volibris; *Norw.*: Volibris; *NZ*: Volibris; *Pol.*: Volibris; *Port.*: Volibris; *Spain*: Volibris; *Swed.*: Volibris; *Switz.*: Volibris; *UK*: Volibris; *USA*: Letairis.

Amezinium Metilsulfate *(rINN)* ⊗

Ametsiniummetilsulfaatti; Amezinii Metilsulfas; Amezinio, metilsulfato de; Amezinium Methylsulphate; Amézinium, Métilsulfate d'; Ameziummetilsulfat; Metilsulfato de amezinio; Амезиния Метилсульфат.

4-Amino-6-methoxy-1-phenylpyridazinium methylsulfate.

$C_{12}H_{15}N_3O_5S$=313.3

CAS — 30578-37-1.

ATC — C01CA25.

ATC Vet — QC01CA25.

UNII — 03NR868ICX.

Profile

Amezinium metilsulfate is a sympathomimetic (p. 1507.3) used for its vasopressor effects in the treatment of hypotensive states (p. 1277.2). It is given orally in a usual dose of 10 mg up to three times daily. It has also been given by slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Regulton; *Ger.*: Regulton; Supratonin†; *Jpn*: Risumic.

Amiloride Hydrochloride

(BANM, USAN, rINNM) ⊗

Amilorid Hidroklorür; Amilorid hydrochlorid dihydrát; Amilorida, hidrocloruro de; Amiloride, Chlorhydrate d'; Amilorid-hidroklorid; Amiloridhydrochlorid; Amiloridhydroklorid; Amiloridi Hydrochloridum; Amiloridi Hydrochloridum Dihydricum; Amiloridihydrokloridi; Amilorido hidrocloridas; Amilorydu chlorowodorek; Amipramizide; Cloridrato de Amilorida; Hidrocloruro de amilorida; MK-870; Амилорида Гидрохлорид.

N-Amidino-3,5-diamino-6-chloropyrazine-2-carboxamide hydrochloride dihydrate.

$C_6H_8ClN_7O,HCl,2H_2O$=302.1

CAS — 2609-46-3 (amiloride); 2016-88-8 (anhydrous amiloride hydrochloride); 17440-83-4 (amiloride hydrochloride dihydrate).

ATC — C03DB01.

ATC Vet — QC03DB01.

UNII — FZJ37245UC.

NOTE. Compounded preparations of amiloride hydrochloride may be represented by the following names:

- Co-amilofruse (*BAN*)—amiloride hydrochloride 1 part and furosemide 8 parts (w/w)
- Co-amilozide (*BAN*)—amiloride hydrochloride 1 part and hydrochlorothiazide 10 parts (w/w)
- Co-amilozide (*PEN*)—amiloride hydrochloride and hydrochlorothiazide.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Amiloride Hydrochloride). A pale yellow to greenish-yellow powder. Slightly soluble in water and in dehydrated alcohol. Protect from light.

USP 36: (Amiloride Hydrochloride). A yellow to greenish-yellow, odourless or practically odourless, powder. Slightly soluble in water; insoluble in acetone, in chloroform, in ether, and in ethyl acetate; freely soluble in dimethyl sulfoxide; sparingly soluble in methyl alcohol.

Uses and Administration

Amiloride is a weak diuretic that appears to act mainly on the distal renal tubules. It is described as potassium-sparing since, like spironolactone, it increases the excretion of sodium and reduces the excretion of potassium. Unlike spironolactone, however, it does not act by specifically antagonising aldosterone. Amiloride does not inhibit carbonic anhydrase. It takes effect about 2 hours after oral dosage and its diuretic action reaches a peak in 6 to 10 hours and has been reported to persist for about 24 hours.

Amiloride diminishes the kaliuretic effects of other diuretics, and may produce an additional natriuretic effect. It is mainly used as an adjunct to thiazide diuretics such as hydrochlorothiazide and loop diuretics such as furosemide, to conserve potassium in those at risk from hypokalaemia during the long-term treatment of oedema associated with hepatic cirrhosis (including ascites, p. 1276.2) and heart failure (p. 1262.3). It is also used with other diuretics in the treatment of hypertension (p. 1251.1). Diuretic-induced hypokalaemia and its management, including the role of potassium-sparing diuretics such as amiloride, is discussed under Effects on Electrolyte Balance in the Adverse Effects of Hydrochlorothiazide, p. 1404.2. Amiloride is sometimes used to manage hypokalaemia in primary hyperaldosteronism (p. 1501.1).

Amiloride by inhalation has also been investigated in the management of cystic fibrosis patients with lung disease (see below).

In the treatment of **oedema** amiloride is given orally as the hydrochloride and doses are expressed in terms of the anhydrous substance. 1 mg of anhydrous hydrochloride is equivalent to about 1.14 mg of the hydrated substance. Treatment may be started with a dose of 5 to 10 mg daily, increased, if necessary, to a maximum of 20 mg daily. An initial dose of 2.5 mg once daily may be used in patients already taking other diuretics or antihypertensives. Similar doses to those given for oedema are used to reduce potassium loss in patients receiving thiazide or loop diuretics.

Potassium supplements should not be given.

For doses in children, see below.

Administration in children. Although amiloride is unlicensed in the UK for use in children, the *BNFC* suggests that it may be given with thiazides or loop diuretics in the treatment of oedema or congestive heart failure in neonates, infants, and children at an oral dose of 100 to 200 micrograms/kg twice daily (maximum total daily dose of 20 mg).

Cystic fibrosis. Pulmonary disease is the major cause of mortality in cystic fibrosis (p. 177.2). Experimental treatment aimed at modifying the pulmonary disease process has included giving amiloride by inhalation.[1,2] No evidence of pulmonary or systemic toxicity was seen in 14 patients treated for 25 weeks.[1] The mechanism of action is unclear but could be the sodium-channel blocking effect[1] or anti-inflammatory effects[3] of amiloride. Concern has been expressed[4] over possible consequences of the inhibition of endogenous urokinase by amiloride although others[3] considered this to be unlikely at the concentrations studied. However, a systematic review[5] found no evidence that amiloride was of clinical benefit.

1. Knowles MR, *et al.* A pilot study of aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med* 1990; 322: 1189–94.
2. App EM, *et al.* Acute and long-term amiloride inhalation in cystic fibrosis lung disease: a rational approach to cystic fibrosis therapy. *Am Rev Respir Dis* 1990; 141: 605–12.
3. Gallo RL. Aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med* 1990; 323: 996–7.
4. Henkin J. Aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med* 1990; 323: 997.
5. Knowles MR, *et al.* Aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med* 1990; 323: 997–8.
6. Burrows E, *et al.* Sodium channel blockers for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 28/04/08).

Diabetes insipidus. Thiazide diuretics are commonly used in nephrogenic diabetes insipidus (p. 2348.2) and NSAIDs may also be employed; both result in an overall decrease in urine production. Hydrochlorothiazide with amiloride has been reported to be at least as effective as hydrochlorothiazide plus indometacin in 5 patients.[1] In addition, amiloride obviated the need for potassium supplements. Hydrochlorothiazide with amiloride was also effective and well tolerated in a group of 4 children with nephrogenic diabetes insipidus who were treated for up to 5 years.[2]

1. Knoers N, Monnens LAH. Amiloride-hydrochlorothiazide versus indomethacin-hydrochlorothiazide in the treatment of nephrogenic diabetes insipidus. *J Pediatr* 1990; 117: 499–502.
2. Kirchlechner V, *et al.* Treatment of nephrogenic diabetes insipidus with hydrochlorothiazide and amiloride. *Arch Dis Child* 1999; 80: 548–52.

Renal calculi. Patients with idiopathic hypercalciuria and a history of renal calculi (p. 2350.3) are usually given a thiazide diuretic such as hydrochlorothiazide to reduce calcium excretion. In patients with calcium oxalate calculi an inherited cellular defect in oxalate transport may also be involved and this might be corrected by amiloride.[1]

1. Baggio B, *et al.* An inheritable anomaly of red-cell oxalate transport in "primary" calcium nephrolithiasis correctable with diuretics. *N Engl J Med* 1986; 314: 599–604.

Adverse Effects

Amiloride can cause hyperkalaemia, particularly in elderly patients, diabetics, and patients with renal impairment. Hyponatraemia has been reported in patients taking amiloride with other diuretics. Amiloride may cause nausea, vomiting, abdominal pain, diarrhoea or constipation, paraesthesia, thirst, dizziness, rashes, pruritus, weakness, muscle cramps, headache, and minor psychiatric or visual changes. Orthostatic hypotension and rises in blood-urea-nitrogen concentrations have been reported. Other adverse effects of amiloride may include alopecia, cough, dyspnoea, jaundice, encephalopathy, impotence, angina pectoris, arrhythmias, and palpitations.

Effects on electrolyte balance. There have been reports of metabolic acidosis associated with amiloride or triamterene[1] and with co-amilozide.[2]

1. Kushner RF, Sitrin MD. Metabolic acidosis: development in two patients receiving a potassium-sparing diuretic and total parenteral nutrition. *Arch Intern Med* 1986; 146: 343–5.
2. Wan HH, Lye MDW. Moduretic-induced metabolic acidosis and hyperkalaemia. *Postgrad Med J* 1980; 56: 348–50.

POTASSIUM. Hyperkalaemia is the main adverse effect when amiloride is given alone but may also occur when amiloride is given with a potassium-wasting diuretic. Severe hyperkalaemia has been reported during co-amilozide therapy, particularly in patients with renal impairment[1,2] and has been accompanied by metabolic acidosis in one such patient.[3]

1. Whiting GFM, *et al.* Severe hyperkalaemia with Moduretic. *Med J Aust* 1979; 1: 409.
2. Jaffey L, Martin A. Malignant hyperkalaemia after amiloride/hydrochlorothiazide treatment. *Lancet* 1981; 1: 1272.
3. Wan HH, Lye MDW. Moduretic-induced metabolic acidosis and hyperkalaemia. *Postgrad Med J* 1980; 56: 348–50.

SODIUM. For reports of severe hyponatraemia in patients taking diuretics such as amiloride with potassium-wasting diuretics, see Hydrochlorothiazide, p. 1404.3.

Effects on the skin. For a report of photosensitivity reactions in patients taking co-amilozide, see Hydrochlorothiazide, p. 1405.3.

Precautions

Amiloride has the same precautions as spironolactone with regard to hyperkalaemia (see p. 1502.1). It should be stopped at least 3 days before glucose-tolerance tests are performed in patients who may have diabetes mellitus because of the risks of provoking severe hyperkalaemia.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amiloride as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

There is an increased risk of hyperkalaemia if amiloride is given with potassium supplements or with other potassium-sparing diuretics. Hyperkalaemia may also occur in patients given amiloride with ACE inhibitors, angiotensin II receptor antagonists, NSAIDs, ciclosporin, or trilostane. In patients taking amiloride with NSAIDs or ciclosporin the risk of nephrotoxicity may also be increased. Diuretics may increase the risk of lithium toxicity by reducing its excretion, but such toxicity does not appear to occur with amiloride. Severe hyponatraemia may occur in patients taking a potassium-sparing diuretic with a thiazide; this risk may be increased in patients taking chlorpropamide. Amiloride may reduce the ulcer-healing properties of carbenoxolone. As with other diuretics, amiloride may enhance the effects of other antihypertensive drugs.

Digoxin. For the effects of amiloride on digoxin clearance and inotropic activity, see p. 1357.2.

Quinidine. For a report of amiloride producing arrhythmias in patients receiving quinidine, see p. 1483.2.

Pharmacokinetics

Amiloride is incompletely absorbed from the gastrointestinal tract; bioavailability is about 50% and is reduced by food. It is not significantly bound to plasma proteins and has a plasma half-life of 6 to 9 hours; the terminal half-life may be 20 hours or more. It is excreted unchanged by the kidneys.

General references.

1. Weiss P, *et al.* The metabolism of amiloride hydrochloride in man. *Clin Pharmacol Ther* 1969; 10: 401–6.

Hepatic impairment. In patients with acute hepatitis the terminal half-life of amiloride was 33 hours compared with 21 hours in healthy subjects.[1] The proportion of the dose excreted in the urine was increased from 49 to 80%.

1. Spahn H, *et al.* Pharmacokinetics of amiloride in renal and hepatic disease. *Eur J Clin Pharmacol* 1987; 33: 493–8.

Renal impairment. Studies of the pharmacokinetics of amiloride[1,2] have reported an increase in terminal elimination half-life from 20 hours in healthy subjects to 100 hours in patients with end-stage renal disease. The natriuretic effect of amiloride was reduced[1] in patients with creatinine clearance below 50 mL/minute. In patients with renal impairment amiloride could aggravate potassium retention due to renal disease. Studies in elderly patients have found increased half-life[3] and steady-state concentrations[4] associated with reduced renal function.

1. Knauf H, *et al.* Limitation on the use of amiloride in early renal failure. *Eur J Clin Pharmacol* 1985; 28: 61–6.
2. Spahn H, *et al.* Pharmacokinetics of amiloride in renal and hepatic disease. *Eur J Clin Pharmacol* 1987; 33: 493–8.
3. Sabanathan K, *et al.* A comparative study of the pharmacokinetics and pharmacodynamics of atenolol, hydrochlorothiazide and amiloride in normal young and elderly subjects and elderly hypertensive patients. *Eur J Clin Pharmacol* 1987; 32: 53–60.
4. Ismail Z, *et al.* The pharmacokinetics of amiloride-hydrochlorothiazide combination in the young and elderly. *Eur J Clin Pharmacol* 1989; 37: 167–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bisdiur; *Austral.*: Kaluril; Midamor†; *Canad.*: Midamor; *China*: Bi Da Shu (必达舒); Cz.: Amiclaran†; *Fr.*: Modamide; *NZ*: Midamor†; *UK*: Amilamont; *USA*: Midamor.

Multi-ingredient Preparations. *Arg.*: Diflux; Diur Pot; Diurex A; Errolon A; Hidrenox A; Lasiride; Moduretic; Nuriban A; Plenacor D; Ren-Ur; Vericordin Compuesto; *Austral.*: Amizide;

Moduretic; *Austria*: Amiloretik; Amilorid comp; Amilostad HCT; Loradur; Moducrin†; Moduretic; *Belg.*: Co-Amiloride; Prusamil; Moduretic; *Braz.*: Amilorid; Amiretic; Ancloric; Diupress; Diurezin-A; Diurisa; Moduretic; *Canad.*: Apo-Amilzide; Gen-Amilazide†; Moduret†; Novamilor; Nu-Amilzide; *Chile*: Purdituren; Hidrium; Hidropid†; *China*: Puluobi (福洛必); Mengdaqing (蒙达清); Wu Du Li (武都力); *Cz.*: Amidoton; Amilorid/HCT; Apo-Amilzide; Loradur; Moduretic; Rheftuin; *Denm.*: Amilco; Frusamil; Sparkal; *Fin.*: Amitrid; Diuramin; Diurex; Miloride; Sparkal; *Fr.*: Logirene; Moducren; Moduretic; *Ger.*: Amilocomp beta†; Amiloretik†; Amilorid comp; Amilorid/HCT†; Diaphal; Diursan†; Moducrin; Moduretik†; Tensoflux; *Gr.*: Prumil; Ividol; Moduretic; Scandrex; Tiaden; *Hong Kong*: Amithiazide; Apo-Amilzide; Moducren†; Moduretic; Navispare; Sefaretic; *Hung.*: Amilorid Comp; Amilozid-B; *India*: Amifru; Amilochlor; Amimide; Beta-Biduret; Biduret; Bp-Loride; Exna-K; Prumil; Hipres-D; Lasiride; *Indon.*: Lorinid; *Irl.*: Buram†; Fru-Co; Prumil; Moducren†; Moduret; *Israel*: Kaluril; *Ital.*: Moduretic; *Malaysia*: Ami-Hydrotride; Amizide†; Apo-Amilzide; Moduretic; Moduride; *Mex.*: Moduretic *Neth.*: Moduretic; *Norw.*: Moduretic; Normorix; *NZ*: Amizide†; Prumil; Moduretic; *Pol.*: Tialorid; *Port.*: Diurene†; Moduretic *S.Afr.*: Adco-Retic; Amiloretic Betaretic; GSA-Retic Hexaretic†; Moducren†; Moduretic; Servatrin; *Singapore*: Apo-Amilzide; *Spain*: Ameride; Diuzine; Kalten; *Swed.*: Amiloferm; Moduretic†; Normorix; Sparkal; *Switz.*: Amiloride/HCT†; Comilorid; Ecodurex; Escoretic†; Grodurex; Kalten†; Moduretic; Rheftuin; *Thai.*: Amilozide; Bilduretic; Buretic; Hydroride Plus; Hyperretic; Meditic; Miduret; Minitic; Miretic; Modupac; Moduretic; Moure-M†; Mourinate; Poli-Uretic; Renase†; Sefaretic†; *Turk.*: Moduretic; *UK*: Amil-Co; Aridil; Fru-Co; Prumil; Kalten; Komil; Moduret; Moduretic; Navispare; *USA*: Moduretic; *Venez.*: Furdiuren; Moduretic.

Pharmacopoeial Preparations

BP 2014: Amiloride Tablets; Co-amilofruse Tablets; Co-amilozide Oral Solution; Co-amilozide Tablets;

USP 36: Amiloride Hydrochloride and Hydrochlorothiazide Tablets; Amiloride Hydrochloride Tablets.

Amiodarone *(BAN, USAN, rINN)*

Amiodaron; Amiodarona; Amiodaroni; Amiodaronum; L-3428; 51087-N; SKF-33134-A; Амиодарон

2-Butylbenzofuran-3-yl 4-(2-diethylaminoethoxy)-3,5-diiodophenyl ketone

$C_{25}H_{29}I_2NO_3$=645.3

CAS — 1951-25-3.

ATC — C01BD01.

ATC Vet — QC01BD01.

UNII — N3RQ532IUT.

Amiodarone Hydrochloride *(BANM, rINNM)*

Amiodaron hidroklorür; Amiodarona, hidrocloruro de; Amiodarone chlorhydrate d'; Amiodaron-hidroklorid; Amiodaronhydrochlorid; Amiodaron-hydrochlorid; Amiodaronhydroklorid; Amiodaroni Hydrochloridum; Amiodaronihydroklorid; Amiodarono hidrochloridas; Hidrocloruro de amiodarona; Амиодарона Гидрохлорид

$C_{25}H_{29}I_2NO_3$,HCl=681.8

CAS — 19774-82-4.

ATC — C01BD01.

ATC Vet — QC01BD01.

UNII — 976728SY6Z.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Amiodarone Hydrochloride). A white or almost white, fine crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane; soluble in methyl alcohol. Store at a temperature not exceeding 30 degrees. Protect from light.

USP 36: (Amiodarone Hydrochloride). White or almost white, fine, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; soluble in methyl alcohol; freely soluble in dichloromethane. A 5% solution in water has a pH of 3.2 to 3.8. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Adsorption. Amiodarone is known to be adsorbed by PVC, although the amount of adsorption has varied in different studies. A study[1] using amiodarone hydrochloride 600 micrograms/mL in glucose 5% found that the concentration fell by 10% in 3 hours followed by a steady decrease to 60% of the initial concentration after 5 days when stored in flexible PVC bags at ambient temperature.[1] However, another study[2] using amiodarone hydrochloride 1.8 to 2 mg/mL in glucose 5% found only that the concentration remained 97.3% of the initial value after 24 hours in PVC infusion bags. In the first study, perfusion of the solution through PVC giving sets resulted in the concentration falling to 82% after 15 minutes, whereas the second study found the concentration fell to 95.1% after 1 hour but then returned to the initial value. No loss was noted in either study when glass or rigid PVC containers were used, suggesting that the losses were caused by the plasticiser, di-2-ethylhexylphthalate (DEHP). Amiodarone may also leach out DEHP and other plasticisers, and it has been suggested that bags and tubing containing DEHP should not be used for giving amiodarone in order to minimise patient exposure.

1. Weir SJ, *et al.* Sorption of amiodarone to polyvinyl chloride infusion bags and administration sets. *Am J Hosp Pharm* 1985; 42: 2679–83.
2. Peters PG, Hayball PJ. A comparative analysis of the loss of amiodarone from small and large volume PVC and non-PVC infusion systems. *Anaesth Intensive Care* 1990; 18: 241–5.

Incompatibility. Amiodarone injection has been reported to be incompatible with aminophylline,[1] flucloxacillin,[2] heparin,[3] and sodium bicarbonate.[4] A further study[5] reported incompatibility with ampicillin/sulbactam sodium, ceftazidime sodium, digoxin, furosemide, imipenem/cilastatin sodium, magnesium sulfate, piperacillin sodium, piperacillin/tazobactam sodium, potassium phosphate, and sodium phosphate. UK licensed product information states that it is incompatible with sodium chloride solutions.

1. Hasegawa GR, Eder JF. Visual compatibility of amiodarone hydrochloride injection with other injectable drugs. *Am J Hosp Pharm* 1984; 41: 1379–80.
2. Taylor A, Lewis R. Amiodarone and injectable drug incompatibility. *Pharm J* 1992; 248: 533.
3. Cairns CJ. Incompatibility of amiodarone. *Pharm J* 1986; 236: 68.
4. Korth-Bradley JM. Incompatibility of amiodarone hydrochloride and sodium bicarbonate injections. *Am J Health-Syst Pharm* 1995; 52: 2340.
5. Chalmers JR, *et al.* Visual compatibility of amiodarone hydrochloride injection with various intravenous drugs. *Am J Health-Syst Pharm* 2001; 58: 504–6.

Stability. An oral suspension prepared from tablets[1] and containing amiodarone hydrochloride 5 mg/mL was stable for 3 months at 4 degrees and 6 weeks at 25 degrees.

1. Nahata MC. Stability of amiodarone in an oral suspension stored under refrigeration and at room temperature. *Ann Pharmacother* 1997; 31: 851–2.

Uses and Administration

Amiodarone is an antiarrhythmic with mainly class III properties (see p. 1243.1). It is used in the control of ventricular and supraventricular arrhythmias, including arrhythmias associated with Wolff-Parkinson-White syndrome. It has been tried for the prevention of arrhythmias in patients with myocardial infarction or heart failure.

Amiodarone hydrochloride is given orally in initial doses of 200 mg three times daily for a week, then 200 mg twice daily for a week, and then a usual maintenance dosage of 200 mg or less daily, according to response. In the USA, amiodarone is only licensed for ventricular arrhythmias and higher doses are used: loading doses of amiodarone hydrochloride are up to 1.6 g daily for 1 to 3 weeks, followed by 600 to 800 mg daily for a month, then a usual maintenance dose of 400 mg daily. Consideration should be given to potential adverse effects, and patients should be given the minimum effective dose.

Amiodarone hydrochloride may be given intravenously where facilities for close monitoring of cardiac function and resuscitation are available. It is usually given as a dilute solution in glucose 5%. Solutions containing less than 600 micrograms/mL are unstable but high concentrations are irritating to the veins, and solutions containing more than 2 mg/mL should be given via a central catheter; a central catheter is also preferred if repeated or continuous infusion is required. The usual dose is 1 to 1.2 g over 24 hours, given by intermittent or continuous infusion as follows:

- in the UK, an initial infusion of 5 mg/kg in 250 mL of glucose 5% is given over 20 to 120 minutes; the infusion may be repeated if required, up to a total dose of 1.2 g in 24 hours, diluted in up to 500 mL of glucose 5%
- in the USA, an initial dose of 150 mg in 100 mL of glucose 5% is given over 10 minutes, followed by 900 mg in 500 mL of glucose 5% over 24 hours, given at a rate of 1 mg/minute for 6 hours and then 500 micrograms/minute for 18 hours; if necessary the maintenance infusion may be continued at a rate of 500 micrograms/minute using a 1 to 6 mg/mL solution
- In emergencies, amiodarone hydrochloride may be given in doses of 150 to 300 mg in 10 to 20 mL of glucose 5% by slow intravenous injection over a period of not less than 3 minutes; a second injection should not be given until at least 15 minutes after the first

For the use of amiodarone in children, see below.

General references.

1. Goldschlager N, *et al.* Practical guidelines for clinicians who treat patients with amiodarone. *Arch Intern Med* 2000; 160: 1741–8.
2. Anonymous. Using oral amiodarone safely. *Drug Ther Bull* 2003; 41: 9–12. Correction. *ibid.*; 40.
3. Siddoway LA. Amiodarone: guidelines for use and monitoring. *Am Fam Physician* 2003; 68: 2189–96.
4. Vassallo P, Trohman RG. Prescribing amiodarone: an evidence-based review of clinical indications. *JAMA* 2007; 298: 1312–22.

Administration. Addition of amiodarone hydrochloride to an intravenous infusion solution reduces the drop size delivered[1,2] and the reduction in size is greater as the concentration of amiodarone is increased. This resulted[1] in a reduction of about 30% in the expected delivery rate when amiodarone hydrochloride 1.2 g was given in 500 mL of glucose 5%. The reduction in drop size has been attributed to a reduction in surface tension caused by inclusion of Tween 80 (polysorbate 80) in the standard intravenous formulation.[1] Allowances should be made for the changes in drop size causing a reduction of the delivery rate of infusions of amiodarone hydrochloride. US licensed product information for the standard formulation (*Cordarone; Wyeth-Ayerst*) contra-indicates the use of drop-counter infusion sets and requires the use of a volumetric infusion pump when intravenous amiodarone is given. Aqueous formulations of amiodarone that do not contain polysorbate 80 have been developed and may be available in some countries, including the USA (*Nexterone; Prism*).

1. Capps PA, Robertson AL. Influence of amiodarone injection on the delivery rate of intravenous fluids. *Pharm J* 1985; 234: 14–15.
2. Chouhan UM, Lynch E. Amiodarone intravenous infusion. *Pharm J* 1985; 235: 466.

Administration in children. Amiodarone has been used orally and intravenously in infants and children[1-3] (but see Precautions, p. 1303.1 for a warning about benzyl alcohol in some intravenous preparations). In the management of cardiac arrhythmias, amiodarone hydrochloride may be given orally in a loading dose of 10 to 20 mg/kg daily (or 500 mg/m^2 daily) for 7 to 10 days, followed by the lowest possible maintenance dose, ranging from 5 to 10 mg/kg daily (or 250 mg/m^2 daily) according to response. It has also been given intravenously in a loading dose of 5 mg/kg given over 20 minutes to 2 hours, followed by a maintenance dose of 10 to 15 mg/kg daily. The *BNFC* suggests intravenous infusions of 5 mg/kg given over 30 minutes and repeated every 12 to 24 hours for neonates, and 5 to 10 mg/kg given over 20 minutes to 2 hours and followed by continuous infusion of 300 micrograms/kg per hour (maximum 1.5 mg/kg per hour) for infants and children up to 18 years. An intravenous injection of 5 mg/kg (maximum 300 mg) given over at least 3 minutes may be used in neonates and children up to 18 years for the termination of ventricular fibrillation or pulseless ventricular tachycardia that is unresponsive to defibrillation.

1. Shuler CO, *et al.* Efficacy and safety of amiodarone in infants. *Am Heart J* 1993; 125: 1430–2.
2. Figa FH, *et al.* Clinical efficacy and safety of intravenous amiodarone in infants and children. *Am J Cardiol* 1994; 74: 573–7.
3. Saul JP, *et al.* Intravenous amiodarone for incessant tachyarrhythmias in children: a randomized, double-blind, antiarrhythmic drug trial. *Circulation* 2005; 112: 3470–7.

Advanced cardiac life support. Cardiac arrest should be treated by starting full life support measures (see p. 1268.3). Amiodarone may be considered in cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia that is refractory to rapid defibrillation. Although higher doses have been used, guidelines[1-3] now recommend an intravenous dose of 300 mg, with a further dose of 150 mg if necessary; it may be given by intraosseous injection if the intravenous route is not available. In the UK[3] and European guidelines,[2] this may be followed by an infusion of 900 mg over 24 hours. A study[4] in patients with cardiac arrest outside hospital found that amiodarone improved survival to admission, while another study[5] found that it was more effective than lidocaine in this setting. Retrospective studies[6,7] of its use in cardiac arrest occurring in hospital, however, have not found it to be of benefit.

1. The American Heart Association. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010; 122 (suppl 3): S639–S946. Also available at: http://circ.ahajournals.org/content/vol122/18_suppl_3/ (accessed 21/01/11)
2. European Resuscitation Council. European Resuscitation Council guidelines for resuscitation 2010. *Resuscitation* 2010; 81: 1219–1451. Also available at: http://www.cprguidelines.eu/2010 (accessed 07/02/11)
3. Resuscitation Council (UK). 2010 Resuscitation Guidelines. Available at: http://www.resus.org.uk/pages/GL2010.pdf (accessed 21/01/11)
4. Kudenchuk PJ, *et al.* Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 1999; 341: 871–8.
5. Dorian P, *et al.* Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med* 2002; 346: 884–90. Correction. *ibid.*; 347: 955.
6. Pollak PT, *et al.* The use of amiodarone for in-hospital cardiac arrest at two tertiary care centres. *Can J Cardiol* 2006; 22: 199–202.
7. Rea RS, *et al.* Comparing intravenous amiodarone or lidocaine, or both, outcomes for inpatients with pulseless ventricular arrhythmias. *Crit Care Med* 2006; 34: 1617–23.

Cardiac arrhythmias. Amiodarone is an effective drug for the treatment of symptomatic supraventricular and ventricular arrhythmias[1,2] (p. 1266.1); it has a relatively low risk of cardiovascular adverse effects and may be particularly useful in patients with structural heart disease. It is also used to prevent recurrence of both supraventricular and ventricular arrhythmias, although non-cardiac toxicity

may limit its long-term use;[2] a small study[3] suggested that short-term use (4 weeks) delayed the recurrence of atrial fibrillation after electrical cardioversion, but the benefits of this approach require confirmation in larger studies. Amiodarone has been used in children (see p. 1300.3), and has been given by various routes to terminate fetal arrhythmias.[4,5]

Perioperative use[6-8] reduces the incidence of atrial fibrillation and other arrhythmias after cardiac surgery. Amiodarone may also have a role in the management of **cardiac arrest** (see Advanced Cardiac Life Support, p. 1300.3); it has been tried for its antiarrhythmic effect in the management of **heart failure** (see below).

Amiodarone has been used for the prevention of sudden cardiac death in patients with asymptomatic ventricular arrhythmias following myocardial infarction, in patients with a history of aborted sudden cardiac death, and in patients with hypertrophic cardiomyopathy or other cardiac disorders that place them at high risk. Although amiodarone may reduce mortality the effect appears to be small,[2,9,10] and early use of high doses after myocardial infarction may be detrimental.[11] For long-term prophylaxis, implantable cardioverter defibrillators are more effective than antiarrhythmic drugs and are usually preferred; amiodarone may have a role as an adjunct to implantable cardioverter defibrillators to prevent frequent shocks,[12] and may also be used in patients who cannot be given an implantable cardioverter defibrillator.

While amiodarone can cause torsade de pointes it appears to do so rarely[13] and patients who have had this form of ventricular tachycardia as a result of other antiarrhythmic therapy have been given amiodarone subsequently without a recurrence.[14]

1. Desai AD, *et al.* The role of intravenous amiodarone in the management of cardiac arrhythmias. *Ann Intern Med* 1997; 127: 294–303. Correction. *ibid.* 1998; 128: 505.
2. Connolly SJ. Evidence-based analysis of amiodarone efficacy and safety. *Circulation* 1999; 100: 2025–34.
3. Boos C, *et al.* A short course of oral amiodarone improves sinus rhythm maintenance post-cardioversion for atrial fibrillation. *Heart* 2004; 90: 1063–4.
4. Flack NJ, *et al.* Amiodarone given by three routes to terminate fetal atrial flutter associated with severe hydrops. *Obstet Gynecol* 1993; 82: 714–16.
5. Strasburger JF, *et al.* Amiodarone therapy for drug-refractory fetal tachycardia. *Circulation* 2004; 109: 375–9.
6. Aasbo JD, *et al.* Amiodarone prophylaxis reduces major cardiovascular morbidity and length of stay after cardiac surgery: a meta-analysis. *Ann Intern Med* 2005; 143: 327–36.
7. Mitchell LB, *et al.* Prophylactic oral amiodarone for the prevention of arrhythmias that begin early after revascularization, valve replacement, or repair: PAPABEAR: a randomized controlled trial. *JAMA* 2005; 294: 3093–3100.
8. Khanderia U, *et al.* Amiodarone for atrial fibrillation following cardiac surgery: development of clinical practice guidelines at a university hospital. *Clin Cardiol* 2008; 31: 6–10.
9. Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. *Lancet* 1997; 350: 1417–24.
10. Hilleman DE, Bauman JL. Role of antiarrhythmic therapy in patients at risk for sudden cardiac death: an evidence-based review. *Pharmacotherapy* 2001; 21: 556–75.
11. Elizari MV, *et al.* Morbidity and mortality following early administration of amiodarone in acute myocardial infarction. *Eur Heart J* 2000; 21: 198–205.
12. Connolly SJ, *et al.* Comparison of β-blockers, amiodarone plus β-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. *JAMA* 2006; 295: 165–71.
13. Hohnloser SH, *et al.* Amiodarone-associated proarrhythmic effects: a review with special reference to torsade de pointes tachycardia. *Ann Intern Med* 1994; 121: 529–35.
14. Mattioni TA, *et al.* Amiodarone in patients with previous drug-mediated torsade de pointes: long-term safety and efficacy. *Ann Intern Med* 1989; 111: 574–80.

Heart failure. Sudden deaths in patients with severe heart failure (p. 1262.3) have been attributed to ventricular arrhythmias but routine use of antiarrhythmics is not recommended since many have a negative inotropic effect. Amiodarone, which is not a negative inotrope, is usually the drug of choice in patients with heart failure and symptomatic arrhythmias, but its role for prophylaxis is less clear. In the GESICA study (Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina)[1] amiodarone appeared to reduce mortality in patients with severe chronic heart failure who were without symptomatic ventricular arrhythmias. The decrease in mortality appeared to be greater than could be expected from antiarrhythmic activity alone. However, in the CHF-STAT study (Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure)[2] involving patients with heart failure and premature ventricular contractions, overall survival did not appear to be improved by amiodarone. A meta-analysis[3] including these and 3 further studies concluded that amiodarone reduced the rate of arrhythmic or sudden death in high-risk patients and that this resulted in an overall reduction in mortality. However, further studies[4,5] found that amiodarone had no effect on long-term survival, whereas implantable cardioverter defibrillators reduced mortality by about 25%, and a retrospective analysis[6] of a study in patients with heart failure after acute myocardial infarction found that mortality was higher in those taking amiodarone. Although some studies[1,7,8] have suggested that amiodarone may also improve cardiac function, adverse effects limit its use, and it is not currently recommended in heart failure except in patients with symptomatic ventricular arrhythmias.

1. Doval HC, *et al.* Randomised trial of low-dose amiodarone in severe congestive heart failure. *Lancet* 1994; 344: 493–8.
2. Singh SN, *et al.* Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. *N Engl J Med* 1995; 333: 77–82.
3. Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. *Lancet* 1997; 350: 1417–24.
4. Bardy GH, *et al.* Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; 352: 225–37.
5. Packer DL, *et al.* Impact of implantable cardioverter-defibrillator, amiodarone, and placebo on the mode of death in stable patients with heart failure: analysis from the Sudden Cardiac Death in Heart Failure Trial. *Circulation* 2009; 120: 2170–6.
6. Thomas KL, *et al.* Amiodarone use after acute myocardial infarction complicated by heart failure and/or left ventricular dysfunction may be associated with excess mortality. *Am Heart J* 2008; 155: 87–93.
7. Takemura K, *et al.* Low-dose amiodarone for patients with advanced heart failure who are intolerant of beta-blockers. *Circ J* 2002; 66: 441–4.
8. Choo DC, *et al.* Amiodarone rescue therapy for severe decompensated heart failure initially unsuitable for beta-blockers. *J Cardiovasc Pharmacol Ther* 2003; 8: 187–92.

Adverse Effects and Treatment

Adverse effects are common with amiodarone. Many are dose-related and reversible with reduction in dose; however, because of its long half-life this can take some time and adverse effects may develop after treatment is stopped.

Adverse cardiovascular effects associated with amiodarone include severe bradycardia, sinus arrest, and conduction disturbances. Severe hypotension may follow intravenous use, particularly (though not exclusively) at rapid infusion rates. Amiodarone may also produce ventricular tachyarrhythmias; torsade de pointes has been reported but appears to be less of a problem with amiodarone than other antiarrhythmics. Rarely, heart failure may be precipitated or aggravated.

Amiodarone reduces the peripheral transformation of thyroxine (T_4) to tri-iodothyronine (T_3) and increases the formation of reverse-T_3. It can affect thyroid function and may induce hypo- or hyperthyroidism.

There have been reports of severe pulmonary toxicity including pulmonary fibrosis and interstitial pneumonitis; these effects are usually reversible on withdrawal of amiodarone but are potentially fatal. Pulmonary haemorrhage has also been noted rarely.

Amiodarone can adversely affect the liver. There may be abnormal liver function tests and cirrhosis or hepatitis; fatalities have been reported.

Prolonged use of amiodarone causes the development of benign yellowish-brown corneal microdeposits in the majority of patients, sometimes associated with coloured haloes of light; these are reversible on stopping therapy. Photosensitivity reactions are also common and more rarely blue-grey discoloration of the skin may occur.

Other adverse effects reported include benign intracranial hypertension, haemolytic or aplastic anaemia, peripheral neuropathy, paraesthesias, myopathy, ataxia, tremor, nausea, vomiting, a metallic taste, nightmares, headaches, sleeplessness, fatigue, and epididymitis.

Thrombophlebitis can occur if amiodarone is injected regularly or infused for prolonged periods into a peripheral vein. Rapid intravenous injection has been associated with anaphylactic shock, hot flushes, sweating, and nausea.

It has been suggested that amiodarone-induced phospholipidosis may explain some of its adverse effects. Amiodarone's iodine content contributes to its thyrotoxicity.

Reviews of the adverse effects of amiodarone.

1. Naccarelli GV, *et al.* Adverse effects of amiodarone: pathogenesis, incidence and management. *Med Toxicol Adverse Drug Exp* 1989; 4: 246–53.
2. Kerin NZ, *et al.* Long-term efficacy and toxicity of high- and low-dose amiodarone regimens. *J Clin Pharmacol* 1989; 29: 418–23.
3. Perkins MW, *et al.* Intraoperative complications in patients receiving amiodarone: characteristics and risk factors. *DICP Ann Pharmacother* 1989; 23: 757–63.
4. Vrobel TR, *et al.* A general overview of amiodarone toxicity: its prevention, detection, and management. *Prog Cardiovasc Dis* 1989; 31: 393–426.
5. Morgan DJR. Adverse reactions profile: amiodarone. *Prescribers' J* 1991; 31: 104–11.
6. CSM/MCA. Amiodarone (Cordarone X). *Current Problems* 1996; 22: 3–4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20244585&RevisionSelectionMethod=LatestReleased (accessed 21/06/07)
7. Vorperian VR, *et al.* Adverse effects of low dose amiodarone: a meta-analysis. *J Am Coll Cardiol* 1997; 30: 791–8.
8. Bongard V, *et al.* Incidence rate of adverse drug reactions during long-term follow-up of patients newly treated with amiodarone. *Am J Ther* 2006; 13: 315–19.

Effects on electrolyte balance. Hyponatraemia associated with the syndrome of inappropriate secretion of antidiuretic hormone has been reported[1-4] in patients taking amiodarone. In each case, the hyponatraemia improved when the dose was reduced or amiodarone was stopped.

1. Odeh M, *et al.* Hyponatremia during therapy with amiodarone. *Arch Intern Med* 1999; 159: 2599–2600.
2. Ikegami H, *et al.* Syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by amiodarone: a report on two cases. *J Cardiovasc Pharmacol Ther* 2002; 7: 25–8.
3. Patel GP, Kasiar JB. Syndrome of inappropriate antidiuretic hormone-induced hyponatremia associated with amiodarone. *Pharmacotherapy* 2002; 22: 649–51.
4. Aslam MK, *et al.* Syndrome of inappropriate antidiuretic hormone secretion induced by amiodarone therapy. *Pacing Clin Electrophysiol* 2004; 27: 831–2.

Effects on the eyes. Slit-lamp examination showed corneal abnormalities in 103 of 105 patients treated with amiodarone for 3 months to 7 years.[1] The most advanced abnormality comprised whorled patterns with uniform granular opacities. The corneal deposits became denser if amiodarone dosage was increased and regressed if dosage was reduced. Ocular symptoms were reported in only 12 patients. Photophobia was reported in 3 patients, while 2 had visual haloes, 1 had blurring of vision, and a further 6 had lid irritation. However, lid irritation was considered a photosensitive skin reaction and blurred vision was probably not due to amiodarone. No patient had any deterioration in visual acuity attributable to amiodarone. In 16 patients amiodarone was withdrawn with complete clearing of corneal abnormalities within 7 months and routine ophthalmological monitoring was considered unnecessary in patients without ocular symptoms. Optic neuropathy[2-4] and neuritis with visual impairment have also been reported with amiodarone although it has been suggested[5] that the association is dubious and that the incidence of optic neuropathy in patients given amiodarone is low enough to support a hypothesis that the drug actually reduces the risk of idiopathic anterior ischaemic optic neuropathy. Nonetheless, licensed product information recommends that annual ophthalmological examinations should be performed.

A sicca syndrome with diminished tear and saliva production has been reported[6] during amiodarone treatment.

1. Ingram DV, *et al.* Ocular changes resulting from therapy with amiodarone. *Br J Ophthalmol* 1982; 66: 676–9.
2. Feiner LA, *et al.* Optic neuropathy and amiodarone therapy. *Mayo Clin Proc* 1987; 62: 702–17.
3. Macaluso DC, *et al.* Features of amiodarone-induced optic neuropathy. *Am J Ophthalmol* 1999; 127: 610–12.
4. Johnson LN, *et al.* The clinical spectrum of amiodarone-associated optic neuropathy. *J Natl Med Assoc* 2004; 96: 1477–91.
5. Mindel JS. Amiodarone and optic neuropathy. *Am Heart J* 2008; 156: 411–13.
6. Dickinson EJ, Wolman RL. Sicca syndrome associated with amiodarone therapy. *BMJ* 1986; 293: 510.

Effects on the genitalia. Epididymal swelling and scrotal pain have been reported with amiodarone.[1-3] Time to onset varied from 7 to 71 months after starting treatment, and resolution occurred within 10 weeks despite continuation of amiodarone in some patients. The mechanism of the reaction is unknown, but in 1 patient[2] the concentration of desethylamiodarone in semen was fivefold that in serum.

Brown discoloration of semen and sweat has also been associated with amiodarone therapy.[4]

1. Gasparich JP, *et al.* Non-infectious epididymitis associated with amiodarone therapy. *Lancet* 1984; ii: 1211–12.
2. Ward MJ, *et al.* Association of seminal desethylamiodarone concentration and epididymitis with amiodarone treatment. *BMJ* 1988; 296: 19–20.
3. Sadek I, *et al.* Amiodarone-induced epididymitis: report of a new case and literature review of 12 cases. *Can J Cardiol* 1993; 9: 833–6.
4. Adams PC, *et al.* Amiodarone in testis and semen. *Lancet* 1985; i: 341.

Effects on the heart. Amiodarone has the potential to provoke arrhythmias; it prolongs the QT interval and there have been reports of torsade de pointes. However, a review of the literature[1] indicated that the frequency of proarrhythmic events was low. The risk of torsade de pointes also appears to be lower with amiodarone than with other class III antiarrhythmics, possibly due to additional actions of amiodarone such as blockade of calcium channels.[2]

1. Hohnloser SH, *et al.* Amiodarone-associated proarrhythmic effects: a review with special reference to torsade de pointes tachycardia. *Ann Intern Med* 1994; 121: 529–35.
2. Brendorp B, *et al.* A benefit-risk assessment of class III antiarrhythmic agents. *Drug Safety* 2002; 25: 847–65.

Effects on lipid metabolism. Amiodarone increases phospholipid concentrations in tissues and this may be responsible for some of its adverse effects.[1] Although hyperlipidaemia may result from hypothyroidism, amiodarone can also increase serum-cholesterol concentrations independently of any effect on the thyroid.[2,3] The effect on triglyceride concentrations is not clear.[3]

1. Kodavanti UP, Mehendale HM. Cationic amphiphilic drugs and phospholipid storage disorder. *Pharmacol Rev* 1990; 42: 327–54.
2. Wiersinga WM, *et al.* An increase in plasma cholesterol independent of thyroid function during long-term amiodarone therapy: a dose-dependent relationship. *Ann Intern Med* 1991; 114: 128–32.

3. Lakhdar AA, *et al.* Long-term amiodarone therapy raises serum cholesterol. *Eur J Clin Pharmacol* 1991; 40: 477–80.

Effects on the liver. Plasma concentrations of liver enzymes are often increased in patients taking amiodarone but this is usually asymptomatic. However, there have been reports of hepatic injury,[1-3] including hepatitis and cirrhosis, with histological changes resembling alcoholic liver disease.[1] Fatal cirrhosis has been reported, usually in patients receiving high doses or long-term therapy,[4-9] and may develop after stopping amiodarone. However, rapidly progressive fatal hepatic failure has occurred[10] only one month after starting treatment. There have also been reports of severe cholestasis, including a case that was reversible,[11] and another that was fatal, despite amiodarone being stopped.[12] Acute hepatitis occurring within 24 hours of intravenous amiodarone has been reported,[13-15] but in 1 case[14] did not recur with subsequent oral therapy, suggesting that the reaction may have been related to the vehicle used in the intravenous formulation.

1. Simon JB, *et al.* Amiodarone hepatotoxicity simulating alcoholic liver disease. *N Engl J Med* 1984; 311: 167–72.
2. Babatin M, *et al.* Amiodarone hepatotoxicity. *Curr Vasc Pharmacol* 2008; 6: 228–36.
3. Raja K, *et al.* Drug-induced steatohepatitis leading to cirrhosis: long-term toxicity of amiodarone use. *Semin Liver Dis* 2009; 29: 423–8.
4. Lim PK, *et al.* Neuropathy and fatal hepatitis in a patient receiving amiodarone. *BMJ* 1984; 288: 1638–9.
5. Tordjman K, *et al.* Amiodarone and the liver. *Ann Intern Med* 1985; 102: 411–12.
6. Rinder HM, *et al.* Amiodarone hepatotoxicity. *N Engl J Med* 1986; 314: 318–19.
7. Richer M, Robert S. Fatal hepatotoxicity following oral administration of amiodarone. *Ann Pharmacother* 1995; 29: 582–6.
8. Singhal A, *et al.* Low dose amiodarone causing pseudo-alcoholic cirrhosis. *Age Ageing* 2003; 32: 224–5.
9. Oikawa H, *et al.* Liver cirrhosis induced by long-term administration of a daily low dose of amiodarone: a case report. *World J Gastroenterol* 2005; 11: 5394–7.
10. Lwakatare JM, *et al.* Fatal fulminating liver failure possibly related to amiodarone treatment. *Br J Hosp Med* 1990; 44: 60–1.
11. Morse RM, *et al.* Amiodarone-induced liver toxicity. *Ann Intern Med* 1988; 109: 838–40.
12. Chang C-C, *et al.* Severe intrahepatic cholestasis caused by amiodarone toxicity after withdrawal of the drug: a case report and review of the literature. *Arch Pathol Lab Med* 1999; 123: 251–6.
13. Pye M, *et al.* Acute hepatitis after parenteral amiodarone administration. *Br Heart J* 1988; 59: 690–1.
14. James PR, Hardman SMC. Acute hepatitis complicating parenteral amiodarone does not preclude subsequent oral therapy. *Heart* 1997; 77: 583–4.
15. Chan AL, *et al.* Fatal amiodarone-induced hepatotoxicity: a case report and literature review. *Int J Clin Pharmacol Ther* 2008; 46: 96–101.

Effects on the lungs. Pulmonary toxicity is one of the most severe adverse effects associated with amiodarone therapy. Reviews have suggested that it may occur in 5%[1] to up to 10%[2] of patients (although the incidence in controlled studies appears to be lower[3]) and fatalities have been reported.[1,4,5] The onset is usually chronic, and patients often present several months after starting amiodarone with increasing dyspnoea, cough, and pleuritic chest pain; however, the onset may also be more acute, and in one patient[6] occurred within days of starting amiodarone. Acute reactions have also developed in patients undergoing surgery or other procedures;[3,7] two patients with amiodarone pulmonary toxicity died less than 1 hour and 24 hours, respectively after pulmonary angiography.[8] Different forms of toxicity have been reported, including interstitial and alveolar infiltration,[9] fibrosis,[4] pneumonitis,[10] and pleural effusion;[11,12] amiodarone-induced asthma has also been reported.[13] The mortality rate is estimated to be about 10% in those with pneumonitis; mortality is highest (about 50%) in patients who develop symptoms suggestive of acute respiratory distress syndrome.[1] Toxicity has been associated with increasing age, duration of treatment, and dose,[1,9,14] but it has also occurred at low doses,[15] and different mechanisms may be involved;[2,7] some patients have evidence of direct toxicity, while in others[10] an immunological reaction appears to be involved. Most patients recover gradually if amiodarone is stopped, but treatment with corticosteroids may be given if necessary,[1,2,9] and has been particularly recommended[7] in acute lung injury.

1. Papiris SA, *et al.* Amiodarone: review of pulmonary effects and toxicity. *Drug Safety* 2010; 33: 539–58.
2. Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity: recognition and pathogenesis. *Chest* 1988; 93: 1067–75 (part 1) and 1242–8 (part 2).
3. Sunderji R, *et al.* Pulmonary effects of low dose amiodarone: a review of the risks and recommendations for surveillance. *Can J Cardiol* 2000; 16: 1435–40.
4. Morera J, *et al.* Amiodarone and pulmonary fibrosis. *Eur J Clin Pharmacol* 1983; 24: 591–3.
5. CSM. Recurrent ventricular tachycardia: adverse drug reactions. *BMJ* 1986; 292: 50.
6. Goldstein I, *et al.* Very early onset of acute amiodarone pulmonary toxicity presenting with hemopysis. *Chest* 1997; 111: 1446–7.
7. Ashrafian H, Davey P. Is amiodarone an underrecognized cause of acute respiratory failure in the ICU? *Chest* 2001; 120: 275–82.
8. Wood DL, *et al.* Amiodarone pulmonary toxicity: report of two cases associated with rapidly progressive fatal adult respiratory distress syndrome after pulmonary angiography. *Mayo Clin Proc* 1985; 60: 601–3.
9. Marchlinski FE, *et al.* Amiodarone pulmonary toxicity. *Ann Intern Med* 1982; 97: 839–45.
10. Venet A, *et al.* Five cases of immune-mediated amiodarone pneumonitis. *Lancet* 1984; I: 962–3.
11. Mittal SR, Maheshwari M. Amiodarone-induced exudative pleural effusion—a case report and review of literature. *Indian Heart J* 2006; 58: 352–5.
12. Uong V, *et al.* Amiodarone-induced loculated pleural effusion: case report and review of the literature. Abridged version: *Pharmacotherapy* 2010; 30: 218. Full version: http://www.pharmacotherapy.org/Case_Reports/Pharm3002e_Uong-CR.pdf (accessed 16/02/10)
13. Yavuzgil O, *et al.* New-onset bronchial asthma induced by low-dose amiodarone. *Ann Pharmacother* 2005; 39: 385–6.
14. Ernawati DK, *et al.* Amiodarone-induced pulmonary toxicity. *Br J Clin Pharmacol* 2008; 66: 82–7.
15. Ott MC, *et al.* Pulmonary toxicity in patients receiving low-dose amiodarone. *Chest* 2003; 123: 646–51.

Effects on mental state. There have been isolated reports of patients (age range 54 to 80 years) developing delirium within about 4 to 17 days of starting amiodarone therapy.[1-3] Mental status improved on withdrawal of amiodarone. Amiodarone-associated depression has also been reported.[4,5]

1. Trohman RG, *et al.* Amiodarone-induced delirium. *Ann Intern Med* 1988; 108: 68–9.
2. Barry JJ, Franklin K. Amiodarone-induced delirium. *Am J Psychiatry* 1999; 156: 1119.
3. Athwal H, *et al.* Amiodarone-induced delirium. *Am J Geriatr Psychiatry* 2003; 11: 696–7.
4. Ambrose A, Salib E. Amiodarone-induced depression. *Br J Psychiatry* 1999; 174: 366–7.
5. Cheesman N, Taylor D. Psychosis and depression associated with alteration to amiodarone therapy. *J Psychopharmacol* 2010; 24: 131–3.

Effects on the nervous system. Neurological toxicity is a recognised adverse effect of amiodarone. A study[1] in 10 patients treated with amiodarone for more than 2 years found that 3 had evidence of peripheral neuropathy, possibly correlated with high doses and high serum concentrations of amiodarone. A later analysis[2] based on retrospective review of records for 707 patients treated with amiodarone found the cumulative incidence of neurotoxic events possibly related to the drug to be just under 3%; these included tremor, ataxia, peripheral neuropathy, and cognitive impairment. The main risk factor was considered to be duration of treatment.

1. Fraser AG, McQueen INF. Adverse reactions during treatment with amiodarone hydrochloride. *BMJ* 1983; 287: 612.
2. Orr CF, Ahlskog JE. Frequency, characteristics, and risk factors for amiodarone neurotoxicity. *Arch Neurol* 2009; 66: 865–9.

Effects on the pancreas. Pancreatitis has been reported[1] in a patient 4 days after starting amiodarone. Symptoms resolved after withdrawal of the drug but returned on re-exposure.

1. Bosch X, Bernadich O. Acute pancreatitis during treatment with amiodarone. *Lancet* 1997; 350: 1300.

Effects on the skin and hair. The most common adverse skin reaction associated with amiodarone is photosensitivity. This is a phototoxic rather than a photoallergic reaction[1-3] and the wavelengths responsible extend from the long-wave ultraviolet (UVA) into the visible light range.[1] Affected patients should be advised to wear protective clothing and avoid exposure to sunlight. Topical sunblock preparations, such as those containing zinc or titanium oxides, may reduce the risk of reaction and a reduction in amiodarone dosage may also be useful.[1] Although pyridoxine has been reported[4] to protect against amiodarone-induced photosensitivity, results from a double-blind placebo-controlled study[5] indicated that it may enhance the photosensitivity. Photosensitivity may continue for several weeks after withdrawal of amiodarone due to its extensive distribution, and persistence for longer periods has been reported.[6] There have also been reports[7] of basal cell carcinoma, possibly related to amiodarone-induced photosensitivity.

Blue-grey[2,3,8] and golden-brown[3] pigmentation of light-exposed skin have been reported during long-term amiodarone use. The pigmentation is usually slowly reversible on withdrawing amiodarone but may not completely disappear. The mean concentrations of amiodarone and its desethyl metabolite in light-exposed pigmented skin have been found to be 10 times the concentrations in non-exposed skin.[2] Discoloration of semen and sweat has also been noted (see Effects on the Genitalia, p. 1301.3).

Cutaneous vasculitis,[9,10] exfoliative dermatitis,[11] and fatal toxic epidermal necrolysis[12,13] have been reported. Alopecia[14,15] has been associated with amiodarone but increased hair growth,[3] possibly due to the vasodilator activity of amiodarone, has also been reported. Extravasation of amiodarone injection has caused severe skin necrosis.[16]

1. Ferguson J, *et al.* Prevention of amiodarone-induced photosensitivity. *Lancet* 1984; II: 414.
2. Zachary CB, *et al.* The pathogenesis of amiodarone-induced pigmentation and photosensitivity. *Br J Dermatol* 1984; 110: 451–6.
3. Ferguson J, *et al.* A study of cutaneous photosensitivity induced by amiodarone. *Br J Dermatol* 1985; 113: 537–49.
4. Kaufmann G. Pyridoxine against amiodarone-induced photosensitivity. *Lancet* 1984; I: 51–2.
5. Mulrow JP, *et al.* Pyridoxine and amiodarone-induced photosensitivity. *Ann Intern Med* 1985; 103: 68–9.
6. Yones SS, *et al.* Persistent severe amiodarone-induced photosensitivity. *Clin Exp Dermatol* 2005; 30: 500–502.
7. Hall MA, *et al.* Basalioma after amiodarone therapy—not only in Britain. *Br J Dermatol* 2004; 151: 932–3.
8. Ammoury A, *et al.* Photodistribution of blue-gray hyperpigmentation after amiodarone treatment: molecular characterization of amiodarone in the skin. *Arch Dermatol* 2008; 144: 92–6.
9. Starke ID, Barbatis C. Cutaneous vasculitis associated with amiodarone therapy. *BMJ* 1985; 291: 940.
10. Gutierrez R, *et al.* Vasculitis associated with amiodarone treatment. *Ann Pharmacother* 1994; 28: 537.
11. Moots RJ, Banerjee A. Exfoliative dermatitis after amiodarone treatment. *BMJ* 1988; 296: 1332–3.
12. Bencini PL, *et al.* Toxic epidermal necrolysis and amiodarone treatment. *Arch Dermatol* 1985; 121: 838.
13. Yung A, *et al.* Two unusual cases of toxic epidermal necrolysis. *Australas. Dermatol* 2002; 43: 35–8.
14. Samanta A, *et al.* Adverse reactions during treatment with amiodarone hydrochloride. *BMJ* 1983; 287: 503.
15. Samuel LM, *et al.* Amiodarone and hair loss. *Postgrad Med J* 1992; 68 771.
16. Russell SJ, Saltissi S. Amiodarone induced skin necrosis. *Heart* 2006; 92 1395.

Effects on thyroid function. Amiodarone has complex effects on thyroid function[1-5] and, while the majority of euthyroid patients receiving amiodarone remain clinically euthyroid, both hypo- and hyperthyroidism may occur. Amiodarone has direct effects on the thyroid gland, but also alters serum concentrations of thyroid hormones complicating the interpretation of thyroid function tests. Use of amiodarone results in a reduction of the peripheral conversion of thyroxine (T_4) to tri-iodothyronine (T_3) with a resulting increase in T_4, a modest fall in T_3, and an increase in reverse-T_3 concentrations; the basal serum-TSH (thyroid-stimulating hormone; thyrotrophin) concentration rises initially but tends to return to normal after about 3 months of treatment.

The prevalence of clinical hypo- and hyperthyroidism appears to correlate with dietary iodine intake, with hypothyroidism being more common in areas of adequate iodine intake and hyperthyroidism in areas of lower intake. The overall incidence of thyroid disorders has been suggested[2] to be anywhere between 1 to 32%. Although the exact mechanism for the toxicity is unknown, amiodarone has a high iodine content (about 75 mg of iodine in each 200-mg tablet) and the large iodine load may affect the thyroid, particularly in patients with an underlying subclinical thyroid defect. Auto-immune mechanisms may also contribute and antithyroid antibodies have been detected during amiodarone therapy. The high iodine load appears to be the main mechanism for hypothyroidism, but for hyperthyroidism two mechanisms may be involved. Type I amiodarone-induced thyrotoxicosis appears to be precipitated by the iodine load, whereas type II amiodarone-induced thyrotoxicosis is a destructive thyroiditis that is probably caused by a direct toxic effect on the thyroid gland.

Assessment of thyroid function is recommended in patients before starting amiodarone treatment and periodically during treatment; TSH concentrations should be measured, along with free T_3 and T_4.

Amiodarone-induced hypothyroidism usually presents similarly to other forms of hypothyroidism[1-3] and treatment is with levothyroxine, starting with a low dose and gradually increasing until control is achieved; amiodarone may be continued.

Amiodarone-induced hyperthyroidism is a more complex problem and may be difficult to diagnose and manage.[1-3,6] Patients may present with classical symptoms such as tachycardia, tremor, weight loss, nervousness, and irritability, but in other cases reappearance of angina, or a worsening of arrhythmia may be the only indication. Amiodarone is usually stopped if clinical hyperthyroidism develops, but may be continued if necessary while the hyperthyroidism is treated.[1-3,6-8] Management depends on whether the patient has *type I* or *type II hyperthyroidism*. Treatment of type I is usually with the thiourea drugs carbimazole, thiamazole, or propylthiouracil; in resistant cases potassium perchlorate may be used with a thiourea to reduce the thyroid iodine load. Lithium carbonate has been used as an alternative, but its role is not yet established.[1,2] In type II thyrotoxicosis, treatment is usually with corticosteroids, and they may also be used with thioureas where the type is mixed or unclear.[8] Oral cholecystographic contrast media such as iopanoic acid have also been used, but appear to be less effective.[9] Radio-iodine can be used but may not be effective if the uptake of radio-iodine by the thyroid is low due to the iodine load from amiodarone; radio-iodine has also been used[10] to allow amiodarone to be restarted in patients with a history of amiodarone-induced hyperthyroidism. Thyroidectomy may have a role[1-3,6,8,11] in the treatment of resistant amiodarone-induced hyperthyroidism.

1. Loh K-C. Amiodarone-induced thyroid disorders: a clinical review. *Postgrad Med J* 2000; 76: 133–40.
2. Martino E, *et al.* The effects of amiodarone on the thyroid. *Endocr Rev* 2001; 22: 240–54.
3. Basaria S, Cooper DS. Amiodarone and the thyroid. *Am J Med* 2005; 118 706–14.

4. Eskes SA, Wiersinga WM. Amiodarone and thyroid. *Best Pract Res Clin Endocrinol Metab* 2009; 23: 735–51.
5. Cohen-Lehman J, *et al.* Effects of amiodarone therapy on thyroid function. *Nat Rev Endocrinol* 2010; 6: 34–41.
6. Bartalena L, *et al.* Diagnosis and management of amiodarone-induced thyrotoxicosis in Europe: results of an international survey among members of the European Thyroid Association. *Clin Endocrinol (Oxf)* 2004; 61: 494–502.
7. Uzan L, *et al.* Continuation of amiodarone therapy despite type II amiodarone-induced thyrotoxicosis. *Drug Safety* 2006; 29: 231–6.
8. Bahn RS, *et al.* Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Thyroid* 2011; 21: 593–646. Also printed in *Endocr Pract* 2011; 17: 456–520. Also available at: https://www.aace.com/sites/default/files/HyperGuidelines2011.pdf (accessed 28/06/11)
9. Bogazzi F, *et al.* Treatment of type II amiodarone-induced thyrotoxicosis by either iopanoic acid or glucocorticoids: a prospective, randomized study. *J Clin Endocrinol Metab* 2003; 88: 1999–2002.
10. Hermida J-S, *et al.* Radioiodine ablation of the thyroid to allow the reintroduction of amiodarone treatment in patients with a prior history of amiodarone-induced thyrotoxicosis. *Am J Med* 2004; 116: 345–8.
11. Gough IR, Gough J. Surgical management of amiodarone-associated thyrotoxicosis. *Med J Aust* 2002; 176: 128–9.

Lupus. There have been reports[1-3] of lupus developing in patients treated with amiodarone; the condition improved when amiodarone was stopped.

1. Susano R, *et al.* Amiodarone induced lupus. *Ann Rheum Dis* 1999; 58: 655–6.
2. Sheikhzadeh A, *et al.* Drug-induced lupus erythematosus by amiodarone. *Arch Intern Med* 2002; 162: 834–6.
3. Kundu AK. Amiodarone-induced systemic lupus erythematosus. *J Assoc Physicians India* 2003; 51: 216–17.

Precautions

Amiodarone should not be given to patients with bradycardia, sino-atrial block, AV block or other severe conduction disorders (unless the patient has a pacemaker), severe hypotension, or severe respiratory failure. It may be used, but with caution, in patients with heart failure. Electrolyte disorders should be corrected before starting treatment. The use of amiodarone should be avoided in patients with iodine sensitivity, or evidence or history of thyroid disorders. Patients taking amiodarone should avoid exposure to sunlight.

Thyroid function should be monitored regularly in order to detect amiodarone-induced hyper- or hypothyroidism. Thyroxine, tri-iodothyronine, and thyrotrophin (thyroid-stimulating hormone; TSH) concentrations should be measured; clinical assessment is important but is unreliable alone. See also Effects on Thyroid Function under Adverse Effects and Treatment, p. 1302.3.

Tests of liver and pulmonary function should also be carried out regularly in patients on long-term therapy. Ophthalmological examinations should be performed annually. Although urinary excretion is not a major route for the elimination of amiodarone or its metabolites, there is a possibility of iodine accumulation in renal impairment.

Intravenous injections of amiodarone should be given slowly: if prolonged or repeated infusions are envisaged, the use of a central venous catheter should be considered. Some intravenous preparations of amiodarone contain benzyl alcohol, a preservative that has caused fatal 'gasping syndrome' in neonates (see Neonates, under Benzyl Alcohol, p. 1741.1), and should be avoided in infants and children up to 3 years old.

Some of the contra-indications for amiodarone may not apply when it is given intravenously in emergency situations.

Administration. For the problems of controlling the delivery rate of amiodarone by intravenous infusion, see under Uses and Administration, p. 1300.3.

Breast feeding. Amiodarone is distributed into breast milk[1,2] and significant amounts may be ingested if infants are breast fed. Licensed product information therefore contra-indicates the use of amiodarone during breast feeding, and the American Academy of Pediatrics considers[3] that the use of amiodarone may be of concern due to the risk of hypothyroidism in the infant. In one study,[2] amiodarone was still detectable in breast milk several weeks after amiodarone was stopped, suggesting that caution is still required. However, there has been a report[4] of an infant who was successfully breast fed with close monitoring of thyroid function; the mother stopped amiodarone at delivery.

1. Pitcher D, *et al.* Amiodarone in pregnancy. *Lancet* 1983; i: 597–8.
2. Plomp TA, *et al.* Use of amiodarone during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1992; 43: 201–7.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)
4. Hall CM, McCormick KPB. Amiodarone and breast feeding. *Arch Dis Child Fetal Neonatal Ed* 2003; 88: F255–F258.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amiodarone as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pregnancy. Each 200-mg tablet of amiodarone contains about 75 mg of iodine. The potential effect of this iodine load on the fetus has limited the use of amiodarone in pregnancy since iodine freely crosses the placenta and may cause thyroid disorders in the fetus. In addition, amiodarone and desethylamiodarone both cross the placenta, with respective concentrations in cord blood at delivery of about 10% and 25% of the maternal plasma concentrations, and direct effects on the fetus are therefore possible. However, a review[1] of 64 reported cases of amiodarone use during pregnancy found no evidence of an increased incidence of fetal malformations; hypothyroidism occurred in 14 neonates (22%), but only 2 had detectable goitre, and 2 neonates had transient hyperthyroidism. Neurodevelopmental follow-up was limited, but mild abnormalities were reported in some cases; this appeared to be independent of thyroid status, suggesting it may have been due to a direct effect of amiodarone.

1. Bartalena L, *et al.* Effects of amiodarone administration during pregnancy on neonatal thyroid function and subsequent neurodevelopment. *J Endocrinol Invest* 2001; 24: 116–30.

Interactions

Amiodarone should be used with caution with other drugs liable to induce bradycardia, such as beta blockers or calcium-channel blockers, and with other antiarrhythmic drugs. Use with arrhythmogenic drugs, particularly drugs that prolong the QT interval such as fluoroquinolones, phenothiazine antipsychotics, tricyclic antidepressants, halofantrine, and terfenadine, should be avoided. Drugs that cause hypokalaemia or hypomagnesaemia may also increase the risk of arrhythmias with amiodarone. Amiodarone is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2C8 and interactions may occur with inhibitors of these enzymes, particularly with inhibitors of CYP3A4 such as HIV-protease inhibitors, cimetidine, and grapefruit juice. Enzyme inducers such as rifampicin and phenytoin may reduce amiodarone concentrations. In addition, amiodarone is an inhibitor of some cytochrome P450 isoenzymes, including CYP3A4 and CYP2D6, resulting in higher plasma concentrations of other drugs metabolised by these enzymes. Examples of these include ciclosporin, clonazepam, digoxin, flecainide, phenytoin, procainamide, quinidine, simvastatin, and warfarin. Amiodarone also inhibits P-glycoprotein and could affect drugs that are P-glycoprotein substrates.

Reviews.

1. Marcus FI. Drug interactions with amiodarone. *Am Heart J* 1983; 106: 924–30.
2. Lesko LJ. Pharmacokinetic drug interactions with amiodarone. *Clin Pharmacokinet* 1989; 17: 130–40.

Agalsidase. For the effect of the use of amiodarone with *agalsidase alfa* or *beta*, see p. 2438.1.

Antibacterials. Palpitations and activation of an implantable cardioverter defibrillator occurred[1] in a woman receiving amiodarone when *rifampicin* was added. Serum concentrations of amiodarone were reduced, probably due to induction of metabolising enzymes by rifampicin.

1. Zarembski DG, *et al.* Impact of rifampin on serum amiodarone concentrations in a patient with congenital heart disease. *Pharmacotherapy* 1999; 19: 249–51.

Antiepileptics. The interaction between *phenytoin* and amiodarone resulting in increased plasma-phenytoin concentrations is widely recognised (see p. 542.3). However, phenytoin is a hepatic enzyme inducer and has been reported[1] to decrease serum-amiodarone concentrations by 32 and 49% after 1 and 2 weeks of use respectively.

1. Nolan PE, *et al.* Effect of phenytoin on the clinical pharmacokinetics of amiodarone. *J Clin Pharmacol* 1990; 30: 1112–19.

Antivirals. A potential interaction has been suggested between amiodarone and HIV-protease inhibitors due to inhibition of amiodarone metabolism. Raised serum concentrations of amiodarone have been reported[1] in a patient given *indinavir* for postexposure prophylaxis; no clinical signs of toxicity occurred.

1. Lohman JJHM, *et al.* Antiretroviral therapy increases serum concentrations of amiodarone. *Ann Pharmacother* 1999; 33: 645–6.

Contrast media. For mention of prolonged QT intervals in patients taking amiodarone who were given *iohexol*, see p. 1590.2.

Grapefruit juice. A study[1] in healthy subjects reported that grapefruit juice decreased the metabolism of amiodarone; the area under the plasma concentration-time curve (AUC) and the peak plasma concentration of amiodarone were both increased.

1. Libersa CC, *et al.* Dramatic inhibition of amiodarone metabolism induced by grapefruit juice. *Br J Clin Pharmacol* 2000; 49: 373–8.

Histamine H_2-antagonists. *Cimetidine* inhibits hepatic metabolism and an increase in the serum-amiodarone concentration has been reported[1] in 8 out of 12 patients given amiodarone and cimetidine.

1. Hogan C, *et al.* Cimetidine-amiodarone interaction. *J Clin Pharmacol* 1988; 28: 909.

Theophylline. For a report of increased serum-theophylline concentrations and resultant adverse effects in a patient when amiodarone was added to therapy, see Antiarrhythmics, p. 1234.1.

Pharmacokinetics

Amiodarone is absorbed variably and erratically from the gastrointestinal tract; the average bioavailability is about 50%, but varies widely, and both the rate and extent of absorption are increased by food. It is extensively distributed to body tissues and accumulates notably in fat as well as in skeletal muscles and highly perfused tissues such as liver, lungs, and spleen; it has been reported to be about 96% bound to plasma proteins. The terminal elimination half-life is about 50 days with a range of about 20 to 100 days due to its extensive tissue distribution. On stopping prolonged amiodarone therapy a pharmacological effect is evident for a month or more. A major metabolite, desethylamiodarone, has antiarrhythmic properties. There is very little urinary excretion of amiodarone or its metabolites, the major route of excretion being in faeces via the bile; some enterohepatic recycling may occur. Amiodarone and desethylamiodarone are reported to cross the placenta and to be distributed into breast milk.

After intravenous injection the maximum effect occurs within 1 to 30 minutes and persists for 1 to 3 hours.

Reviews.

1. Latini R, *et al.* Clinical pharmacokinetics of amiodarone. *Clin Pharmacokinet* 1984; 9: 136–56.
2. Roden DM. Pharmacokinetics of amiodarone: implications for drug therapy. *Am J Cardiol* 1993; 72: 45F–50F.
3. Pollak PT, *et al.* Population pharmacokinetics of long-term oral amiodarone therapy. *Clin Pharmacol Ther* 2000; 67: 642–52.
4. Kotake T, *et al.* Serum amiodarone and desethylamiodarone concentrations following nasogastric versus oral administration. *J Clin Pharm Ther* 2006; 31: 237–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Amiocar; Angoten; Asulbian; Atlansil; Cistimela†; Coronax; Coronovo; Miodarona; Miotenk; Ritmocardyl; *Austral.*: Aratac; Cardinorm†; Cordarone X; Rithmik; *Austria*: Sedacoron; *Belg.*: Cordarone; *Braz.*: Amiobal; Amioron; Ancoron; Angiodarona; Angyton; Atlansil; Cardicoron; Cor Mio; Diodarone†; Hiperterona; Miocor; Miocoron; Miodaren; Miodarid; Miodaron; Miodon; *Canad.*: Cordarone; *Chile*: Atlansil; Cordarone; Ritmocardyl; *China*: Cordarone (可达龙); *Cz.*: Amiohexal; Amiokordin; Cordarone; Ritmopuls†; Rivodaron; Sedacoron; *Denm.*: Amiodar†; Angoron; Cordan; Cordarone; *Fin.*: Cordarone; *Fr.*: Corbionax; Cordarone; *Ger.*: Amiodarex†; Amiogamma; Amiohexal†; Cordarex†; Cornaron†; *Gr.*: Angoron; *Hong Kong*: Aratac†; Cordarone; Sedacoron; *Hung.*: Cordarone; Sedacoron†; *India*: Aldarone; Amiodar; Amiodon; Biodaron; Cardasol; Cardichek; Cordarone; Duron; Eurythmic; Panaron; *Indon.*: Cordarone; Kendaron; Tiaryt; *Irl.*: Cordarone X; *Israel*: Amiocor; Amiodacore; Procor; *Ital.*: Amiodar; Angoron; Cordarone; *Jpn*: Ancaron; *Malaysia*: Aratac†; Cardilor; Cordarone; *Mex.*: Braxan; Cordarone; Forken; Keritmon; Sinarona; *Neth.*: Cordarone; *Norw.*: Cordarone; *NZ*: Aratac; Cordarone X; *Philipp.*: Amio; Anoion; Arrythgo; Cordarone; Myodial; *Pol.*: Amiokordin; Cordarone; Opacorden; *Port.*: Corbionax; Cordarone; Miodrone; *Rus.*: Amiokordin (Амиокордин); Cardiodarone (Кардиодарон); Cordarone (Кордарон); Rhythmiodarone (Ритмиодарон); Rythmorest (Ритморест); Sedacoron (Седакорон); *S.Afr.*: Adcorone; Amiotach; Arycor; Cordarone X; Hexarone; *Singapore*: Aratac; Cordarone; *Spain*: Trangorex; *Swed.*: Cordarone; *Switz.*: Amiodar; Cordarone; Escodaron; Rivodarone; *Thai.*: Aldarone; Amdarone†; Amidarone 200; Aratac†; Cardilor; Cordarone; *Turk.*: Cordarone; *UAE*: Amirone; *UK*: Amyben; Cordarone X; *Ukr.*: Amidaron (Амидарон); Amiokordin (Амиокордин); Aritmil (Аритмил); Cardiodaron (Кардиодарон); Cordarone (Кордарон); Miorytmil (Миоритмил); *USA*: Cordarone; Nexterone; Pacerone; *Venez.*: Coradona; Diarona; Eudarona; Novarona; Trangorex.

Multi-ingredient Preparations. *Ukr.*: Tiodaron (Тиодарон).

Pharmacopoeial Preparations

BP 2014: Amiodarone Infusion; Amiodarone Oral Suspension; Amiodarone Tablets;

USP 36: Amiodarone Hydrochloride Oral Suspension.

Amlodipine *(BAN, rINN)*

Amlodipilini; Amlodipin; Amlodipina; Amlodipino; Amlodipinum; Амлодипин.

3-Ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate.

$C_{20}H_{25}ClN_2O_5$=408.9.

CAS — 88150-42-9.

ATC — C08CA01.

ATC Vet — QC08CA01.

UNII — 1J444QC288.

Amlodipine Besilate *(BANM, rINNM)*

Amlodipilinibesilaatti; Amlodipin Besilat; Amlodipinbesilat; Amlodipin-besylát; Amlodipin-bezilát; Amlodipine; Bésilate d'; Amlodipine Besylate (USAN); Amlodipini Besilas; Amlodipino besilatas; Amlodipino, besilato de; Besilato de amlodipino; UK-48340-26; Амлодипина безилат.

$C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$=567.0

CAS — 111470-99-6.

ATC — C08CA01.

ATC Vet — QC08CA01.

UNII — 864V2Q084H.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Amlodipine Besilate). A white or almost white powder. Slightly soluble in water and in isopropyl alcohol; sparingly soluble in dehydrated alcohol; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Amlodipine Besylate). A white or almost white powder. Slightly soluble in water and isopropyl alcohol; sparingly soluble in alcohol; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

Amlodipine Maleate *(BANM, USAN, rINNM)*

Amlodipine, Maléate d'; Amlodipini Maleas; Maleato de amlodipino; UK-48340-11; Амлодипина малеат.

$C_{20}H_{25}ClN_2O_5.C_4H_4O_4$=525.0

CAS — 88150-47-4.

ATC — C08CA01.

ATC Vet — QC08CA01.

UNII — CQ27G28ZJM.

Uses and Administration

Amlodipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p. 1447.2). It is used in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3).

Amlodipine is given orally as the besilate, but doses are usually expressed in terms of the base; amlodipine besilate 6.9 mg is equivalent to about 5 mg of amlodipine. The camsilate, maleate, and mesilate are also used.

In hypertension the usual initial dose is 5 mg once daily, increased, if necessary, to 10 mg once daily. Similar doses are given in the treatment of stable angina and Prinzmetal's angina. Lower initial doses may be used in elderly patients and those with hepatic impairment (see below).

Levamlodipine besilate, the (*S*)-isomer of amlodipine besilate, has also been used.

Amlodipine has been investigated for its apparent antibacterial activity.

Reviews.

1. Murdoch D, Heel RC. Amlodipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cardiovascular disease. *Drugs* 1991; 41: 478–505.
2. Haria M, Wagstaff AJ. Amlodipine: a reappraisal of its pharmacological properties and therapeutic use in cardiovascular disease. *Drugs* 1995; 50: 560–86.
3. Siragy HM. Improving vascular function in hypertension: potential benefits of combination therapy with amlodipine and renin-angiotensin-aldosterone system blockers. *J Hypertens* 2010; 28: 2–8.

Administration in children. Several studies have examined dosing regimens of amlodipine in children and adolescents with hypertension.[1-4] Amlodipine clearance is faster in younger children[5] and they need proportionally higher doses than older children.[3,4] Some younger children may also benefit from twice-daily dosing.[4] Amlodipine was well-tolerated in each of the studies; it also appears to be safe and effective when given long-term.[6]

US licensed product information suggests that for the treatment of hypertension in children aged 6 to 17 years, an oral dose of 2.5 to 5 mg once daily may be given. Amlodipine is not licensed for use in children in the UK; however, the *BNFC* suggests the following doses for the treatment of hypertension:

- an initial oral dose of 100 to 200 micrograms/kg once daily may be given to those aged 1 month to 12 years; this may be increased if necessary, at intervals of 1 to 2 weeks, to a maximum dose of 400 micrograms/kg or 10 mg once daily
- older children may be given the usual adult dose (see above)

1. Pfammatter JP, *et al.* Amlodipine once-daily in systemic hypertension. *Eur J Pediatr* 1998; 157: 618–21.
2. Flynn JT, *et al.* A randomized, placebo-controlled trial of amlodipine in children with hypertension. *J Pediatr* 2004; 145: 353–9.
3. Tallian KB, *et al.* Efficacy of amlodipine in pediatric patients with hypertension. *Pediatr Nephrol* 1999; 13: 304–10.
4. Flynn JT, *et al.* Treatment of hypertensive children with amlodipine. *Am J Hypertens* 2000; 13: 1061–6.
5. Flynn JT, *et al.* Population pharmacokinetics of amlodipine in hypertensive children and adolescents. *J Clin Pharmacol* 2006; 46: 905–16.
6. Flynn JT. Efficacy and safety of prolonged amlodipine treatment in hypertensive children. *Pediatr Nephrol* 2005; 20: 631–5.

Administration in hepatic impairment. The clearance of amlodipine is reduced in patients with hepatic impairment and lower doses should be considered; US licensed product information recommends an initial oral dose of 2.5 mg once daily.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2).

Incidence of adverse effects. Of 1091 patients prescribed amlodipine for hypertension, 128 (11.7%) stopped the drug because of adverse effects.[1] The commonest adverse effects were ankle oedema, flushing, headache, rash, and fatigue.

1. Benson E, Webster J. The tolerability of amlodipine in hypertensive patients. *Br J Clin Pharmacol* 1995; 39: 578P–579P.

Heart failure. Calcium-channel blockers are normally avoided in patients with heart failure but amlodipine has not been found to have any adverse effects on morbidity or mortality in patients with severe heart failure receiving the drug.[1] Therefore, its use to treat angina pectoris or hypertension may be possible in such patients.

1. Packer M, *et al.* Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med* 1996; 335: 1107–14.

Porphyria. Although there have been reports[1,2] of the successful use of amlodipine in patients with porphyria, acute exacerbation has also occurred.[3] The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, nevertheless classifies amlodipine as probably not porphyrinogenic and considers that it may be used as a drug of first choice and no precautions are needed.[4]

1. Gorchein A. Drug treatment of hypertension in acute intermittent porphyria: doxazosin and amlodipine. *Br J Clin Pharmacol* 1997; 43: 339–40.
2. Cinemre H, *et al.* Safety of amlodipine use in patients with acute intermittent porphyria. *Br J Clin Pharmacol* 2007; 64: 246–7.
3. Kepple A, Cernek PK. Amlodipine-induced acute intermittent porphyria exacerbation. *Ann Pharmacother* 1997; 31: 253.
4. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Pharmacokinetics

Amlodipine is well absorbed after oral doses and peak blood concentrations occur after 6 to 12 hours. The bioavailability varies but is usually about 60 to 65%. Amlodipine is reported to be about 98% bound to plasma proteins. It has a prolonged terminal elimination half-life of 35 to 50 hours and steady-state plasma concentrations are not achieved until after 7 to 8 days of use. Amlodipine is extensively metabolised in the liver; metabolites are mostly excreted in urine, with less than 10% of a dose as unchanged drug. Amlodipine is not removed by dialysis.

References.

1. Meredith PA, Elliott HL. Clinical pharmacokinetics of amlodipine. *Clin Pharmacokinet* 1992; 22: 22–31.
2. Kang D, *et al.* Population analyses of amlodipine in patients living in the community and patients living in nursing homes. *Clin Pharmacol Ther* 2006; 79: 114–24.
3. Flynn JT, *et al.* PATH-2 Investigators. Population pharmacokinetics of amlodipine in hypertensive children and adolescents. *J Clin Pharmacol* 2006; 46: 905–16.

Absorption. Results of studies involving 24 healthy subjects indicated that absorption of amlodipine from a capsule was equivalent to that from a solution, suggesting that the slow transfer of amlodipine into the blood is a property of the drug not of the dosage form; absorption was not affected by food.[1]

1. Faulkner JK, *et al.* Absorption of amlodipine unaffected by food: solid dose equivalent to solution dose. *Arzneimittelforschung* 1989; 39: 799–801.

Metabolism. The metabolites of amlodipine have been characterised in *animals* and in human subjects.[1] Metabolism of amlodipine is complex and extensive, and in common with other dihydropyridines oxidation to the pyridine analogue represents a major step. About 5% of a dose was recovered from urine as unchanged amlodipine.

1. Beresford AP, *et al.* Biotransformation of amlodipine. *Arzneimittelforschung* 1989; 39: 201–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Abloom; Amloc; Amlocard; Amlodine; Amlotens; Amze; Anexa; Angiofilina; Angipress; Arteriosan; Calpres; Carboplex†; Cardiorex; Cardivas; Corovell; Dronalden; Fabocef; Hipertensal; Ilduc; Mitokor; Nexoten; Nikor; Pelmec; Pultex; Tensimed; Terloc; Tervalon; Zundec; *Austral.*: Amlo; Nordip; Norvapine; Norvasc; Oziodip; Perivac; *Austria*: Amlodibene; Amlodilan; Amlodinova; Amlohyt†; Amlotyrol†; Coradipin†; Edidipin†; Norvasc; *Belg.*: Amlor; *Braz.*: Amilopil; Amlocor; Amlodil; Amlovasc; Anlo; Anlodibil; Anlodil†; Besilapin; Cordarex; Cordipina; Lodipen; Lodipi†; Nicord; Norvasc; Pressat; Roxflan; Tendipina; Tensaliv; Tensilpin†; Tensodin; *Canad.*: Norvasc; *Chile*: Amdipin; Amloc; Mylsicor; Norvasc; Presilam; Presovasc; Terloc; *China*: An Nei Zhen (安内真); Ao Wan Lu (奥万路); Fuleqing (伏络清); Ke Ping (可平); Lan Di (兰迪); Ning Li Ping (宁立平); Norvasc (络活喜); Nuo Er Ma (诺尔玛); Ping Neng (平能); Shi Hui Da (施慧达); Xi Luo Ning (西络宁); XinLuoPing (欣络平); Xinshu (欣舒); Xinta (欣他); Ya Shi Da (压氏达); Ya Si Ke Ping (亚斯克平); Cz.: Aten; Agen; Alozur; Amilostad; Amlodigamma†; Amlopin; Amloratio; Amlotenz†; Amlozek; Apo-Amlo; Cardilopin; Genam; Hipres; Normodipine; Norvasc†; Orcal; Recotens; Tensigal; Torella; Zeppeliton; Zorem; Zufalm; *Denm.*: Amdepin†; Amdin†; Amlobesyl; Amlohexal; Amlokamman†; Amlomat; Amlopharm; Dipinohex; Dipinosticht; Norvasc; *Fin.*: Amloratio; Beslodipin†; Coveram; Norvasc; *Fr.*: Amlor; *Ger.*: Amlo Tad†; Amlo-Isis†; Amlo-Q†; Amlobesilat†; Amlobeta; Amlocard†; Amloclair; Amlodigamma; Amlodoc†; AmloLich†; Amparo; Norvasc; *Gr.*: Abesyl; Aggovask; Aldosion; Alister; Amlopad; Amlibon; Amlodil; Amlodin; Amlopen; Amlopress; Amloretin; Amlosilat; Amlotens; Amodipan; Angioretic; Awadik; Axyplot; Baruden; Beglaryl; Dafor; Evangio; Flodil; Hypertel; Karpin; Lavi-Press; Lodipin; Naxuril; Nolvac; Nordex; Norfan; Normodin; Norvagen; Norvalet; Norvasc; Pidolen; Precardin; Ramlet; Rovoxid; Vascodin; *Hong Kong*: A-phine; Actapin; Amdol; Amedin; Amlod; Amlodigamma; Amlong; Amlopin†; Amlopres; Amlovas; Amlozen; CP-Lovac; Derox; Hypress; Lofral; Norvasc; Stadovas; Zynor; *Hung.*: Agen; Alozur; Amlipin; Amlobesyl; Amlodep; Amlodigamma; Amlodipress; Amlodowin; Amlozek; Cardilopin; Normodipine; Norvasc; Tenox; *India*: Aamin; Acord; Adipin; ADP; Aglodepin; Alodip; Am; Amcard; Amchek; Amdepin; Amdip; Amlan; Amlibon; Amlin; Amlip; Amlo CB; Amloact; Amlocan; Amlocom; Amlocor; Amlodac; Amlogard; Amlogen; Amlokath; Amlokind; Amlokos; Amlol; Amlong; Amlopin; Amlopres; Amlosafe; Amlostat; Amlosun; Amlosyl; Amloz; Amlotab; Amlotal; Amlotrac; Amlotrust; Amlovas; Amlovin; Amloz; Amodep; Amone; Amopin; Ampine; Amrap; Amsach; Amset; Amsyn; Amtas; Amzel; Angicam.; Angiguard; Atemos; Bp-Mide; C-Amlo; Calchek; Camlo; Candez; Card; Cardpin; Carvasc; Corvadil; Defidin; Diavasc; Dilsave; Dip; Dipal; Diplom; Dipress; Emadine; Esamlovin; Gamlo; Klodip; Lama; Lodi; Malodip; Milopin; Myamlo; Myodura; Myozar; Nicol; Norvate; Numlo; Nusar-AM; *Indon.*: A-B Vask; Actapin; Amcor; Amdixal; Calsivas; Cardicap; Cardisan; Cardivask; Comdipin; Divask; Ethivask; Gensia; Gravask; Intervask; Lopiten; Lovask; Normoten; Norvask; Pehavask; Sandovask; Simvask; Tensivask; Theravask; Vasgard; *Irl.*: Amlid; Amlist; Amlode; Amlotan; Istin; Istolde; Myostin; Rustin; *Israel*: Amlow; Caduet; Norvasc; *Ital.*: Abis; Almidis; Amlopol; Antacal; Balarm; Krudipin; Makadip; Monopina; Norvasc; Pressac; Zauris; *Jpn*: Amlodin; Norvasc; *Malaysia*: Amlibon; Amlodac; Amlong; Amvaz; Anlodin; Avevasc; Camlodin; Covasc; Hovasc; Lofral; Nordipine; Norvasc; Sunvasc; Vamlo; Zynor; *Mex.*: Aken; Amlibon Bes; Amlibon; Amtev; Avistar; Cropinex; Inivical; Lodicord; Nexus; Norpled; Norvas; Oralcam; Pequisy; Poltroon; Preslopin; Presone-1; Sistopres; Spinodin; Zadivonal; Zagapsol; Zaxinat; *Neth.*: Amlober; Amlodno; Amlostad; Amlosyl†; Norvasc; *Norw.*: Norvasc; *NZ*: Calvasc; Norvasc; *Philipp.*: Aforbes; Amaday; Ambes; Ambesyl; Ambloc; Amcal; Amlix; Amlobes; Amlocor; Amlodac; Amlodine; Amlonex; Amlong; Amlopine; Amlosyl; Amnique; Amvasc; Asomex; Besylon; Bezam; Calbloc; Calcheck; Calcivas; Corvex; Dailyvasc; Derox; Hartvasc; Lodicap; Lodip; Lopicard; Medipin; Norbloc; Norvasc; Odasyl; Provasc; Sedipin; Stalip; Stamlo; Swamlo; Teneze; Vasalat; Vaselec; Vasprim; *Pol.*: Adipine; Agen; Aldan; Amlonor; Amlopin; Amloratio; Amlozek; Apo-Amlo; Cardilopin; Lofral; Normodipine; Norvasc; Suplar; Tenox; Vilpin; *Port.*: Adivaz†; Amlocor; Cardionox; Dilocea; Drime; Freccia; Ibotec†; Mibral; Monodin†; Norvasc; Orexene; Tencemed; Teufin†; Tifiodipina†; Vasoplus†; Zabart†; *Rus.*: Agen (Аген); Akridipin (Акридипин); Amlodac (Амлодак); Amlodil (Амлодил)†; Amlong (Амлонг); Amlonorm (Амлонорм); Amlorus (Амлорус); Amlotop (Амлотоп); Amlovas (Амловас); Calchek (Калчек); Cardilopin (Кардилопин); Cordi Cor (Кордн Кор); Corvadil (Корвадил); EsCordi Cor (ЭсКордн Кор); Normodipine (Нормодипин); Norvadin (Норвадин); Norvasc (Норвасс); Omelar Cardio (Омелар Кардио); Stamlo M (Стамло М); Tenox (Тенокс); *S.Afr.*: Almadin; Amlate; Amloc; Amlodac; Amlosyn; Amtas; Calbloc; Ciplavasc; Corvadil; Keysal; Klodip; Lomanor; Norcard; Norvasc; Stamlo; *Singapore*: Actapin; Amloc; Amlong; Amlotens; Amtas; Avevasc; Norvasc; Stamlo; *Spain*: Amlor†; Arainno; Astudal; Norvas; Presdeten†; Zabart; *Swed.*: Amlarrow; Amlobesyl†; Amloratio; Norvasc; *Switz.*: Amlo eco†; Amlopin†; Amlovasc; Norvasc; *Thai.*: Ambes; Amcardia; Amlod; Amlodac; Amlopine;

Amvas; Deten; Lovas; Narvin; Norvasc; *Turk.*: Amlodis; Amlohex; Amlokard; Amlovas; Biocard†; Dilopin; Lipinox; Monovas; Nipidol; Norlopin; Normopres; Norvadin; Norvasc; Penvasc; Vasocard; Vasonorm; Vazkor; *UAE*: Amlophar; *UK*: Amlostin; Istin; *Ukr.*: Agen (Агея); Aladin (Аладин); Amlodil (Амлодил); Amlong (Амлонг); Amlopril (Амлоприл); Amlosandoz (Амлосандоз); Asomex (Азомекс); Duactin (Дуактин); Emlodin (Эмлодин); Norvadin (Норвадин)†; Norvasc (Норваск); Stamlo (Стамло); Tenox (Тенокс); *USA*: Norvasc; *Venez.*: Amlibon; Amlip; Amlopin; Amlovas; Angiovan; Dilotex; Lodipin; Norvasc; Pinam.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations
USP 36: Amlodipine and Benazepril Hydrochloride Capsules; Amlodipine Besylate Tablets; Amlodipine Oral Suspension.

Amosulalol Hydrochloride *(rINNM)* ⊗

Amosulalol, Chlorhydrate d'; Amosulalol, hidrocloruro de; Amosulalolі Hydrochloridum; Hidrocloruro de amosulalol; YM-09538; Амосулалола Гидрохлорид.
(±)-5-{1-Hydroxy-2-[[2-(o-methoxyphenoxy)ethyl]amino] ethyl}-o-toluenesulphonamide hydrochloride.
$C_{18}H_{24}N_2O_5S,HCl$=416.9
CAS — 85320-68-9 (amosulalol); 70958-86-0 (amosulalol hydrochloride); 93633-92-2 (amosulalol hydrochloride).
UNII — 4O45698PEE.

NOTE. The name Lowgan has been used as a trade mark for amosulalol hydrochloride.

Pharmacopoeias. In *Jpn.*

Profile

Amosulalol is a beta blocker (p. 1316.3); it also has alpha-blocking activity. It has been given orally as the hydrochloride in the management of hypertension.

Amrinone *(BAN, rINN)*

Amrinon; Amrinona; Amrinoni; Amrinonum; Inamrinone (USAN); Win-40680; Амринон.
5-Amino-3,4'-bipyridyl-6(1*H*)-one.
$C_{10}H_9N_3O$=187.2
CAS — 60719-84-8.
ATC — C01CE01.
ATC Vet — QC01CE01.
UNII — JUT23379TN.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Inamrinone). A pale yellow to tan powder; odourless or with a faint odour. Practically insoluble in water and in chloroform; slightly soluble in methyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Amrinone Lactate *(BANM, rINNM)*

Amrinona, lactato de; Amrinone, Lactate d'; Amrinoni Lactas; Lactato de amrinona; Амринона Лактат.
$C_{10}H_9N_3O,C_3H_6O_3$=277.3
CAS — 75898-90-7.
ATC — C01CE01.
ATC Vet — QC01CE01.
UNII — I229274Y5B.

Incompatibility. The manufacturer has reported that amrinone lactate injection is physically incompatible with glucose-containing solutions and with furosemide.

Precipitation occurred[1] when amrinone was mixed with sodium bicarbonate injection, probably because of the reduced solubility of amrinone in alkaline solutions.

1. Riley CM, Junkin P. Stability of amrinone and digoxin, procainamide hydrochloride, propranolol hydrochloride, sodium bicarbonate, potassium chloride, or verapamil hydrochloride in intravenous admixtures. *Am J Hosp Pharm* 1991; 48: 1245–52.

Uses and Administration

Amrinone is a phosphodiesterase type 3 inhibitor that has vasodilator and positive inotropic properties. It is used in the management of heart failure (p. 1262.3). Although amrinone is effective when given orally this route has been associated with an unacceptable level of adverse effects, and the drug is now only given intravenously for the short-term management of heart failure unresponsive to other forms of therapy.

The mode of action is not fully known, but appears to involve an increase in cyclic adenosine monophosphate concentration secondary to inhibition of phosphodiesterase, leading to an increased contractile force in cardiac muscle.

Amrinone is given intravenously as the lactate and doses are expressed in terms of the base. Amrinone lactate 1.48 mg is equivalent to about 1 mg of amrinone. The initial loading dose is 750 micrograms/kg by slow intravenous injection over 2 to 3 minutes. This is followed by a maintenance infusion, although the loading dose may be repeated after 30 minutes if necessary. Maintenance doses are 5 to 10 micrograms/kg per minute by infusion to a usual maximum total dose (including loading doses) of 10 mg/kg in 24 hours. Doses of up to 18 mg/kg daily have been used for short periods in a limited number of patients.

Administration in children. Pharmacokinetic and pharmacodynamic studies[1,2] in infants undergoing cardiac surgery indicated that the dose needed for infants to achieve a plasma-amrinone concentration of 2 to 7 micrograms/mL was an initial intravenous bolus of 3 to 4.5 mg/kg in divided doses followed by a continuous infusion of 10 micrograms/kg per minute. Neonates appear to eliminate amrinone more slowly than infants, possibly due to their immature renal function;[1,3] it was therefore suggested[1] that neonates should receive a similar bolus dose to infants, followed by a continuous infusion of 3 to 5 micrograms/kg per minute. In a further study[4] that included mainly infants and older children, amrinone clearance and volume of distribution varied widely between patients but did not appear to be related to age.

1. Lawless S, *et al.* Amrinone in neonates and infants after cardiac surgery. *Crit Care Med* 1989; 17: 751–4.
2. Lawless ST, *et al.* The acute pharmacokinetics and pharmacodynamics of amrinone in pediatric patients. *J Clin Pharmacol* 1991; 31: 800–3.
3. Laitinen P, *et al.* Pharmacokinetics of amrinone in neonates and infants. *J Cardiothorac Vasc Anesth* 2000; 14: 378–82.
4. Allen-Webb EM, *et al.* Age-related amrinone pharmacokinetics in a pediatric population. *Crit Care Med* 1994; 22: 1016–24.

Adverse Effects

Amrinone produces gastrointestinal disturbances that may necessitate withdrawal of treatment. It produces dose-dependent thrombocytopenia. Hepatotoxicity may occur, particularly during long-term oral treatment. Hypotension and cardiac arrhythmias have been reported. Other adverse effects include headache, fever, chest pain, nail discoloration, and decreased tear production. Hypersensitivity reactions including myositis and vasculitis have been reported. Local pain and burning may occur at the site of intravenous injection.

The adverse effects associated with oral use have made this route unacceptable and amrinone is now only given intravenously for short-term use. Studies with other inotropic phosphodiesterase inhibitors have shown that their prolonged oral use can increase the mortality rate.

References.
1. Wynne J, *et al.* Oral amrinone in refractory congestive heart failure. *Am J Cardiol* 1980; 45: 1245–9.
2. Wilmshurst PT, Webb-Peploe MM. Side effects of amrinone therapy. *Br Heart J* 1983; 49: 447–51.
3. Wilmshurst PT, *et al.* The effects of amrinone on platelet count, survival and function in patients with congestive cardiac failure. *Br J Clin Pharmacol* 1984; 17: 317–24.
4. Silverman BD, *et al.* Clinical effects and side effects of amrinone: a study of 24 patients with chronic congestive heart failure. *Arch Intern Med* 1985; 145: 825–9.
5. Webster MWI, Sharpe DN. Adverse effects associated with the newer inotropic agents. *Med Toxicol* 1986; 1: 335–42.
6. Mattingly PM, *et al.* Pancytopenia secondary to short-term, high-dose intravenous infusion of amrinone. *DICP Ann Pharmacother* 1990; 24: 1172–4.
7. Ross MP, *et al.* Amrinone-associated thrombocytopenia: pharmacokinetic analysis. *Clin Pharmacol Ther* 1993; 53: 661–7.

Precautions

Amrinone should be used with caution in severe obstructive aortic or pulmonary valvular disease or in hypertrophic cardiomyopathy. Blood pressure and heart rate should be monitored during parenteral use. The fluid and electrolyte balance should be maintained. Platelet counts and liver function should also be monitored.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amrinone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pharmacokinetics

Although amrinone is rapidly absorbed from the gastrointestinal tract it is no longer given orally. The half-life is variable and after intravenous injection has been reported to be about 4 hours in healthy subjects and about 6 hours in patients with heart failure. Binding to plasma proteins is generally low. Amrinone is partially metabolised in the liver and excreted in the urine as unchanged drug and metabolites; up to about 40% is excreted as unchanged drug after intravenous use. About 18% of an oral dose has been detected in the faeces over 72 hours.

General references.
1. Rocci ML, Wilson H. The pharmacokinetics and pharmacodynamics of newer inotropic agents. *Clin Pharmacokinet* 1987; 13: 91–109. Correction. *ibid.* 1988; 14:(contents page).

Infants. For reference to the pharmacokinetics of amrinone in neonates and infants, see Administration in children under Uses and Administration, above.

Renal impairment. Studies in a child with multi-organ failure and anuria[1] and in 3 adults with anuria after cardiac surgery[2] have shown that amrinone is effectively removed by haemofiltration but clearance varies widely between patients. Non-renal clearance may also be altered in critically ill patients and monitoring of plasma-amrinone concentrations has been suggested.[2]

1. Lawless S, *et al.* Effect of continuous arteriovenous haemofiltration on pharmacokinetics of amrinone. *Clin Pharmacokinet* 1993; 25: 80–2.
2. Hellinger A, *et al.* Elimination of amrinone during continuous veno-venous haemofiltration after cardiac surgery. *Eur J Clin Pharmacol* 1995; 48: 57–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Amicor; Amrisol; Cardiotone; *Israel*: Inocor†; *Mex.*: Inocor†; *USA*: Inocor.

Pharmacopoeial Preparations
USP 36: Inamrinone Injection.

Anacetrapib *(USAN, rINN)*

Anacétrapib; Anacetrapibum; MK-0859; Анацетрапиб.
(4*S*,5*R*)-5-[3,5-Bis(trifluoromethyl)phenyl]-3-{[4'-fluoro-2'-methoxy-5'-(propan-2-yl)-4-(trifluoromethyl)(1,1'-biphenyl)-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one.
$C_{30}H_{25}F_{10}NO_3$=637.5
CAS — 875446-37-0.
UNII — P7T269PR6S.

Profile

Anacetrapib is an inhibitor of cholesteryl ester transfer protein (CETP) that is under investigation for the treatment of dyslipidaemias and atherosclerosis.

References.
1. Bloomfield D, *et al.* Efficacy and safety of the cholesteryl ester transfer protein inhibitor anacetrapib as monotherapy and coadministered with atorvastatin in dyslipidemic patients. *Am Heart J* 2009; 157: 352–360.e2.
2. Masson D. Anacetrapib, a cholesterol ester transfer protein (CETP) inhibitor for the treatment of atherosclerosis. *Curr Opin Investig Drugs* 2009; 10: 980–7.
3. Cannon CP, *et al.* Determining the Efficacy and Tolerability Investigators. Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med* 2010; 363: 2406–15.
4. Kumar S, *et al.* Metabolism and excretion of anacetrapib, a novel inhibitor of the cholesteryl ester transfer protein, in humans. *Drug Metab Dispos* 2010; 38: 474–83.
5. Miyares MA. Anacetrapib and dalcetrapib: two novel cholesteryl ester transfer protein inhibitors. *Ann Pharmacother* 2011; 45: 84–94.

Ancrod *(BAN, USAN, rINN)*

Ancrodo; Ancrodum; Анкрод.
CAS — 9046-56-4.
ATC — B01AD09.
ATC Vet — QB01AD09.
UNII — EL55307L15.

Description. Ancrod is an enzyme obtained from the venom of the Malayan pit-viper (*Calloselasma rhodostoma* = *Agkistrodon rhodostoma*).

Uses and Administration

Ancrod is an anticoagulant. It reduces the blood concentration of fibrinogen by the cleavage of microparticles of fibrin which are rapidly removed from the circulation by fibrinolysis or phagocytosis. It reduces blood viscosity but has no effect on established thrombi. Haemostatic concentrations of fibrinogen are normally restored in about 12 hours and normal concentrations in 10 to 20 days.

Ancrod has been used in the management of thromboembolic disorders, particularly in the prevention and treatment of deep-vein thrombosis (p. 1274.1) in hospitalised patients, including as an alternative to heparin in those with heparin-induced thrombocytopenia. It has also been given for priapism. Ancrod has been investigated in ischaemic stroke, with disappointing results.

References.
1. Sherman DG, *et al.* Intravenous ancrod for treatment of acute ischemic stroke: the STAT study: a randomized controlled trial. *JAMA* 2000; 283: 2395–2403.
2. Hennerici MG, *et al.* ESTAT Investigators. Intravenous ancrod for acute ischaemic stroke in the European Stroke Treatment with Ancrod Trial: a randomised controlled trial. *Lancet* 2006; 368: 1871–8.
3. Levy DB, *et al.* Ancrod Stroke Program (ASP) Study Team. Ancrod for acute ischemic stroke: a new dosing regimen derived from analysis of prior ancrod stroke studies. *J Stroke Cerebrovasc Dis* 2009; 18: 23–7.

4. Levy DE, *et al.* Ancrod in acute ischemic stroke: results of 500 subjects beginning treatment within 6 hours of stroke onset in the Ancrod Stroke Program. *Stroke* 2009; 40: 3796–3803.

Adverse Effects and Treatment

Haemorrhage may occur during treatment with ancrod and usually responds to its withdrawal. If haemorrhage is severe, cryoprecipitate can be used to raise plasma fibrinogen concentrations; plasma may be used if cryoprecipitate is not available. An antivenom has been used to neutralise ancrod.

Rashes, transient chills, and fever have been reported with the use of ancrod.

Precautions

As for Heparin, p. 1399.3.

Ancrod should not be given to patients with severe infections or disseminated intravascular coagulation. It should be used cautiously in patients with cardiovascular disorders that may be complicated by defibrination. It is very important that when ancrod is given by intravenous infusion it should be given slowly to prevent the formation of large amounts of unstable fibrin.

Ancrod is not recommended during pregnancy; high doses in *animals* have caused placental haemorrhage and fetal death.

Interactions

Ancrod should not be used with antifibrinolytics such as aminocaproic acid or with plasma volume expanders such as dextrans.

Angiotensinamide *(BAN, rINN)*

Angiotensiiniamidi; Angiotensin Amide (USAN); Angiotensina Amida; Angiotensinamid; Angiotensinamida; Angiotensinamidum; NSC-107678; Ангиотензинамид.

Asn-Arg-Val-Tyr-Val-His-Pro-Phe; [1-Asparagine,5-valine] angiotensin II.

$C_{49}H_{70}N_{14}O_{11}$=1031.2

CAS — 11128-99-7 (angiotensin II); 53-73-6 (angiotensinamide).

ATC — C01CX06.

ATC Vet — QC01CX06.

UNII — 7WAL1X78KV.

Profile

Angiotensinamide is a vasopressor related to the naturally occurring peptide angiotensin II. It increases the peripheral resistance mainly in cutaneous, splanchnic, and renal blood vessels. The increased blood pressure is accompanied by a reflex reduction in heart rate, and cardiac output may also be reduced.

Angiotensinamide has been used in the treatment of hypotension associated with shock. It has also been given in the management of overdosage of ACE inhibitors, when conventional therapy has been ineffective.

Angiotensinamide should not be given to patients being treated with an MAOI or within 14 days of stopping such treatment as a hypertensive crisis may be precipitated.

References.
1. Jackson T, *et al.* Enalapril overdose treated with angiotensin infusion. *Lancet* 1993; 341: 703.
2. Newby DE, *et al.* Enalapril overdose and the corrective effect of intravenous angiotensin II. *Br J Clin Pharmacol* 1995; 40: 103–4.
3. Yunge M, Petros A. Angiotensin for septic shock unresponsive to noradrenaline. *Arch Dis Child* 2000; 82: 388–9.

Anistreplase *(BAN, USAN, rINN)*

Anisoylated Plasminogen Streptokinase Activator Complex; Anistreplaasi; Anistreplas; Anistreplasa; Anistreplasum; APSAC; BRL-26921; Анистреплаза.

p-Anisoylated (human) lys-plasminogen streptokinase activator complex (1:1).

CAS — 81669-57-0.

ATC — B01AD03.

ATC Vet — QB01AD03.

UNII — 5O8V54THJ6.

Storage. The manufacturer has recommended that anistreplase should be stored at 2 degrees to 8 degrees.

Uses and Administration

Anistreplase is a thrombolytic drug. It consists of a complex of the lys-form of plasminogen and streptokinase with the addition of a *p*-anisoyl group. After intravenous injection the anisoyl group undergoes deacylation at a steady rate to release the active complex which converts plasminogen to plasmin, resulting in fibrinolysis and dissolution of clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p. 1124.3.

Anistreplase has been used similarly to streptokinase (p. 1503.1) in the treatment of acute myocardial infarction (p. 1257.1). It has been given as a single intravenous injection in a dose of 30 units over 5 minutes, as soon as possible after the onset of symptoms.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p. 1505.1. Like streptokinase, anistreplase appears to be antigenic and may be neutralised by streptokinase antibodies.

Back pain. For references to back pain associated with anistreplase infusion, see under Streptokinase, p. 1505.1.

Interactions

As for Streptokinase, p. 1507.1.

Pharmacokinetics

Anistreplase is reported to be cleared from plasma at about half the rate of streptokinase and has a fibrinolytic half-life of about 90 minutes. It is metabolised to the plasminogen-streptokinase complex at a steady rate.

References.
1. Gemmill JD, *et al.* A comparison of the pharmacokinetic properties of streptokinase and anistreplase in acute myocardial infarction. *Br J Clin Pharmacol* 1991; 31: 143–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Eminase†; *Gr.*: Eminase.

Apixaban *(USAN, rINN)*

Apixabán; Apixabanum; BMS-562247-01; Апиксабан.

1-(4-Methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide.

$C_{25}H_{25}N_5O_4$=459.5

CAS — 503612-47-3.

ATC — B01AF02.

ATC Vet — QB01AF02.

UNII — 3Z9Y7UWC1J.

Uses and Administration

Apixaban is an oral direct inhibitor of factor Xa (activated factor X) with actions and uses similar to those of rivaroxaban (p. 1487.2).

For the prevention of venous thromboembolism (p. 1274.1) in patients undergoing hip or knee replacement surgery, apixaban is given at a dose of 2.5 mg twice daily. The initial dose should be given 12 to 24 hours after surgery, and the recommended duration of treatment is 10 to 14 days after knee surgery and 32 to 38 days after hip surgery.

For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (see Thromboembolic Diseases, below), a dose of 5 mg twice daily is given long term. A lower dose of 2.5 mg twice daily is recommended for patients who also have at least 2 of the following characteristics: aged ≥80 years, body-weight ≤60 kg, or serum-creatinine ≥1.5 mg per 100 mL (133 micromoles/litre). See also Administration in Renal Impairment (below) for further details on dose adjustment. A dose of 2.5 mg twice daily has also been recommended when apixaban is given with strong dual inhibitors of the cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein; such combinations should be avoided in patients already taking apixaban 2.5 mg twice daily.

References.
1. Watson J, *et al.* Apixaban: first global approval. *Drugs* 2011; 71: 2079–89.

Administration in renal impairment. An apixaban dose of 2.5 mg orally twice daily should be used for the prevention of stroke in patients with non-valvular atrial fibrillation who have severe renal impairment (creatinine clearance 15 to 29 mL/minute). Apixaban should also be used with caution in patients with severe impairment who are given it for the prevention of venous thromboembolism after hip or knee replacement surgery. It is not recommended in patients with creatinine clearance of less than 15 mL/minute and those undergoing haemodialysis because of a lack of information.

No dose adjustment is considered necessary in mild or moderate renal impairment (but see also Uses and Administration, above, for dose adjustment in patients with renal impairment who are elderly or have low body-weight).

Thromboembolic diseases. Apixaban has been compared with enoxaparin in the prophylaxis of venous thromboembolism in patients undergoing hip[1] or knee[2,3] replacement surgery, and its use in this indication has been reviewed.[4] Apixaban may also be used in the prevention of stroke and embolic events in patients with atrial fibrillation (see Cardiac Arrhythmias, p. 1266.1). In the ARISTOTLE study[5] apixaban was found to reduce the risk of stroke or systemic embolism by 21%, major bleed by 31%, and death by 11% compared with warfarin in patients with atrial fibrillation and at least one other risk factor for stroke. Among patients for whom warfarin therapy was inappropriate, the AVERROES study[6] found apixaban to substantially reduce the risk of stroke and other embolic events compared with aspirin without significantly increasing the risk of major bleeding or intracranial hemorrhage. In both trials, a dose of 5 mg orally twice daily was used for most patients, although the dose was halved for patients with at least two of the following criteria: advanced age (≥80 years), low body-weight (≤60 kg), and renal dysfunction (serum creatinine ≥133 micromoles/litre).[5,6]

Apixaban has been investigated as an anticoagulant in the management of several other thromboembolic diseases.[7,8] It has also been investigated in the management of acute coronary syndromes (p. 1254.2), with disappointing results.[9]

1. Lassen MR, *et al.* ADVANCE-3 Investigators. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med* 2010; 363: 2487–98.
2. Lassen MR, *et al.* Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med* 2009; 361: 594–604.
3. Lassen MR, *et al.* Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet* 2010; 375: 807–15.
4. Deeks ED. Apixaban: a review of its use in the prevention of venous thromboembolism after knee or hip replacement surgery. *Drugs* 2012; 72: 1271–91.
5. Granger CB, *et al.* ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365: 981–92.
6. Connolly SJ, *et al.* AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011; 364: 806–17.
7. Goldhaber SZ, *et al.* ADOPT Trial Investigators. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med* 2011; 365: 2167–77.
8. Prom R, Spinler SA. The role of apixaban for venous and arterial thromboembolic disease. *Ann Pharmacother* 2011; 45: 1262–83.
9. Alexander JH, *et al.* APPRAISE-2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med* 2011; 365: 699–708.

Adverse Effects, Treatment, and Precautions

As for Rivaroxaban, p. 1488.1. Apixaban should be used with caution in mild or moderate hepatic impairment (Child-Pugh score A or B). It is not recommended in severe hepatic impairment. The dose of apixaban may need adjustment in renal impairment. Apixaban should be stopped at least 48 hours before surgery or invasive procedures with a moderate or high risk of bleeding, and at least 24 hours before those with a low bleeding risk; it should be restarted as soon as possible after the surgery or procedure provided there is adequate haemostasis.

Interactions

As for Rivaroxaban, p. 1488.1. The dose of apixaban should be adjusted when it is given with strong inhibitors of the cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein (see Uses and Administration, above).

Pharmacokinetics

Apixaban is rapidly absorbed with an absolute bioavailability of about 50% and peak plasma concentrations occurring 3 to 4 hours after an oral dose. Plasma protein binding is about 87%. Apixaban is metabolised in the liver mainly via the P450 cytochromes CYP3A4 and CYP3A5, and is excreted renally and in the faeces as unchanged drug and inactive metabolites. The half-life is about 12 hours. Apixaban is a substrate of the transport protein P-glycoprotein.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Eliquis; *Canad.*: Eliquis; *Denm.*: Eliquis; *Fr.*: Eliquis; *Ger.*: Eliquis; *Irl.*: Eliquis; *Israel*: Eliquis; *Jpn*: Eliquis; *Neth.*: Eliquis; *Norw.*: Eliquis; *Spain*: Eliquis; *Swed.*: Eliquis; *Switz.*: Eliquis; *UK*: Eliquis; *USA*: Eliquis.

Aprindine Hydrochloride *(BANM, USAN, rINNM)*

AC-1802; Aprindina, hidrocloruro de; Aprindine, Chlorhydrate d'; Aprindini Hydrochloridum; Compound 83846; Compound 99170 (aprindine); Hidrocloruro de aprindina; Априндина Гидрохлорид.

N-(3-Diethylaminopropyl)-*N*-indan-2-ylaniline hydrochloride; *NN*-Diethyl-*N'*-indan-2-yl-*N'*-phenyltrimethylenediamine hydrochloride.
$C_{22}H_{30}N_2$,HCl=359.0
CAS — 37640-71-4 (aprindine); 33237-74-0 (aprindine hydrochloride).
ATC — C01BB04.
ATC Vet — QC01BB04.
UNII — PB5EKT7Q2V.

NOTE. The names Aspenon and Apritone have been used as trade marks for aprindine.

Uses and Administration

Aprindine is a class Ib antiarrhythmic (p. 1243.1) used in the management of ventricular and supraventricular arrhythmias (p. 1266.1).

Aprindine is given orally as the hydrochloride. Therapy should be monitored by ECG during initial stabilisation of the dose and intermittently thereafter. Aprindine has also been given intravenously.

Adverse Effects and Precautions

Adverse effects of aprindine are usually dose-related and most commonly affect the CNS. They include tremor, vertigo, ataxia, diplopia, memory impairment, hallucinations, and convulsions. Gastrointestinal effects include nausea, vomiting, and bloating. There have been reports of agranulocytosis, including fatalities. Hepatitis and cholestatic jaundice have occasionally been reported; blood and liver function tests should be performed during treatment.

Aprindine is contra-indicated in patients with advanced heart failure or severe conduction disturbances. Some licensed product information has recommended that aprindine should not be used in patients with parkinsonism or convulsive disorders. It should be used with caution in patients with bradycardia, hypotension, and hepatic or renal impairment.

Effects on the nervous system. A study[1] in Japanese patients suggested that neurological adverse effects (such as dizziness and tremor) were present in about half of patients in whom serum concentrations of aprindine were above 1 microgram/mL, but almost absent in those whose concentrations were maintained below this value.

1. Tsuchishita Y, *et al.* Relationship between serum aprindine concentration and neurologic side effects in Japanese. *Biol Pharm Bull* 2009; 32: 637–9.

Interactions

Antiarrhythmics. Steady-state plasma-aprindine concentrations increased in 2 patients after starting *amiodarone* and this coincided with the appearance of adverse effects.[1]

1. Southworth W, *et al.* Possible amiodarone-aprindine interaction. *Am Heart J* 1982; 104: 323.

Pharmacokinetics

Aprindine is readily absorbed from the gastrointestinal tract. It has a long plasma half-life, usually between 20 and 27 hours, and is about 85 to 95% bound to plasma proteins. It is excreted in the urine and the bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Fiboran; *Neth.*: Fiboran†.

Aranidipine *(rINN)*

Aranidipino; Aranidipinum; MPC-1304; Аранидипин.
(±)-Acetonyl methyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate.
$C_{19}H_{20}N_2O_7$=388.4
CAS — 86780-90-7.
UNII — 4Y7UR6X2PO.

Profile

Aranidipine is a dihydropyridine calcium-channel blocker used orally in the management of hypertension.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Bec; Sapresta.

Ardeparin Sodium *(USAN, rINN)*

Ardeparina sódica; Ardéparine Sodique; Ardeparinum Natricum; Wy-90493-BD; Ардепарин Натрий.
CAS — 9041-08-1.
UNII — N3927D01P8.

Description. Ardeparin sodium is prepared by peroxide degradation of heparin obtained from the intestinal mucosa of pigs. The end chain structure appears to be the same as the starting material with no unusual sugar residues present. The molecular weight of 98% of the components is between 2000 and 15 000 and the average molecular weight is about 5500 to 6500. The degree of sulfation is about 2.7 per disaccharide unit.

Profile

Ardeparin sodium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant activity that has been used for the prevention of postoperative venous thromboembolism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Indeparin.

Argatroban *(BAN, USAN, rINN)*

Argatrobana; Argatrobanum; Argipidine; DK-7419; GN-1600; MCI-9038; MD-805; Аргатробан.
(2*R*,4*R*)-4-Methyl-1-[(*S*)-*N*^{2}-[(*RS*)-1,2,3,4-tetrahydro-3-methyl-8-quinolyl]sulfonyl]arginyl]pipecolic acid.
$C_{23}H_{36}N_6O_5S$=508.6
CAS — 74863-84-6 (anhydrous argatroban); 141396-28-3 (argatroban monohydrate).
ATC — B01AE03.
ATC Vet — QB01AE03.
UNII — OCY3U280Y3 (anhydrous argatroban); IY90U61Z3S (argatroban monohydrate).

Incompatibility. Trace evidence of precipitation was seen immediately after mixing solutions of argatroban and amiodarone.[1] No visual incompatibility was noted for solutions of argatroban with furosemide, nesiritide, sodium nitroprusside, or a total parenteral nutrition solution, but changes in pH occurred over 24 hours, suggesting such mixtures should be used with caution.[1]

1. Honisko ME, *et al.* Compatibility of argatroban with selected cardiovascular agents. *Am J Health-Syst Pharm* 2004; 61: 2415–18.

Uses and Administration

Argatroban is a synthetic direct thrombin inhibitor (see Lepirudin, p. 1418.2) with anticoagulant and antiplatelet activity. It is used for the treatment and prophylaxis of thromboembolism in patients with heparin-induced thrombocytopenia (see Effects on the Blood under Heparin, p. 1399.1), and as an adjunct in patients undergoing percutaneous coronary interventions (see Reperfusion and Revascularisation Procedures, p. 1259.2) who have or are at risk of heparin-induced thrombocytopenia. It has also been used in other thromboembolic disorders.

In the management of heparin-induced thrombocytopenia, argatroban is given by intravenous infusion in an initial dose of 2 micrograms/kg per minute, adjusted according to the activated partial thromboplastin time (APTT), to a maximum dose of 10 micrograms/kg per minute.

In percutaneous coronary interventions in patients at risk of or with heparin-induced thrombocytopenia, argatroban is given by intravenous infusion in an initial dose of 25 micrograms/kg per minute, and an intravenous injection of 350 micrograms/kg is given simultaneously over 3 to 5 minutes. Close monitoring of the activated clotting time (ACT) is required. If necessary, additional intravenous bolus doses of 150 micrograms/kg may be given, and the infusion rate adjusted to between 15 and 40 micrograms/kg per minute.

Doses should be reduced in patients with hepatic impairment (see below).

For doses in children, see below.

References.

1. McKeage K, Plosker GL. Argatroban. *Drugs* 2001; 61: 515–22.
2. Verme-Gibboney CN, Hursting MJ. Argatroban dosing in patients with heparin-induced thrombocytopenia. *Ann Pharmacother* 2003; 37: 970–5.
3. Lewis BE, *et al.* Effects of argatroban therapy, demographic variables, and platelet count on thrombotic risks in heparin-induced thrombocytopenia. *Chest* 2006; 129: 1407–16.
4. Bartholomew JR, *et al.* Argatroban anticoagulation for heparin-induced thrombocytopenia in elderly patients. *Drugs Aging* 2007; 24: 489–99.
5. Beiderlinden M, *et al.* Argatroban in extracorporeal membrane oxygenation. *Artif Organs* 2007; 31: 461–5.
6. Ansara AJ, *et al.* Weight-based argatroban dosing nomogram for treatment of heparin-induced thrombocytopenia. *Ann Pharmacother* 2009; 43: 9–18.
7. Babuin L, Pengo V. Argatroban in the management of heparin-induced thrombocytopenia. *Vasc Health Risk Manag* 2010; 6: 813–19.

Administration in children. Case reports of the use of argatroban in children were reviewed.[1] Argatroban appeared to provide therapeutic levels of anticoagulation in a variety of settings including thromboprophylaxis and treatment, cardiac catheterisation, haemodialysis, and extracorporeal membrane oxygenation. However, argatroban was associated with an unacceptably high bleeding risk in patients undergoing cardiopulmonary bypass.

Based on a study[2] in 18 children aged from birth to 16 years, US licensed product information suggests the following doses of argatroban in children with heparin-induced thrombocytopenia:

- in those with normal liver function, a continuous infusion of 750 nanograms/kg per minute, adjusted in increments of 100 to 250 nanograms/kg per minute according to the activated partial thromboplastin time.
- in those with impaired liver function, a continuous infusion of 200 nanograms/kg per minute, adjusted in increments of no more than 50 nanograms/kg per minute according to the activated partial thromboplastin time.

1. Hursting MJ, *et al.* Argatroban anticoagulation in pediatric patients: a literature analysis. *J Pediatr Hematol Oncol* 2006; 28: 4–10.
2. Madabushi R, *et al.* Pharmacokinetic and pharmacodynamic basis for effective argatroban dosing in pediatrics. *J Clin Pharmacol* 2011; 51: 19–28.

Administration in hepatic impairment. In patients with heparin-induced thrombocytopenia with hepatic impairment the initial dose of argatroban should be reduced.[1] US licensed product information recommends an initial dose of 500 nanograms/kg per minute in moderate hepatic impairment. Reversal of anticoagulant effects after stopping argatroban may take more than 4 hours, due to decreased clearance and increased elimination half-life. High doses of argatroban should not be used in patients with significant hepatic impairment undergoing percutaneous coronary interventions.

Reduced initial doses have also been suggested for those with conditions that might *indirectly* decrease hepatic function—see Critical Illness under Adverse Effects and Precautions, below.

1. Levine RL, *et al.* Argatroban therapy in heparin-induced thrombocytopenia with hepatic dysfunction. *Chest* 2006; 129: 1167–75.

Administration in renal impairment. Argatroban is not significantly excreted by the kidneys and dosage adjustment is not usually required in renal impairment, although excessive anticoagulation has been reported in critically ill patients, including some with compromised renal function (see Critical Illness under Adverse Effects, below). The use of argatroban in patients with renal impairment has been reviewed.[1]

For a discussion of the use of direct thrombin inhibitors, including argatroban, as alternatives to heparin in patients undergoing haemodialysis or haemofiltration, see Extracorporeal Circuits under Lepirudin, p. 1418.2.

1. Hursting MJ, Murray PT. Argatroban anticoagulation in renal dysfunction: a literature analysis. *Nephron Clin Pract* 2008; 109: c80–c94.

Adverse Effects, Treatment, and Precautions

As for Lepirudin, p. 1419.2.

If argatroban and warfarin are given together there is an effect on the measurement of the INR values. The manufacturer provides guidelines for interpreting the INR during the change from combined therapy to warfarin alone.

Critical illness. Critically ill patients appear to be particularly sensitive to argatroban and may require doses lower than those licensed. Four critically ill patients became excessively anticoagulated[1] when treatment with argatroban was started after cardiac surgery, despite use of only the recommended doses or lower. All 4 had relatively normal hepatic function. Clearance of the drug appeared to be prolonged after it was stopped. In a patient[2] who had no significant direct hepatic dysfunction but severe hepatic congestion secondary to acute renal failure, the effect of argatroban was prolonged and reduction in dose was necessary. Haemodialysis had little or no effect on clearance. Further cases of excessive anticoagulation have been reported in patients with multiple organ failure,[3] and in an elderly patient with multiple comorbidities.[4] In a subsequent study, of 53 patients given argatroban for heparin-induced thrombocytopenia (HIT), 47 (of whom 33 were classed as critically ill) required doses lower than the licensed doses, and 16 (of whom 15 were classed as critically ill) required doses lower than 500 nanograms/kg per minute.[5] A review[6] of argatroban in HIT considered that reduced initial doses should be given to those with conditions that might indirectly decrease hepatic function, and that for many patients doses within the range of 0.5 to 1.2 micrograms/kg per minute appeared to be adequate.

1. Reichert MG, *et al.* Excessive argatroban anticoagulation for heparin-induced thrombocytopenia. *Ann Pharmacother* 2003; 37: 652–4.

2. de Denus S, Spinler SA. Decreased argatroban clearance unaffected by hemodialysis in anasarca. *Ann Pharmacother* 2003; 37: 1237–40.
3. Beiderlinden M, *et al.* Argatroban anticoagulation in critically ill patients. *Ann Pharmacother* 2007; 41: 749–54.
4. Kubiak DW, *et al.* Extensive prolongation of aPTT with argatroban in an elderly patient with improving renal function, normal hepatic enzymes, and metastatic lung cancer. *Ann Pharmacother* 2005; 39: 1119–23.
5. Keegan SP, *et al.* Effects of critical illness and organ failure on therapeutic argatroban dosage requirements in patients with suspected or confirmed heparin-induced thrombocytopenia. *Ann Pharmacother* 2009; 43: 19–27.
6. Hursting MJ, Soffer J. Reducing harm associated with anticoagulation: practical considerations of argatroban therapy in heparin-induced thrombocytopenia. *Drug Safety* 2009; 32: 203–18.

Overdosage. A critically ill patient receiving low-dose continuous intravenous argatroban for thromboembolism prophylaxis was mistakenly given an additional infusion of 125 mg of argatroban over 1 hour (26.1 micrograms/kg per minute).[1] He was given repeated doses of fresh frozen plasma and no bleeding complications occurred, but the prothrombin time remained prolonged for over 48 hours. Although the total dose given was comparable to doses used in other indications, critically ill patients may be particularly sensitive to the effects of argatroban (see p. 1307.3).

1. Yee AJ, Kuter DJ. Successful recovery after an overdose of argatroban. *Ann Pharmacother* 2006; 40: 336–9.

Interactions

As for Lepirudin, p. 1419.3.

Warfarin. Although caution is necessary in interpreting the INR when argatroban and warfarin are given together (see Adverse Effects and Precautions, p. 1307.3), a study in healthy subjects[1] showed no pharmacokinetic interaction.

1. Brown PM, Hursting MJ. Lack of pharmacokinetic interactions between argatroban and warfarin. *Am J Health-Syst Pharm* 2002; 59: 2078–83.

Pharmacokinetics

Argatroban is about 54% bound to plasma proteins. Metabolism, mainly hydroxylation and aromatisation, takes place in the liver, with the main metabolite having weak anticoagulant activity. Anticoagulant effects are seen immediately upon starting infusion; steady-state concentrations occur within 1 to 3 hours and are maintained until the infusion is stopped or the dose adjusted. The terminal elimination half-life of argatroban is between 39 and 51 minutes. It is excreted primarily in the faeces, via the bile as metabolites and as unchanged drug. About 16% of a dose is excreted unchanged in the urine, and at least 14% unchanged in faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Argatra; *China*: Da Bei (达贝); Novastan (诺保思泰); *Denm.*: Novastan; *Fin.*: Novastan; *Fr.*: Arganova; *Ger.*: Argatra; *Ital.*: Novastan; *Jpn*: Argaron; Gartban; Novastan; Slonnon; Slovastan†; *Neth.*: Arganova; *Norw.*: Novastan; *Swed.*: Novastan; *UK*: Exembol.

Arotinolol Hydrochloride *(rINNM)* ⊗

Arotinolol Chlorhydrate d'; Arotinolol, hidrocloruro de; Arotinololi Hydrochloridum; Hidrocloruro de arotinolol; S-596; Аротинолола Гидрохлорид.

(±)-5-[2-[[3-(*tert*-Butylamino)-2-hydroxypropyl]thio]-4-thiazolyl]-2-thiophenecarboxamide hydrochloride.

$C_{15}H_{21}N_3O_2S_3$,HCl=408.0.

CAS — 68377-92-4 (arotinolol); 68377-91-3 (arotinolol hydrochloride).

UNII — 9DO1HT306.

NOTE. The names Acemail, Alochinon, Arotinoil, Astonil, and Ceonomal have been used as trade marks for arotinolol hydrochloride.

Pharmacopoeias. In *Jpn*.

Profile

Arotinolol is a non-cardioselective beta blocker (p. 1316.3); it also has alpha$_1$-blocking activity. It is used as the hydrochloride in the management of hypertension (p. 1251.1), angina pectoris (p. 1254.3), cardiac arrhythmias (p. 1266.1), and essential tremor (p. 1318.3). The usual oral dose is 20 mg daily in 2 divided doses although up to 30 mg daily may be given. The initial dose for essential tremor is 10 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Almarl (阿尔马尔); *Jpn*: Almarl.

Atenolol *(BAN, USAN, rINN)* ⊗

Ateénolol; Atenololi; Atenololis; Atenololum; ICI-66082; Ateneton.

2-(*p*-[2-Hydroxy-3-(isopropylamino)propoxy]phenyl)acetamide.

$C_{14}H_{22}N_2O_3$=266.3.

CAS — 29122-68-7; 60966-51-0.

ATC — C07AB03.

ATC Vet — QC07AB03.

UNII — 50VV3VW0TI.

NOTE. Compounded preparations of atenolol may be represented by the following names:

- Co-tenidone (*BAN*)—atenolol 4 parts and chlortalidone 1 part (w/w)
- Co-tenidone (*PEN*)—atenolol and chlortalidone.

Distinguish atenolol from Atenenol, which has been used as a trade mark for alprenolol hydrochloride (p. 1296.3).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Atenolol). A white or almost white powder. Sparingly soluble in water; soluble in dehydrated alcohol; slightly soluble in dichloromethane.

USP 36: (Atenolol). White or practically white, odourless powder. Slightly soluble in water and in isopropyl alcohol; sparingly soluble in alcohol; freely soluble in methyl alcohol.

Uses and Administration

Atenolol is a cardioselective beta blocker (p. 1316.3). It is reported to lack intrinsic sympathomimetic activity and membrane-stabilising properties.

Atenolol is used in the management of hypertension (p. 1251.1), angina pectoris (p. 1254.3), cardiac arrhythmias (p. 1266.1), and myocardial infarction (p. 1257.1). It may also be used for the prophylaxis of migraine (p. 670.3).

In **hypertension** atenolol is given orally in a dose of 25 to 100 mg daily, as a single dose, although doses over 50 mg daily are rarely needed. The full effect is usually evident within 1 to 2 weeks.

The usual dose for **angina pectoris** is 50 to 100 mg daily orally, given as a single dose or in divided doses. Additional benefit is not usually obtained from higher doses of atenolol although up to 200 mg daily has been given.

For the emergency treatment of **cardiac arrhythmias** atenolol may be given by intravenous injection in a dose of 2.5 mg injected at a rate of 1 mg/minute, repeated if necessary every 5 minutes to a maximum total dosage of 10 mg. Alternatively atenolol may be given by intravenous infusion over 20 minutes in a dose of 150 micrograms/kg. The injection or infusion procedure may be repeated every 12 hours if necessary. When control is achieved maintenance oral doses of 50 to 100 mg daily may be given.

Atenolol is also used in the early management of acute **myocardial infarction**. Treatment should be given within 12 hours of the onset of chest pain; atenolol 5 to 10 mg should be given by slow intravenous injection at a rate of 1 mg/minute, followed after 15 minutes with 50 mg orally, provided no adverse effects result from the injection; alternatively an intravenous dose of 5 mg may be repeated after 10 minutes followed by an oral dose of 50 mg after a further 10 minutes. A further 50 mg may be given orally after 12 hours, and subsequent dosage maintained, after a further 12 hours, with 100 mg daily.

In the prophylaxis of **migraine** an oral dose of 50 to 200 mg daily has been used.

Reduced doses may be required in patients with impaired renal function (see below).

For doses in children, see Administration in Children, below.

The *S* (-)-isomer of atenolol, esatenolol (p. 1377.2), is used similarly to atenolol.

Administration in children. Atenolol may be given orally to children in the treatment of hypertension or arrhythmias. The *BNFC* recommends the following doses, given as a single dose once daily or in 2 divided doses:

- neonates and children up to 12 years: 0.5 to 2 mg/kg daily up to the maximum adult dose of 100 mg daily, although doses higher than 50 mg daily rarely necessary for hypertension
- children from 12 to 18 years may be given the usual oral adult dose for these indications, see Uses and Administration, above

Administration in renal impairment. The dose of atenolol should be reduced in patients with renal impairment, depending on the creatinine clearance (CC) as follows:

- CC 15 to 35 mL/minute per 1.73 m^2: 50 mg daily orally or 10 mg once every two days intravenously
- CC less than 15 mL/minute per 1.73 m^2: 25 mg daily or 50 mg on alternate days orally or 10 mg once every four days intravenously
- dialysis patients: 25 to 50 mg orally after each dialysis.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Breast feeding. Atenolol is distributed into breast milk and there has been a report of cyanosis and bradycardia in a breast-fed neonate whose mother had been taking atenolol (see under Pharmacokinetics, below). The American Academy of Pediatrics therefore considers[1] that it should be given with caution to breast-feeding mothers.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Effects on the eyes. Visual symptoms without headache were associated with atenolol for migraine prophylaxis in a patient who had had a similar reaction with nadolol.[1]

1. Kumar KL, Cooney TG. Visual symptoms after atenolol therapy for migraine. *Ann Intern Med* 1990; 112: 712–13. Correction. *ibid.*; 113: 257.

Effects on the heart. Beta blockers are used in the management of cardiac arrhythmias. However, atenolol 2.5 mg by intravenous injection induced atrial fibrillation in 6 of 12 predisposed patients.[1]

1. Rassmussen K, *et al.* Atrial fibrillation induced by atenolol. *Eur Heart J* 1982; 3: 276–81.

Effects on lipid metabolism. For a report of acute pancreatitis due to hypertriglyceridaemia in a patient taking metoprolol followed by atenolol, see p. 1320.1.

Effects on the liver. Adverse hepatic reactions in patients receiving atenolol have included reversible cholestatic hepatitis in one[1] and hepatic dysfunction in another.[2]

1. Schwartz MS, *et al.* Atenolol-associated cholestasis. *Am J Gastroenterol* 1989; 84: 1084–6.
2. Yusuf SW, Mishra RM. Hepatic dysfunction associated with atenolol. *Lancet* 1995; 346: 192.

Overdosage. Atenolol appears to lack membrane-stabilising activity and may have fewer adverse cardiac effects than some other beta blockers. However, cardiovascular toxicity has been noted after massive overdosage: ventricular asystole[1] and hypotension with ECG abnormalities[2] have been reported. Severe cardiovascular effects also occurred[3] in a patient with mixed overdosage including atenolol and diltiazem, and were attributed to additive toxicity.

1. Stinson J, *et al.* Ventricular asystole and overdose with atenolol. *BMJ* 1992; 305: 693.
2. Love JN, Elshami J. Cardiovascular depression resulting from atenolol intoxication. *Eur J Emerg Med* 2002; 9: 111–14.
3. Snook CP, *et al.* Severe atenolol and diltiazem overdose. *J Toxicol Clin Toxicol* 2000; 38: 661–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies atenolol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria: Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

About 50% of an oral dose of atenolol is absorbed. Peak plasma concentrations occur in 2 to 4 hours. Atenolol has low lipid solubility. It crosses the placenta and is distributed into breast milk where concentrations higher than those in maternal plasma have been achieved. Only small amounts are reported to cross the blood-brain barrier, and plasma-protein binding is minimal. The plasma half-life is about 6 to 7 hours. Atenolol undergoes little or no hepatic metabolism and is excreted mainly in the urine. It is removed by haemodialysis.

Breast feeding. Atenolol diffuses into breast milk in concentrations similar[1] to or higher[2] than those in maternal blood. Cyanosis and bradycardia associated with ingestion of atenolol in breast milk has been reported in a 5-day-old term infant. The baby improved when breast feeding was stopped.[3]

1. Thorley KJ, McAinsh J. Levels of the beta-blockers atenolol and propranolol in the breast milk of women treated for hypertension in pregnancy. *Biopharm Drug Dispos* 1983; 4: 299–301.
2. White WB, *et al.* Atenolol in human plasma and breast milk. *Obstet Gynecol* 1984; 63: 42S–44S.
3. Schimmel MS, *et al.* Toxic effects of atenolol consumed during breast feeding. *J Pediatr* 1989; 114: 476–8.

Pregnancy. Creatinine clearance increases during pregnancy, and a study in 17 pregnant patients found that the elimination half-life was shorter and renal clearance of

atenolol faster during the second and third trimesters compared with three months post partum.[1] In another study,[2] postpartum samples were taken from the maternal and umbilical serum of 6 women who had been taking atenolol for at least 6 days before delivery; atenolol was detected in both maternal and cord blood in about equal concentrations. Atenolol was not detected in the maternal or cord blood of another patient who had stopped taking atenolol one day before delivery; the authors concluded that atenolol levels in the mother and fetus are equal at steady state, and that fetal accumulation does not occur. Atenolol concentrations in 35 term neonates whose mothers had received atenolol were examined.[3] It was found that the elimination rate for the neonates was 4 times slower than in adults, possibly because of immaturity of renal function. Transient bradycardia developed in 14 neonates.

1. Hebert MF, *et al.* Pharmacokinetics and pharmacodynamics of atenolol during pregnancy and postpartum. *J Clin Pharmacol* 2005; 45: 25–33.
2. Melander A, *et al.* Transplacental passage of atenolol in man. *Eur J Clin Pharmacol* 1978; 14: 93–4.
3. Rubin PC, *et al.* Atenolol elimination in the neonate. *Br J Clin Pharmacol* 1983; 16: 659–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Atel†; Atelan†; Atenoblock; Atenopharma; Atenovit; Cardioblock; Corpaz; Fabotenol; Felobits; Ilaten; Myocord; Plenacor; Prenormine; Telvodin; Tensiol†; Tozolden; Vericordin; *Austral.*: Anselol; Atehexal†; Noten; Tenormin; Tensig; *Austria*: Atehexal; Atenolan; Tenormin; *Belg.*: Atenotop†; Docateno†; Tenormin; *Braz.*: Ablok; Angiless; Angipress; Atecard; Atenegran; Ateneo; Ateneum; Atenobal; Atenokin†; Atenol; Atenolab; Atenopress; Atenorm; Atenoton; Atensiol; Atenuol; Atepress; Plenacor; Telol; *Canad.*: Apo-Atenol; Novo-Atenol†; Nu-Atenol; Tenormin; *Chile*: Atomex; Betacar; Grifotenol; Labotensil; Sotacor; *Cz.*: Apo-Atenol; Atehexal; Atenobene; Tenormin; *Denm.*: Atenet†; Atenodan; Atenor†; Tenormin; Uniloc; *Fin.*: Atenblock; Tenoblock; Tenoprin; *Fr.*: Betatop; Tenormine; *Ger.*: Ate Lich†; Atebeta; Atehexal†; Ateno†; Atenogamma†; Juvental†; Tenormin; *Gr.*: Adenamin; Azectol; Blikonol; Blocotenol; Eptonal; Estanolin; Fealin; Galol; Hemon; Londofis; Mesonex; Mezarid; Neocardon; Osel; Presentil; Silder; Synarome; Tenormin; Tradiver; Umoder; *Hong Kong*: Apo-Atenol; Artenol†; Atenemeal†; CP-Atenol; Hajimet†; Hypernol; Lo-Ten; Martenol†; Normaten; Nortelol; Noten†; Oraday†; Telol; Tenormin; Tensig†; Ternolol; Totamol†; Tredol; Vascoten; Velorin; *Hung.*: Atenobene; Atenomel; Blokium†; Prinorm; *India*: Agloten; Alinor; Anol; Atbeta; Atcardil; Atcom; Atecard; Atekind; Atelol; Aten; Atenex; Atenij; Atenova; Atensia; Atepres; Atezys; Atol; Atop; Atormin; Atpark; Atzee; B-Bloc; Beta; Betacard; Beten; Biduten; Bp Norm; Bp-Act; Bp-Nol; Bpgard; C-Tol; Cadpres; Cardaten; Carden; Catenol; Coronol; Dilcare; Esamlo AT; Etopres; G-Ten; Harten; Hibesor; Hipres; Hyten; Lakten; Lonol; Manoten; Natenol; Novaten; O-Beta; Odinol; Teno; Tenolol; Tenormin; Tensimin; *Indon.*: Betablok; Farnormin; Hiblok; Internolol; Tenblok; Tenormin; Tensinorm†; Zumablok; *Irl.*: Amolin; Atecor; Ateni; Atenogen; Atenomel; Nortenolol; Tenormin; Trantalol; *Israel*: Normalol; Normiten; *Ital.*: Atenol; Atermin†; Seles Beta; Tenomax; Tenormin; Tensiblock; *Malaysia*: Apo-Atenol; Aveten; Beten; Loten†; Normaten; Noten†; Ranlol; Tenormin; Urosin; Vascoten; Velorin; *Mex.*: Atenol†; Atoken; Betadure; Biofilen; Blotex; Lesaten; Min-T; Nosbal; Tenormin; Trebanol; *Norw.*: Tenormin; Uniloc; *NZ*: Lo-Ten†; *Philipp.*: Aloten; Aten; Atestad; Cardioten; Durabeta; Tenor-Bloc; Tenormin; Tenorvas; Tenostat†; Tensimin; Therabloc; Trubloc; Velorin; Zenolen†; *Pol.*: Normocard†; *Port.*: Bril; Corzil; Tenormin; Tessifol†; *Rus.*: Atenolan (Атенолан)†; Betacard (Бетакард); Catenol (Катенол)†; Estekor (Эстекор); Hypoten (Хайпотен)†; Prinorm (Принорм); Tenolol (Тенолол); Tenormin (Тенормин); *S.Afr.*: Atenoblok†; B-Block; Hexa-Blok; Ten-Bloka; Tenopress; Tenormin; Venapulse†; *Singapore*: Aiti; Alonet; Apo-Atenol; Catenol; Hypernol; Normaten; Noten; Prenolol; Pretenol; Tenol; Tenolol; Tenormin; Tensig; Ternolol; Urosin; Vascoten; Velorin; *Spain*: Blokium; Neatenol†; Tanser†; Tenormin; *Swed.*: Tenormin; *Switz.*: Atenil; Cardaxen†; Selobloc; Tenormin; *Thai.*: Atcard; Atenol; Betaday; Coratol†; Daynol†; Enolol; Eutensin; Nolol†; Nortelol†; Oraday; Prelol; Prenolol; Tenocard; Tenocor†; Tenol†; Tenolol; Tenormin; Tenrol; Tetalin; Tolol; Vascoten†; Velorin; *Turk.*: Atoiteva; Nortan; Tensidif†; Tensinor; *UAE*: Tensotin; *UK*: Antipressan; Atenix†; Tenormin; *Ukr.*: Atenobene (Атенобене); *USA*: Tenormin; *Venez.*: Beloc; Blokium; Ritmilan; Tenormin.

Multi-ingredient Preparations. *Arg.*: Plenacor D; Prenoretic; Vericordin Compuesto; *Austria*: Atenolan comp; Atenolol comp; Beta-Adalat; Nif-Ten; Polinorm†; Tenoretic; *Belg.*: Tenif; Tenoretic; *Braz.*: Ablok Plus; Anaten; Angipress CD; Atelidona; Atenorese; Atenoric; Atenuol CRT; Betacard Plus; Betalor; Diublok; Nifelat; Tenoretic; *Canad.*: Apo-Atenidone; Novo-Atenolthalidone†; Tenoretic; *Cz.*: Tenoretic; *Denm.*: Tenidon; Tenoretic; *Fin.*: Nif-Ten†; *Fr.*: Beta-Adalate; Tenordate; Tenoretic; *Ger.*: Ate Lich comp†; Atehexal comp†; Atel†; AteNif beta†; Ateno comp†; Atenogamma comp†; Atenolol comp; Bresben†; Diu-Atenolol†; Nif-Ten; Nifatenol†; Teneretic; TRI-Normin; *Gr.*: Apress; Chlotenor; Merendal; Obosan; Ogerol; Tenoretic; Typofen; Vagosinol; *Hong Kong*: Nif-Ten; Target†; Tenoret; Tenoretic; *Hung.*: Blokium Diu; *India*: Aamin-A; Acord-A; Adpine-AT; Aglodepin-AT; Alodip-AT; Amcard-AT; Amchek AT; Amdepin-AT; Amdip-AT; Amdonex-AT; Amfast-AT; Amlat; Amlip Beta; Amlo-AT; Amloact-AT; Amlobet; Amlocal-AT; Amlocan-TN; Amlocard Forte; Amlocom-AT; Amlodac-AT; Amlogen-AT; Amlokath-A; Amlokind-AT; Amlokos-AT; Amlong-A; Amlonol; Amlonova; Amlopin-AT; Amlopres AT; Amlosafe-AT; Amlostat-AT; Amlot-AT; Amlotal-AT; Amlotec-AT; Amloten; Amlovas-AT; Amloz AT; Amodep-AT; Amone-AT; Amozen-AT; Ampine-AT; Amrap-AT; Amset-XT; Amsten; Amtas-AT; Amtenol; Angicam-Beta; Angitol Plus; Angizaar-AT; Anol-AD; Anol-Plus; Asomex-AT; Atamo; Atecard-AM; Atecard-D; Atelol-D; Atemos-AT; Aten-AM; Aten-D; Aten-H; Atenex-AM; Atenodip; Atenova H; Atenova-SA; Atensia-AM; Atloma; Atol-AM; Atzee-AM; Beta Amlol; Beta-Bidure; Beta-Nicardia; Beta-Nifedipine; Betacard H; Betacard-AM; Betanif; Betatrop; Beten-AM; Bibidip; Bp-Cure-AT; Bp-Loride; Bp-Mide Plus; C-Amlo Plus; Cardif Beta†; Cardipin-AT; Cardules Plus; Carvasc-A; Cinamat; Coronol-AM; Corvadil-A; Coslo; Defidin-A; Depten; Diavasc-AT; Dipal-AT; Dipress-Plus; Emadine AT; Esam AT; Esdil AT; Eslo-AT; Espin-AT; Etopres-AT; Etotan-AT; Gamlo AT; Hipres-D; Hypernorm; Inat; Indap-AT; Joglit; Losar-Beta-H; Losar-Beta; Lotensyl-AT; Maat; Maldip-AT; Melol; Moldep-AT; Myamlo-AT; Myo-24; Natenol-AM; NBal-AT; Neocard-Atn; Nicol-AT; Nifetolol; Nilol; Novadep-AT; Numlo-AT; Nusar-ATN; Odinol-AM; Olpine-AT; Presolar; Tenochek; Tenoclor; Tenofed; Tenolol-AM; Tenolol-D; Tenoric; *Indon.*: Nif-Ten; Tenoret†; Tenoretic†; *Irl.*: Atecor CT; Atenetic; Beta-Adalat; Nif-Ten; Tenoret; Tenoretic; *Ital.*: Atenigron; Carmian; Clortanol; Diube; Eupres; Igroseles; Nif-Ten; Normopress; Target; Tenoretic; *Malaysia*: Apo-Atenidone; Pretenol C; Target; Tenoret; Tenoretic; *Mex.*: Higroton Blok; Plenacor; Tenoretic; *Philipp.*: Nif-Ten†; Tenoretic; *Port.*: Tenoretic; *Rus.*: Atehexal Compositum (Атегексал Композитум); Atenolol Compositum (Атенолол Композитум); Tenochek (Теночек); Tenonorm (Тенонорм); Tenoretic (Теноретик); Tenoric (Тенорик); Tenorox (Тенорокс); *S.Afr.*: Adco-Loten; Tenchlor; Tenoret; Teneretic; *Singapore*: Beta Nicardia; Nif-Ten; Nifetex; Pretenol C; Target; Tenoret†; Tenoretic†; *Spain*: Blokium Diu; Kalten; Neatenol Diu; Neatenol Diuvas†; Normopresil; Teneretic; *Switz.*: Atedurex; Beta-Adalat; Cardaxen plus; Co-Atenolol; Cotenolol-Neo; Kalten†; Nif-Ten; Teneretic; *Thai.*: Catenol; *Turk.*: Atexal; Tenoretic; *UK*: AtenixCo; Beta-Adalat; Kalten; Tenchlor; Tenif; Tenoret; Tenoretic; Totaretic; *Ukr.*: Dinorik (Диноpик); Neocard-Atn (Неокард-Атн)†; Tenochek (Теночек); Tenoric (Тенорик); Tonorma (Тонорма); *USA*: Tenoretic; *Venez.*: Blokiuret; Tenoretic.

Pharmacopoeial Preparations

BP 2014: Atenolol Injection; Atenolol Oral Solution; Atenolol Tablets; Co-tenidone Tablets;

USP 36: Atenolol and Chlorthalidone Tablets; Atenolol Injection; Atenolol Oral Solution; Atenolol Tablets.

Atorvastatin Calcium

(BANM, USAN, rINNM)

Atorvastatina cálcica; Atorvastatine calcique; Atorvastatinum calcicum; Calcii Atorvastatinum; CI-981; Кальций Аторвастатин.

Calcium (βR,δR)-2-(*p*-fluorophenyl)-β,δ-dihydroxy-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrole-1-heptanoic acid (1:2) trihydrate.

$C_{66}H_{68}CaF_2N_4O_{10}3H_2O$=1209.4

CAS — 134523-00-5 (atorvastatin); 134523-03-8 (atorvastatin calcium); 344423-98-9 (atorvastatin calcium trihydrate).

ATC — C10AA05.

ATC Vet — QC10AA05.

UNII — 48A5M73Z4Q (atorvastatin calcium hydrate); C0GEJ5QCSO (anhydrous atorvastatin calcium).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Atorvastatin Calcium Trihydrate). A white or almost white powder. It exhibits polymorphism. Very slightly soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane.

USP 36: (Atorvastatin Calcium). A white to off-white, crystalline powder. Very slightly soluble in water, in pH 7.4 phosphate buffer, and in acetonitrile; insoluble in aqueous solutions of pH 4 and below; slightly soluble in alcohol; freely soluble in methyl alcohol.

Uses and Administration

Atorvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p. 1489.3). It is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the treatment of hyperlipidaemia (p. 1248.1), including hypercholesterolaemias and combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias), hypertriglyceridaemia (type IV), and dysbetalipoproteinaemia (type III). Atorvastatin can be effective as adjunctive therapy in patients with homozygous familial hypercholesterolaemia who have some LDL-receptor function. It is also used for primary and secondary prophylaxis of cardiovascular events (see Cardiovascular Risk Reduction, p. 1246.1) in patients with multiple risk factors, including diabetes mellitus.

Atorvastatin is given orally as the calcium salt although doses are expressed in terms of the base (atorvastatin magnesium has also been used); 10.82 mg of atorvastatin calcium trihydrate is equivalent to 10 mg of base. The usual initial dose is 10 to 20 mg of atorvastatin once daily; an initial dose of 40 mg daily may be used in patients who require a large reduction in LDL-cholesterol. The dose may be adjusted at intervals of at least 4 weeks up to a maximum of 80 mg daily.

For patients taking drugs that interact with atorvastatin, dose reduction is advised as follows:

- patients taking *ciclosporin*, maximum dose 10 mg once daily
- patients taking *clarithromycin*, initial dose 10 mg once daily and maximum dose 20 mg once daily
- patients taking *itraconazole*, initial dose 10 mg once daily and maximum dose 40 mg once daily
- patients taking *ritonavir-boosted lopinavir* or *ritonavir-boosted saquinavir*, doses above 20 mg once daily should be used with caution

For the use of atorvastatin in children and adolescents, see below.

General reviews.

1. Lea AP, McTavish D. Atorvastatin: a review of its pharmacology and therapeutic potential in the management of hyperlipidaemias. *Drugs* 1997; 53: 828–47.
2. Malinowski JM. Atorvastatin: a hydroxymethylglutaryl-coenzyme A reductase inhibitor. *Am J Health-Syst Pharm* 1998; 55: 2253–67.
3. Malhotra HS, Goa KL. Atorvastatin: an updated review of its pharmacological properties and use in dyslipidaemia. *Drugs* 2001; 61: 1835–81.
4. Croom KF, Plosker GL. Atorvastatin: a review of its use in the primary prevention of cardiovascular events in patients with type 2 diabetes mellitus. *Drugs* 2005; 65: 137–52.
5. Doggrell SA. Is atorvastatin superior to other statins? Analysis of the clinical trials with atorvastatin having cardiovascular endpoints. *Rev Recent Clin Trials* 2006; 1: 143–53.
6. Poli A. Atorvastatin: pharmacological characteristics and lipid-lowering effects. *Drugs* 2007; 67 (suppl 1): 3–15.
7. Bybee KA, *et al.* Cumulative clinical trial data on atorvastatin for reducing cardiovascular events: the clinical impact of atorvastatin. *Curr Med Res Opin* 2008; 24: 1217–29.
8. Acharjee S, Welty FK. Atorvastatin and cardiovascular risk in the elderly—patient considerations. *Clin Interv Aging* 2008; 3: 299–314.

Administration in children. In patients aged 10 to 17 years with hypercholesterolaemia or combined (mixed) hyperlipidaemia, atorvastatin is licensed for use orally in an initial dose of 10 mg once daily, adjusted if necessary at intervals of at least 4 weeks to a maximum dose of 20 mg once daily. A 6-month study[1] with this dose regimen in children with familial or severe hypercholesterolaemia found that atorvastatin was both safe and effective. Atorvastatin has also been used in children with hyperlipidaemia associated with renal[2] or heart[3] transplantation.

1. McCrindle BW, *et al.* Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *J Pediatr* 2003; 143: 74–80.
2. Argent E, *et al.* Atorvastatin treatment for hyperlipidemia in pediatric renal transplant recipients. *Pediatr Transplant* 2003; 7: 38–42.
3. Chin C, *et al.* Efficacy and safety of atorvastatin after pediatric heart transplantation. *J Heart Lung Transplant* 2002; 21: 1213–17.

Adverse Effects and Precautions

As for Simvastatin, p. 1492.1 and p. 1494.1, respectively.

General references.

1. Black DM, *et al.* An overview of the clinical safety profile of atorvastatin (Lipitor), a new HMG-CoA reductase inhibitor. *Arch Intern Med* 1998; 158: 577–84.
2. Bernini F, *et al.* Safety of HMG-CoA reductase inhibitors: focus on atorvastatin. *Cardiovasc Drugs Ther* 2001; 15: 211–18.
3. Waters DD. Safety of high-dose atorvastatin therapy. *Am J Cardiol* 2005; 96 (suppl 5A): 69F–75F.
4. Arca M. Atorvastatin: a safety and tolerability profile. *Drugs* 2007; 67 (suppl 1): 63–9.

Effects on the skin. Toxic epidermal necrolysis apparently caused by atorvastatin has been reported.[1] The authors were not aware of this adverse effect previously having been associated with any of the statin lipid regulating drugs.

1. Pfeiffer CM, *et al.* Toxic epidermal necrolysis from atorvastatin. *JAMA* 1998; 279: 1613–14.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies atorvastatin as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Simvastatin, p. 1494.2.

Pharmacokinetics

Atorvastatin is rapidly absorbed from the gastrointestinal tract. It has low absolute bioavailability of about 12% due to presystemic clearance in the gastrointestinal mucosa and/or first-pass metabolism in the liver, its primary site of action. Atorvastatin is metabolised by the cytochrome P450 isoenzyme CYP3A4 to several active metabolites. It is 98% bound to plasma proteins. The mean plasma elimination half-life of atorvastatin is about 14 hours although the half-life of inhibitory activity for HMG-CoA reductase is about 20 to 30 hours due to the contribution of the active metabolites. Atorvastatin is excreted as metabolites, primarily in the bile.

Reviews.

1. Lennernäs H. Clinical pharmacokinetics of atorvastatin. *Clin Pharmacokinet* 2003; **42**: 1141–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ampliar; Atarva; Ateroclar; Atormax; Atorvastan; Faboxim; Finlipol; Liparex; Lipibec; Lipifen; Lipitor; Lipocambi; Lipofin; Lipokemia; Liponorm; Lipostop; Lipovastatin; Normalip; Normolipol; Plan; Sincol; Tecoplax; Tialipol†; Torivas; Trimstat; Vanator; Vastina; Zarator; *Austral.*: Lipitor; *Austria*: Sortis; *Belg.*: Lipitor; *Braz.*: Atorless; Citalor; Kolevas; Lipigran; Lipistat; Lipitor; Volunta; Zarator; *Canad.*: Lipitor; *Chile*: Atenfar; Atorlip; Dislipor; Hipolixan; Lipitor; Lipotropic; Lipox; Lowden; Zarator; Zurinel†; *China*: Ale (阿乐); Lipitor (立普妥); You Jia (尤佳); Cz.: Atogal†; Atorgamma; Atoris; Atorpharm; Atraven; Bisatum†; Corat; Larus; Pharmtina; Sortis; Spatizalex; Torvacard; Torvazin; Triglyx; Tulip; Vaston†; Voredanin; Xippatin†; *Denm.*: Atorin; Erostatin; Lipitor; Prevencor; Sortis; Tahor†; Torvast; Zarator; *Fin.*: Atorvaratio; Lipitor; Orbeos; *Fr.*: Tahor; *Ger.*: Sortis; *Gr.*: Altoram; Antorcin; Arvastatil; Ator-Chol; Atorgon; Atorlip; Atorlonga; Atorstat; Atorval; Atorvalet; Atorvanox; Atorvin; Atrost; Atrosterol; Atrovita; Biger; Card-OK; Danelip; Delipost; Doss; Fluxol; Hollsten; Latrovin; Lipigan; Lipitor; Lipium-Raldex; Lipizem; Lipodial; Lipostatin; Lipovast; Lorvaten; Rotova; Torvaplus; Torvastin; Vastazor; Xanator; Zarator; *Hong Kong*: Atacor; Lipitor; *Hung.*: Atorgamma; Atoris; Atorva; Atorvep; Atorvox; Copator; Decholest; Dislipat; Hypolip; Liprimar†; Obradon; Sortis; Torvacard; Torvalipin; *India*: A-Vin; Alip; Alnavas; Altovas; Aova; Aqualip; Arpitor; Astin; Asvasin; Atba; Atchol; Atevan; Atheart; Atherochek; Atix; Ato; Atocor; Atofast; Atone; Atorbest; Atordin; Atorec; Atorem; Atorfit; Atoril; Atorin; Atoriv; Atorlip; Atormac; Atornet; Atoroll; Atorsi; Atortin; Atortus; Atorva; Atorvasia; Atorvik; Atosar; Atover; Atozide; Atria; Atrolar; Atrostat; Atstat; Attor; Atv; Atvas; Avas; Avascare; Avastin; Avistatin; Aztor; Barostatin; Biostat; Caat; Carato; Cardinova; Cardistat; Cholecheck; Cholestat; Dipolip; Dyslip; Dysliptin; Elvas; Esia; Eto; Etovas; Gatovas; Genlip; Genxvast; Hartor; Hivas; Jvastor; Kobit; LDTor; Lesstrol; Lipichek; Lipicon; Lipicor; Lipicure; Lipid; Lipidrop; Lipikind; Lipiles; Lipira; Lipiric; Lipirol; Lipitab; Lipivas; Lipofix; Liponorm; Liporest; Lipvas; Ministat; Modlip; Monotorva; Noclog; Nustat; Omnitor; Orvas; Ostin; Xtor; *Indon.*: Atofar; Atorsan; Lipitor; Stator; Truvaz; *Irl.*: Atorvas; Lipitor; Lipvastin; Torvacol; *Israel*: Caduet; Lipitor; Litorva; Torid; *Ital.*: Atosener; Brouclast; Haepcard; Lipitor; Rovas; Sopavi; Torastin; Torvast; Totalip; Tovanira; Xarator; *Jpn*: Lipitor; *Malaysia*: Lipitor; Rotaqor; Storvas; *Mex.*: Lipitor; *Neth.*: Atofloc; Atolux; AtoraB; Lipitor; Prevencor†; Sortis†; *Norw.*: Lipitor; *NZ*: Lipitor; *Philipp.*: Atopitar; Ator; Atroact; Avamax; Carvastin; Lipitor; Redulip; Stallp; *Pol.*: Apo-Atorva; Atorgamma; Atoris; Atorvasterol; Atorvox; Atractin; Atrox; Corator; Larus; Sortis; Storvas; Torvacard; Torvalipin; Tulip; Xavitor; *Port.*: Atorvan; Avarte; Colip†; Kalcor; Kasitrin†; Minilip†; Sortis†; Telvarte; Texzor; Vartrual; Vastor; Zarator; *Rus.*: Anvistat (Анвистат); Atomax (Атомакс); Atoris (Аторис); Atorvox (Аторвокс); Lipoford (Липофорд); Lipona (Липона); Liprimar (Липримар); Liptonorm (Липтонорм); Torvacard (Торвакард); Tulip (Тулип); *S.Afr.*: Aspavor; Atolip; Lipitor; Lipogen; *Singapore*: Lipitor; *Spain*: Atoris; Cardyl; Prevencor; Thervan; Zarator; *Swed.*: Atorbir; Atorstad; Lipitor; Tavara; *Switz.*: Atorva; Sortis; *Thai.*: Atorsan; Lipitor; *Turk.*: Alvastin; Ateroz; Ator; Avitorel; Cardyn; Cholvast; Colastin-L; Divator; Kolestor; Lipidra; Lipitaksin; Lipitor; Saphire; Tarden; Torvaxal; *UAE*: Lipigard; *UK*: Lipitor; *Ukr.*: Amvastan (Амвастан); Astin (Астин); Atocor (Атокор); Atoris (Аторис); Atorvacor (Аторвакор); Atorvasterol (Аторвастерол); Liprimar (Липримар); Livostor (Ливостор); Storvas (Сторвас); Tolevas (Толевас); Torvacard (Торвакард); Tulip (Тулип); *USA*: CTR; Lipitor; *Venez.*: Atovarol; Glustar; Lipitor; Tarimyl.

Multi-ingredient Preparations. *Arg.*: Ampliar Duo; Ampliar Plus; Ateroclar Combi; Ateroclar Duo; Colmibe; Hipertensal Combi; Liparex Duo; Liparex Plus; Lipibec Duo; Lipibec Plus; Lipoarteriosan; Lipocambi Plus; Liponorm Duo; Pelmec Plus; Plan Duo; Temax; Torimibe; Torivas AT; *Austral.*: Caduet; *Austria*: Caduet; *Braz.*: Caduet; *Canad.*: Caduet; *Chile*: Caduet; *China*: Caduet (多达一); Cz.: Caduet; *Fr.*: Caduet; *Hong Kong*: Caduet; *Hung.*: Caduet; *India*: A-Vin-AS; A1A; AFP; Alip-AM; Alnavas-A; Alnavas-EZ; Altovas-EZ; Amat; Amdepin Duo; Amlopin Plus; Amtor; Aova-EZ; Aova-P; Atchol Asp; Atchol-P; Atheart-EZ; Atherochek-10; Atherochek-5; Atherotwo; Atix-EZ; Atofast-EZ; Atofast-P; Atofast-M; Atoplus; Atorem-F; Atorfen; Atorin-EZ; Atorin-F; Atorlip-EZ; Atorlip-F; Atormac-TG; Atornet-F; Atoroll-EZ; Atortus-EZ; Atorva-TG; Atorvik-EZ; Atosa; Atozide-F; Avas AM; Avas EZ; Avas Plus; Avascare-EZ; Aztor Asp; Aztor EZ; Bitorva; Caduet; Cardipill; Cardisoz-AT; Deplatt-CV; Diakit-4; Dilutex Plus; Dipilitor; Duocad; Dyslip-EZ; Dyslip-TG; Dysliptin-EZ; Dysliptin-TG; Ecosprin Gold; Ecosprin-AV; Ecostat; Eslova; Etovas-EZ; Ezemax-A; Ezevas; Fenostat; Fibator EZ; Fibator; Fibrovas; Genlip-EZ; Genxvast-F; Gissistat; Inovas-F; Jstat; Jvastor-EZ; Kobit-AS; Kobit-M; LDTor-Z; Lesstrol-AM; Lesstrol-EZ; Lesstrol-N; Lipi-EZ; Lipicard AV; Lipicure-AS; Lipidrop-V; Lipifol Plus; Lipikind-AM; Lipikind-EZ; Lipivas EZ; Liplofin; Lipofix-EX; Liponorm-EZ; Lorisk; Lorlip-EZ; Lorlip; Modlip Asp; Modlip-AM; Modlip-EZ; Niyat; Noclog-EZ; Noklot-CV; Nurokind Hart; Omnitor-EZ; Orvaz-EZ; Orvaz-FT; Zeditor; *Indon.*: Caduet; *Malaysia*: Caduet; *Mex.*: Caduet; *Philipp.*: Envacar; *Port.*: Caduet; *Rus.*: Caduet (Кадуэт); *S.Afr.*: Caduet; *Singapore*: Caduet; *Spain*: Astucor; Caduet; *Switz.*: Caduet; *Thai.*: Caduet; *Turk.*: Caduet; *Ukr.*: Azi-Ator (Ази-Атор); Caduet (Кадует); *USA*: Caduet; Liptruzet; *Venez.*: Caduet.

Atropine *(BAN)*

Atropiini; Atropin; Atropină; Atropina; Atropinas; Atropinum; DL-Hiosciámina; Атропин; (±)-Hiosciamina; (±)-Hyoscyamine.

(1*R*,3*r*,5*S*,8*r*)-Tropan-3-yl (*RS*)-tropate.

$C_{17}H_{23}NO_3$=289.4

CAS — 51-55-8.

ATC — A03BA01; S01FA01.

ATC Vet — QA03BA01; QS01FA01.

UNII — 7C0697DR9I.

Description. Atropine is an alkaloid that may be obtained from solanaceous plants, or prepared by synthesis.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Atropine). A white or almost white, crystalline powder or colourless crystals. Very slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Atropine). White crystals, usually needle-like, or white crystalline powder. Soluble 1 in 460 of water, 1 in 90 of water at 80 degrees, 1 in 2 of alcohol, 1 in 1 of chloroform, and 1 in 25 of ether; soluble in glycerol. Its saturated solution in water is alkaline to phenolphthalein. Store in airtight containers. Protect from light.

Atropine Methobromide *(BANM)*

Atropina, metilbromuro de; Atropine Methylbromide; Methylatropine Bromide; Méthylatropine, bromure de; Methylatropini Bromidum; Methylatropinii Bromidum; Methylatropinium Bromatum; Methylatropinium-bromid; Methylatropiniumbromid; Metilatropin-bromid; Metilatropino bromidas; Metylatropinbromid; Metyylatropiinibromidi; Mydriasine; Атропина Метобромид.

(1*R*,3*r*,5*S*)-8-Methyl-3-[(±)-tropoyloxy]tropanium bromide.

$C_{18}H_{26}BrNO_3$=384.3

CAS — 2870-71-5.

ATC — A03BA01.

ATC Vet — QA03BA01.

UNII — 63IFTDXX9N.

Atropine Methonitrate *(BANM, rINN)*

Atrop. Methonit.; Atropiinimetonitraatti; Atropina, metilnitrato de; Atropine, Méthonitrate d'; Atropini Methonitras; Atropinmetonitrat; Methylatropine Nitrate (USAN); Methylatropine Nitrate; Méthylatropine, nitrate de; Methylatropini nitras; Methylatropinii Nitras; Methylatropinium nitrát; Methylatropiniumnitrat; Metilatropin-nitrát; Metilatropino nitratas; Metilnitrato de atropina; Metonitrato de atropina; Metylatropiinnitraatti; Metyylatropiininitraatti; Атропина Метонитрат.

(1*R*,3*r*,5*S*)-8-Methyl-3-[(±)-tropoyloxy]tropanium nitrate.

$C_{18}H_{26}N_2O_6$=366.4

CAS — 52-88-0.

ATC — A03BB02.

ATC Vet — QA03BB02.

UNII — Q48D9J47K2.

Stability. Aqueous solutions of atropine methonitrate are unstable; stability is enhanced in acid solutions of pH below 6.

Atropine Sulfate *(BANM)*

Atrop. Sulph.; Atropiinisulfaatti; Atropin Sülfat; Atropina, sulfato de; Atropine, sulfate d'; Atropine Sulphate; Atropini sulfas; Atropini Sulfas Monohydricus; Atropino sulfatas; Atropinsulfat; Atropin-sulfát monohydrát; Atropin-szulfát; Atropiny siarczan; Атропина Сульфат.

$(C_{17}H_{23}NO_3)_2.H_2SO_4.H_2O$=694.8

CAS — 55-48-1 (anhydrous atropine sulfate); 5908-99-6 (atropine sulfate monohydrate).

ATC — A03BA01; S01FA01.

ATC Vet — QA03BA01; QS01FA01.

UNII — KAE4PSB0Z3 (anhydrous atropine sulfate); 03J5ZE7KA5 (atropine sulfate monohydrate).

NOTE. Compounded preparations of atropine sulfate may be represented by the following names:

- Co-phenotrope (*BAN*)—atropine sulfate 1 part and diphenoxylate hydrochloride 100 parts (w/w).

ATR is a code approved by the BP 2014 for use on single unit dose eye drops containing atropine sulfate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Atropine Sulfate). A white or almost white crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol. A 2% solution in water has a pH of 4.5 to 6.2. Protect from light.

USP 36: (Atropine Sulfate). Odourless, colourless crystals or white crystalline powder. It effloresces in dry air. Soluble 1 in 0.5 of water, 1 in 2.5 of boiling water, 1 in 5 of alcohol, and 1 in 2.5 of glycerol. Store in airtight containers. Protect from light.

Incompatibility. Incompatibility between atropine sulfate and hydroxybenzoate preservatives has been seen,[1] resulting in a total loss of the atropine in 2 to 3 weeks.

1. Deeks T. Oral atropine sulphate mixtures. *Pharm J* 1983; **230**: 481.

Uses and Administration

Atropine is a tertiary amine antimuscarinic alkaloid with both central and peripheral actions (see below). It is usually given as the sulfate. It first stimulates and then depresses the CNS and has antispasmodic actions on smooth muscle and reduces secretions, especially salivary and bronchial secretions; it also reduces perspiration, but has little effect on biliary or pancreatic secretion. Atropine depresses the vagus and thereby increases the heart rate. When given orally atropine reduces smooth-muscle tone and diminishes gastric and intestinal motility but has little effect on gastric secretion in usual therapeutic doses. Quaternary ammonium derivatives, such as the methonitrate, have less effect on the CNS but strong ganglion-blocking activity.

Because of its effects on heart rate, atropine is used in the treatment of bradycardia and asystole of various causes (p. 1311.2), including in acute cardiopulmonary resuscitation procedures. It has also had many other uses, including: in anaesthetic practice as a premedicant and to counteract the muscarinic effects of anticholinesterases such as neostigmine and other parasympathomimetics (p. 1311.1); as an antispasmodic in gastrointestinal disorders (p. 1311.2); as an adjunct to opioid analgesics for the symptomatic relief of biliary or renal colic (p. 1311.2); to treat or prevent bronchospasm (p. 1312.1); and in the treatment of poisoning with mushrooms that contain muscarine and in organophosphorus pesticide poisoning (p. 1311.3). Atropine is used topically as a mydriatic and cycloplegic in ophthalmology (p. 1311.2).

Actions of antimuscarinics. Antimuscarinic drugs such as atropine are competitive inhibitors of the actions of acetylcholine at the muscarinic receptors of autonomic effector sites innervated by parasympathetic (cholinergic postganglionic) nerves; they are also inhibitors of the action of acetylcholine on smooth muscle lacking cholinergic innervation. They have been described as parasympatholytic, atropinic, atropine-like, and as anticholinergic, although the latter term should encompass compounds that also have antinicotinic actions.

At least 5 different pharmacologically identifiable types of **muscarinic receptor** (M_1, M_2, M_3, M_4, and M_5) have been described as have 5 different molecular forms (m_1, m_2, m_3, m_4, and m_5) of these receptors. While the traditional antimuscarinics appear to be relatively non-specific, newer compounds like pirenzepine and telenzepine have a selective action on the M_1 receptors within ganglia supplying cholinergic postganglionic nerves to the gastrointestinal tract.

Antimuscarinics can be classified as **tertiary amine** or **quaternary ammonium** compounds. Atropine and other naturally occurring alkaloids such as hyoscine and hyoscyamine are tertiary amines, that is they have a tertiary nitrogen atom; semisynthetic derivatives or synthetic antimuscarinics may be either tertiary (e.g. homatropine or trihexyphenidyl) or quaternary ammonium (e.g. homatropine methylbromide or ipratropium) compounds.

At therapeutic doses tertiary amine antimuscarinics have little effect on the actions of acetylcholine at nicotinic receptors. However, the quaternary ammonium antimuscarinics have a greater degree of antinicotinic potency, and some of their effects at high doses are due to ganglionic blockade; excessively high doses may even produce neuromuscular block. There are also pharmacokinetic

differences between tertiary amine and quaternary ammonium antimuscarinics. Quaternary ammonium compounds are less lipid soluble than tertiary amines; their gastrointestinal absorption is poor and they do not readily pass the blood-brain barrier or conjunctiva.

Antimuscarinics can produce a wide range of effects at therapeutic doses. The **peripheral** antimuscarinic effects that are produced as the dose increases are:

- decreased production of secretions from the salivary, bronchial, and sweat glands
- dilatation of the pupils (mydriasis) and paralysis of accommodation (cycloplegia)
- increased heart rate
- inhibition of micturition and reduction in gastrointestinal tone
- inhibition of gastric acid secretion

As for **central** effects, with the exception of hyoscine, which causes CNS depression at therapeutic doses, tertiary amines stimulate the medulla and higher cerebral centres producing mild central vagal excitation and respiratory stimulation. At toxic doses all tertiary amines, including hyoscine, cause stimulation of the CNS with restlessness, disorientation, hallucinations, and delirium. As the dose increases stimulation is followed by central depression and death from respiratory paralysis. Synthetic tertiary amines are less potent in their central effects than natural tertiary amines; quaternary ammonium compounds have negligible central effects.

Anaesthesia. Antimuscarinics, including *atropine, hyoscine,* and *glycopyrronium,* have been used pre-operatively to inhibit salivation and excessive secretions of the respiratory tract during anaesthesia (p. 1899.1), although this use is less important now that less irritating anaesthetics are used. Atropine and glycopyrronium are also given to reduce intra-operative bradycardia and hypotension induced by drugs such as suxamethonium, halothane, or propofol, or after vagal stimulation. Glycopyrronium causes less tachycardia than atropine when given intravenously. When hyoscine is used as a premedicant it also provides some amnesia, sedation, and antiemesis but, unlike atropine, may cause bradycardia rather than tachycardia. Atropine or, preferably, glycopyrronium is also used before, or with, anticholinesterases such as neostigmine to prevent their muscarinic adverse effects (see Uses and Administration of Neostigmine, p. 687.2).

For **premedication** 300 to 600 micrograms of atropine sulfate may be given by subcutaneous or intramuscular injection, usually 30 to 60 miniutes before anaesthesia. Alternatively 300 to 600 micrograms of atropine sulfate may be given intravenously immediately before induction of anaesthesia.

The *BNFC* suggests that suitable paediatric subcutaneous or intramuscular premedication doses of atropine sulfate are:

- neonates: 10 micrograms/kg
- children aged 1 month to 12 years: 10 to 30 micrograms/kg (minimum 100 micrograms, maximum 600 micrograms)
- children aged 12 to 18 years: the adult dose

It also suggests the following intravenous doses:

- neonates: 10 micrograms/kg
- children aged 1 month to 12 years: 20 micrograms/kg (minimum 100 micrograms, maximum 600 micrograms)
- children aged 12 to 18 years: the adult dose

The *BNFC* also lists oral doses to be given 1 to 2 hours before induction:

- neonates: 20 to 40 micrograms/kg
- children aged 1 month to 18 years: 20 to 40 micrograms/kg (maximum 900 micrograms).

For intra-operative **bradycardia** the *BNF* states that 300 to 600 micrograms may be given intravenously; larger doses may be used in emergencies.

The *BNFC* suggests that a suitable intravenous dose is:

- neonates and children aged 1 month to 12 years: 10 to 20 micrograms/kg
- children aged 12 to 18 years: the adult dose.

To counteract the muscarinic effects of **anticholinesterases** when they are used to reverse the effects of competitive muscle relaxants, adults are given atropine sulfate 0.6 to 1.2 mg by intravenous injection before or with neostigmine; the *BNF* considers the 0.6 mg dose to be sufficient with edrophonium.

The *BNFC suggests* that a suitable intravenous dose for use with neostigmine is:

- neonates and children aged 1 month to 12 years: 20 micrograms/kg (maximum 1.2 mg)
- children aged 12 to 18 years: the adult dose

and that a suitable intravenous dose for use with edrophonium is:

- children aged 1 month to 18 years: 7 micrograms/kg (maximum 600 micrograms)

Biliary and renal colic. Atropine has been used as an adjunct to opioid analgesics for symptomatic relief of biliary or renal colic (see p. 6.3).

Cardiac disorders. Atropine depresses the vagus and thereby increases the heart rate. It is therefore used in a variety of disorders or circumstances in which bradyarrhythmias occur. It is frequently used in sudden onset bradyarrhythmias and although it may also be given for the initial treatment of chronic arrhythmias (p. 1266.1), cardiac pacing is generally preferred for long-term control. Examples of acute use include the prevention and treatment of arrhythmias associated with anaesthesia (see above), the treatment of other drug-induced arrhythmias, and in bradycardia after cardiac arrest (p. 1268.3). Atropine sulfate has been used in the management of bradycardia of acute myocardial infarction; however, caution is required, as atropine may exacerbate ischaemia or infarction in these patients.

In **bradycardia** after cardiac arrest, atropine is given[1-3] in doses of 500 micrograms intravenously repeated every 3 to 5 minutes to a total dose of 3 mg. Doses lower than 500 micrograms may paradoxically slow the heart.[1-3]

If an intravenous line cannot be established, atropine can be given via an endotracheal tube, although this route is considered less reliable and higher doses are generally required. For children, a suggested dose is 30 micrograms/kg, flushed with 5 mL of sodium chloride 0.9% followed by 5 manual ventilations.[2]

1. The American Heart Association. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010; 122 (18 suppl 3): S639–S946. Also available at: http://ctrc.ahajournals.org/content/vol122/18_suppl_3/ (accessed 21/01/11)
2. European Resuscitation Council. European Resuscitation Council guidelines for resuscitation 2010. *Resuscitation* 2010; 81: 1219–1451. Also available at: www.cprguidelines.eu/2010 (accessed 07/02/11)
3. Resuscitation Council (UK). 2010 Resuscitation Guidelines. Available at: http://www.resus.org.uk/pages/GL2010.pdf (accessed 21/01/11)

Eye disorders. Ophthalmic application of atropine produces mydriasis and cycloplegia (p. 2000.2). One local application takes up to 40 minutes or more to produce mydriasis, which lasts for 7 or more days; marked cycloplegia is obtained in 1 to 3 hours with recovery in 6 to 12 days. Atropine is used to prevent the formation of adhesions and relieve painful ciliary muscle spasm in inflammatory eye disorders such as uveitis (p. 1615.1). It is used to prevent or reverse amblyopia (lazy eye) by producing cycloplegia in the stronger eye, for example in those with strabismus (p. 2000.3), and may be considered as effective as conventional occlusion.[1] It has also been used to aid ophthalmic examination, for example in the determination of refraction; however, other antimuscarinics such as cyclopentolate, homatropine, or tropicamide are usually preferred, especially in adults, because of their faster onset and shorter duration of action.

Atropine sulfate eye drops are usually available in a strength of 1%, although a 0.5% solution or a 1% ointment are obtainable in some countries and may be more suitable where the avoidance of systemic absorption is important, for example in infants and young children. Systemic absorption may also be reduced by compressing the lachrymal sac after instillation.

In the treatment of **inflammatory eye disorders** such as uveitis, atropine sulfate is applied to the eye(s) 1 to 4 times daily. To prevent or reverse **amblyopia**, atropine sulfate may be applied to the stronger eye once daily, although its long duration of action may permit less frequent application.[2-4] To aid **determination of refraction** and other ophthalmic examinations, atropine sulfate is applied to the eye(s) twice daily for up to 3 days before the procedure.

Daily application of atropine sulfate 1% in 400 children aged from 6 to 12 years was shown[5] to slow the progression of myopia, although the same treatment in a similar study did not show an effect on astigmatism.[6]

Atropine borate has also been used in ophthalmic preparations.

1. Li T, Shotton K. Conventional occlusion versus pharmacologic penalization for amblyopia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 22/04/10).
2. Stolovitch C, *et al.* Atropine cycloplegia: how many instillations does one need? *J Pediatr Ophthalmol Strabismus* 1992; 29: 175–6.
3. Repka MX, *et al.* Pediatric Eye Disease Investigator Group. A randomized trial of atropine regimens for treatment of moderate amblyopia in children. *Ophthalmology* 2004; 111: 2076–85.
4. Repka MX, *et al.* Pediatric Eye Disease Investigator Group. Treatment of severe amblyopia with weekend atropine: results from 2 randomized clinical trials. *J AAPOS* 2009; 13: 258–63.
5. Chua WH, *et al.* Atropine for the treatment of childhood myopia. *Ophthalmology* 2006; 113: 2285–91.
6. Chia A, *et al.* Effect of topical atropine on astigmatism. *Br J Ophthalmol* 2009; 93: 799–802.

Gastrointestinal disorders. Antimuscarinics may be used in gastrointestinal disorders as antispasmodics (see p. 1806.3), because of their marked inhibitory effect on gastrointestinal motility, and for their antisecretory effects. Atropine (as the sulfate or quaternary derivatives such as the methobromide or methonitrate) has been used to reduce smooth-muscle tone and diminish motility, but has little effect on gastric secretion at usual therapeutic doses. It has been tried as an adjunct to the treatment of benign gastric and duodenal ulcers and the antispasmodic action of atropine has been used to facilitate radiological examination of the gut. Atropine sulfate has also been used in the treatment of irritable bowel syndrome. Atropine oxide hydrochloride is also used for gastrointestinal disorders.

Poisoning. Atropine is used in the management of overdosage or poisoning due to anticholinesterase compounds including organophosphorus pesticides,[1,2] chemical warfare nerve gases,[3] and parasympathomimetics such as neostigmine. It is also used to antagonise the effects of cholinomimetic substances in the treatment of overdosage with parasympathomimetics such as bethanechol, and in the treatment of poisoning with mushrooms that contain muscarine. Atropine blocks the action of these compounds at muscarinic receptors, reversing bradycardia and decreasing tracheobronchial secretions, bronchoconstriction, intestinal secretions, and intestinal motility.

- In the treatment of poisoning with organophosphorus **pesticides** or chemical warfare **nerve gases** atropine sulfate may be given to adults in an initial intravenous dose of 2 mg every 5 minutes until muscarinic effects disappear or signs of atropine toxicity are seen. In severe poisoning, some sources have suggested doubling the dose of atropine every 5 to 10 minutes until improvement is seen. Continuous infusion has also been used.[4,5] Some have suggested a dose of at least 50 micrograms/kg intravenously or intramuscularly for children affected by nerve agents;[6] the *BNFC* includes an intravenous dose of 20 micrograms/kg (maximum 2 mg) given every 5 to 10 minutes for pesticide poisoning.
- In moderate to severe poisoning a state of atropinisation is usually maintained for at least 2 days and continued for as long as symptoms are evident. In severely poisoned patients this may entail prolonged treatment.[7,8] As large amounts of atropine may be required it is important to use a preservative-free preparation to avoid the potential toxicity associated with use of excess quantities of preservatives such as benzyl alcohol or chlorobutanol.
- Since atropine is ineffective against any nicotinic effects of these compounds a cholinesterase reactivator such as pralidoxime (p. 1571.2) may be used as an adjunct.

The use of atropine in poisoning or overdosage with **other compounds** having muscarinic actions is similar to that for organophosphorus pesticides but the duration of treatment necessary is usually shorter. An initial dose of 1 to 2 mg given subcutaneously, intramuscularly, or intravenously and repeated every 2 to 4 hours may be adequate for overdosage with cholinomimetics such as bethanechol.

1. Singh S, *et al.* Is atropine alone sufficient in acute severe organophosphorus poisoning: experience of a North West Indian hospital. *Int J Clin Pharmacol Ther* 1995; 33: 628–30.
2. Eddleston M, *et al.* Management of severe organophosphorus pesticide poisoning. *Crit Care* 2002; 6: 259.
3. Anonymous. Treatment of nerve gas poisoning. *Med Lett Drugs Ther* 1995; 37: 43–4.
4. Ram JS, *et al.* Continuous infusion of high doses of atropine in the management of organophosphorus compound poisoning. *J Assoc Physicians India* 1991; 39: 190–3.
5. Sungur M, Güven M. Intensive care management of organophosphate insecticide poisoning. *Crit Care* 2001; 5: 211–15.
6. Rotenberg JS, Newmark J. Nerve agent attacks on children: diagnosis and management. *Pediatrics* 2003; 112: 648–58.
7. Golsousidis H, Kokkas V. Use of 19 590 mg of atropine during 24 days of treatment after a case of unusually severe parathion poisoning. *Hum Toxicol* 1985; 4: 339–40.
8. Afzaal S, *et al.* High dose atropine in organophosphorus poisoning. *Postgrad Med J* 1990; 66: 70–1.

Reflex anoxic seizures. A reflex anoxic seizure[1,2] is a paroxysmal event triggered by a noxious stimulus which, by vagal stimulation, causes pronounced bradycardia or cardiac arrest and consequent relative cerebral ischaemia. Depending on the degree of vagal hypersensitivity or noxious stimulus, attacks may occur infrequently or several times daily. Certain features of the attack may lead to a misdiagnosis of epilepsy. To avoid confusion with epileptic seizures (p. 506.1), reflex anoxic seizures have also been called white, pallid, or type 2 breath holding attacks. In susceptible individuals, a reflex anoxic seizure may provoke a true epileptic seizure, but this is rare.[3]

Infants and young children are mainly affected and the condition usually resolves by early childhood. It is generally benign and children do not suffer cardiac or cerebral damage. Treatment is seldom necessary, but atropine has been advocated to prevent vagal hypersensitivity in those children with frequent, persistent attacks. As atropine may require frequent doses with an attendant risk of overdosage, transdermal hyoscine has been tried as an alternative;[4] cardiac pacing has also been used successfully.[5,6]

1. Appleton RE. Reflex anoxic seizures. *BMJ* 1993; 307: 214–5.
2. Stephenson JB. Anoxic seizures: self-terminating syncopes. *Epileptic Disord* 2001; 3: 3–6.

3. Horrocks IA, *et al.* Anoxic-epileptic seizures: observational study of epileptic seizures induced by syncopes. *Arch Dis Child* 2005; 90: 1283–7.
4. Palm L, Blennow G. Transdermal anticholinergic treatment of reflex anoxic seizures. *Acta Paediatr Scand* 1985; 74: 803–4.
5. McLeod KA, *et al.* Cardiac pacing for severe childhood neurally mediated syncope with reflex anoxic seizures. *Heart* 1999; 82: 721–5.
6. Wilson D, *et al.* Cardiac pacing in the management of severe pallid breath-holding attacks. *J Paediatr Child Health* 2005; 41: 228–30.

Respiratory-tract disorders. Although atropine is a potent bronchodilator its use in the management of reversible airways obstruction has largely been replaced by other antimuscarinics such as ipratropium (p. 1211.3). Atropine is sometimes used in combination preparations with antihistamines and decongestants for the symptomatic relief of symptoms of the common cold.

References.

1. Sur S, *et al.* A random double-blind trial of the combination of nebulized atropine methylnitrate and albuterol in nocturnal asthma. *Ann Allergy* 1990; 65: 384–8.
2. Vichyanond P, *et al.* Efficacy of atropine methylnitrate alone and in combination with albuterol in children with asthma. *Chest* 1990; 98: 637–42.

Adverse Effects

The pattern of adverse effects seen with atropine and other antimuscarinics can mostly be related to their pharmacological actions at muscarinic and, at high doses, nicotinic receptors (see Actions of Antimuscarinics, p. 1310.3). These effects are dose-related and are usually reversible when therapy is stopped. The **peripheral** effects of atropine and other antimuscarinics are a consequence of their inhibitory effect on muscarinic receptors within the autonomic nervous system. At therapeutic doses, adverse effects include dryness of the mouth with difficulty in swallowing and talking, thirst, reduced bronchial secretions, dilatation of the pupils (mydriasis) with loss of accommodation (cycloplegia) and photophobia, flushing and dryness of the skin, transient bradycardia followed by tachycardia, with palpitations and arrhythmias, and difficulty in micturition, as well as reduction in the tone and motility of the gastrointestinal tract leading to constipation. Some of the **central** effects of atropine and other tertiary antimuscarinics seen at toxic doses (see below) may also occur at therapeutic doses.

In **overdosage**, the peripheral effects become more pronounced and other symptoms such as hyperthermia, hypertension, increased respiratory rate, and nausea and vomiting may occur. A rash may appear on the face or upper trunk. Toxic doses also cause CNS stimulation marked by restlessness, confusion, excitement, ataxia, incoordination, paranoid and psychotic reactions, hallucinations and delirium, and occasionally seizures. However, in severe intoxication, central stimulation may give way to CNS depression, coma, circulatory and respiratory failure, and death.

There is considerable variation in susceptibility to atropine; recovery has occurred even after 1 g, whereas deaths have been reported from doses of 100 mg or less for adults and 10 mg for children.

Quaternary ammonium antimuscarinics, such as atropine methobromide or methonitrate and propantheline bromide, have some ganglion-blocking activity and high doses may cause orthostatic hypotension and impotence; in toxic doses non-depolarising neuromuscular block may be produced.

Systemic toxicity may be produced by the **local** instillation of antimuscarinic eye drops, particularly in children and in the elderly. Prolonged application of atropine to the eye may lead to local irritation, hyperaemia, oedema, and conjunctivitis. An increase in intra-ocular pressure may occur, especially in patients with angle-closure glaucoma.

Hypersensitivity to atropine is not uncommon and may occur as conjunctivitis or a rash.

Effects on body temperature. Atropine can cause hyperthermia as a result of inhibition of sweating. This may be attenuated by atropine's ability to dilate cutaneous blood vessels. However, there has been a report of hypothermia in a 14-year-old feverish patient after intravenous use of atropine.[1]

For reports of fatal heat stroke in patients taking an antimuscarinic with an antipsychotic see under Interactions in Benzatropine, p. 895.1.

1. Lacouture PG, *et al.* Acute hypothermia associated with atropine. *Am J Dis Child* 1983; 137: 291–2.

Effects on the eyes. In addition to the expected ocular effects of atropine (see above) there have been instances of acute angle-closure glaucoma in patients receiving nebulised atropine.[1]

1. Berdy GJ, *et al.* Angle closure glaucoma precipitated by aerosolized atropine. *Arch Intern Med* 1991; 151: 1658–60.

Effects on the gastrointestinal tract. Antimuscarinics reduce gastrointestinal tone and paralytic ileus has been reported[1] in a 77-year-old man with Parkinson's disease who had been receiving atropine sulfate orally to control excess salivation. An increased risk of oesophageal cancer has also been reported[2] with antimuscarinics, possibly due to reductions in lower oesophageal sphincter tone increasing the risk of gastro-oesophageal reflux.

1. Beatson N. Atropine and paralytic ileus. *Postgrad Med J* 1982; 58: 451–3.
2. Lagergren J, *et al.* Association between medications that relax the lower esophageal sphincter and risk for esophageal adenocarcinoma. *Ann Intern Med* 2000; 133: 165–75.

Effects on the heart. Atropine sulfate, to a total of 1 mg per 70 kg body-weight, given intravenously to 79 patients before surgery produced arrhythmias in over 20% of patients, especially in the young.[1] Atrioventricular dissociation was the most common disturbance in adults and in children atrial rhythm disturbances were common. In another study[2] premedication including atropine or glycopyrronium given intramuscularly resulted in a significantly greater incidence of tachycardia during anaesthetic induction and intubation compared with controls who received no antimuscarinic drug. Patients who received glycopyrronium also had a higher incidence of tachycardia during surgery than the controls. No significant difference in bradycardia or extrasystoles was found in the atropine- or the glycopyrronium-treated patients. Atrial fibrillation has been reported in 2 elderly glaucoma patients after post-surgical application of atropine ointment or eye drops to the eye.[3]

1. Dauchot P, Gravenstein JS. Effects of atropine on the electrocardiogram in different age groups. *Clin Pharmacol Ther* 1971; 12: 274–80.
2. Shipton EA, Roelofse JA. Effects on cardiac rhythm of premedication with atropine or glycopyrrolate. *S Afr Med J* 1984; 66: 287–8.
3. Meril GJ, *et al.* Cardiac dysrhythmias associated with ophthalmic atropine. *Arch Intern Med* 1986; 146: 45–7.

Effects on mental function. A study[1] in patients with Parkinson's disease and healthy control subjects suggested that although short-term memory was impaired in patients receiving long-term antimuscarinic therapy the effect was reversible on stopping. An epidemiological study[2] similarly reported lower cognitive performance in elderly patients receiving antimuscarinics.

See also under Trihexyphenidyl (p. 918.1) and under Oxybutynin (p. 2362.1).

1. Van Herwaarden G, *et al.* Short-term memory in Parkinson's disease after withdrawal of long-term anticholinergic therapy. *Clin Neuropharmacol* 1993; 16: 438–43.
2. Lechevallier-Michel N, *et al.* Drugs with anticholinergic properties and cognitive performance in the elderly: results from the PAQUID Study. *Br J Clin Pharmacol* 2005; 59: 143–51.

Hypersensitivity. A report[1] of anaphylactic shock developing in a 38-year-old woman after an intravenous injection of atropine.

1. Aguilera L, *et al.* Anaphylactic reaction after atropine. *Anaesthesia* 1988; 43: 955–7.

Overdosage. Reports of atropine poisoning or overdosage have included a respiratory therapist[1] who had given 10 atropine sulfate aerosol treatments in the preceding 24 hours and children who had taken overdoses of a preparation containing diphenoxylate and atropine.[2]

1. Larkin GL. Occupational atropine poisoning via aerosol. *Lancet* 1991; 337: 917.
2. McCarron MM, *et al.* Diphenoxylate-atropine (Lomotil) overdose in children: an update (report of eight cases and review of the literature). *Pediatrics* 1991; 87: 694–700.

Treatment of Adverse Effects

If a patient presents within an hour of an oral overdose of atropine the stomach may be emptied or activated charcoal given to reduce absorption. Supportive therapy (p. 1537.1) should be given as required; in particular, hypoxia and hypotension should be corrected. Metabolic acidosis that persists despite correction of hypoxia and adequate fluid replacement may require treatment with intravenous sodium bicarbonate. Arrhythmias are best managed by correction of hypoxia and acidosis; antiarrhythmics should not be given. Diazepam has been used to manage repeated or prolonged convulsions (lorazepam has also been given), and for sedation in agitated adults.

Physostigmine has been tried for antimuscarinic poisoning (see p. 2010.1) but such use can be hazardous and is not generally recommended.

Precautions

Atropine should be used with caution in children and the elderly, who may be more susceptible to its adverse effects. It is contra-indicated in patients with prostatic enlargement, in whom it may lead to urinary retention, and in those with paralytic ileus or pyloric stenosis. In patients with ulcerative colitis its use may lead to ileus or megacolon, and its effects on the lower oesophageal sphincter may exacerbate reflux. Caution is generally advisable in any patient with diarrhoea. It should not be given to patients with myasthenia gravis except to reduce adverse muscarinic effects of an anticholinesterase.

Atropine should not be given to patients with angle-closure glaucoma or with a narrow angle between the iris and the cornea, since it may raise intra-ocular pressure and precipitate an acute attack. Acute angle-closure glaucoma has been reported in patients receiving nebulised atropine. Some licensed product information recommends that atropine eye drops should not be used in infants aged less than 3 months due to the possible association between them induced cycloplegia and the development of amblyopia. Systemic reactions have followed the absorption of atropine from eye drops; overdosage is less likely if the eye ointment is used. In the event of blurred vision after topical application of atropine to the eye patients should not drive or operate machinery. Systemic use of antimuscarinics may also cause blurred vision, dizziness, and other effects that may impair a patient's ability to perform skilled tasks such as driving.

Because of the risk of provoking hyperthermia, atropine should not be given to patients, especially children, when the ambient temperature is high. It should also be used cautiously in patients with fever.

Atropine and other antimuscarinics need to be used with caution in conditions characterised by tachycardia such as thyrotoxicosis, heart failure, and in cardiac surgery, where they may further accelerate the heart rate. Care is required in patients with acute myocardial infarction, as ischaemia and infarction may be made worse, and in patients with hypertension.

Atropine may cause confusion, especially in the elderly. Reduced bronchial secretion caused by systemic atropine may be associated with the formation of mucous plugs.

In the treatment of parkinsonism, increases in dosage and transfer to other forms of treatment should be gradual and the antimuscarinic should not be withdrawn abruptly. Minor reactions may be controlled by reducing the dose until tolerance has developed.

Persons with Down's syndrome appear to have an increased susceptibility to some of the actions of atropine, whereas those with albinism may have a reduced susceptibility.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving atropine, and the last available guidance from the American Academy of Pediatrics[1] considered that it was therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/06/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies atropine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

The effects of atropine and other antimuscarinics may be enhanced by use with other drugs having antimuscarinic properties, such as amantadine, some antihistamines, phenothiazine antipsychotics, and tricyclic antidepressants. Inhibition of drug-metabolising enzymes by MAOIs may possibly enhance the effects of antimuscarinics. The reduction in gastric motility caused by antimuscarinics may affect the absorption of other drugs. Antimuscarinics may also antagonise the gastrointestinal effects of cisapride, domperidone, and metoclopramide. Antimuscarinics and parasympathomimetics may counteract each others effects.

Pharmacokinetics

Atropine is readily absorbed from the gastrointestinal tract; it is also absorbed from mucous membranes, the eye, and to some extent through intact skin. It is rapidly cleared from the blood and is distributed throughout the body. It crosses the blood-brain barrier. It is incompletely metabolised in the liver and is excreted in the urine as unchanged drug and metabolites. A half-life of about 4 hours has been reported. Atropine crosses the placenta and traces appear in breast milk.

Quaternary ammonium salts of atropine, such as the methonitrate, are less readily absorbed after oral doses. They are highly ionised in body fluids and being poorly soluble in lipids they do not readily cross the blood-brain barrier.

Pregnancy. Studies of the pharmacokinetics of atropine in mother and fetus in late pregnancy[1-3] indicated that atropine rapidly crosses the placenta. However, whereas peak concentrations of atropine in fetal cord blood were reached about 5 minutes after intravenous doses, the max-

imum effect on fetal heart rate occurred after about 25 minutes.

1. Barrier G, *et al.* La pharmacocinétique de l'atropine chez la femme enceinte et le foetus en fin de grossesse. *Anesth Analg Reanim* 1976; 33: 795–800.
2. Onnen I, *et al.* Placental transfer of atropine at the end of pregnancy. *Eur J Clin Pharmacol* 1979; 15: 443–6.
3. Kanto J, *et al.* Placental transfer and pharmacokinetics of atropine after a single maternal intravenous and intramuscular administration. *Acta Anaesthesiol Scand* 1981; 25: 85–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Endotropina; Klonatropina; ***Austral.***: Atropt; ***Belg.***: Stellatropine; ***Braz.***: Atropion; Santropina; ***China***: Di Shan (迪善); ***Ger.***: Dysurgal; ***India***: Atp; Atro; Atroren-P; Atrosun; Bell Pino-Atrin†; ***Indon.***: Isotic Cycloma; ***Israel***: Atrospan; ***Mex.***: Atro Grin; Atro Ofteno; Atropisa†; Tropyn; ***NZ***: Atropt; ***Philipp.***: Anespin; Atropol; ***Port.***: Atropocil; ***Singapore***: Atrosol; ***Switz.***: Bellafit N; ***Thai.***: Atroren-P; ***Turk.***: Atrosol; ***USA***: AtroPen; Ocu-Tropine†; Sal-Tropine†.

Multi-ingredient Preparations. ***Arg.***: Asmopul; Neoastrin; Yanal; ***Austral.***: Donnagel; Donnalix; Donnatab; ***Braz.***: Espasmocron†; Neogrein; Ormigrein; Tonaton; Vagostesyl; ***Chile***: Buton; Colicor; Dipatropin; Dolospam; ***Fr.***: Ineurope; ***Hong Kong***: Alubar†; Alutal†; Virulex Forte; ***India***: Atrisolon; Atrocin; Brovon; Deco-AT; Pino-Cort†; ***Indon.***: Aludonna; ***Israel***: Spasmalgin; ***Ital.***: Cardiostenol; Deltamidrina; ***Mex.***: Paliatil; Redotex NF; Redotex; ***Pol.***: Tolargin†; ***S.Afr.***: Colstat; Donnatal†; Famucaps†; Millerspast†; ***Spain***: Abdominol†; Midriatico†; Sulmetin Papaver†; Tabletas Quimpe†; ***Swed.***: Palladon Comp†; ***Switz.***: Spasmosol†; ***Thai.***: Alkamine†; Alumag; Alupep; ANH Mat; Droximag-P; Sinlumag; Stomac†; ***UK***: Actonorm; Brovon; Nerve Agent Antidote L4A1; Valonorm; ***USA***: Alkabel; Antispasmodic Elixir; Atrosept; Bellahist-D; Bellatal; Donnatal; DuoDote; Emergent-Ez; Hyosophen; MHP-A; PB-Hyos; Quadrapax; Se-Donna PB HYOS; Servira; Stahist; Susano; UAA; Uriseptic; Uritact; ***Venez.***: Butropina; Carbargal con Atropina; Eumidral.

Used as an adjunct in. ***Austral.***: Lofenoxal; Lomotil; ***Braz.***: Colestase; Lomotil; ***Canad.***: Lomotil; ***Cz.***: Reasec; ***Gr.***: Reasec; ***Hong Kong***: Dhamotil; Diamotil†; Diarest†; Diatrol†; Dimotil; Lomotil; Syncomil†; ***Hung.***: Reasec; ***India***: Lomofen; Lomotil; ***Irl.***: Lomotil; ***Malaysia***: Beamotil; Dhamotil; Diphenoxylate A; ***NZ***: Diastop; ***Pol.***: Reasec; ***S.Afr.***: Lomotil; ***Singapore***: Beamotil; Dhamotil; Sun-Dianox; ***Thai.***: Ditropine; Lomotil; Spasil; ***Turk.***: Lomotil; ***UAE***: Intard; ***UK***: Dymotil; Lomotil; ***USA***: Enlon-Plus; Logen; Lomotil; Lonox; Motofen; Neostigmine Min-I-Mix.

Homoeopathic Preparations. ***Austria***: Meditonsin; Tonsiotren; ***Canad.***: Ervopax†; ***Cz.***: Spascupreel S†; ***Fr.***: Apomorphinum Complexe No 97†; Argentum Complexe no 98; Bilinum Complexe No 113; Billerol; Nervopax; Oenanthe Crocata Complexe No 78; ***Ger.***: Cefaspasmon N†; Cefatropin N†; Hevertotox; Meditonsin; Migrane Hevert; Rufebran allergo†; Rufebran gastro†; Sensiotin; Spascupreel; Tonsiotren H; ***Hung.***: Spascupreel; ***Rus.***: Tonsilotren (Тонзилотрен); ***Ukr.***: Tonsilotren (Тонзилотрен).

Pharmacopoeial Preparations
BP 2014: Atropine Eye Drops; Atropine Eye Ointment; Atropine Injection; Atropine Tablets; Morphine and Atropine Injection; **USP 36:** Atropine Sulfate Injection; Atropine Sulfate Ophthalmic Ointment; Atropine Sulfate Ophthalmic Solution; Atropine Sulfate Tablets; Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution; Diphenoxylate Hydrochloride and Atropine Sulfate Tablets.

Azamethonium Bromide *(BAN, rINN)*

Azamethonii Bromidum; Azaméthonium, Bromure d'; Bromuro de azametonio; Pentamethazene Bromide; Pentaminum; Азаметония бромид.

2,2′-Methyliminobis(diethyldimethylammonium) dibromide.

$C_{13}H_{33}Br_2N_3$=391.2

CAS — 60-30-0 (azamethonium); 306-53-6 (azamethonium bromide).

UNII — 4K6NEIOMSR.

Profile

Azamethonium bromide is a ganglion blocker that has been used in the treatment of hypertension.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Pentamin (Пентамин).

Azapetine Phosphate *(BANM)*

Atsapetiinifosfaatti; Azapetine Phosphate; Azapetina, fosfato de; Azapetinfosfat; Azépine Phosphate; Ro-2-3248; Азапетина фосфат.

6-Allyl-6,7-dihydro-5*H*-dibenz[*c,e*]azepine dihydrogen phosphate.

$C_{17}H_{17}N.H_3PO_4$=333.3

CAS — 146-36-1 (azapetine); 130-83-6 (azapetine phosphate).

ATC — C04AX30.

ATC Vet — QC04AX30.

UNII — 0N2U15U85W.

Profile

Azapetine is a vasodilator that has been used, as the phosphate, in peripheral vascular disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Peridil.

Azelnidipine *(rINN)*

Azelnidipino; Azelnidipinum; CS-905; Азелнидипин.

3-[1-(Diphenylmethyl)-3-azetidinyl] 5-isopropyl (±)-2-amino-1,4-dihydro-6-methyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate.

$C_{33}H_{34}N_4O_6$=582.7

CAS — 123524-52-7.

UNII — PV23P19YUG.

Profile

Azelnidipine is a long-acting dihydropyridine calcium-channel blocker used in the management of hypertension.

References.
1. Wellington K, Scott LJ. Azelnidipine. *Drugs* 2003; 63: 2613–21.
2. Yamamoto T, *et al.* Azelnidipine-induced chyloperitoneum in a patient with microscopic polyangiitis. *Clin Exp Nephrol* 2010; 14: 496–500.
3. Zhao X, *et al.* Azelnidipine and amlodipine: a comparison of their effects and safety in a randomized double-blinded clinical trial in Chinese essential hypertensive patients. *Clin Exp Hypertens* 2010; 32: 372–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Beiqi (贝琪); ***Jpn***: Calblock.

Azilsartan *(USAN, rINN)*

Azilsartán; Azilsartanum; TAK-536; Азилсартан.

2-Ethoxy-1-[[2′-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1,1′-biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic acid.

$C_{25}H_{20}N_4O_5$=456.5

CAS — 147403-03-0.

UNII — F9NUX55P23.

Azilsartan Kamedoxomil *(USAN, rINNM)*

Azilsartan Medoxomil Potassium; TAK-491.

Potassium 3-(4′-[[2-ethoxy-7-[[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy]carbonyl]-1*H*-benzimidazol-1-yl)methyl]biphenyl-4-yl]-5-oxo-1,2,4-oxadiazol-4(5*H*)-ide.

$C_{30}H_{23}KN_4O_8$=606.6

CAS — 863031-24-7.

UNII — WEC6IZK1FC.

Azilsartan Medoxomil *(USAN, rINN)*

Azilsartan Médoxomil; Azilsartan Medoxomilo; Azilsartanum Medoxomilum; TAK-491; Азильсартан медоксомил.

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-[[2′-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1,1′-biphenyl-4-yl]methyl]-1*H*-benzimidazol-7-carboxylate.

$C_{30}H_{24}N_4O_8$=568.5

CAS — 863031-21-4.

UNII — LL0G25K7I2.

Uses and Administration

Azilsartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p. 1422.2). It is used in the management of hypertension (p. 1251.1).

Azilsartan is given as the potassium salt of the medoxomil ester but doses are expressed in terms of the ester; azilsartan kamedoxomil 10.7 mg is equivalent to about 10 mg of azilsartan medoxomil. A starting dose corresponding to azilsartan medoxomil 40 mg is given orally once daily, particularly in patients also taking high doses of diuretics. A starting dose of 20 mg once daily may be considered necessary in patients over 75 years of age, who can be at risk of hypotension, and in patients with volume or salt depletion. The dose may be increased to 80 mg once daily. Reduced doses may also be considered in patients with hepatic impairment (see below).

References.
1. Zaiken K, Cheng JW. Azilsartan medoxomil: a new angiotensin receptor blocker. *Clin Ther* 2011; 33: 1577–89.
2. Baker WL, White WB. Azilsartan medoxomil: a new angiotensin II receptor antagonist for treatment of hypertension. *Ann Pharmacother* 2011; 45: 1506–15.
3. Takagi H, *et al.* A meta-analysis of randomized controlled trials of azilsartan therapy for blood pressure reduction. *Hypertens Res* 2013. Available at: doi:10.1038/hr.2013.142

Administration in hepatic impairment. There is limited experience of the use of azilsartan in patients with hepatic impairment, but exposure to the drug may be slightly increased. A starting dose equivalent to azilsartan medoxomil 20 mg orally once daily may be considered in patients with mild to moderate hepatic impairment, and use of the drug possibly avoided in those with severe impairment.

Adverse Effects and Precautions

As for Losartan Potassium, p. 1424.1 and p. 1424.3.

Interactions

As for Losartan Potassium, p. 1424.3.

Pharmacokinetics

Azilsartan medoxomil is hydrolysed in the gastrointestinal tract to its active metabolite azilsartan, which is then absorbed with a bioavailability of about 60%. Peak plasma concentrations occur within 1.5 to 3 hours. Azilsartan is highly bound to plasma proteins (> 99%). It is metabolised in the liver by *O*-dealkylation and decarboxylation, mainly via the cytochrome P450 isoenzyme CYP2C9, to its inactive metabolites. The elimination half-life of azilsartan is about 11 hours. About 55% of a dose is excreted in the faeces and about 42% in the urine, 15% as azilsartan. It is not removed by haemodialysis.

Studies in *rats* indicate that azilsartan crosses the placenta and is distributed to the fetus. It is also distributed into the milk of lactating *rats*.

References.
1. Angeli F, *et al.* Pharmacokinetic evaluation and clinical utility of azilsartan medoxomil for the treatment of hypertension. *Expert Opin Drug Metab Toxicol* 2013; 9: 379–85.
2. Preston RA, *et al.* Single-center evaluation of the single-dose pharmacokinetics of the angiotensin II receptor antagonist azilsartan medoxomil in renal impairment. *Clin Pharmacokinet* 2013; 52: 347–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Irl.***: Edarbi; ***Jpn***: Azilva; ***Neth.***: Edarbi; ***Prez***: Edarbi; ***Switz.***: Edarbi; ***UK***: Edarbi; ***USA***: Edarbi.

Multi-ingredient Preparations. ***USA***: Edarbyclor.

Azimilide Hydrochloride *(BANM, rINNM)*

Azimilida, hidrocloruro de; Azimilide, Chlorhydrate d'; Azimilide Dihydrochloride (USAN); Azimilidi Hydrochloridum; Hidrocloruro de azimilida; NE-10064; Азимилида гидрохлорид.

1-[[5-(*p*-Chlorophenyl)furfurylidene]amino]-3-[4-(4-methyl-1-piperazinyl)butyl]hydantoin dihydrochloride.

$C_{23}H_{28}ClN_5O_3.2HCl$=530.9

CAS — 149908-53-2 (azimilide); 149888-94-8 (azimilide hydrochloride).

UNII — 6E6VJP68KR.

Profile

Azimilide hydrochloride is a class III antiarrhythmic (p. 1243.1) being studied in the management of supraventricular arrhythmias. It has also been tried in ventricular arrhythmias.

References.
1. Clemett D, Markham A. Azimilide. *Drugs* 2000; 59: 271–7.
2. Pritchett ELC, *et al.* Effects of azimilide on heart rate and ECG conduction intervals during sinus rhythm in patients with a history of atrial fibrillation. *J Clin Pharmacol* 2002; 42: 388–94.
3. Connolly SJ, *et al.* Symptoms at the time of arrhythmia recurrence in patients receiving azimilide for control of atrial fibrillation or flutter: results from randomized trials. *Am Heart J* 2003; 146: 489–93.
4. Singer I, *et al.* Azimilide decreases recurrent ventricular tachyarrhythmias in patients with implantable cardioverter defibrillators. *J Am Coll Cardiol* 2004; 43: 39–43.
5. Camm AJ, *et al.* Mortality in patients after a recent myocardial infarction: a randomized, placebo-controlled trial of azimilide using heart rate variability for risk stratification. *Circulation* 2004; 109: 990–6.
6. Dorian P, *et al.* Placebo-controlled, randomized clinical trial of azimilide for prevention of ventricular tachyarrhythmias in patients with an implantable cardioverter defibrillator. *Circulation* 2004; 110: 3646–54.
7. Pritchett ELC, *et al.* Antiarrhythmic efficacy of azimilide in patients with atrial fibrillation: maintenance of sinus rhythm after conversion to sinus rhythm. *Am Heart J* 2006; 151: 1043–9.
8. Kerr CR, *et al.* Efficacy of azimilide for the maintenance of sinus rhythm in patients with paroxysmal atrial fibrillation in the presence and absence of structural heart disease. *Am J Cardiol* 2006; 98: 215–18.
9. Pratt CM, *et al.* Cumulative experience of azimilide-associated torsades de pointes ventricular tachycardia in the 19 clinical studies comprising the azimilide database. *J Am Coll Cardiol* 2006; 48: 471–7.
10. Lombardi F, *et al.* Azimilide vs. placebo and sotalol for persistent atrial fibrillation: the A-COMET-II (Azimilide-CardiOversion MaintEnance Trial-II) trial. *Eur Heart J* 2006; 27: 2224–31.

11. Page RL, *et al.* Azimilide for the treatment of atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia: results of a randomized trial and insights on the concordance of symptoms and recurrent arrhythmias. *J Cardiovasc Electrophysiol* 2008; 19: 172–7.

Azosemide *(USAN, rINN)* ⊗

Azosemida; Azosémide; Azosemidum; BM-02001; Ple-1053; Азосемид.
2-Chloro-5-(1*H*-tetrazol-5-yl)-4-(2-thenylamino)benzenesulphonamide.
$C_{12}H_{11}ClN_6O_2S_2$=370.8
CAS — 27589-33-9.
UNII — MR40VT1L8Z.

NOTE. The names Azoselic, Daitalic, and Diart have been used as trade names for azosemide.

Profile

Azosemide is a diuretic with actions similar to those of furosemide (p. 1387.1) that has been used in the management of oedema.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ya Li (雅利).

Bamethan Sulfate *(BANM, USAN, rINNM)*

Bametán, sulfato de; Bametanu siarczan; Baméthan, Sulfate de; Bamethan Sulphate; Bamethani Sulfas; Sulfato de bametán; Баметана Сульфат.
2-Butylamino-1-(4-hydroxyphenyl)ethanol sulfate.
$(C_{12}H_{19}NO_2)_2H_2SO_4$=516.6
CAS — 3703-79-5 (bamethan); 5716-20-1 (bamethan sulfate).
ATC — C04AA31.
ATC Vet — QC04AA31.
UNII — W2L3E1W827.

Pharmacopoeias. In *Jpn* and *Pol.*

Profile

Bamethan sulfate is a vasodilator used in the management of peripheral vascular disorders.

Bamethan nicotinate and bamethan succinate have been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dilartan; *Braz.*: Vasculat.

Multi-ingredient Preparations. *Arg.*: Flaval; Grafic Forte; *Fr.*: Escimogel†.

Barnidipine Hydrochloride *(rINNM)*

Barnidipine, Chlorhydrate de; Barnidipini Hydrochloridum; Barnidipino, hidrocloruro de; Hidrocloruro de barnidipino; LY-198561; Mepirodipine Hydrochloride; YM-730; YM-09730-5; Барнидипина Гидрохлорид.
(+)-(3′*S*,4*S*)-1-Benzyl-3-pyrrolidinyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate hydrochloride.
$C_{27}H_{29}N_3O_6HCl$=528.0
CAS — 104713-75-9 (barnidipine); 104757-53-1 (barnidipine hydrochloride).
ATC — C08CA12.
ATC Vet — QC08CA12.
UNII — 7LZ6R3AEM1.

Profile

Barnidipine is a dihydropyridine calcium-channel blocker with general properties similar to those of nifedipine (p. 1447.2). It is given orally as the hydrochloride in the management of hypertension (p. 1251.1). The initial dose is 5 to 10 mg once daily, increased, according to response, to a usual maintenance dose of 10 to 20 mg once daily.

Reviews.

1. Malhotra HS, Plosker GL. Barnidipine. *Drugs* 2001; 61: 989–96.
2. Liau CS. Barnidipine: a new calcium channel blocker for hypertension treatment. *Expert Rev Cardiovasc Ther* 2005; 3: 207–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Vasexten; *China*: Hypoca (合普卡); *Cz.*: Vasexten; *Gr.*: Vasexten; *Ital.*: Libradin; Osipine; Vasexten; *Jpn*: Hypoca; *Neth.*: Cyress; Libradin; Vasexten; *Philipp.*: Hypoca†; *Port.*: Cyress; Libradin†; Vasexten†; *Spain*: Barnix; Libradin†; *Thai.*: Hypoca†; *Turk.*: Libradin.

Bemetizide *(BAN, rINN)* ⊗

Bemetizida; Bémétizide; Bemetizidum; Diu-60; Беметизид.
6-Chloro-3,4-dihydro-3-(α-methylbenzyl)-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.
$C_{15}H_{16}ClN_3O_4S_2$=401.9
CAS — 1824-52-8.
UNII — EZN4D2O31B.

Profile

Bemetizide is a thiazide diuretic (see Hydrochlorothiazide, p. 1403.2) that is used, often with triamterene, in the treatment of oedema and hypertension.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ger.*: dehydro sanol tri; Diucomb.

Bemiparin Sodium *(BAN, rINN)*

Bemiparina sódica; Bémiparine Sodique; Bemiparinum Natricum; Бемипарин Натрий.
CAS — 9041-08-1.
ATC — B01AB12.
ATC Vet — QB01AB12.

Description. Bemiparin sodium is prepared by alkaline degradation of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-4-enepyranosuronic acid structure at the non-reducing end and a 2-*N*,6-*O*-disulfo-D-glucosamine structure at the reducing end of their chain. The average relative molecular mass is about 3600 (3000 to 4200). The degree of sulfation is about 2 per disaccharide unit.

Units

As for Low-molecular-weight Heparins, p. 1426.2.

Uses and Administration

Bemiparin sodium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant activity. It is used for the prevention and treatment of venous thromboembolism (p. 1274.1), and to prevent clotting during extracorporeal circulation.

In the *prophylaxis* of **venous thromboembolism** during general surgery with moderate risk, bemiparin sodium is given subcutaneously in a dose of 2500 units once daily, with the first dose given 2 hours before or 6 hours after surgery; in patients undergoing orthopaedic surgery with high risk of thromboembolism the dose should be 3500 units initially and then once daily. Prophylaxis should be continued for at least 7 to 10 days and until the patient is fully ambulant. For *treatment* of thromboembolism, a dose of 115 units/kg is given subcutaneously once daily.

In some countries bemiparin sodium is used for prophylaxis in non-surgical patients at moderate or high risk of venous thromboembolism, a dose of 2500 or 3500 units being given daily according to risk. Bemiparin sodium is also used in some countries for secondary prevention of venous thromboembolism in patients with transitory risk factors, a dose of 3500 units being given daily for up to 3 months as an alternative to oral anticoagulant therapy.

For the prevention of clotting in the extracorporeal circulation during **haemodialysis**, bemiparin sodium is given into the arterial side of the dialyser in a single dose of 2500 units for patients weighing less than 60 kg and 3500 units for patients weighing more than 60 kg.

An oral formulation of bemiparin is under investigation.

References.

1. Chapman TM, Goa KL. Bemiparin: a review of its use in the prevention of venous thromboembolism and treatment of deep vein thrombosis. *Drugs* 2003; 63: 2357–77.
2. Martínez-González J, *et al.* Bemiparin: second-generation, low-molecular-weight heparin for treatment and prophylaxis of venous thromboembolism. *Expert Rev Cardiovasc Ther* 2008; 6: 793–802.
3. Rullan M, *et al.* Treatment of chronic diabetic foot ulcers with bemiparin: a randomized, triple-blind, placebo-controlled, clinical trial. *Diabet Med* 2008; 25: 1090–5.
4. Martínez-González J, Rodríguez C. New challenges for a second-generation low-molecular-weight heparin: focus on bemiparin. *Expert Rev Cardiovasc Ther* 2010; 8: 625–34.
5. Sánchez-Ferrer CF. Bemiparin: pharmacological profile. *Drugs* 2010; 70 (suppl 2): 19–23.
6. Abad Rico JI, *et al.* Clinical experience with bemiparin. *Drugs* 2010; 70 (suppl 2): 25–33.
7. Monreal Bosch M, *et al.* Bemiparin in oncology. *Drugs* 2010; 70 (suppl 2): 35–42.
8. Boj JF. New frontiers with bemiparin: use in special populations. *Drugs* 2010; 70 (suppl 2): 43–7.

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p. 1426.3.

Severe bleeding with bemiparin sodium may be reducec by intravenous protamine sulfate; 1.4 mg of protamine sulfate is stated to inhibit the effects of about 100 units of bemiparin sodium.

Interactions

As for Low-molecular-weight Heparins, p. 1427.2.

Pharmacokinetics

Bemiparin sodium is rapidly absorbed after subcutaneous injection with a bioavailability of about 96%. Peak plasma activity occurs in about 2 to 4 hours, depending on the dose. The elimination half-life is about 5 to 6 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Badyket; *Austria*: Ivor; Ivorat; *Cz.*: Zibor; *Gr.*: Ivor; Ivormax; *Hung.*: Zibor; *India*: Hibor; *Irl.*: Zibor; *Ital.*: Ivor; *Port.*: Ivor; *Rus.*: Cibor (Цибор); *Spain*: Hepadren; Hibor; *Turk.*: Hibor; *UK*: Zibor†; *Ukr.*: Zibor (Цибор).

Benazepril Hydrochloride

(BANM, USAN, rINNM)

Benatsepriilihydrokloridi; Bénazépril, chlorhydrate de; Benazepril, hidrocloruro de; Benazepril Hidroklorür; Benazeprilhydrochlorid; Benazeprilhydroklorid; Benazeprili Hydrochloridum; CGS-14824A (benazepril or benazepril hydrochloride); Hidrocloruro de benazepril; Беназеприла Гидрохлорид.
((3*S*)-3-[(1*S*)-1-Ethoxycarbonyl-3-phenylpropylamino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-1-yl)acetic acid hydrochloride; 1-Carboxymethyl-3-[1-ethoxycarbonyl-3-phenyl-(1*S*)-propylamino]-2,3,4,5-tetrahydro-1*H*-1(3*S*)-benzazepin-2-one hydrochloride.
$C_{24}H_{28}N_2O_5HCl$=461.0
CAS — 86541-75-5 (benazepril); 86541-74-4 (benazepril hydrochloride).
ATC — C09AA07.
ATC Vet — QC09AA07.
UNII — N1SN99T69T.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Benazepril Hydrochloride). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Slightly soluble in water; freely soluble in dehydrated alcohol; practically insoluble in cyclohexane; very slightly soluble in ethyl acetate. Store in airtight containers. Protect from light.

USP 36: (Benazepril Hydrochloride). A white to off-white crystalline powder. Soluble in water, in alcohol, and in methyl alcohol. Store at a temperature below 30 degrees, preferably between 15 degrees and 30 degrees.

Uses and Administration

Benazepril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1) and heart failure (p. 1262.3).

Benazepril owes its activity to benazeprilat to which it is converted after oral dosage. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after about 2 to 4 hours, although the full effect may not develop for 1 to 2 weeks during chronic dosing. The haemodynamic action lasts for about 24 hours, allowing once-daily dosing. Benazepril is given orally as the hydrochloride.

In the treatment of **hypertension**, the usual initial dose of benazepril hydrochloride is 10 mg once daily. An initial dose of 5 mg once daily is suggested for patients with renal impairment (see p. 1315.1) or who are receiving a *diuretic*; if possible the diuretic should be withdrawn 2 or 3 days before benazepril is started and resumed later if necessary.

The usual maintenance dose is 20 to 40 mg daily, which may be given in 2 divided doses if control is inadequate with a single dose; doses of up to 80 mg daily have been used.

In the treatment of **heart failure** the usual initial dose of benazepril hydrochloride is 2.5 mg once daily, adjusted according to response to a maximum dose of 20 mg daily.

Administration in children. Experience with benazepril in children is limited. US licensed product information recommends an initial oral dose of 200 micrograms/kg once daily for hypertension in children 6 years of age and over. Maintenance doses up to 600 micrograms/kg daily (maximum 40 mg daily) have been studied. Insufficient evidence is available to recommend doses for younger children or for any children with creatinine clearance below 30 mL/minute.

Administration in renal impairment. In patients with a creatinine clearance of less than 30 mL/minute, the initial dose of benazepril hydrochloride for hypertension is 5 mg once daily and the maintenance dose should not exceed 40 mg daily.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Benazepril acts as a prodrug of the diacid benazeprilat, its active metabolite. At least 37% of an oral dose of benazepril is absorbed. Benazepril is almost completely metabolised in the liver to benazeprilat. Peak plasma concentrations of benazeprilat after an oral dose of benazepril have occurred in 1 to 2 hours in the fasting state or 2 to 4 hours in the nonfasting state. Both benazepril and benazeprilat are about 95% bound to plasma proteins. Benazeprilat is excreted mainly in the urine; about 11 to 12% is excreted in the bile. The effective half-life for accumulation of benazeprilat is 10 to 11 hours after multiple doses of benazepril. The elimination of benazeprilat is slowed in renal impairment, although biliary excretion may compensate to some extent. Small amounts of benazepril and benazeprilat are distributed into breast milk.

References.

1. Kaiser G, *et al.* Pharmacokinetics of the angiotensin converting enzyme inhibitor benazepril HCl (CGS 14 824A) in healthy volunteers after single and repeated administration. *Biopharm Drug Dispos* 1989; 10: 365–76.
2. Kaiser G, *et al.* Pharmacokinetics of a new angiotensin-converting enzyme inhibitor, benazepril hydrochloride, in special populations. *Am Heart J* 1989; 117: 746–51.
3. Kaiser G, *et al.* Pharmacokinetics and pharmacodynamics of the ace inhibitor benazepril hydrochloride in the elderly. *Eur J Clin Pharmacol* 1990; 38: 379–85.
4. Macdonald N-J, *et al.* A comparison in young and elderly subjects of the pharmacokinetics and pharmacodynamics of single and multiple doses of benazepril. *Br J Clin Pharmacol* 1993; 36: 201–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Boncordin; *Belg.*: Cibacen; *Braz.*: Lotensin; *Canad.*: Lotensin; *China*: Di Ya Ping (敌亚平); Lotensin (洛汀新); Pu Li Duo (普力多); Zaprace (倍尼); *Denm.*: Cibacen; Jenaril; Lazeril; *Fr.*: Briem; Cibacene; *Ger.*: Cibacen; *Gr.*: Cibacen; *Hung.*: Lotensin; *India*: Benace; *Indon.*: Cibacen†; *Irl.*: Cibacen; *Ital.*: Cibacen; Tenkuoren; Tensanil†; Zinadril; *Mex.*: Lotensin; *Neth.*: Cibacen; *Philipp.*: Cibacen; *Pol.*: Lisonid; Lotensin; *Rus.*: Lotensin (Лотензин); *S.Afr.*: Cibace; *Spain*: Cibacen; Labopal†; *Switz.*: Cibacen; *Turk.*: Cibacen; *USA*: Lotensin.

Multi-ingredient Preparations. *Arg.*: Amlopril; Arteriosan Plus; Coroval B; Ilduc Duo; Pelmec Duo; Terloc Duo; *Braz.*: Lotensin H; Press Plus; *China*: Cibadrex (依思汀); Zaprace-D (双赛普利); *Fr.*: Briazide; Cibadrex; *Ger.*: Benazeplus†; Benazepril comp; Cibadrex; *Gr.*: Cibadrex; *Hung.*: Lotensin HCT; *India*: Amace-BP; Amlo-B; *Ital.*: Cibadrex; Tensadiur; Zinadiur; *Mex.*: Amlipril†; *Neth.*: Cibadrex; *Pol.*: Lisonid HCT; Lotensin HCT; *S.Afr.*: Cibadrex; *Spain*: Cibadrex; Labodrex†; *Switz.*: Cibadrex; *Turk.*: Cibadrex; *USA*: Lotensin HCT; Lotrel; *Venez.*: Amlibon B.

Pharmacopoeial Preparations

USP 36: Amlodipine and Benazepril Hydrochloride Capsules; Benazepril Hydrochloride Tablets.

Bencyclane Fumarate *(rINNM)*

Benciclano, fumarato de; Bencyclane, Fumarate de; Bencyclane Hydrogen Fumarate; Bencyclani Fumaras; Bensiklan Hidrojen Fumarat; Fumarato de benciclano; Бенциклана Фумарат.

3-(1-Benzylcycloheptyloxy)-*NN*-dimethylpropylamine hydrogen fumarate.

$C_{19}H_{31}NO.C_4H_4O_4$=405.5

CAS — 2179-37-5 (bencyclane); 14286-84-1 (bencyclane fumarate).

ATC — C04AX11.

ATC Vet — QC04AX11.

UNII — OZN2MG334O.

Profile

Bencyclane fumarate is a vasodilator used in the management of peripheral (p. 1272.3) and cerebral vascular disorders (p. 1269.2) in usual oral doses of 100 to 200 mg three times daily. It has also been given intravenously.

Bencyclane acefyllinate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Fludilat; *Gr.*: Diacyclan; Fludilat; *Hung.*: Halidor; *Indon.*: Fludilat; *Pol.*: Halidor; *Rus.*: Halidor (Галидор); *Thal.*: Fludilat†; *Turk.*: Angiodel; *Ukr.*: Halidor (Галидор); *Venez.*: Fludilat.

Bendroflumethiazide *(BAN, rINN)* ⊗

Bendidroflumetiazida; Bendilhidroflumetiazida; Bendrofluaz; Bendrofluazida; Bendrofluazide; Bendroflumethiazid; Bendroflumethiazide; Bendroflumethiazidum; Bendroflumetiatsidi; Bendroflumetiazid; Bendroflumetiazida; Bendroflumetiazidas; Benzydroflumethiazide; FT-81; Бендрофлуметиазид.

3-Benzyl-3,4-dihydro-6-trifluoromethyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_{15}H_{14}F_3N_3O_4S_2$=421.4

CAS — 73-48-3.

ATC — C03AA01.

ATC Vet — QC03AA01.

UNII — SQ52X6KCJL.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Bendroflumethiazide). A white or almost white crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone.

USP 36: (Bendroflumethiazide). A white to cream-coloured, finely divided, crystalline powder. Is odourless or has a slight odour. Practically insoluble in water; soluble 1 in 23 of alcohol and 1 in 200 of ether; freely soluble in acetone. Store in airtight containers.

Uses and Administration

Bendroflumethiazide is a thiazide diuretic with actions and uses similar to those of hydrochlorothiazide (p. 1403.2). It is used for hypertension (p. 1251.1), either alone or with other antihypertensives such as ACE inhibitors and beta blockers. It is also used for oedema, including that associated with heart failure (p. 1262.3), and with renal or hepatic disorders. Other indications have included the suppression of lactation.

Bendroflumethiazide is given orally; diuresis starts in about 2 hours after a dose, peaks after about 3 to 6 hours, and lasts for 12 to 18 hours or longer.

In the treatment of **hypertension** bendroflumethiazide 2.5 mg daily, either alone or with other antihypertensives, is usually adequate although initial doses of up to 20 mg daily have sometimes been suggested.

In the treatment of **oedema** the usual initial dose is 5 to 10 mg daily or on alternate days; in some cases initial doses of up to 20 mg may be necessary. Maintenance dosage schedules have varied from 5 to 30 mg weekly in divided doses in the UK, to 2.5 to 5 mg daily or intermittently in the USA.

For doses in children, see below.

Doses of 5 mg twice daily for about 5 days have been used to **suppress lactation.**

In the management of **idiopathic hypercalciuria** (see Renal Calculi, p. 2350.3) the *BNF* considers that, with increased fluid intake, a sufficient dose is 2.5 mg daily.

Administration in children. In the UK, bendroflumethiazide may be given to children in the treatment of oedema or hypertension in the following initial oral doses according to age, and adjusted according to response:

- 1 month to 2 years: 50 to 100 micrograms/kg daily
- 2 to 12 years: 50 to 400 micrograms/kg daily (maximum of 10 mg), followed by 50 to 100 micrograms/kg daily, adjusted according to response
- 12 to 18 years: hypertension, 2.5 mg daily; oedema, 5 to 10 mg daily or on alternate days

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p. 1404.2.

Breast feeding. Bendroflumethiazide has been used to suppress lactation (see Uses above). However, the American Academy of Pediatrics considers[1] that it is usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bendroflumethiazide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Overdosage. Tonic-clonic convulsions occurred in a previously healthy 14-year-old girl after ingestion of bendroflumethiazide 150 to 200 mg.[1] The convulsions were not associated with any measurable disturbance of serum electrolytes.

1. Hine KR, *et al.* Bendrofluazide convulsions. *Lancet* 1982; i: 564.

Interactions

As for Hydrochlorothiazide, p. 1406.1.

Pharmacokinetics

Bendroflumethiazide has been reported to be completely absorbed from the gastrointestinal tract and to have a plasma half-life of about 3 or 4 hours. It is highly bound to plasma proteins. There are indications that bendroflumethiazide is fairly extensively metabolised; about 30% is excreted unchanged in the urine.

References.

1. Beermann B, *et al.* Pharmacokinetics of bendroflumethiazide. *Clin Pharmacol Ther* 1977; 22: 385–8.
2. Beermann B, *et al.* Pharmacokinetics of bendroflumethiazide in hypertensive patients. *Eur J Clin Pharmacol* 1978; 13: 119–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Aprinox†; *Denm.*: Centyl†; *Gr.*: Aprinox; Pluryl; *Irl.*: Centyl; *Norw.*: Centyl†; *NZ*: Neo-NaClex; *Swed.*: Salures; *UK*: Aprinox; Neo-NaClex†.

Multi-ingredient Preparations. *Arg.*: Pertenso; Sumal; *Austria*: Sall-Aldopur; *Braz.*: Diserim; *Denm.*: Centyl med Kaliumklorid; *Fr.*: Precyclan†; Tensionorme; *Ger.*: Dociretic; Pertenso N; Tensoflux; *Gr.*: Centyl K; Corzide; *Irl.*: Centyl K; Low Centyl K; Prestim; *Mex.*: Corgaretic; *Norw.*: Centyl med Kaliumklorid; *S. Afr.*: Corgaretic†; *Spain*: Neatenol Diu; Neatenol Diuvas†; *Swed.*: Centyl K; *UK*: Centyl K†; Neo-NaClex-K; Prestim; *USA*: Corzide.

Pharmacopoeial Preparations

BP 2014: Bendroflumethiazide Tablets;

USP 36: Bendroflumethiazide Tablets; Nadolol and Bendroflumethiazide Tablets.

Benfluorex Hydrochloride *(BANM, pINNM)* ⊗

Benfluoreksihydroklorid; Benfluorekso hidrochloridas; Benfluorex, Chlorhydrate de; Benfluorex, hidrocloruro de; Benfluorex-hidroklorid; Benfluorex-hydrochlorid; Benfluorex-hydroklorid; Benfluorexi Hydrochloridum; Hidrocloruro de benfluorex; JP-992; SE-780; Бенфлуорекса Гидрохлорид.

2-[α-Methyl-3-(trifluoromethyl)phenethylamino]ethyl benzoate hydrochloride.

$C_{19}H_{20}F_3NO_2$,HCl=387.8

CAS — 23602-78-0 (benfluorex); 35976-51-3 (± benfluorex); 23642-66-2 (benfluorex hydrochloride).

ATC — A10BX06.

ATC Vet — QA10BX06.

UNII — X7O165XZ00.

Profile

Benfluorex hydrochloride is a lipid regulating drug used in the treatment of hyperlipidaemias (p. 1248.1). It has also been used as an adjunct in the management of type 2 diabetes mellitus (p. 459.1). Benfluorex is structurally related to fenfluramine (p. 2322.3) and has been used similarly as an anorectic like fenfluramine, it has been associated with cardiovascular adverse effects (see below).

Benfluorex hydrochloride has been given orally in usual doses of 150 mg three times daily with meals.

Adverse effects. Fenfluramine and dexfenfluramine were withdrawn from the world market after cardiovascular adverse effects including pulmonary hypertension and valvular heart disease were associated with their use (for a discussion, see p. 2322.3). There have been reports[1-4] of similar adverse effects with benfluorex, a related compound, and in 2009 the EMEA recommended the withdrawal of benfluorex from the European market.[5]

1. Nolze P, *et al.* Valvular heart disease in a patient taking benfluorex. *Fundam Clin Pharmacol* 2006; 20: 577–8.
2. Boutet K, *et al.* Fenfluramine-like cardiovascular side-effects of benfluorex. *Eur Respir J* 2009; 33: 684–8.
3. Frachon I, *et al.* Benfluorex and unexplained valvular heart disease: a case-control study. *PLoS One* 2010; 5: e10128. Available at: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0010128 (accessed 10/06/10)
4. Anonymous. Benfluorex: increasing reports of valve disorders. *Prescrire Int* 2010; 19: 17.
5. EMEA. European Medicines Agency recommends withdrawal of benfluorex from the market in European Union (issued 18th December 2009). Available at: http://www.ema.europa.eu/pdfs/human/referral/benfluorex/Benfluorex_81503309en.pdf (accessed 10/06/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Mediator†; *Gr.*: Lipophoral; *Hong Kong*: Mediaxal; *Malaysia*: Axal; Mediaxal†; *Port.*: Mediator†; *Singapore*: Mediaxal†; *Venez.*: Lipascor.

Benidipine Hydrochloride *(rINNM)*

Benidipine, Chlorhydrate de; Benidipini Hydrochloridum; Benidipino, hidrocloruro de; Hidrocloruro de benidipino; KW-3049; Nakadipine Hydrochloride; Бенидипина гидрохлорид.

(±)-1-(*R*)-3-[(*R*)-1-Benzyl-3-piperidyl]methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate hydrochloride.

$C_{28}H_{31}N_3O_6HCl$=542.0

CAS — 105979-17-7 (benidipine); 91599-74-5 (benidipine hydrochloride).

ATC — C08CA15.

ATC Vet — QC08CA15.

UNII — 0A6746FWDL.

Pharmacopoeias. In *Jpn*.

Profile

Benidipine is a dihydropyridine calcium-channel blocker with general properties similar to those of nifedipine (p. 1447.2). It is given orally as the hydrochloride in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3). In hypertension, the usual dose is 2 to 4 mg once daily, increased to 8 mg once daily if necessary. In angina pectoris, the usual dose is 4 mg twice daily.

References.

1. Yao K, *et al.* Pharmacological, pharmacokinetic, and clinical properties of benidipine hydrochloride, a novel, long-acting calcium channel blocker. *J Pharmacol Sci* 2006; **100**: 243–61.
2. Suzuki H, *et al.* Clinical efficacy of benidipine for vasospastic angina pectoris. *Arzneimittelforschung* 2007; **57**: 20–5.
3. Wang HY, *et al.* Efficacy and safety of benidipine therapy of essential hypertension in elderly Chinese patients. *Arzneimittelforschung* 2008; **58**: 505–9.
4. Ohta M, *et al.* Effects of benidipine, a long-acting T-type calcium channel blocker, on home blood pressure and renal function in patients with essential hypertension: a retrospective, 'real-world' comparison with amlodipine. *Clin Drug Invest* 2009; **29**: 739–46.
5. Peng T, *et al.* A comparative study of the renoprotective effects of benidipine and valsartan in primary hypertensive patients with proteinuria. *Arzneimittelforschung* 2009; **59**: 647–50.
6. Miyagawa K, *et al.* Renoprotective effect of calcium channel blockers in combination with an angiotensin receptor blocker in elderly patients with hypertension. A randomized crossover trial between benidipine and amlodipine. *Clin Exp Hypertens* 2010; **32**: 1–7.
7. Olkawa Y, *et al.* Effects of treatment with once-daily nifedipine CR and twice-daily benidipine on prevention of symptomatic attacks in patients with coronary spastic angina pectoris—Adalat Trial vs Conicl in Tokyo against Coronary Spastic Angina (ATTACK CSA). *J Cardiol* 2010; **55**: 238–47.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Coniel (可力洛); Yuan Zhi (元洛); *India*: Caritec; *Jpn*: Coniel; *Philipp.*: Coniel; *Turk.*: Coniel.

Benzthiazide *(BAN, rINN)* ⊗

Benzthiazidum; Benztiazida; P-1393; Бензтиазид.

3-Benzylthiomethyl-6-chloro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_{15}H_{14}ClN_3O_4S_3$=431.9

CAS — 91-33-8.

UNII — 1TD848L61.

Profile

Benzthiazide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (p. 1403.2). It is used for oedema, including that associated with heart failure (p. 1262.3), and has also been used for hypertension (p. 1251.1). It has been given alone but is often given with triamterene. The usual initial oral dose for oedema is 75 mg daily, although higher doses have been given. The dose is reduced for maintenance; intermittent dosing may be adequate.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *India*: Ditide; *Switz.*: Dyrenium compositum†; *UK*: Dytide†.

Benzylhydrochlorothiazide ⊗

Su-6227.

3-Benzyl-6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_{14}H_{14}ClN_3O_4S_3$=387.9

CAS — 1824-50-6.

UNII — 176437APQH.

Profile

Benzylhydrochlorothiazide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (p. 1403.2). It is used for oedema, including that associated with heart failure (p. 1262.3), and for hypertension (p. 1251.1). The usual initial oral dose is 4 to 8 mg twice daily reduced to two or three times weekly for maintenance therapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Behyd.

Multi-ingredient Preparations. *Jpn*: Behyd-RA.

Bepridil Hydrochloride *(BANM, USAN, rINNM)*

Bepridilihydrokloridi; Bépridil, Chlorhydrate de; Bepridil, hidrocloruro de; Bepridilhydroklorid; Bepridilii Hydrochloridum; CERM-1978; Hidrocloruro de bepridil; Org-5730; Бепридила гидрохлорид.

N-Benzyl-*N*-(3-isobutoxy-2-pyrrolidin-1-ylpropyl)aniline hydrochloride monohydrate.

$C_{24}H_{34}N_2O.HCl.H_2O$=421.0

CAS — 64706-54-3 (bepridil); 49571-04-2 (bepridil); 64616-81-5 (anhydrous bepridil hydrochloride); 74764-40-2 (bepridil hydrochloride monohydrate).

ATC — C08EA02.

ATC Vet — QC08EA02.

UNII — 4W2P15D93M.

Profile

Bepridil is a calcium-channel blocker (p. 1244.2). It has similar properties to nifedipine (p. 1447.2) but reduces the heart rate and does not usually cause reflex tachycardia. It also has antiarrhythmic activity. It is not related chemically to other calcium-channel blockers such as diltiazem, nifedipine, or verapamil.

Bepridil is used as the hydrochloride in the management of angina pectoris (p. 1254.3) and cardiac arrhythmias (p. 1266.1). Ventricular arrhythmias, including torsade de pointes, and agranulocytosis have been associated with bepridil and, as a result, it has usually been reserved for patients who have not responded adequately to other anti-anginal drugs. Frequent ECG monitoring has been advised, and reducing or stopping doses should be considered if QT-interval prolongation occurs.

Bepridil hydrochloride has been given in oral doses of 100 to 300 mg daily.

References.

1. Hollingshead LM, *et al.* Bepridil: a review of its pharmacological properties and therapeutic use in stable angina pectoris. *Drugs* 1992; **44**: 835–57.
2. Awni WM, *et al.* Pharmacokinetics of bepridil and two of its metabolites in patients with end-stage renal disease. *J Clin Pharmacol* 1995; **35**: 379–83.
3. Yasuda M, *et al.* Clinical evaluation of adverse effects during bepridil administration for atrial fibrillation and flutter. *Circ J* 2006; **70**: 662–6.
4. Taguchi M, *et al.* Nonlinear mixed effects model analysis of the pharmacokinetics of routinely administered bepridil in Japanese patients with arrhythmias. *Biol Pharm Bull* 2006; **29**: 517–21.
5. Izumi D, *et al.* Bepridil for drug-refractory ventricular tachyarrhythmias. *Intern Med* 2007; **46**: 119–24.
6. Miyaji K, *et al.* Efficacy and safety of the additional bepridil treatment in patients with atrial fibrillation refractory to class I antiarrhythmic drugs. *Circ J* 2007; **71**: 1250–7.
7. Imai S, *et al.* Use of bepridil in combination with Ic antiarrhythmic agent in converting persistent atrial fibrillation to sinus rhythm. *Circ J* 2008; **72**: 709–15.
8. Yamashita T, *et al.* Dose-response effects of bepridil in patients with persistent atrial fibrillation monitored with transtelephonic electrocardiograms: a multicenter, randomized, placebo-controlled,double-blind study (J-BAF Study). *Circ J* 2009; **73**: 1020–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Kaike (开克); *Fr.*: Unicordium†; *Jpn*: Bepricor.

Beraprost Sodium *(USAN, rINNM)*

Beraprost sódico; Béraprost Sodique; ML-1129; ML-1229 (beraprost); Natrii Beraprostum; TRK-100; Натрий Беапрост.

Sodium (±)-(1*R*,2*R*,3a*S*,8b*S*)-2,3,3a,8b-tetrahydro-2-hydroxy-1-[(*E*)-(3*S*,4*RS*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-1*H*-cyclopenta[*b*]benzofuran-5-butyrate.

$C_{24}H_{29}NaO_5$=420.5

CAS — 88430-50-6 (beraprost); 88475-69-8 (beraprost sodium).

ATC — B01AC19.

ATC Vet — QB01AC19.

UNII — 15K99VDU5F.

Profile

Beraprost is a synthetic analogue of epoprostenol (prostacyclin) that causes vasodilatation and prevents platelet aggregation. It is given orally as the sodium salt in the management of pulmonary hypertension (p. 1278.2). It has also been promoted for peripheral vascular disorders (p. 1272.3) although good evidence of value is lacking.

In pulmonary arterial hypertension, beraprost sodium is given in an initial dose of 60 micrograms daily in three divided doses; this may be increased gradually if necessary to 180 micrograms daily in three or four divided doses. For peripheral vascular disease a dose of 120 micrograms daily in three divided doses has been used.

Adverse effects of beraprost include headache, flushing, nausea, diarrhoea, and increased liver enzyme, bilirubin, and triglyceride concentrations.

Cardiovascular disorders. References to the use of beraprost for pulmonary hypertension or intermittent claudication:[1-8] results of studies for the latter indication have been conflicting. It has been tried with sildenafil in patients with pulmonary hypertension.[9,10]

1. Nagaya N, *et al.* Effect of orally active prostacyclin analogue on survival of outpatients with primary pulmonary hypertension. *J Am Coll Cardiol* 1999; **34**: 1188–92.
2. Lievre M, *et al.* Oral beraprost sodium, a prostaglandin I_2 analogue, for intermittent claudication: a double-blind, randomized, multicenter controlled trial. *Circulation* 2000; **102**: 426–31.
3. Mellan EB, Goa KL. Beraprost: a review of its pharmacology and therapeutic efficacy in the treatment of peripheral arterial disease and pulmonary arterial hypertension. *Drugs* 2002; **62**: 107–33.
4. Galiè N, *et al.* Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2002; **39**: 1496–1502.
5. Mohler ER, *et al.* Treatment of intermittent claudication with beraprost sodium, an orally active prostaglandin I_2 analogue: a double-blinded, randomized, controlled trial. *J Am Coll Cardiol* 2003; **41**: 1679–86.
6. Barst RJ, *et al.* Beraprost therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2003; **41**: 2119–25.
7. Hashiguchi M, *et al.* Studies on the effectiveness and safety of cilostazol, beraprost sodium, prostaglandin E1 for the treatment of intermittent claudication. *Yakugaku Zasshi* 2004; **124**: 321–32.
8. Oyamada J, *et al.* Long-term administration of beraprost sodium for pulmonary arterial hypertension associated with congenital heart disease. *Intern Med* 2009; **48**: 1531–4.
9. Ikeda D, *et al.* Addition of oral sildenafil to beraprost is a safe and effective therapeutic option for patients with pulmonary hypertension. *J Cardiovasc Pharmacol* 2005; **45**: 286–9.
10. Kim SY, *et al.* Sildenafil and beraprost combination therapy in patients with pulmonary hypertension undergoing valvular heart surgery. *J Heart Valve Dis* 2010; **19**: 333–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Dorner (德纳); *Indon.*: Dorner; *Jpn*: Belnari; Beplarid†; Beradorlin; Berastolin; Berasus; Beruler; Bestorner†; Careload; Dornalin; Dorner; Procylin; Prodoner; Promer; Prosner; Prostalin; Senaprost; *Philipp.*: Dorner; *Thai.*: Dorner.

Beta Blockers ⊗

β-Bloqueantes; Бета-блокаторы.

Beta blockers (beta-adrenoceptor blocking drugs or antagonists) are competitive antagonists of catecholamines at beta-adrenergic receptors in a wide range of tissues. Although they have broadly similar properties they differ in their affinity for beta$_1$ or beta$_2$ receptor subtypes, intrinsic sympathomimetic activity, membrane-stabilising activity, blockade of alpha-adrenergic receptors, and pharmacokinetic properties including differences in lipid solubility (see Table 4, p. 1317, for some of these characteristics). These differences may affect the choice of drug in specific situations.

Uses and Administration

Beta blockers are competitive antagonists of the effects of catecholamines at beta-adrenergic receptor sites. The different types of adrenergic receptor are described under the Actions and Uses of Sympathomimetics (see p. 1507.3). Blockade of beta receptors has the following effects:

- beta$_1$ blockade mainly affects the heart, reducing heart rate, myocardial contractility, and rate of conduction of impulses through the conducting system (class II antiarrhythmic effect, see p. 1243.1). It also leads to suppression of adrenergic-induced renin release and lipolysis

Table 4. Characteristics of beta blockers.

Beta blocker	$Beta_1$ selectivity	ISA*	MSA**	Vasodilator activity
Acebutolol	+	+	+	0
Alprenolol	0	+	0	0
Atenolol	+	0	0	0
Betaxolol	+	0	0	0
Bisoprolol	+	0	0	0
Carteolol	0	+	0	0
Carvedilol	0	0	0	+
Celiprolol	+	+	–	+
Esmolol	+	0	0	0
Labetalol	0	0	0	+
Levobunolol	0	0	0	0
Metipranolol	0	0	0	0
Metoprolol	+	0	0	0
Nadolol	0	0	0	0
Nebivolol	+	0	0	+
Oxprenolol	0	+	+	0
Penbutolol	0	0	0	0
Pindolol	0	++	0	0
Propranolol	0	0	++	0
Sotalol	0	0	0	0
Timolol	0	0	0	0

0 = absent or low; + = moderate; ++ = high; – = no information
* ISA = Intrinsic sympathomimetic activity
** MSA = Membrane-stabilising activity

- $beta_2$ blockade leads to increased bronchial resistance and inhibition of catecholamine-induced glucose metabolism; there may also be an effect on heart rate. $Beta_2$ blockade also appears to be the main mechanism for the reduction in intra-ocular pressure associated with beta blockers
- the role of $beta_3$ blockade is not clear

Beta blockers differ in their affinity for the subtypes of beta receptor, as well as in their actions at other receptors and ancillary properties (see Table 4, above). The cardiovascular effects of beta blockers relate to their action at $beta_1$ receptors, and all clinically used beta blockers are $beta_1$ antagonists. Propranolol and other nonselective beta blockers also have antagonist effects at $beta_2$ receptors, and this may be responsible for many of their adverse effects. Beta blockers with a higher affinity for $beta_1$ than $beta_2$ receptors, such as atenolol and metoprolol, cause fewer noncardiovascular effects and are described as cardioselective or second generation. However, selectivity is relative and, as doses are increased, activity at $beta_2$ receptors becomes clinically important. Beta blockers with additional properties such as vasodilatation have been described as third generation, and include carvedilol, celiprolol, and nebivolol.

Beta blockers such as acebutolol, celiprolol, oxprenolol, and pindolol also possess intrinsic (partial) sympathomimetic activity in that they activate beta receptors in the absence of catecholamines and are therefore partial agonists. Beta blockers with intrinsic sympathomimetic activity produce less resting bradycardia than beta blockers without.

At high blood concentrations, propranolol and some other beta blockers also possess a membrane-stabilising effect. This effect may not be evident at therapeutic doses but may be important in overdose. The non-cardioselective beta blocker sotalol also has class III antiarrhythmic activity.

Beta blockers that cause vasodilatation may do so by several mechanisms: carvedilol and labetalol block $alpha_1$ receptors; celiprolol has $beta_2$ agonist effects; and nebivolol has a direct action on the endothelium, possibly involving nitric oxide release.

Beta blockers are used in the treatment of hypertension (p. 1251.1), angina pectoris (p. 1254.3), cardiac arrhythmias (p. 1266.1), and myocardial infarction (p. 1257.1) and also have a role in heart failure (p. 1318.1). They are also used to control symptoms of sympathetic overactivity in the management of alcohol withdrawal (p. 1735.1), in anxiety disorders (below), in hyperthyroidism (p. 2332.2), and in tremor (p. 1318.3). Beta blockers are used in the prophylaxis of migraine (p. 1318.2) and of variceal bleeding associated with portal hypertension (p. 2563.1). They are also used, with an alpha blocker, in the initial management of phaeochromocytoma (p. 1318.3). Some beta blockers are used as eye drops in the management of glaucoma and ocular hypertension (p. 1318.1).

Choice of beta blocker. The selection of a specific beta blocker for an individual patient depends on the condition being treated and patient characteristics such as liver and kidney function or existing disease such as diabetes. Patient tolerance also varies for different beta blockers. The characteristics of the beta blocker, for example, $beta_1$ selectivity and intrinsic sympathomimetic activity may also influence selection, as may additional pharmacological properties such as vasodilator activity. Although the clinical significance of these differences has been debated, only certain beta blockers have a proven benefit in some conditions (for example, heart failure) and this will also influence choice.

References.
1. Anonymous. Which beta-blocker? *Med Lett Drugs Ther* 2001; 43: 9–11.
2. Brown MJ. A rational basis for selection among drugs of the same class. *Heart* 2003; 89: 687–94.

Anxiety disorders. Beta blockers have been used in patients with various anxiety disorders,[1] including generalised anxiety disorder (p. 1028.1), panic disorder (p. 1029.1), and performance anxiety[1] (see under Phobic Disorders, p. 1029.1). However, their benefits do not appear to be particularly great and they are probably most useful in reducing symptoms such as tremor or palpitations that are mediated through beta stimulation. Improvement usually occurs within 1 to 2 hours with relatively low doses of beta blockers (propranolol 40 mg, oxprenolol 40 to 80 mg, nadolol 40 mg). Some patients require higher doses and longer periods of treatment for a beneficial effect.

1. Tyrer P. Current status of β -blocking drugs in the treatment of anxiety disorders. *Drugs* 1988; 36: 773–83.

Burns. Beta blockers have been tried in major burn injury (p. 1683.1) to attenuate the hypermetabolism and marked catabolism that may result. A study[1] in children with severe burns found that oral propranolol reduced energy expenditure and muscle-protein catabolism, suggesting beta blockers could have an anabolic effect.

1. Herndon DN, *et al.* Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med* 2001; 345: 1223–9.

Cardiomyopathy. See Heart Failure, p. 1318.1.

Cardiovascular risk reduction. Beta blockers have established benefits in patients with *ischaemic heart disease*,[1] and long-term therapy with beta blockers has an important role in reducing cardiovascular risk in patients with angina pectoris (p. 1254.3), and particularly in patients who have had a myocardial infarction (p. 1257.1). They have also been used to reduce ischaemia and cardiac events in patients undergoing surgery, but their benefits in this situation are less clear.

Perioperative use of beta blockers is controversial (see Precautions, p. 1320.3); they reduce the risk of ischaemia and arrhythmias, but increase the risk of hypotension, and they have often been stopped pre-operatively to enable better control of blood pressure during surgery. However, there is some evidence that continuing or starting beta blockers perioperatively may be of benefit in patients at risk of cardiovascular events, although not all studies have come to the same conclusions. A systematic review[2] of studies with beta blockers suggested a reduction in myocardial ischaemia, non-fatal myocardial infarction, and mortality from cardiovascular causes in patients at high cardiovascular risk undergoing major noncardiac surgery, and a retrospective study[3] also suggested that perioperative beta blockers reduced in-hospital mortality in high-risk patients, although there was no benefit (and possible harm) in low-risk patients. However, another systematic review and meta-analysis[4] concluded that, while the evidence for the use of beta blockers was encouraging, it was too unreliable for definitive conclusions to be drawn. More recent studies[5,6] using perioperative metoprolol have found no benefit, and a further large study (the POISE study)[7] and subsequent meta-analyses[8,9] found fewer cardiac events but a higher risk of stroke and death in patients given beta blockers, although meta-analysis may be heavily weighted by the results from POISE. A regimen of high-dose, long-acting metoprolol started on the day of surgery in the POISE study has been criticised,[10-14] and the resulting hypotension and bradycardia may have contributed to the higher mortality in the active arm. Another meta-analysis[9] that included the results of POISE suggested that the increased risk of stroke with perioperative beta blockers was greatest in those with the lowest baseline risk of the condition.

The conflicting conclusions may relate to the wide range of protocols used in the beta blocker studies, whether patients were already taking beta blockers, and the different selection criteria used for the reviews and analyses. Recognising these limitations, consensus guidelines for non-cardiac surgery in the USA recommend[15] that beta blockers should be continued perioperatively in patients receiving them for accepted indications, and that patients undergoing vascular surgery who are at high risk of cardiovascular events (confirmed by pre-operative testing) should probably have beta blockers started; in patients at lower risk, use of beta blockers may be considered, but there is less evidence of benefit. All patients in whom beta blockers are started require careful dose titration well before the procedure with the aim of avoiding hypotension and bradycardia. It is not clear which beta blockers should be preferred, but a retrospective study[16] found that patients who took atenolol pre- and postoperatively had a lower risk of events than patients who took metoprolol. Some suggest that short-acting,[17] cardioselective[18] beta blockers should be chosen.

Beta blockers may also have benefits in patients undergoing cardiac surgery. Observational studies have found that prior[19] or pre-operative[20] use of beta blockers reduces ischaemic complications, while perioperative[21] and postoperative[22] beta blockers have been shown to reduce the risk of atrial fibrillation, although one study found[23] that the effects on atrial fibrillation only applied to patients already taking beta blockers pre-operatively.

Although beta blockers effectively lower blood pressure, they do not reduce cardiovascular events to the same extent as some other antihypertensives and may not be first choice for *hypertension* (p. 1251.1).[24,25]

1. Ellison KE, Gandhi G. Optimising the use of β -adrenoceptor antagonists in coronary artery disease. *Drugs* 2005; 65: 787–97.
2. Auerbach AD, Goldman L. β -Blockers and reduction of cardiac events in noncardiac surgery: scientific review. *JAMA* 2002; 287: 1435–44.
3. Lindenauer PK, *et al.* Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med* 2005; 353: 349–61.
4. Devereaux PJ, *et al.* How strong is the evidence for the use of perioperative β blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials. *BMJ* 2005; 331: 313–16.
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24. Lindholm LH, *et al.* Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005; 366: 1545–53.
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Extrapyramidal disorders. Beta blockers (in low doses) have been suggested for the management of antipsychotic-induced akathisia although evidence of benefit is limited (see under Chlorpromazine, p. 1049.2).

Glaucoma and ocular hypertension. Topical beta blockers are often the drugs of first choice for the initial treatment and maintenance of open-angle glaucoma and other chronic glaucomas (p. 1999.1). They are believed to inhibit beta receptors in the ciliary epithelium and reduce the secretion of aqueous humour. Clinical studies have established that betaxolol, carteolol, levobunolol, metipranolol, and timolol are effective, generally reducing intra-ocular pressure to a similar extent,[1-5] although a meta-analysis suggested that timolol might be slightly more effective than betaxolol in lowering intra-ocular pressure.[6] The possibility of systemic effects after topical use needs to be borne in mind (see Effects after Ophthalmic Use, p. 1320.1), especially in the elderly.[7]

Beta blockers have also been used for prophylaxis of postoperative ocular hypertension.[8,9]

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Heart failure. Beta blockers have negative inotropic properties and have in the past been contra-indicated in patients with heart failure (p. 1262.3). However, evidence shows that their inhibition of the persistent activation of the sympathetic nervous system associated with disease progression can outweigh this. Reviews,[1-4] meta-analyses,[5,6] and long-term studies[7,8] have confirmed that the beta blockers bisoprolol, carvedilol, and long-acting preparations of metoprolol all improve mortality in patients with chronic heart failure, and another study[9] has shown benefit with nebivolol in elderly patients. A further meta-analysis[10] found that fewer patients were withdrawn from treatment with beta blockers than placebo, suggesting that the benefits outweigh their adverse effects. Sub-group analysis[11] of one of the large studies also confirmed that metoprolol was well tolerated and of benefit in diabetics, despite potential effects on diabetic control (see Effects on Carbohydrate Metabolism under Adverse Effects, p. 1319.2). Beta blockers have also improved functional status in patients with chronic heart failure.[12] Selected beta blockers are therefore now recommended, as part of standard therapy, given with ACE inhibitors and diuretics, in all patients with clinically stable heart failure due to left ventricular systolic dysfunction where there are no contra-indications; the benefit in patients with preserved left ventricular function is less clear, although the empirical use of beta blockers to reduce heart rate and improve myocardial ischaemia has been suggested.[13]

The benefit of beta blockers in heart failure may not be a class effect, and in general only those with an established benefit should be used. Not all beta blockers have been studied in heart failure, but there is also evidence that some are ineffective; a study[14] with bucindolol was stopped early because no mortality benefit was found. For those that have been shown to improve mortality, it is not clear if they are all equally effective.[15] A meta-analysis[16] has suggested that vasodilating beta blockers such as carvedilol have a greater effect on overall mortality than those that do not produce vasodilatation, and a large study[17] comparing carvedilol with metoprolol also found a greater mortality reduction with carvedilol, although the equivalence of the doses used in the study was questioned.[18] The optimum dose is also unclear; many patients are unable to tolerate the target doses used in clinical studies, but an analysis[19] of a study with metoprolol suggested that the mortality benefit was equal in those receiving low or high doses and a meta-analysis[20] found that the magnitude of survival benefit seen with beta blockers was associated with the magnitude of heart rate reduction rather than the dose.

Beta blockers may also be of value in some patients with heart failure due to cardiomyopathy (p. 1261.3). Some beta blockers have provided symptomatic benefit in idiopathic dilated cardiomyopathy, and the heart failure studies that showed a mortality benefit included patients with dilated cardiomyopathy. In hypertrophic cardiomyopathy, beta blockers may be of value for symptomatic management to curtail tachycardia, reduce anginal pain, and prevent syncope.

1. Foody JM, *et al.* β-Blocker therapy in heart failure: scientific review. *JAMA* 2002; 287: 883–9.
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5. Lechat P, *et al.* Clinical effects of β-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 1998; 98: 1184–91.
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9. Flather MD, *et al.* Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005; 26: 215–25.
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19. Wikstrand J, *et al.* Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure (MERIT-HF). *J Am Coll Cardiol* 2002; 40: 491–8.
20. McAlister FA, *et al.* Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med* 2009; 150: 784–94.

Hypotension. Beta blockers have a hypotensive effect and are usually used to reduce blood pressure in patients with hypertension, or occasionally to produce controlled hypotension during surgery. Paradoxically, however, they may be used in the management of neurally mediated hypotension in patients who require drug therapy (see p. 1277.2), although there is limited evidence to support their use, and adverse effects may be a concern. Beta blockers with partial agonist activity have been used in orthostatic hypotension due to autonomic failure (p. 1634.3) but are potentially dangerous.

Migraine and tension type headache. Beta blockers (usually propranolol or metoprolol) are considered[1] by many to be the drugs of choice in patients requiring prophylactic treatment for migraine (p. 670.3). Their mechanism of action in this disorder is not fully understood. Other beta blockers reported to be effective include atenolol, nadolol, and timolol; those with intrinsic sympathomimetic activity may not be effective.

Beta blockers may sometimes also be of benefit in patients with chronic tension-type headache (p. 671.3).

Propranolol has been tried in the treatment of children with abdominal migraine (see under Pizotifen, p. 678.2).

1. Limmroth V, Michel MC. The prevention of migraine: a critical review with special emphasis on β-adrenoceptor blockers. *Br J Clin Pharmacol* 2001; 52: 237–43.

Peripheral vascular disease. Beta blockers may cause coldness of the extremities and have been reported to induce secondary Raynaud's syndrome. However, they may be of some help in the management of erythromelalgia (see under Vasospastic Arterial Disorders on p. 1275.3).

Phaeochromocytoma. Beta blockers are used, with an alpha blocker, in the initial management of phaeochromocytoma (p. 1278.1). Beta blockers reduce the responses to the beta-adrenoceptor stimulating effects of adrenaline. Treatment must be started with the alpha blocker and only when alpha blockade is successfully established can tachycardia be controlled by the cautious use of a beta blocker. A $beta_1$-selective blocker is preferred so that peripheral $beta_2$-mediated vasodilatation is unaffected. In most cases modest doses are sufficient although higher doses may be required for a tumour that is mainly adrenaline-secreting.

Tetanus. Autonomic overactivity, usually due to excessive catecholamine release, may occur as a complication of tetanus and is usually controlled with sedation (see p. 2029.2). Beta blockers have also been used but may produce severe hypertension and are therefore not usually recommended. Labetalol has both alpha- and beta-blocking properties and intravenous labetalol has been used successfully to control the cardiovascular effects of tetanus,[1] although it has not been shown to offer any advantage over propranolol in this situation. Esmolol, a short-acting beta blocker, has also been used.[2]

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Tetralogy of Fallot. For the use of beta blockers in the management of tetralogy of Fallot, see under Uses of Propranolol, p. 1479.3.

Tremor. Tremor is a rhythmical oscillation of part of the body caused by involuntary contraction of opposing muscles. It may occur during action, maintenance of posture, or at rest, and varies in frequency and amplitude. Resting tremor is associated mainly with parkinsonism (p. 889.1), whereas action tremor, which includes postural tremor and kinetic tremor, occurs in a wide variety of disorders. Treatment of the underlying disorder may remove the tremor. Drugs such as bronchodilators, tricyclic antidepressants, lithium, and caffeine may induce tremor; withdrawal of the causative drug usually alleviates the tremor. However, tremor often has no known underlying cause. Such tremor is referred to as **essential tremor** or benign essential tremor; it is usually postural and tends to affect the hands, head, voice, and sometimes the legs and trunk. It is exacerbated by emotional stress and anxiety. Essential tremor may appear at any age and is a lifelong condition that may progress with increasing age. In many cases there is a family history of the disorder (familial essential tremor).

Mild cases of essential tremor may not require regular drug treatment. Single doses of a beta blocker or a benzodiazepine may be useful in acute circumstances to control exacerbations provoked by stress. A single dose of propranolol usually produces a maximum effect after 1 to 2 hours and the effect may persist for several hours. Small amounts of alcohol may also provide effective temporary relief of essential tremor, although its regular use is obviously discouraged.

For more severe cases of essential tremor long-term drug treatment may be required (and may also be tried in other forms of tremor).[1-5] A beta blocker (usually a non-cardioselective beta blocker such as propranolol) is often the first drug used. Up to 70% of people have been reported to respond, although the average tremor reduction is only about 50 to 60%. The beneficial effect appears to be mainly due to blockade of peripheral $beta_2$ receptors on extrafusal muscle fibres and muscle spindles, although there may also be a CNS effect. Adverse effects may be troublesome on long-term use. Primidone may also be tried[6] although there may be a high incidence of acute adverse reactions after initial doses. Concern has been expressed that patients may become tolerant to these drugs given long-term. However, 3 small studies found a reduced response on long-term therapy in only a few patients.[7-9]

Local injection of botulinum A toxin has been tried in refractory essential tremor. Benzodiazepines, and antimuscarinic or dopaminergic antiparkinsonian drugs may be effective in some forms of tremor.[1] Other drugs that have shown some benefit include gabapentin and topiramate.[1-4,10] Many other drugs have been tried, but there is little evidence to support their use.[10] In very severe disabling cases, surgery (thalamotomy or deep brain stimulation) may have to be considered.

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6. Koller WC, Royse VL. Efficacy of primidone in essential tremor. *Neurology* 1986; 36: 121–4.
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Adverse Effects

Beta blockers are generally well tolerated and most adverse effects are mild and transient. Reactions may be more severe after intravenous than oral doses; ocular use has also been associated with systemic adverse effects. The most frequent and serious adverse effects are related to their beta-adrenergic blocking activity. Among the most serious adverse effects are heart failure, heart block, and bronchospasm. Troublesome subjective effects include fatigue and coldness of the extremities; when beta blockers are used for long-term treatment of asymptomatic diseases such as hypertension, such effects may be an important determinant of patient compliance.

Cardiovascular effects include bradycardia and hypotension; heart failure or heart block may be precipitated or worsened in patients with underlying cardiac disorders. Abrupt withdrawal of beta blockers may exacerbate angina and may lead to sudden death. (For further details on withdrawal of beta blockers, see Precautions, p. 1320.3.)

Bronchospasm, shortness of breath, and dyspnoea may be precipitated, particularly in patients with a history of obstructive airways disease, due to blockade of $beta_2$ receptors in bronchial smooth muscle. Drugs with selectivity for $beta_1$ receptors or with intrinsic sympathomimetic activity at $beta_2$ receptors may be less likely to induce bronchospasm (but see Precautions, p. 1320.3). Pneumonitis, pulmonary fibrosis, and pleurisy have also been reported.

CNS effects include headache, depression, dizziness, hallucinations, confusion, amnesia, and sleep disturbances including nightmares. Coma and convulsions have been reported after beta-blocker overdosage. Beta blockers that are lipid soluble are more likely to enter the brain and would be expected to be associated with a higher incidence of CNS adverse effects, although this is not proven.

Fatigue is a common adverse-effect of beta blockers. Paraesthesia, arthralgia, and myopathies, including muscle cramps, have been reported. Reduced peripheral circulation can produce coldness of the extremities and may exacerbate peripheral vascular disease such as Raynaud's syndrome.

Adverse gastrointestinal effects include nausea and vomiting, diarrhoea, constipation, and abdominal cramping.

Beta blockers interfere with carbohydrate and lipid metabolism and can produce hypoglycaemia, hyperglycaemia, and changes in blood concentrations of triglycerides and cholesterol (see under Effects on Carbohydrate Metabolism, below and Effects on Lipid Metabolism, p. 1320.1 for further details).

Rashes, pruritus, exacerbation of psoriasis, excess sweating, and reversible alopecia have occurred with use of beta blockers.

Decreased tear production, blurred vision, conjunctivitis, and soreness are among the ocular symptoms that have been reported. Adverse effects specific to ocular use are also discussed on p. 1320.1.

Haematological reactions include nonthrombocytopenic purpura, thrombocytopenia, and rarely agranulocytosis. Transient eosinophilia can occur.

An asymptomatic increase in antinuclear antibodies has occurred with many beta blockers; SLE has also been reported. Other adverse effects reported with some beta blockers include dry mouth, raised liver enzymes, male impotence, sclerosing peritonitis, and retroperitoneal fibrosis.

Effects on bones and joints. Adverse effects on the bones and joints have occurred in patients receiving beta blockers. Five cases of arthralgia associated with the use of metoprolol had been reported to the FDA;[1] there had also been 6 reports of similar symptoms with propranolol, and 1 with atenolol. A case of polymyalgia rheumatica-like syndrome has also been reported.[2]

However, epidemiological studies have also suggested that beta blockers may increase bone mineral density[3] and reduce the risk of fractures,[3,4] although another study[5] could not confirm this effect.

1. Sills JM, Bosco L. Arthralgia associated with β-adrenergic blockade. *JAMA* 1986; 255: 198–9.
2. Snyder S. Metoprolol-induced polymyalgia-like syndrome. *Ann Intern Med* 1991; 114: 96–7.
3. Pasco JA, *et al.* β-Adrenergic blockers reduce the risk of fracture partly by increasing bone mineral density: Geelong Osteoporosis Study. *J Bone Miner Res* 2004; 19: 19–24.
4. Schlienger RG, *et al.* Use of β-blockers and risk of fractures. *JAMA* 2004; 292: 1326–32.
5. Reid IR, *et al.* β-Blocker use, BMD, and fractures in the study of osteoporotic fractures. *J Bone Miner Res* 2005; 20: 613–18.

Effects on the breast. A 54-year-old woman developed breast pain and swelling a few weeks after starting atenolol for hypertension;[1] it resolved when the atenolol was stopped.

1. Kelleher JA. Atenolol-induced breast pain in a woman with hypertension. *Ann Pharmacother* 2006; 40: 990–2.

Effects on carbohydrate metabolism. The sympathetic nervous system is involved in the control of carbohydrate metabolism and beta blockers can interfere with carbohydrate and insulin regulation; both hypoglycaemia and hyperglycaemia have been reported in patients with no history of diabetes, as well as in patients with types 1 or 2 diabetes mellitus.

Beta blockers cause hypoglycaemia in non-diabetics, possibly by increasing peripheral glucose uptake through increased insulin sensitivity.[1] Those most at risk include fasting or nutritionally-compromised patients, haemodialysis patients, neonates after maternal treatment with beta blockers, and patients with liver disease;[1] those undertaking vigorous exercise[2] and children may also be at risk. Glucose metabolism is controlled by the action of catecholamines at the $beta_2$ receptor, and therefore cardioselective beta blockers are less likely to cause hypoglycaemia than their non-cardioselective counterparts;[1] however, hypoglycaemia was reported[3] in a non-diabetic patient given the cardioselective beta blocker metoprolol pre-operatively for cardiovascular protection.

Traditionally beta blockers have been considered unsafe in diabetics because of reports that they may precipitate and prolong hypoglycaemia, an effect that was first seen in the 1960s in adult type 1 diabetics taking propranolol; however, in a long-term study[4] in type 2 diabetics, there was no difference in the incidence of hypoglycaemia in patients receiving captopril or the cardioselective beta blocker atenolol, and both significantly improved outcome. A case-control study[5] and a review[6] of the use of beta blockers in diabetic patients both concluded that the incidence of hypoglycaemia was not increased and that beta blockers were appropriate therapy for diabetics. Nonetheless, beta blockers may mask the adrenaline-mediated symptoms of hypoglycaemia such as tachycardia and tremor, and non-cardioselective beta blockers may delay recovery in patients given glucose for hypoglycaemia;[6] cardioselective beta blockers are less likely to mask the signs of hypoglycaemia and are therefore preferred in diabetics.[7]

Both cardioselective and non-cardioselective beta blockers may increase fasting blood glucose concentrations in non-diabetic hypertensive patients,[8,9] and epidemiological studies have shown that the risk of developing diabetes mellitus is increased by beta blockers.[10-12] The mechanism is possibly through inhibition of pancreatic insulin release,[1,13] although it has been suggested that hypertensive patients are predisposed to diabetes mellitus and beta blockers act as a precipitating factor;[10,14] changes in body-weight in some of the studies may also have confounded the results.[6] Hyperglycaemia can also occur in diabetic patients treated with beta blockers;[14] however, the established benefits generally outweigh the risk.

Although the adverse effects of beta blockers on carbohydrate metabolism are well-established, there is some evidence that the newer, vasodilating beta blockers, such as carvedilol[15,16] and nebivolol,[17,18] may have beneficial effects on insulin resistance or glucose control, and weight gain may be less with carvedilol.[19] New onset diabetes was also more likely to occur with metoprolol than carvedilol in a study on patients with heart failure.[20]

1. Pandit MK, *et al.* Drug-induced disorders of glucose tolerance. *Ann Intern Med* 1993; 118: 529–39.
2. Holm G, *et al.* Severe hypoglycaemia during physical exercise and treatment with beta-blockers. *BMJ* 1981; 282: 1360.
3. Brown DR, Brown MJ. Hypoglycemia associated with preoperative metoprolol administration. *Anesth Analg* 2004; 99: 1427–8.
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5. Thamer M, *et al.* Association between antihypertensive drug use and hypoglycemia: a case-control study of diabetic users of insulin or sulfonylureas. *Clin Ther* 1999; 21: 1387–1400.
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16. Giugliano D, *et al.* Metabolic and cardiovascular effects of carvedilol and atenolol in non-insulin-dependent diabetes mellitus and hypertension: a randomized, controlled trial. *Ann Intern Med* 1997; 126: 955–9.
17. Celik T, *et al.* Comparative effects of nebivolol and metoprolol on oxidative stress, insulin resistance, plasma adiponectin and soluble P-selectin levels in hypertensive patients. *J Hypertens* 2006; 24: 591–6.
18. Poirier L, *et al.* Effects of nebivolol and atenolol on insulin sensitivity and haemodynamics in hypertensive patients. *J Hypertens* 2001; 19: 1429–35.
19. Messerli FH, *et al.* Body weight changes with beta-blocker use: results from GEMINI. *Am J Med* 2007; 120: 610–15.
20. Torp-Pedersen C, *et al.* Effects of metoprolol and carvedilol on pre-existing and new onset diabetes in patients with chronic heart failure: data from the Carvedilol Or Metoprolol European Trial (COMET). *Heart* 2007; 93: 968–73.

Effects on the circulation. Hypotension is a recognised adverse effect of beta blockers, and severe reactions have been reported. Near-fatal shock occurred[1] in an elderly patient with chronic bronchitis and angina pectoris within 40 minutes of taking acebutolol 400 mg. (For discussion of hypotension possibly associated with increased mortality in patients given beta blockers perioperatively see Cardiovascular Risk Reduction, under Uses, p. 1317.2.) Hypotension, leading to a rise in serum creatinine indicative of kidney ischaemia, occurred[2] in 2 women after a single oral dose of atenolol 100 mg or 2 oral doses of atenolol 50 mg; both had presented with severe hypertension, hyponatraemia, hypokalaemia, and high renin activity. Renal artery thrombosis believed to be due to the hypotensive effect of atenolol was reported[3] in a 70-year-old man with a history of circulatory and cardiac disorders. He had received atenolol 100 mg for treatment of moderate hypertension.

Beta blockers have been tried in neurally mediated hypotension (see Hypotension under Uses, p. 1318.2), but this may be hazardous: a 27-year-old man had[4] ten episodes of syncope with severe bradycardia after taking atenolol for recurrent vasovagal syncope; episodes ceased on stopping the atenolol. The authors suggested that the atenolol aggravated the vasovagal syncope, and recommended careful monitoring of patients given beta blockers for this condition.

1. Tirlapur VG, *et al.* Shock syndrome after acebutolol. *Br J Clin Pract* 1986; 40: 33–4.
2. Kholeif M, Isles C. Profound hypotension after atenolol in severe hypertension. *BMJ* 1989; 298: 161–2.
3. Shaw AB, Gopalka SK. Renal artery thrombosis caused by antihypertensive treatment. *BMJ* 1982; 285: 1617.
4. Wang C-C, *et al.* Worsening of vasovagal syncope after beta-blocker therapy. *Chest* 1994; 106: 963–5.

Effects on the gastrointestinal tract. Sclerosing peritonitis was noted as part of the 'oculomucocutaneous syndrome' that occurred with practolol. However, while both sclerosing peritonitis and retroperitoneal fibrosis have also been reported with some other beta blockers, including atenolol,[1,2] metoprolol,[3,4] oxprenolol,[5] propranolol,[6,7] sotalol,[8] and timolol,[9,10] a review[11] of 100 cases of retroperitoneal fibrosis concluded that beta blockers could not be considered as the cause.

Abdominal pain and bloody diarrhoea were reported[12] in a patient the day after treatment was started with propranolol; symptoms were attributed to splanchnic vasoconstriction caused by the drug, which may have exacerbated pre-existing mesenteric ischaemia.

1. Nielsen BV, Pedersen KG. Sclerosing peritonitis associated with atenolol. *BMJ* 1985; 290: 518.
2. Johnson JN, McFarland J. Retroperitoneal fibrosis associated with atenolol. *BMJ* 1980; 280: 864.

3. Thompson J, Julian DG. Retroperitoneal fibrosis associated with metoprolol. *BMJ* 1982; 284: 83–4.
4. Clark CV, Terris R. Sclerosing peritonitis associated with metoprolol. *Lancet* 1983; i: 937.
5. McCluskey DR, *et al.* Oxprenolol and retroperitoneal fibrosis. *BMJ* 1980; 281: 1459–60.
6. Pierce JR, *et al.* Propranolol and retroperitoneal fibrosis. *Ann Intern Med* 1981; 95: 244.
7. Kalra S, *et al.* Sclerosing encapsulating peritonitis associated with propranolol usage: a case report and review of the literature. *J Dig Dis* 2009; 10: 332–5.
8. Laakso M, *et al.* Retroperitoneal fibrosis associated with sotalol. *BMJ* 1982; 285: 1085–6.
9. Baxter-Smith DC, *et al.* Sclerosing peritonitis in patient on timolol. *Lancet* 1978; ii: 149.
10. Rimmer E, *et al.* Retroperitoneal fibrosis associated with timolol. *Lancet* 1983; i: 300.
11. Pryor JP, *et al.* Do beta-adrenoceptor blocking drugs cause retroperitoneal fibrosis? *BMJ* 1983; 287: 639–41.
12. Köksal AŞ, *et al.* Propranolol-exacerbated mesenteric ischemia in a patient with hyperthyroidism. *Ann Pharmacother* 2005; 39: 559–62.

Effects on lipid metabolism. The adrenergic system is involved in the control of lipid metabolism and beta blockers may therefore have effects on plasma-lipid concentrations. In general, beta blocker therapy results in increased concentrations of very-low-density lipoprotein and triglycerides, a reduction in high-density lipoprotein, and no change in low-density lipoprotein.[1] These effects may be less pronounced with beta$_1$ cardioselective drugs, beta blockers with intrinsic sympathomimetic activity, and beta blockers that also block alpha-adrenergic receptors. For example, pindolol,[2,3] a beta blocker with intrinsic sympathomimetic activity, and arotinolol[4] and carvedilol,[5] which possess alpha-adrenergic blocking properties, are reported to have no adverse effects on plasma-lipid concentrations, although acute pancreatitis due to severe hypertriglyceridaemia has been reported[6] in a patient treated with metoprolol followed by atenolol. However, the effects on lipid concentrations are generally fairly small, and a review of the subject[7] concluded that there was little or no evidence that such effects negated the beneficial effects of beta blockers on cardiovascular outcomes.

1. Krone W, Nägele H. Effects of antihypertensives on plasma lipids and lipoprotein metabolism. *Am Heart J* 1988; 116: 1729–34.
2. Hunter Hypertension Research Group. Effects of pindolol, or a pindolol/clopamide combination preparation, on plasma lipid levels in essential hypertension. *Med J Aust* 1989; 150: 646–52.
3. Terént A, *et al.* Long-term effect of pindolol on lipids and lipoproteins in men with newly diagnosed hypertension. *Eur J Clin Pharmacol* 1989; 36: 347–50.
4. Sasaki J, *et al.* Effects of arotinolol on serum lipid and apolipoprotein levels in patients with mild essential hypertension. *Clin Ther* 1989; 11: 580–3.
5. Sharp RP, *et al.* Impact of carvedilol on the serum lipid profile. *Ann Pharmacother* 2008; 42: 564–71.
6. Durrington PN, Cairns SA. Acute pancreatitis: a complication of beta-blockade. *BMJ* 1982; 284: 1016.
7. Weir MR, Moser M. Diuretics and β-blockers: is there a risk for dyslipidemia? *Am Heart J* 2000; 139: 174–84.

Effects on mental state. Beta blockers can cross the blood-brain barrier and there are many reports of adverse psychiatric effects. Theoretically this is more likely with lipophilic drugs (such as propranolol, timolol, and metoprolol) but there have also been reports of psychosis[1] and delirium[2] with atenolol.

Although beta blockers have been associated with depression,[3] the risk may not be as high as has sometimes been suggested; a review[4] of randomised studies in myocardial infarction, heart failure, or hypertension, which included over 35 000 patients, found no significant increase in the risk of depression in those taking beta blockers.

1. Viadero JJ, *et al.* Acute psychotic behavior associated with atenolol. *Am J Psychiatry* 1983; 140: 1382.
2. Arber N, *et al.* Delirium induced by atenolol. *BMJ* 1988; 297: 1048.
3. Parker WA. Propranolol-induced depression and psychosis. *Clin Pharm* 1985; 4: 214–18.
4. Ko DT, *et al.* β-Blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA* 2002; 288: 351–7.

Effects after ophthalmic use. Ophthalmic use of beta blockers may produce ocular irritation (including hypersensitivity), blepharitis, keratitis, decreased corneal sensitivity, visual disturbances, diplopia, photophobia, and ptosis. Hypersensitivity to ophthalmic beta blockers has caused allergic conjunctivitis and contact dermatitis; cross-sensitivity between beta blockers has been reported.[1] Uveitis has been reported with metipranolol eye drops.[2] Iris depigmentation has occurred[3] after the use of topical levobunolol. Older patients using topical beta blockers may be at greater risk of decreased corneal sensitivity or corneal anaesthesia with the consequent risk of keratitis.[4]

Systemic absorption may occur after the use of beta blockers in eye drops. Excess drug can drain into the lachrymal ducts to be absorbed through the nasal mucosa. Absorption also occurs via the ophthalmic and facial veins. After such absorption the beta blocker reaches the systemic circulation without undergoing first-pass hepatic metabolism.

The main systemic effects associated with topical ocular use of beta blockers are on the pulmonary, cardiovascular, and central nervous systems.[5,6]

Both cardioselective and non-cardioselective topical beta blockers have been shown to cause pulmonary effects, and these can occur in patients without a history of obstructive airways disease.[7] Reported events include acute pulmonary oedema associated with use of metipranolol eye drops,[8] and wheezing after a single dose of topical levobunolol, which developed into severe respiratory distress requiring hospitalisation after a second dose.[9] Myocardial infarction has been reported[10] shortly after a single dose of betaxolol eye drops; the patient was also taking atenolol and indapamide for hypertension. Systemic effects have also been reported in patients using timolol eye drops, including depression and bradycardia, with a rise in blood pressure and neurological signs of stroke after rapid withdrawal of the drops,[11] syncope and falls,[12] and severe nausea and vomiting, which resolved within a few days of withdrawal but recurred on rechallenge.[13] Cases of alopecia associated with ocular use of beta blockers have also been reported.[14]

1. Jappe U, *et al.* Allergic contact dermatitis due to β-blockers in eye drops: a retrospective analysis of multicentre surveillance data 1993–2004. *Acta Derm Venereol* 2006; 86: 509–14.
2. Akingbehin T, Villada JR. Metipranolol-associated granulomatous anterior uveitis. *Br J Ophthalmol* 1991; 75: 519–23.
3. Doyle E, Liu C. A case of acquired iris depigmentation as a possible complication of levobunolol eye drops. *Br J Ophthalmol* 1999; 83: 1405–6.
4. Weissman SS, Asbell PA. Effects of topical timolol (0.5%) and betaxolol (0.5%) on corneal sensitivity. *Br J Ophthalmol* 1990; 74: 409–12.
5. Everitt DE, Avorn J. Systemic effects of medications used to treat glaucoma. *Ann Intern Med* 1990; 112: 120–5.
6. Vander Zanden JA, *et al.* Systemic adverse effects of ophthalmic β-blockers. *Ann Pharmacother* 2001; 35: 1633–7.
7. Kirwan JF, *et al.* Do selective topical β antagonists for glaucoma have respiratory side effects? *Br J Ophthalmol* 2004; 88: 196–8.
8. Johns MD, Ponte CD. Acute pulmonary edema associated with ocular metipranolol use. *Ann Pharmacother* 1995; 29: 370–3.
9. Stubbs GM. Betagan drops. *Med J Aust* 1994; 161: 576.
10. Chamberlain TJ. Myocardial infarction after ophthalmic betaxolol. *N Engl J Med* 1989; 321: 1342.
11. Rao MR, *et al.* Systemic hazards of ocular timolol. *Br J Hosp Med* 1993; 50: 553.
12. Müller ME, *et al.* Syncope and falls due to timolol eye drops. *BMJ* 2006; 332: 960–1.
13. Wollhagen FEJ, *et al.* Severe nausea and vomiting with timolol eye drops. *Lancet* 1998; 352: 373.
14. Praunfelder FT, *et al.* Alopecia possibly secondary to topical ophthalmic β-blockers. *JAMA* 1990; 263: 1493–4.

Hypersensitivity. For the suggestion that beta blockers may exacerbate anaphylactic reactions, see under Precautions, p. 1321.1.

See also under Effects after Ophthalmic Use, above.

Overdosage. Many cases of beta-blocker overdosage[1] are uneventful, but some patients develop severe and occasionally fatal cardiovascular depression. Effects can include bradycardia, cardiac conduction block, hypotension, heart failure, and cardiogenic shock. Convulsions, coma, respiratory depression, and bronchoconstriction can also occur, although infrequently. Most reports of serious toxic reactions after overdosage concern beta blockers with significant membrane-stabilising activity, such as propranolol or oxprenolol, which may have quinidine-like effects (see p. 1482.1). Overdosage of beta blockers with intrinsic sympathomimetic activity may present with tachycardia and hypertension. Overdosage of sotalol, a beta blocker with class II and III antiarrhythmic properties, usually presents as ventricular tachyarrhythmia.

1. DeWitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and β-blocker toxicity. *Toxicol Rev* 2004; 23: 223–38.

Treatment of Adverse Effects

Beta blockers are generally well tolerated and adverse effects usually respond to a reduction in dose. In overdosage, use of activated charcoal or gastric lavage should be considered if the patient presents within 1 hour of ingestion. Mild hypotension may respond to intravenous fluids. If hypotension continues, intravenous glucagon should be given; sympathomimetics may be used as an alternative or given with glucagon. Isoprenaline has been the sympathomimetic of choice since it acts mainly at beta receptors, but other sympathomimetics are often used; very high doses may be required (see Overdosage, below). Atropine may be given intravenously for bradycardia; sympathomimetics or a cardiac pacemaker may also be required. Beta$_2$ agonists or xanthines may be given for bronchospasm; hypoglycaemia may respond to glucose or glucagon. Haemodialysis may be of benefit for severe overdosage with renally excreted beta blockers, but is usually unnecessary.

Overdosage. Atropine, glucagon, and sympathomimetics are the mainstay of treatment for severe beta blocker overdosage (see above). Very high doses of sympathomimetics have been used in some patients; a woman[1] who had taken acebutolol, labetalol, and trimipramine required isoprenaline at a rate of 1660 micrograms/minute and dopamine at a rate of 200 micrograms/kg per minute to maintain her blood pressure. However, standard therapy is not effective in all patients and alternatives have been tried.

The phosphodiesterase inhibitor enoximone has been used successfully in patients resistant to standard treatment,[2,3] and a dramatic response to calcium chloride has been reported in a patient with electromechanical dissociation after propranolol overdosage.[4] It has been suggested[5,6] that high doses of insulin given with glucose (hyperinsulinaemia/euglycaemia therapy) may be of benefit, although there is no clinical evidence to support this. There has also been a report[7] of the successful use of sodium bicarbonate in a patient with cardiac arrest after overdosage with multiple drugs, including propranolol; it was suggested that the increased sodium load counteracted the sodium-channel blocking effect of propranolol.

1. Lewis M, *et al.* Survival following massive overdose of adrenergic blocking agents (acebutolol and labetalol). *Eur Heart J* 1983; 4: 328–32.
2. Hoeper MM, Boecker KHW. Overdose of metoprolol treated with enoximone. *N Engl J Med* 1996; 335: 1538.
3. Sandroni C, *et al.* Enoximone in cardiac arrest caused by propranolol: two case reports. *Acta Anaesthesiol Scand* 2006; 50: 759–61.
4. Brimacombe JR, *et al.* Propranolol overdose—a dramatic response to calcium chloride. *Med J Aust* 1991; 155: 267–8.
5. Shepherd G. Treatment of poisoning caused by β-adrenergic and calcium-channel blockers. *Am J Health-Syst Pharm* 2006; 63: 1828–35.
6. Mégarbane B, *et al.* The role of insulin and glucose (hyperinsulinaemia/euglycaemia) therapy in acute calcium channel antagonist and β-blocker poisoning. *Toxicol Rev* 2004; 23: 215–22.
7. Shanker UR, *et al.* Sodium bicarbonate to treat massive β blocker overdose. *Emerg Med J* 2003; 20: 393.

Precautions

Beta blockers should not be given to patients with bronchospasm or asthma or to those with a history of obstructive airways disease. This contra-indication generally applies even to those beta blockers considered to be cardioselective. However, cardioselective beta blockers may be used with extreme caution when there is no alternative treatment (see Obstructive Airways Disease, p. 1321.1). Other contra-indications include metabolic acidosis, cardiogenic shock, hypotension, severe peripheral arterial disease, sinus bradycardia, and second- or third-degree AV block; caution should be observed in first-degree block. Although beta blockers are used in the management of heart failure, they should not be given to patients with uncontrolled heart failure and treatment should be begun with great care, starting with a low dose and cautiously titrating upwards. Patients with phaeochromocytoma should not be given beta blockers without alpha-adrenoceptor blocking therapy as well.

Beta blockers may mask the symptoms of hyperthyroidism and of hypoglycaemia. They may unmask myasthenia gravis. Psoriasis may be aggravated. Beta blockers may increase the number of attacks of chest pain in patients with Prinzmetal's angina; this occurs especially with non-cardioselective beta blockers, which should be avoided. Beta blockers increase sensitivity to allergens and also the severity of anaphylactoid reactions; patients with a history of anaphylaxis to an antigen may be more reactive to repeated challenge with the antigen while taking beta blockers (see Hypersensitivity, p. 1321.1).

Abrupt withdrawal of beta blockers has sometimes resulted in angina, myocardial infarction, ventricular arrhythmias, and death. Patients on long-term treatment with a beta blocker should have their medication stopped gradually over a period of 1 to 2 weeks. In patients undergoing surgery, beta blockers may reduce the risk of arrhythmias but increase the risk of hypotension; the decision to withdraw or continue therapy depends on individual patient risk—see Cardiovascular Risk Reduction, p. 1317.2. If beta blockers are withdrawn, this should take place at least 24 to 48 hours before surgery; if they are continued, atropine may be given to counter increases in vagal tone and anaesthetics causing myocardial depression, such as ether, cyclopropane, and trichloroethylene, are best avoided. It is of the greatest importance that the anaesthetist is aware that beta blockers are being taken.

Use of beta blockers in pregnancy shortly before delivery has occasionally resulted in bradycardia and other adverse effects such as hypoglycaemia and hypotension in the neonate. Many beta blockers are distributed into breast milk.

Similar precautions apply when beta blockers are used as eye drops since systemic absorption can occur.

Cocaine toxicity. Although beta blockers are useful in the acute and chronic management of myocardial ischaemia, the problem of unopposed α-adrenergic stimulation and potential for exacerbating coronary vasoconstriction make them a hazardous choice where ischaemia is induced by cocaine, and fatalities have been reported.[1,2] Some guidelines[3,4] recommend against their use, while others[5] suggest that the cautious use of a combined alpha- and beta-blocking agent such as labetalol may be reasonable if

hypertension and tachycardia are present and the patient has also received a vasodilator;[5] carvedilol has been suggested as an alternative.[2] There is little guidance on the long-term safety of beta blockers after cocaine-induced myocardial ischaemia, but the likelihood of continued cocaine ingestion should be borne in mind.[2]

1. Pareed FN, *et al.* Death temporally related to the use of a beta adrenergic receptor antagonist in cocaine associated myocardial infarction. *J Med Toxicol* 2007; 3: 169–72.
2. Page RL, *et al.* Should β-blockers be used in the treatment of cocaine-associated acute coronary syndrome? *Ann Pharmacother* 2007; 41: 2008–13.
3. Antman EM, *et al.* ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Executive summary: *Circulation* 2004; 110: 588–636. Correction. *ibid.* 2005; 111: 2013. Full guidelines available at: http://circ.ahajournals.org/cgi/reprint/110/9/e82 (accessed 26/01/10)
4. The American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005; 112: (suppl 1): IV1–IV203. Available at: http://intl-circ.ahajournals.org/content/vol112/24_suppl/ (accessed 26/01/10)
5. Anderson JL, *et al.* ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction). Full text: *Circulation* 2007; 116: e148–e304. Also available at: http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.107.181940 (accessed 26/01/10) Executive summary: *Circulation* 2007; 116: 803–77. Also available at: http://circ.ahajournals.org/cgi/reprint/116/7/803 (accessed 26/01/10)

Contact lenses. Beta blockers may reduce tear flow, leading to irritation of the eye in wearers of contact lenses and potentially to the dehydration of soft lenses.[1]

1. McGuire T. Drugs interfering with contact lenses. *Aust J Hosp Pharm* 1987; 17: 55–6.

Hypersensitivity. Anaphylactic reactions to stings and other antigens may be potentiated by beta blockers[1-3] and the risk of serious reactions may be increased. In addition, beta blockers may antagonise the effects of adrenaline in the management of anaphylaxis (see Interactions under Sympathomimetics, p. 1509.1). Particular caution is necessary when beta blockers are used in patients with a history of anaphylaxis.[3]

1. Hannaway PJ, Hopper GDK. Severe anaphylaxis and drug-induced beta-blockade. *N Engl J Med* 1983; 308: 1536.
2. Pedersen DL. Hymenoptera stings and beta-blockers. *Lancet* 1989; ii: 619.
3. Lang DM. Anaphylactoid and anaphylactic reactions: hazards of β-blockers. *Drug Safety* 1995; 12: 299–304.

Obstructive airways disease. Beta blockers may precipitate bronchospasm and are generally contra-indicated in patients with obstructive airways disease.[1,2] However, systematic reviews have suggested that short-term use of cardioselective beta blockers does not produce adverse respiratory effects in patients with mild to moderate asthma[3] or chronic obstructive pulmonary disease.[4] The reviewers concluded that, given the established benefits of beta blockers in cardiovascular disorders, they should not be withheld in such patients, although patients should be carefully monitored since long-term effects were less clear. A retrospective study[5] found that use of beta blockers increased the rate of hospitalisations and emergency department visits in patients with asthma, but not in those with non-asthmatic chronic obstructive pulmonary disease, suggesting that the benefits and risks need to be assessed for each patient individually. Another study[6] found that patients with acute exacerbations of chronic obstructive pulmonary disease who were given beta blockers had lower mortality than those who were not.

1. CSM/MCA. Reminder: beta-blockers contraindicated in asthma. *Current Problems* 1996; 22: 2. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 10/01/08)
2. The Task Force on Beta-Blockers of the European Society of Cardiology. Expert consensus document on β-adrenergic receptor blockers. *Eur Heart J* 2004; 25: 1341–62.
3. Salpeter S, *et al.* Cardioselective beta-blockers for reversible airway disease. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2002 (accessed 10/01/08).
4. Salpeter S, *et al.* Cardioselective beta-blockers for chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2005 (accessed 10/01/08).
5. Brooks TWA, *et al.* Rates of hospitalizations and emergency department visits in patients with asthma and chronic obstructive pulmonary disease taking β-blockers. *Pharmacotherapy* 2007; 27: 684–90.
6. Dransfield MT, *et al.* Use of beta blockers and the risk of death in hospitalised patients with acute exacerbations of COPD. *Thorax* 2008; 63: 301–5.

Pregnancy. Many beta blockers cross the placenta, and use shortly before delivery may result in neonatal adrenergic blockade, with symptoms of bradycardia, hypoglycaemia or hypotension. Furthermore, the treatment of maternal hypertension with beta blockers, particularly atenolol, in early pregnancy or for a long duration has been associated with growth retardation of the fetus.[1-3] However, beta blockers are recommended therapy for maternal conditions such as hypertension, pre-eclampsia, cardiac arrhythmias, and ischaemic heart disease;[4,5] cardioselective agents with no effect on uterine contraction are preferred.[5]

1. Butters L, *et al.* Atenolol in essential hypertension during pregnancy. *BMJ* 1990; 301: 587–9.
2. Lydakis C, *et al.* Atenolol and fetal growth in pregnancies complicated by hypertension. *Am J Hypertens* 1999; 12: 541–7.
3. Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. Available in the Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2003 (accessed 10/01/08).
4. Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of Cardiology. Expert consensus document on management of cardiovascular diseases during pregnancy. *Eur Heart J* 2003; 24: 761–81.
5. Task Force on Beta-Blockers of the European Society of Cardiology. Expert consensus document on β-adrenergic receptor blockers. *Eur Heart J* 2004; 25: 1341–62.

Withdrawal. The abrupt withdrawal of beta blockers may lead to rebound hypertension or overshoot hypertension where the patient's blood pressure is higher than before treatment. Angina can be exacerbated, myocardial infarction induced, and fatalities have occurred.[1,2]

1. Houston MC, Hodge R. Beta-adrenergic blocker withdrawal syndromes in hypertension and other cardiovascular diseases. *Am Heart J* 1988; 116: 515–23.
2. Psaty BM, *et al.* The relative risk of incident coronary heart disease associated with recently stopping the use of β-blockers. *JAMA* 1990; 263: 1653–7.

Interactions

Both pharmacodynamic and pharmacokinetic interactions have been reported with beta blockers. **Pharmacodynamic** interactions may occur with drugs whose actions enhance or antagonise the various effects of beta blockers at $beta_1$ and $beta_2$ receptors, including their antihypertensive effect, cardiodepressant effect, effect on carbohydrate metabolism, or effect on bronchial $beta_2$ receptors. The characteristics of the individual beta blocker must therefore be borne in mind when considering likely interactions; for more details on the characteristics of different beta blockers, see Uses and Administration, p. 1316.3.

Drugs that enhance the antihypertensive effects of beta blockers, such as ACE inhibitors, calcium-channel blockers, and clonidine may be useful in controlling hypertension (but see Antihypertensives, p. 1322.1). Drugs that cause hypotension such as aldesleukin and general anaesthetics also enhance the antihypertensive effects of beta blockers while other drugs, for example NSAIDs, antagonise the antihypertensive effects.

Use of beta blockers with other cardiac depressants such as antiarrhythmics and rate-limiting calcium-channel blockers can precipitate bradycardia and heart block; the combination of intravenous verapamil and beta blockers should especially be avoided. Sotalol is particularly prone to interactions with other drugs affecting cardiac conduction (see p. 1499.2). Beta blockers may potentiate bradycardia due to digoxin.

The interaction between beta blockers and sympathomimetics is complex and depends on the selectivity of both drugs (see under Sympathomimetics, p. 1509.1). Patients taking beta blockers may have an exaggerated hypertensive response to adrenaline, caused by unopposed alpha-mediated vasoconstriction, while the bronchodilator effects are inhibited; the response to adrenaline given for anaphylaxis may also be reduced in patients on long-term treatment with beta blockers.

In diabetic patients beta blockers can reduce the response to insulin and oral hypoglycaemics through their effects on pancreatic beta receptors (see Effects on Carbohydrate Metabolism, p. 1319.2).

Pharmacokinetic interactions occur with drugs that alter the absorption or metabolism of beta blockers. Although these interactions may alter the beta blocker plasma concentration, they are not usually clinically significant since there is little association between plasma concentrations and therapeutic effect or toxicity and there are wide interindividual differences in steady-state plasma concentrations of beta blockers.

Drugs that reduce absorption include aluminium salts (but see also Antacids, below) and bile-acid binding resins such as colestyramine.

Metabolism of some beta blockers can be increased by drugs such as barbiturates and rifampicin and decreased with drugs such as cimetidine, erythromycin, fluvoxamine, and hydralazine. Drugs that alter hepatic blood flow also affect metabolism of some beta blockers. For example, cimetidine and hydralazine decrease hepatic blood flow and this contributes to the decreased hepatic clearance seen with these drugs. Drugs that influence hepatic metabolism affect beta blockers that are extensively metabolised, such as labetalol, propranolol, and timolol, while beta blockers that are excreted largely unchanged, for example atenolol and nadolol, are unaffected.

Since systemic absorption can occur after ocular use of beta blockers the possibility of similar interactions should be considered.

General references.

1. McDevitt DG. Interactions that matter: 12. β-adrenoceptor antagonists. *Prescribers' J* 1988; 28: 25–30.
2. Blaufarb I, *et al.* β-Blockers: drug interactions of clinical significance. *Drug Safety* 1995; 13: 359–70.
3. Brodde OE, Kroemer HK. Drug-drug interactions of beta-adrenoceptor blockers. *Arzneimittelforschung* 2003; 53: 814–22.

Antacids. Bioavailability of metoprolol was increased when given with an antacid containing aluminium and magnesium salts, but the bioavailability of atenolol was reduced. Variable results on bioavailability of propranolol have been reported when aluminium hydroxide was given with propranolol.[1]

1. Gugler R, Allgayer H. Effects of antacids on the clinical pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1990; 18: 210–19.

Antiarrhythmics. Use of beta blockers with antiarrhythmic drugs and other drugs affecting cardiac conduction can precipitate bradycardia and heart block.

Bradycardia, cardiac arrest, and ventricular fibrillation have been reported shortly after starting beta-blocker therapy in patients receiving *amiodarone*.[1] Amiodarone was found to increase plasma-metoprolol concentrations in patients with cardiac arrhythmias, probably through inhibition of the cytochrome P450 isoenzyme CYP2D6 by the metabolite desethylamiodarone.[2] However, an analysis[3] of the CAMIAT and EMIAT studies in patients after myocardial infarction found that patients taking amiodarone and beta blockers had better outcomes than patients on one, or neither, drug, suggesting that any interaction may not always be detrimental. Use of *flecainide* with propranolol produced additive negative inotropic effects on the heart and increased serum concentrations of both drugs.[4] In a pharmacokinetic study in 12 healthy males, giving *propafenone* with propranolol resulted in increases in serum-propranolol concentrations but only modest enhancement of beta-blocking activity.[5] An increase in serum-metoprolol concentration has been reported after use of propafenone with metoprolol.[6] The metabolism of metoprolol may be decreased by *quinidine*.[7] Both quinidine and beta blockers have a negative inotropic action on the heart; bradycardia[8] and hypotension[9] have occurred in patients given quinidine with beta blockers.

For a report of reduced clearance of *disopyramide* by atenolol, see p. 1365.2.

The interactions of sotalol are discussed on p. 1499.2.

1. Lesko LJ. Pharmacokinetic drug interactions with amiodarone. *Clin Pharmacokinet* 1989; 17: 130–40.
2. Fukumoto K, *et al.* Effect of amiodarone on the serum concentration/dose ratio of metoprolol in patients with cardiac arrhythmia. *Drug Metab Pharmacokinet* 2006; 21: 501–5.
3. Boutitie F, *et al.* Amiodarone interaction with β-blockers: analysis of the merged EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) databases. *Circulation* 1999; 99: 2268–75.
4. Holtzman JL, *et al.* The pharmacodynamic and pharmacokinetic interaction of flecainide acetate with propranolol: effects on cardiac function and drug clearance. *Eur J Clin Pharmacol* 1987; 33: 97–9.
5. Kowey PR, *et al.* Interaction between propranolol and propafenone in healthy volunteers. *J Clin Pharmacol* 1989; 29: 512–17.
6. Wagner F, *et al.* Drug interaction between propafenone and metoprolol. *Br J Clin Pharmacol* 1987; 24: 213–20.
7. Leemann T, *et al.* Single-dose quinidine treatment inhibits metoprolol oxidation in extensive metabolizers. *Eur J Clin Pharmacol* 1986; 29: 739–41.
8. Dinai Y, *et al.* Bradycardia induced by interaction between quinidine and ophthalmic timolol. *Ann Intern Med* 1985; 103: 890–1.
9. Loon NR, *et al.* Orthostatic hypotension due to quinidine and propranolol. *Am J Med* 1986; 81: 1101–4.

Antibacterials. Serum-atenolol concentrations in 6 healthy subjects were reduced by a 1-g oral dose of *ampicillin*.[1] Plasma concentrations of propranolol,[2] metoprolol,[3] celiprolol,[4] and bisoprolol[5] may be reduced by *rifampicin*. Licensed product information for *telithromycin* states that it causes increased plasma concentrations of metoprolol.

1. Schäfer-Korting M, *et al.* Atenolol interaction with aspirin, allopurinol, and ampicillin. *Clin Pharmacol Ther* 1983; 33: 283–8.
2. Shaheen O, *et al.* Influence of debrisoquin phenotype on the inducibility of propranolol metabolism. *Clin Pharmacol Ther* 1989; 45: 439–43.
3. Bennett PN, *et al.* Effect of rifampicin on metoprolol and antipyrine kinetics. *Br J Clin Pharmacol* 1982; 13: 387–91.
4. Lilja JJ, *et al.* Rifampicin reduces plasma concentrations of celiprolol. *Eur J Clin Pharmacol* 2004; 59: 819–24.
5. Kirch W, *et al.* Interaction of bisoprolol with cimetidine and rifampicin. *Eur J Clin Pharmacol* 1986; 31: 59–62.

Anticoagulants. For the effect of beta blockers on the pharmacokinetics of some oral anticoagulants, see p. 1533.1.

Antidepressants. Bradycardia and heart block, occurring shortly after starting *fluoxetine* therapy, have been reported in patients receiving metoprolol[1] and propranolol.[2] Possible mechanisms include impaired conduction through the AV node and inhibition by fluoxetine of the oxidative metabolism of beta blockers. Use of fluoxetine also increased the plasma concentration of carvedilol in

patients with heart failure but no clinical effects were noted.[3]

Fluvoxamine and *paroxetine* inhibit oxidative metabolism; increased plasma concentrations of propranolol have been noted in patients also taking fluvoxamine, and of metoprolol[4,5] in those also taking paroxetine. The latter combination has resulted in complete AV block.[5]

For the use of pindolol in augmenting antidepressant therapy, see Psychiatric Disorders under Pindolol, p. 1470.2..

1. Walley T, *et al.* Interaction of metoprolol and fluoxetine. *Lancet* 1993; 341: 967–8.
2. Drake WM, Gordon GD. Heart block in a patient on propranolol and fluoxetine. *Lancet* 1994; 343: 425–6.
3. Graff DW, *et al.* Effect of fluoxetine on carvedilol pharmacokinetics, CYP2D6 activity, and autonomic balance in heart failure patients. *J Clin Pharmacol* 2001; 41: 97–106.
4. Goryachkina K, *et al.* Inhibition of metoprolol metabolism and potentiation of its effects by paroxetine in routinely treated patients with acute myocardial infarction (AMI). *Eur J Clin Pharmacol* 2008; 64: 275–82.
5. Onalan O, *et al.* Complete atrioventricular block associated with concomitant use of metoprolol and paroxetine. *Mayo Clin Proc* 2008; 83: 595–9.

Antihypertensives. An enhanced antihypertensive effect is seen when other antihypertensives are given with beta blockers. However, some combinations should be avoided (see Calcium-channel Blockers, below). Beta blockers can potentiate the severe orthostatic hypotension that may follow the initial dose of alpha blockers such as prazosin and can exacerbate rebound hypertension after withdrawal of clonidine treatment (see Precautions, p. 1341.3).

Antimalarials. Antimalarials such as *halofantrine*, *mefloquine*, and *quinine* can cause cardiac conduction defects and caution is necessary if they are used with beta blockers. Cardiopulmonary arrest has occurred after a single dose of mefloquine in a patient taking propranolol.[1]

1. Anonymous. Mefloquine for malaria. *Med Lett Drugs Ther* 1990; 32: 13–14.

Antimigraine drugs. For the effect of propranolol on *rizatriptan*, see p. 679.2.

See also under Ergotamine Tartrate, p. 675.3, for further interactions with drugs used in the treatment of migraine.

Antineoplastics. Licensed product information for *gefitinib* states that it has been reported to increase exposure to metoprolol by about 30%.

Anxiolytics and antipsychotics. Plasma concentrations of some beta blockers may be reduced by *barbiturates*.[1-3] Increased plasma-propranolol concentrations and bioavailability, and reduced metabolism, have been reported in healthy subjects also given *chlorpromazine*.[4]

See p. 1069.2 for the effect of beta blockers on the pharmacokinetics of some *benzodiazepines*.

1. Sotaniemi EA, *et al.* Plasma clearance of propranolol and sotalol and hepatic drug-metabolizing enzyme activity. *Clin Pharmacol Ther* 1979; 26: 153–61.
2. Haglund K, *et al.* Influence of pentobarbital on metoprolol plasma levels. *Clin Pharmacol Ther* 1979; 26: 326–9.
3. Seideman P, *et al.* Decreased plasma concentrations and clinical effects of alprenolol during combined treatment with pentobarbitone in hypertension. *Br J Clin Pharmacol* 1987; 23: 267–71.
4. Vestal RE, *et al.* Inhibition of propranolol metabolism by chlorpromazine. *Clin Pharmacol Ther* 1979; 25: 19–24.

Calcium-channel blockers. Use of calcium-channel blockers with beta blockers has resulted in hypotension, bradycardia, conduction defects, and heart failure.[1]

Beta blockers should be avoided if possible with rate-limiting calcium-channel blockers such as *verapamil* (see p. 1525.2) and *diltiazem*. Although they are reportedly safe with dihydropyridines such as *nifedipine*,[2] heart failure and severe hypotension have been reported (see under Nifedipine, p. 1453.3). Reported pharmacokinetic interactions include increased plasma concentrations of propranolol and of metoprolol with concurrent use of diltiazem[3] or verapamil,[1] and increased plasma concentrations of propranolol with *nicardipine*.[4]

1. Lam YWF, Shepherd AMM. Drug interactions in hypertensive patients: pharmacokinetic, pharmacodynamic and genetic considerations. *Clin Pharmacokinet* 1990; 18: 295–317.
2. Reid JL. First-line and combination treatment for hypertension. *Am J Med* 1989; 86 (suppl 4A): 2–5.
3. Tateishi T, *et al.* Effect of diltiazem on the pharmacokinetics of propranolol, metoprolol and atenolol. *Eur J Clin Pharmacol* 1989; 36: 67–70.
4. Schoors DF, *et al.* Influence of nicardipine on the pharmacokinetics and pharmacodynamics of propranolol in healthy volunteers. *Br J Clin Pharmacol* 1990; 29: 497–501.

Cardiac glycosides. For reference to interactions between beta blockers and *digoxin*, see p. 1357.2.

Ciclosporin. For the effect of carvedilol on plasma-ciclosporin concentrations, see p. 1957.3.

Ergot derivatives. *Nicergoline* enhanced the cardiac depressant action of propranolol in healthy subjects.[1]

For reports of enhanced vasoconstrictor action in patients taking *ergot alkaloids* and beta blockers, see p. 675.3.

1. Boismare F, *et al.* Potentiation by an alpha-adrenolytic agent, nicergoline, of the cardiac effects of propranolol. *Methods Find Exp Clin Pharmacol* 1983; 5: 83–8.

Food. Studies in healthy subjects found that *grapefruit juice* greatly reduced the plasma concentration of celiprolol[1] and talinolol,[2] but had much less effect on acebutolol.[3] An effect on gastrointestinal absorption was suggested as the mechanism.[1,2] Studies with *orange juice* have found a similar effect on celiprolol[4] and, to a lesser extent, atenolol.[5]

1. Lilja JJ, *et al.* Itraconazole increases but grapefruit juice greatly decreases plasma concentrations of celiprolol. *Clin Pharmacol Ther* 2003; 73: 192–8.
2. Schwarz UI, *et al.* Grapefruit juice ingestion significantly reduces talinolol bioavailability. *Clin Pharmacol Ther* 2005; 77: 291–301.
3. Lilja JJ, *et al.* Effects of grapefruit juice on the pharmacokinetics of acebutolol. *Br J Clin Pharmacol* 2005; 60: 659–63.
4. Lilja JJ, *et al.* Orange juice substantially reduces the bioavailability of the beta-adrenergic-blocking agent celiprolol. *Clin Pharmacol Ther* 2004; 75: 184–90.
5. Lilja JJ, *et al.* Effects of orange juice on the pharmacokinetics of atenolol. *Eur J Clin Pharmacol* 2005; 61 337–40.

General anaesthetics. Beta blockers are usually continued perioperatively although the anaesthetist must be informed of their use (see Precautions, p. 1320.3). However, the hypotensive effects of beta blockers may be potentiated by general anaesthetics, and anaesthetics that cause myocardial depression, such as *ether*, *cyclopropane*, and *trichloroethylene* should preferably be avoided.

Histamine. For the effect of beta blockers, including propranolol, on histamine given exogenously, see p. 2525.3.

Histamine H_2-antagonists. Plasma concentrations of propranolol and metoprolol may be increased by *cimetidine*;[1] pharmacokinetic studies indicate that cimetidine exerts its effect by reducing hepatic blood flow and impairing beta blocker metabolism. Cimetidine has been reported to increase the bioavailability of labetalol,[1] and to increase the systemic effects of timolol eye drops.[2]

1. Smith SR, Kendall MJ. Ranitidine versus cimetidine: a comparison of their potential to cause clinically important drug interactions. *Clin Pharmacokinet* 1988; 15: 44–56.
2. Ishii Y, *et al.* Drug interaction between cimetidine and timolol ophthalmic solution: effect on heart rate and intraocular pressure in healthy Japanese volunteers. *J Clin Pharmacol* 2000; 40: 193–9.

Local anaesthetics. For details of the effect of beta blockers in reducing the clearance of *bupivacaine*, see p. 1986.1, and of *lidocaine*, see p. 1995.1. For the effects of propranolol with *cocaine*, see p. 1990.3.

Neuromuscular blockers. For the effects of beta blockers on the activity of neuromuscular blockers, see under Atracurium, p. 2032.2.

NSAIDs. The antihypertensive effect of beta blockers may be impaired by some NSAIDs, possibly due to their inhibition of renal synthesis of vasodilating prostaglandins. This interaction probably occurs with all beta blockers but may not occur with all NSAIDs. For example, *sulindac* appears to affect blood pressure control less than *indometacin*.[1]

A randomised study[2] in 12 healthy subjects found that *celecoxib* significantly inhibited the metabolism of metoprolol by the cytochrome P450 isoenzyme CYP2D6.

1. Lam YWF, Shepherd AMM. Drug interactions in hypertensive patients: pharmacokinetic, pharmacodynamic and genetic considerations. *Clin Pharmacokinet* 1990; 18: 295–317.
2. Werner U, *et al.* Celecoxib inhibits metabolism of cytochrome P450 2D6 substrate metoprolol in humans. *Clin Pharmacol Ther* 2003; 74: 130–7.

Opioid analgesics. Bioavailability of propranolol and metoprolol was increased in subjects given *dextropropoxyphene*;[1] dextropropoxyphene is an inhibitor of the cytochrome P450 isoenzyme CYP2D6 and was reported[2] to increase serum concentrations of metoprolol, a CYP2D6 substrate, in a patient given both drugs, resulting in bradycardia. Intravenous *morphine* may increase serum concentrations of esmolol.[3]

1. Lundborg P, *et al.* The effect of propoxyphene pretreatment on the disposition of metoprolol and propranolol. *Clin Pharmacol Ther* 1981; 29: 263–4.
2. Marraffa JM, *et al.* Profound metoprolol-induced bradycardia precipitated by acetaminophen-propoxyphene. *Clin Pharmacol Ther* 2006; 79: 282–6.
3. Lowenthal DT, *et al.* Clinical pharmacology, pharmacodynamics and interactions with esmolol. *Am J Cardiol* 1985; 56: 14F–17F.

Oral contraceptives. Plasma-metoprolol concentrations were increased in some women taking oral contraceptives.[1]

1. Kendall MJ, *et al.* Metoprolol pharmacokinetics and the oral contraceptive pill. *Br J Clin Pharmacol* 1982; 14: 120–2.

Parasympathomimetics. For the effect of beta blockers on the response to *anticholinesterases*, see p. 689.1.

Thyroid drugs. For a discussion of thyroid status and its effect on plasma-propranolol concentrations and the effects of propranolol on *thyroid hormone* metabolism, see p. 2341.3.

Xanthines. For details of reduced *theophylline* clearance in patients receiving some beta blockers, see p. 1235.2.

Pharmacokinetics

Beta blockers differ widely in their pharmacokinetic properties. Differences in lipid solubility contribute to these varying pharmacokinetic properties.

Beta blockers with high lipid solubility (lipophilic beta blockers) include alprenolol and propranolol.

Hydrophilic beta blockers, such as atenolol and nadolol, have low lipid solubility and when compared with lipophilic beta blockers generally:

- tend to be less readily absorbed from the gastrointestinal tract
- are less extensively metabolised
- have low plasma-protein binding
- have relatively long plasma half-lives
- cross the blood-brain barrier less readily

Beta blockers cross the placenta and most are known to distribute into breast milk.

There is no clear correlation between plasma concentrations of beta blockers and therapeutic activity, especially when the beta blocker undergoes metabolism to active metabolites.

Betaxolol Hydrochloride

(BANM, USAN, rINNM) ⊗

ALO-1401-02; Betaksolol Hidroklorür; Betaksololihydrokloridi; Betaksololio hidrochloridas; Bétaxolol, Chlorhydrate de; Betaxolol, hidrocloruro de; Betaxolol-hidroklorid; Betaxolol-hydrochlorid; Betaxolol-hydrochlorid; Betaxololhydroklorid; Betaxolol hydrochloridum; Hidrocloruro de betaxolol; SL-75212-10; Бетаксолола Гидрохлорид.

1-[4-[2-(Cyclopropylmethoxy)ethyl]phenoxy]-3-isopropylaminopropan-2-ol hydrochloride.

$C_{18}H_{29}NO_3$,HCl=343.9

CAS — 63659-18-7 (betaxolol); 63659-19-8 (betaxolol hydrochloride).

ATC — C07AB05; S01ED02.

ATC Vet — QC07AB05; QS01ED02.

UNII — 6X97D2XT0O.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Betaxolol Hydrochloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol; soluble in dichloromethane. Protect from light.

USP 36: (Betaxolol Hydrochloride). A white crystalline powder. Freely soluble in water, in alcohol, in chloroform, and in methyl alcohol. pH of a 2% solution in water is between 4.5 and 6.5. Store in airtight containers.

Uses and Administration

Betaxolol is a cardioselective beta blocker (p. 1316.3). It is reported to lack intrinsic sympathomimetic activity and to have little membrane-stabilising activity.

Betaxolol is used as the hydrochloride in the management of hypertension (p. 1251.1), angina pectoris (p. 1254.3), and glaucoma (p. 1999.1).

In **hypertension** betaxolol hydrochloride is given in an initial oral dose of 10 mg once daily, which may be doubled if necessary after 1 to 2 weeks. Doses above 20 mg daily do not usually give additional benefit, but up to 40 mg daily has been tolerated. Similar doses are used in **angina pectoris.**

An initial dose of 5 mg daily is suggested for elderly patients. Reduced dosages should also be used in patients with severe renal impairment (see below).

Eye drops containing the equivalent of 0.25 or 0.5% betaxolol as the hydrochloride are instilled twice daily to reduce raised intra-ocular pressure in ocular hypertension and open-angle **glaucoma.**

General references.

1. Buckley MM-T, *et al.* Ocular betaxolol: a review of its pharmacological properties, and therapeutic efficacy in glaucoma and ocular hypertension. *Drugs* 1990; 40: 75–90.

Administration in children. Betaxolol hydrochloride eye drops can be used in children for the treatment of glaucoma; the *BNFC* suggests that drops can be applied in children as in adults (see Uses and Administration, above).

Administration in renal impairment. The clearance of betaxolol is reduced in patients with renal impairment and the dose may therefore need to be reduced. Licensed US product information recommends an initial dose of betaxolol hydrochloride 5 mg daily in patients with severe

renal impairment or on dialysis; the dose may be increased by 5 mg every 2 weeks, to a maximum of 20 mg daily.

Speech disorders. A 50-year-old man who had stuttered since childhood obtained striking improvement in his stuttering when he was given betaxolol 20 mg daily for essential hypertension.[1]

1. Burris JF, *et al.* Betaxolol and stuttering. *Lancet* 1990; 335: 223.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies betaxolol as possibly porphyrinogenic when used systematically; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients. Eye drops of betaxolol are classified as not porphyrinogenic.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Betaxolol is completely absorbed from the gastrointestinal tract and undergoes only minimal first-pass metabolism, resulting in a high oral bioavailability of about 90%. It has high lipid solubility. Betaxolol is about 50% bound to plasma proteins. It crosses the placenta and is distributed into breast milk where higher concentrations have been achieved than in maternal blood. The plasma elimination half-life of betaxolol ranges from 14 to 22 hours. The primary route of elimination is via hepatic metabolism and urinary excretion; only about 15% is excreted in the urine as unchanged drug.

Pregnancy and breast feeding. The pharmacokinetics of betaxolol were investigated in the perinatal period in 28 pregnant hypertensive patients receiving doses of 10 to 40 mg daily.[1] Pharmacokinetic values were similar to those seen in non-pregnant patients. Umbilical-cord concentrations were similar to maternal blood concentrations and showed a negative correlation between concentration in cord blood and timing of the last dose of betaxolol. Thus the betaxolol concentration in neonates can be considerably reduced by stopping maternal drug use 16 to 18 hours before birth. The blood-betaxolol half-life in the neonates ranged from 14.8 to 38.5 hours. The mean apparent half-life in infants with gestational age less than 36 weeks was about 32% higher than in full-term neonates. Betaxolol concentrations in milk and/or colostrum were determined in 3 mothers. In all samples the milk-to-blood ratio was greater than 2.

1. Morsell PL, *et al.* Placental transfer and perinatal pharmacokinetics of betaxolol. *Eur J Clin Pharmacol* 1990; 38: 477–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Betasel; Tonobexol; *Austral.*: Betoptic; Betoquin; *Austria*: Betoptic; *Belg.*: Betoptic; Kerlone; *Braz.*: Betoptic; Presmin; Visoptic; *Canad.*: Betoptic; *Chile*: Bemaz†; Beof; Betoptic; BTX Ofteno; *China*: Betoptic (贝特舒); Kerlone (卡尔仑); *Cz.*: Betalmic; Betamed; Betaxa; Betoptic; Lokren; *Denm.*: Betoptic; *Fin.*: Betoptic; Kerlon; *Fr.*: Betoptic; Kerlone; *Ger.*: Betoptima; Kerlone; *Gr.*: Armament; Betoptic; Eifel; Kerlone; Pertaxol; *Hong Kong*: Betoptic; *Hung.*: Betoptic; Lokren; *India*: Bulol; Glucoptic; Iobet; Ocubeta; Optipres; *Indon.*: Betoptima; Optibet; *Irl.*: Betoptic; *Israel*: Betoptic; *Ital.*: Betoptic; Kerlon; *Jpn*: Kerlong; *Malaysia*: Axoptic; Betac; Betoptic; Kerlone; *Mex.*: Betoptic; BTX-HA Ofteno; *Neth.*: Betoptic; Kerlon; *Norw.*: Betoptic; *NZ*: Betoptic; *Philipp.*: Betoptic; Kerlone; Oxol; *Pol.*: Betabion†; Betoptic; Lokren; Optibetol; *Port.*: Bertocil; Betoptic; Davixolol†; *Rus.*: Betac (Betak); Betalmic (Беталмик); Betoftan (Бетофтан); Betoptic (Бетоптик); Lokren (Локрен); Xonef (Ксонеф); *S.Afr.*: Betoptic; *Singapore*: Acculol; Betac; Betoptic; Kerlone; *Spain*: Betoptic; *Swed.*: Betoptic; *Switz.*: Betoptic; *Thal.*: Betoptic; *Turk.*: Betoptic; Eifel; *UK*: Betoptic; *Ukr.*: Betacor (Бетакор); Betoptic (Бетоптик S); Lokren (Локрен); *USA*: Betoptic; Kerlone†; *Venez.*: Betaxol; Betoptic.

Pharmacopoeial Preparations

BP 2014: Betaxolol Eye Drops, Solution; Betaxolol Eye Drops, Suspension;

USP 36: Betaxolol Ophthalmic Solution; Betaxolol Tablets.

Bevantolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Bévantolol, Chlorhydrate de; Bevantolol, hidrocloruro de; Bevantololhydrokloridi; Bevantololi Hydrochloridum; Bevantololhydrokloridi; CI-775; Hidrocloruro de bevantolol; NC-1400; Бевантолола Гидрохлорид.

1-(3,4-Dimethoxyphenethylamino)-3-*m*-tolyloxypropan-2-ol hydrochloride.

$C_{20}H_{27}NO_4HCl$=381.9

CAS — 59170-23-9 (bevantolol); 42864-78-8 (bevantolol hydrochloride).

ATC — C07AB06.

ATC Vet — QC07AB06.

UNII — 4VB9HU078C.

Profile

Bevantolol is a cardioselective beta blocker (p. 1316.3). It is reported to lack significant intrinsic sympathomimetic activity but has weak membrane-stabilising properties and also has vasodilator activity. It has been given orally as the hydrochloride in the management of hypertension and angina pectoris.

References.

1. Frishman WH, *et al.* Bevantolol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in hypertension and angina pectoris. *Drugs* 1988; 35: 1–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Calvan (卡理稳); *Jpn*: Calvan.

Bezafibrate *(BAN, USAN, rINN)*

Betsafibraatti; Bezafibrat; Bezafibrát; Bezafibratas; Bézafibrate; Bezafibrato; Bezafibratum; BM-15075; LO-44; Безафибрат.

2-[4-(2-*p*-Chlorobenzamidoethyl)phenoxy]-2-methylpropionic acid.

$C_{19}H_{20}ClNO_4$=361.8

CAS — 41859-67-0.

ATC — C10AB02.

ATC Vet — QC10AB02.

UNII — Y9449Q51XH.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Bezafibrate). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol and in acetone; freely soluble in dimethylformamide; it dissolves in dilute solutions of alkali hydroxides.

Uses and Administration

Bezafibrate, a fibric acid derivative, is a lipid regulating drug. It is used to reduce total cholesterol and triglycerides in the management of hyperlipidaemias (p. 1248.1), including type IIa, type IIb, type III, type IV, and type V hyperlipoproteinaemias. Bezafibrate and other fibrates reduce triglycerides by reducing the concentration of very-low-density lipoprotein (VLDL). They reduce low-density lipoprotein (LDL)-cholesterol to a lesser extent, although the effect is variable, and may also increase high-density lipoprotein (HDL)-cholesterol. Although evidence that this leads to a reduction in cardiovascular events is less good than for statins, some fibrates may have a role in cardiovascular risk reduction (see below).

Bezafibrate is given in a usual oral dose of 200 mg three times daily taken with or after food; gastrointestinal disturbances may be reduced in susceptible patients by increasing the dose gradually over 5 to 7 days; 200 mg twice daily may occasionally be adequate for maintenance particularly in the treatment of hypertriglyceridaemia. A modified-release tablet is also available and is given as a single daily dose of 400 mg.

The dose of bezafibrate should be reduced in patients with renal impairment (see below). See also below for doses in children.

General reviews.

1. Goa KL, *et al.* Bezafibrate: an update of its pharmacology and use in the management of dyslipidaemia. *Drugs* 1996; 52: 725–53.
2. Goldenberg I, *et al.* Update on the use of fibrates: focus on bezafibrate. *Vasc Health Risk Manag* 2008; 4: 131–41.

Action. Bezafibrate is a typical member of the fibric acid derivative group of drugs (the fibrates) used in the treatment of hyperlipidaemias (p. 1248.1). One of the primary actions of the fibrates is to promote the catabolism of triglyceride-rich lipoproteins, in particular very-low-density lipoproteins (VLDL), apparently mediated by an enhanced activity of lipoprotein lipase.[1] They may also interfere with the synthesis of VLDL, possibly by inhibiting hepatic acetyl coenzyme A carboxylase. The effect of fibrates on low-density lipoprotein (LDL)-cholesterol depends on the overall lipoprotein status of the patient but concentrations tend to decrease if high at baseline and increase if low at baseline. High-density lipoprotein (HDL)-cholesterol concentrations are increased, although there have been a few reports of unexpected falls in HDL-cholesterol with bezafibrate[2,3] and ciprofibrate.[4,5]

Fibrates have three actions on sterol metabolism:[1] they inhibit the synthesis of cholesterol, they inhibit the synthesis of bile acids, and they enhance the secretion of cholesterol in bile. It is these latter two effects which are responsible for the raised cholesterol saturation of bile, which may lead to the formation of gallstones in some patients (see Gallstones, under Adverse Effects, p. 1325.1).

The effects of fibrates are mediated by their agonist action at peroxisome proliferator-activated receptors (PPARs).[6,7] Fibrates are agonists of PPAR-α, which plays an important role in fatty acid metabolism; some, such as bezafibrate, may also activate other receptors including PPAR-γ (which plays a role in glucose homoeostasis).[7]

1. Grundy SM, Vega GL. Fibric acids: effects on lipids and lipoprotein metabolism. *Am J Med* 1987; 83 (suppl 5B): 9–20.
2. Capps NE. Lipid profiles on fibric-acid derivatives. *Lancet* 1994; 344: 684–5.
3. McLeod AJ, *et al.* Abnormal lipid profiles on fibrate derivatives. *Lancet* 1996; 347: 261.
4. Chandler HA, Batchelor AJ. Ciprofibrate and lipid profile. *Lancet* 1994; 344: 128–9.
5. McLeod AJ, *et al.* Ciprofibrate and lipid profile. *Lancet* 1994; 344: 955.
6. Pruchart J-C, Duriez P. Mode of action of fibrates in the regulation of triglyceride and HDL-cholesterol metabolism. *Drugs Today* 2006; 42: 39–64.
7. Robinson JG. Should we use PPAR agonists to reduce cardiovascular risk? *PPAR Res* 2008; 2008: 891425.

Administration in children. Bezafibrate is not licensed in the UK for use in children, and the *BNFC* considers that, given the limited evidence supporting its use in children, bezafibrate should be used only when a statin or bile-acid binding drug is unsuitable. For the treatment of hyperlipidaemias including familial hypercholesterolaemia, it suggests that children aged 10 years or over may be given bezafibrate in an oral dose of 200 mg once daily, adjusted according to response, to a maximum of 200 mg three times daily.

Administration in renal impairment. Bezafibrate is mainly excreted in the urine and dosage alterations may be necessary in patients with renal impairment; fibrates may also impair renal function (see Effects on the Kidneys under Adverse Effects, p. 1324.3). Modified-release preparations are contra-indicated in patients with creatinine clearance (CC) below 60 mL/minute and the dosage of conventional-release formulations should be reduced depending on CC, as follows:

- CC 40 to 60 mL/minute: 400 mg daily
- CC 15 to 40 mL/minute: 200 mg daily or on alternate days
- CC less than 15 mL/minute unless on dialysis: contra-indicated
- dialysis patients: 200 mg every 3 days, with careful monitoring

In a study in patients with renal impairment[1] the half-life of bezafibrate was reported to be prolonged to 4.6 hours in 3 patients with CC greater than 40 mL/minute, 7.8 hours in 8 patients with CC of 20 to 40 mL/minute, and 20.1 hours in a patient with CC of 13 mL/minute.

1. Anderson P, Norbeck H-E. Clinical pharmacokinetics of bezafibrate in patients with impaired renal function. *Eur J Clin Pharmacol* 1981; 21: 209–14.

Biliary-tract disorders. Bezafibrate may be able to prevent damage to the biliary tract[1] (perhaps by modulating phospholipid secretion via an action at the peroxisome proliferator-activated receptor-α (PPAR-α)). It has been used[2,3] with ursodeoxycholic acid in the treatment of primary biliary cirrhosis (p. 2638.3); fenofibrate has been tried similarly.[4] Bezafibrate has also been tried in primary sclerosing cholangitis.[5]

1. Nakamuta M, *et al.* Therapeutic effect of bezafibrate against biliary damage: a study of phospholipid secretion via the PPAR α -MDR3 pathway. *Int J Clin Pharmacol Ther* 2010; 48: 22–8.
2. Iwasaki S, *et al.* Study Group of Intractable Liver Diseases for Research on a Specific Disease, Health Science Research Grant, Ministry of Health, Labour and Welfare of Japan. The efficacy of ursodeoxycholic acid and bezafibrate combination therapy for primary biliary cirrhosis: a prospective, multicenter study. *Hepatol Res* 2008; 38: 557–64.
3. Bazzan R, Tur-Kaspa R. Bezafibrate treatment of primary biliary cirrhosis following incomplete response to ursodeoxycholic acid. *J Clin Gastroenterol* 2010; 44: 371–3.
4. Liberopoulos EN, *et al.* Fenofibrate in primary biliary cirrhosis: a pilot study. *Open Cardiovasc Med J* 2010; 4: 120–6.
5. Mizuno S, *et al.* Bezafibrate for the treatment of primary sclerosing cholangitis. *J Gastroenterol* 2010; 45: 758–62.

Cardiovascular risk reduction. Lipid lowering therapy has an important role in patients at risk of cardiovascular disease (p. 1246.1). Although the evidence is less good than for statins, several studies have shown that fibrates may

reduce both the progression of atherosclerosis and the incidence of cardiovascular events.[1]

In the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT)[2,3] treatment with bezafibrate for 5 years in young men (less than 45 years of age) after myocardial infarction resulted in fewer coronary events and slowed the progression of focal coronary atherosclerosis when compared with placebo. However, in older men with peripheral vascular disease,[4] bezafibrate had no effect on the incidence of coronary events and stroke together, although the severity of intermittent claudication was reduced and, in men under 65 years, there were fewer non-fatal coronary events. In the Diabetes Atherosclerosis Intervention Study (DAIS),[5] fenofibrate reduced the angiographic progression of coronary atherosclerosis in type 2 diabetics, and there were also fewer clinical events in those receiving fenofibrate. However, another study in type 2 diabetics, the FIELD study,[6] found no reduction in the risk of major coronary events with fenofibrate, although there were fewer non-fatal myocardial infarctions and revascularisations. A meta-analysis[7] of studies including type 2 diabetics concluded that fibrates reduce the incidence of cardiovascular events, but the effect on mortality was not significant.

The best evidence for a reduction in cardiovascular events is for gemfibrozil. The Helsinki Heart Study[8] assessed gemfibrozil for the primary prevention of ischaemic heart disease in 4081 middle-aged men with hyperlipidaemia. There was an overall reduction of 34% in the incidence of fatal and non-fatal myocardial infarctions and cardiac deaths in the gemfibrozil group compared with the placebo group, with the greatest reduction seen during years 3 to 5. Follow-up for a further 3.5 years[9] suggested that long-term treatment with gemfibrozil seemed to postpone coronary events for about 5 years. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)[10] assessed gemfibrozil for the secondary prevention of ischaemic heart disease in 2531 older men (mean age 64 years) whose primary lipid abnormality was a low HDL-cholesterol level. There was an overall reduction of 22% in the incidence of fatal and non-fatal myocardial infarctions and cardiac deaths in the gemfibrozil group compared with the placebo group, with the beneficial effects of gemfibrozil becoming apparent about 2 years after randomisation. There was also a reduction in the incidence of stroke.[11]

1. Després J-P, *et al.* Role of fibric acid derivatives in the management of risk factors for coronary heart disease. *Drugs* 2004; 64: 2177–98.
2. Ericsson C-G, *et al.* Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male postinfarction patients. *Lancet* 1996; 347: 849–53.
3. Ericsson C-G, *et al.* Effect of bezafibrate treatment over five years on coronary plaques causing 20% to 50% diameter narrowing (The Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT)). *Am J Cardiol* 1997; 80: 1125–9.
4. Meade T, *et al.* Bezafibrate in men with lower extremity arterial disease: randomised controlled trial. *BMJ* 2002; 325: 1139–43.
5. Diabetes Atherosclerosis Intervention Study Investigators. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet* 2001; 357: 905–910. Correction. *ibid.*: 1890.
6. The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; 366: 1849–61. Corrections. *ibid.* 2006; 368: 1415 and 1420.
7. Allemann S, *et al.* Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus: meta-analysis of randomised controlled trials. *Curr Med Res Opin* 2006; 22: 617–23.
8. Frick MH, *et al.* Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; 317: 1237–45.
9. Heinonen OP, *et al.* The Helsinki Heart Study: coronary heart disease incidence during an extended follow-up. *J Intern Med* 1994; 235: 41–9.
10. Bloomfield Rubins H, *et al.* Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 1999; 341: 410–18.
11. Bloomfield Rubins H, *et al.* Reduction in stroke with gemfibrozil in men with coronary heart disease and low HDL cholesterol: The Veterans Affairs HDL Intervention Trial (VA-HIT). *Circulation* 2001; 103: 2828–33.

Dementia. For reference to a possible reduction in the incidence of dementia associated with lipid regulating drugs, including fibrates, see under Uses of Simvastatin, p. 1491.2.

Diabetic complications. In diabetic patients, fibrates may have a role in cardiovascular risk reduction (see p. 1323.3) and there has been interest in their possible effects on microvascular diabetic complications (p. 462.2). The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, designed to assess the effects of fenofibrate on cardiovascular outcomes in type 2 diabetics, included microvascular complications as tertiary outcomes; patients were given fenofibrate or placebo for about 5 years. There was evidence for a reduction in the onset of markers of nephropathy (p. 465.1) such as microalbuminuria or progression to macroalbuminuria, and more regression of albuminuria, in patients given fenofibrate.[1,2] The Diabetes Atherosclerosis Intervention Study (DAIS) also showed reduced progression to microalbuminuria in patients given fenofibrate.[3] Additionally from the FIELD study, the need for first laser treatment of retinopathy (p. 464.2) was reduced in the fenofibrate group.[4] Fenofibrate was also associated with a reduction in the risk of first minor amputation in patients without documented large vessel (atherosclerotic) disease, but for those with large vessel disease the risk of either minor or major amputation was not affected.[5] These effects on microvascular complications in the FIELD study did not seem to be related to plasma-lipid concentrations. Results of a retrospective cohort study in patients treated with bezafibrate compared with patients given other fibrates have also suggested that bezafibrate might have some benefit in preventing or delaying progression of diabetes mellitus itself.[6]

1. The FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; 366: 1849–61. Corrections. *ibid.* 2006; 368: 1415 and 1420.
2. Davis TM, *et al.* Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. *Diabetologia* 2011; 54: 280–90.
3. Ansquer J-C, *et al.* Fenofibrate reduces progression to microalbuminuria over 3 years in a placebo-controlled study in type 2 diabetes: results from the Diabetes Atherosclerosis Intervention Study (DAIS). *Am J Kidney Dis* 2005; 45: 485–93.
4. Keech AC, *et al.* The FIELD Study Investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 2007; 370: 1687–97.
5. Rajamani K, *et al.* The FIELD Study Investigators. Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomised controlled trial. *Lancet* 2009; 373: 1780–8.
6. Flory JH, *et al.* Antidiabetic action of bezafibrate in a large observational database. *Diabetes Care* 2009; 32: 547–51.

Adverse Effects and Precautions

The commonest adverse effects of bezafibrate therapy are gastrointestinal disturbances including anorexia, nausea, and gastric discomfort. Other adverse effects reported to occur less frequently include headache, dizziness, vertigo, fatigue, skin rashes, pruritus, photosensitivity, alopecia, impotence, anaemia, leucopenia, and thrombocytopenia. Raised serum-aminotransferase concentrations have occasionally been reported. Elevated creatine phosphokinase concentrations during bezafibrate therapy may be associated with a syndrome of myositis, myopathy, and rarely rhabdomyolysis; patients with hypoalbuminaemia resulting from nephrotic syndrome or with renal impairment may be at increased risk. Bezafibrate should not be given with statins in patients with risk factors for myopathy. Bezafibrate may increase the lithogenic index, and there have been isolated reports of gallstones, although the risk from fibrates as a class is unclear (see Gallstones, p. 1325.1).

Bezafibrate should not be given to patients with severe hepatic impairment or significant liver disease, gallstones or gallbladder disorders, or hypoalbuminaemic states such as nephrotic syndrome. It should be used with caution in renal impairment and is contra-indicated if creatinine clearance is below 15 mL/minute unless the patient is on dialysis (see under Uses and Administration, p. 1323.3).

Reviews.

1. Davidson MH, *et al.* Safety considerations with fibrate therapy. *Am J Cardiol* 2007; 99(Issue 6 suppl 1): 3C–18C.
2. Florentin M, *et al.* Fibrate-associated adverse effects beyond muscle and liver toxicity. *Curr Pharm Des* 2008; 14: 574–87.

Effects on glucose metabolism. Use of fibrates in diabetic patients has generally been reported to either improve[1-3] or have no effect[4-6] on insulin sensitivity and glucose metabolism, and they are considered a suitable treatment for type 2 diabetics with hypertriglyceridaemia.[7] There is also some evidence that fibrates may reduce the incidence or delay the onset of diabetes in patients with obesity[8] or impaired glucose tolerance.[9] However, there has been a report[10] of recurrent hypoglycaemia in a type 2 diabetic when gemfibrozil was added to high-dose insulin therapy although eventually a reduced insulin dosage, with fibrate therapy, produced good glucose control. Gemfibrozil is contra-indicated in patients receiving repaglinide due to the risk of severe hypoglycaemia (see p. 496.1). Conversely, a study in 20 diabetic patients[11] given gemfibrozil reported a slight increase in requirements for antidiabetic therapy (oral hypoglycaemics or insulin) in 9 and a decrease in 1.

1. Ogawa S, *et al.* Bezafibrate reduces blood glucose in type 2 diabetes mellitus. *Metabolism* 2000; 49: 331–4.
2. Jones IR, *et al.* Lowering of plasma glucose concentrations with bezafibrate in patients with moderately controlled NIDDM. *Diabetes Care* 1990; 13: 855–63.
3. Notarbartolo A, *et al.* Effects of gemfibrozil in hyperlipidemic patients with or without diabetes. *Curr Ther Res* 1993; 53: 381–93.
4. Leaf DA, *et al.* The hypolipidemic effects of gemfibrozil in type V hyperlipidemia. *JAMA* 1989; 262: 3154–60.
5. Pagani A, *et al.* Effect of short-term gemfibrozil administration on glucose metabolism and insulin secretion in non-insulin-dependent diabetics. *Curr Ther Res* 1989; 45: 14–20.
6. Hernández-Mijares A, *et al.* Ciprofibrate effects on carbohydrate and lipid metabolism in type 2 diabetes mellitus subjects. *Nutr Metab Cardiovasc Dis* 2000; 10: 1–6.
7. Buse JB, *et al.* Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation* 2007; 115: 114–26. Also available at: http://circ.ahajournals.org/cgi/reprint/115/1/114.pdf (accessed 28/08/09) Also published in *Diabetes Care* 2007; 30: 162–72. Also available at: http://care.diabetesjournals.org/content/30/1/162.full.pdf (accessed 28/08/09)
8. Tenenbaum A, *et al.* Effect of bezafibrate on incidence of type 2 diabetes mellitus in obese patients. *Eur Heart J* 2005; 26: 2032–8.
9. Tenenbaum A, *et al.* Peroxisome proliferator-activated receptor ligand bezafibrate for prevention of type 2 diabetes mellitus in patients with coronary artery disease. *Circulation* 2004; 109: 2197–2202.
10. Klein J, *et al.* Recurrent hypoglycaemic episodes in a patient with type 2 diabetes under fibrate therapy. *J Diabetes Complications* 2002; 16: 246–8.
11. Konttinen A, *et al.* The effect of gemfibrozil on serum lipids in diabetic patients. *Ann Clin Res* 1979; 11: 240–5.

Effects on the kidneys. Small increases in creatinine concentration are common during treatment with bezafibrate and have also been reported with other fibrates,[1,2] although possibly not with gemfibrozil. Such increases, which are not necessarily associated with changes in renal function, are reversible on stopping the drug, although serum-creatinine values may take several weeks to return to baseline.[2] There have also been reports of acute renal failure associated with treatment with bezafibrate,[3] and with clofibrate,[4,5] and an accelerated decline in renal function has been reported with bezafibrate in patients with chronic renal failure.[6] Renal failure may also occur due to rhabdomyolysis in patients receiving fibrates, including gemfibrozil (see Effects on Skeletal Muscle, p. 1325.1).

1. Broeders N, *et al.* Fibrate-induced increase in blood urea and creatinine: is gemfibrozil the only innocuous agent? *Nephrol Dial Transplant* 2000; 15: 1993–9.
2. Sica DA. Fibrate therapy and renal function. *Curr Atheroscler Rep* 2009; 11: 338–42.
3. Lipkin GW, Tomson CRV. Severe reversible renal failure with bezafibrate. *Lancet* 1993; 341: 371.
4. Dosa S, *et al.* Acute-on-chronic renal failure precipitated by clofibrate. *Lancet* 1976; i: 250.
5. Cumming A. Acute renal failure and interstitial nephritis after clofibrate treatment. *BMJ* 1980; 281: 1529–30.
6. Williams AJ, *et al.* The short term effects of bezafibrate on the hypertriglyceridaemia of moderate to severe uraemia. *Br J Clin Pharmacol* 1984; 18: 361–7.

Effects on the nervous system. Adverse effects on the peripheral nervous system have been reported with fibrates. Peripheral neuropathy has been reported[1] with bezafibrate, and was substantiated by nerve conduction studies. There have also been reports of peripheral neuropathy with clofibrate,[2] and with fenofibrate,[3] which resolved when therapy was withdrawn. In addition, by 1993, the Adverse Drug Reactions Advisory Committee in Australia had received reports of paraesthesia occurring in 6 patients in association with gemfibrozil treatment.[4]

1. Ellis CJ, *et al.* Peripheral neuropathy with bezafibrate. *BMJ* 1994; 309: 929.
2. Gabriel R, Pearce JMS. Clofibrate-induced myopathy and neuropathy. *Lancet* 1976; ii: 906.
3. Corcia P, *et al.* Severe toxic neuropathy due to fibrates. *J Neurol Neurosurg Psychiatry* 1999; 66: 410.
4. Anonymous. Paraesthesia and neuropathy with hypolipidaemic agents. *Aust Adverse Drug React Bull* 1993; 12: 6.

Effects on the pancreas. Acute pancreatitis has been reported[1] in a patient receiving bezafibrate, and recurred on 2 occasions when bezafibrate was restarted. There has also been a report[2] of acute pancreatitis in a patient receiving both fenofibrate and simvastatin, although simvastatin was considered more likely to be responsible. An increased incidence of pancreatitis was also reported with fenofibrate in the FIELD study,[3] although the number of cases was small.

1. Gang N, *et al.* Relapsing acute pancreatitis induced by re-exposure to the cholesterol lowering agent bezafibrate. *Am J Gastroenterol* 1999; 94: 3626–8.
2. McDonald KB, *et al.* Pancreatitis associated with simvastatin plus fenofibrate. *Ann Pharmacother* 2002; 36: 275–9.
3. The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; 366: 1849–61. Corrections. *ibid.* 2006; 368: 1415 and 1420.

Effects on sexual function. Sexual dysfunction has occurred with some fibrates. *Erectile dysfunction* and *loss of libido* has been reported in 3 patients[1-3] during gemfibrozil treatment. In 2 of the men[1,2] bezafibrate did not produce this adverse effect. The UK CSM was reported to be aware of a further 6 cases.[2] Of a further 3 cases of erectile dysfunction associated with gemfibrozil reported from Spain, 1 patient had previously reacted similarly to clofibrate.[4] A systematic review,[5] including these and other reports, supported the conclusion that fibrates could cause erectile dysfunction.

Gynaecomastia was reported[6] in a 56-year-old man receiving fenofibrate and recurred on rechallenge; there were no other effects on sexual function.

1. Pizarro S, *et al.* Gemfibrozil-induced impotence. *Lancet* 1990; 336: 1135.
2. Bain SC, *et al.* Gemfibrozil-induced impotence. *Lancet* 1990; 336: 1389.
3. Bharani A. Sexual dysfunction after gemfibrozil. *BMJ* 1992; 305: 693.
4. Figueras A, *et al.* Gemfibrozil-induced impotence. *Ann Pharmacother* 1993; 27: 982.
5. Rizvi K, *et al.* Do lipid-lowering drugs cause erectile dysfunction? A systematic review. *Fam Pract* 2002; 19: 95–8.
6. Gardette V, *et al.* Gynecomastia associated with fenofibrate. *Ann Pharmacother* 2007; 41: 508–11.

Effects on skeletal muscle. Muscle disorders including myositis and myopathy are well known to occur with lipid regulating drugs such as fibrates.[1] Rhabdomyolysis, presenting as muscle pain with elevated creatine phosphokinase and myoglobinuria leading to renal failure, has also been reported but appears to be rare. Patients with renal impairment, and possibly with hypothyroidism, may be at increased risk of muscle toxicity. The UK CSM has advised[1] that patients treated with fibrates should consult their doctor if they develop muscle pain, tenderness, or weakness, and treatment should be stopped if muscle toxicity is suspected clinically or if creatine phosphokinase is markedly raised or progressively rising.

Other lipid regulating drugs, particularly the statins, have also been associated with myopathy and the risk of muscle toxicity is increased if fibrates and statins are taken together (see Lipid Regulating Drugs under Interactions of Simvastatin, p. 1495.3); combination therapy may be appropriate in some patients but careful monitoring is required.[2]

1. CSM/MCA. Rhabdomyolysis associated with lipid-lowering drugs. *Current Problems* 1995; 21: 3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015418&RevisionSelectionMethod=LatestReleased (accessed 30/05/08)
2. Shek A, Ferrill MJ. Statin-fibrate combination therapy. *Ann Pharmacother* 2001; 35: 908–917.

Gallstones. Fibrates, including fenofibrate[1-3] and gemfibrozil[4] have been reported to increase indices of bile lithogenicity, and some studies[5,6] have suggested an increased risk of gallstones in patients receiving fibrates. However, in the Helsinki Heart Study[7] no significant increase in gallstone operations was reported among 2051 patients taking gemfibrozil compared with 2030 taking placebo, although a follow-up study[8] reported that cholecystectomies were consistently more common in those receiving gemfibrozil during the entire 8.5-year observation period.

1. Brown WV. Treatment of hypercholesterolaemia with fenofibrate: a review. *Curr Med Res Opin* 1989; 11: 321–30.
2. Blane GF. Comparative toxicity and safety profile of fenofibrate and other fibric acid derivatives. *Am J Med* 1987; 83 (suppl 5B): 26–36.
3. Palmer RH. Effects of fibric acid derivatives on biliary lipid composition. *Am J Med* 1987; 83 (suppl 5B): 37–43.
4. Leiss O, *et al.* Effect of gemfibrozil on biliary lipid metabolism in normolipemic subjects. *Metabolism* 1985; 34: 74–82.
5. Mamdani MM, *et al.* Is there an association between lipid-lowering drugs and cholecystectomy? *Am J Med* 2000; 108: 418–21.
6. Caroli-Bosc F-X, *et al.* Role of fibrates and HMG-CoA reductase inhibitors in gallstone formation: epidemiological study in an unselected population. *Dig Dis Sci* 2001; 46: 540–4.
7. Frick MH, *et al.* Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; 317: 1237–45.
8. Huttunen JK, *et al.* The Helsinki Heart Study: an 8.5-year safety and mortality follow-up. *J Intern Med* 1994; 235: 31–9.

Headache. Severe recurrent headaches have been reported[1] in a patient receiving bezafibrate. The headaches started about 24 hours after therapy with bezafibrate began, and recurred about 1 hour after each dose. Headaches occurred 30 to 90 minutes after each dose of gemfibrozil in 2 patients.[2,3] In both patients, the headaches were accompanied by dry mouth, and in 1 also by blurred vision. The headaches stopped when gemfibrozil was withdrawn and recurred one week after re-exposure.

1. Hodgetts TJ, Tunnicliffe C. Bezafibrate-induced headache. *Lancet* 1989; i: 163.
2. Arellano F, *et al.* Gemfibrozil-induced headache. *Lancet* 1988; i: 705.
3. Alvarez-Sabin J, *et al.* Gemfibrozil-induced headache. *Lancet* 1988; ii: 1246.

Hyperhomocysteinaemia. Hyperhomocysteinaemia has been associated with an increased risk for cardiovascular disease. Small studies have found that both bezafibrate[1,2] and fenofibrate[1,3] increase plasma-homocysteine concentrations, although the clinical significance of this is not clear.[4] Folic acid and vitamin B_{12} have been given[4,5] with fenofibrate to reduce homocysteine concentrations, but the role of such treatment is not established.

1. Dierkes J, *et al.* Serum homocysteine increases after therapy with fenofibrate or bezafibrate. *Lancet* 1999; 354: 219–20.
2. Jonkers IJAM, *et al.* Implication of fibrate therapy for homocysteine. *Lancet* 1999; 354: 1208.
3. de Lorgeril M, *et al.* Lipid-lowering drugs and homocysteine. *Lancet* 1999; 353: 209–10.
4. Dierkes J, *et al.* Fenofibrate-induced hyperhomocysteinaemia: clinical implications and management. *Drug Safety* 2003; 26: 81–91.
5. Melenovsky V, *et al.* Effect of folic acid on fenofibrate-induced elevation of homocysteine and cysteine. *Am Heart J* 2003; 146: 110. Full version available at: http://download.journals.elsevierhealth.com/pdfs/journals/0002-8703/PIIS0002870303001224.pdf (accessed 30/05/08)

Photosensitivity. Fibrates have been associated with photosensitivity reactions[1] and there may be cross-sensitivity with ketoprofen (see under Adverse Effects of Ketoprofen, p. 79.3).

1. Serrano G, *et al.* Photosensitivity induced by fibric acid derivatives and its relation to photocontact dermatitis to ketoprofen. *J Am Acad Dermatol* 1992; 27: 204–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bezafibrate as probably not porphyrinogenic: it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

Bezafibrate and other fibrates are highly protein-bound and may displace other drugs from protein binding sites. Interactions may also occur through changes in the activity of cytochrome P450 isoenzymes, particularly CYP3A4.

Fibrates may enhance the effects of oral anticoagulants; the dose of anticoagulant should be reduced when treatment with a fibrate is started, and then adjusted gradually if necessary. Recommendations vary; licensed product information for bezafibrate suggests a reduction of up to 50% in the dosage of anticoagulant. The mechanism of the interaction is unclear; fibrates have been reported to displace warfarin from protein binding sites but other mechanisms are probably also involved.

Other drugs that may be displaced from plasma proteins by fibrates include tolbutamide and other sulfonylurea antidiabetics, phenytoin, and, in patients with hypoalbuminaemia, furosemide. The interaction with antidiabetics is complex since fibrates may alter glucose tolerance in diabetic patients (see Effects on Glucose Metabolism, p. 1324.2). The dosage of antidiabetics may need adjusting during bezafibrate therapy.

There is an increased risk of myopathy if fibrates are used with statins (see Lipid Regulating Drugs under Interactions of Simvastatin, p. 1495.3).

Fibrates may interact with ciclosporin, although reports have been conflicting (see p. 1958.1). However, nephrotoxicity associated with increased ciclosporin concentrations has been reported with bezafibrate and renal function should be monitored.

Cholestasis has been reported in a patient given fenofibrate with raloxifene (see p. 2304.1).

Reviews.

1. Lozada A, Dujovne CA. Drug interactions with fibric acids. *Pharmacol Ther* 1994; 63: 163–76.

Antidiabetics. A paradoxical, reversible decrease in plasma high-density-lipoprotein cholesterol has been reported[1-6] in patients taking fibrates with thiazolidinediones. The mechanism is unclear, although it is unlikely to be a pharmacokinetic interaction.

1. Normén L, *et al.* Combination therapy with fenofibrate and rosiglitazone paradoxically lowers serum HDL cholesterol. *Diabetes Care* 2004; 27: 2241–2.
2. Health Canada. Rosiglitazone (Avandia): decreased high-density lipoprotein cholesterol levels. *Can Adverse React News* 2005; 15 (3): 2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n3-eng.pdf (accessed 04/08/10)
3. Senba H, *et al.* Severe decrease in serum HDL-cholesterol during combination therapy of bezafibrate and pioglitazone. *J Atheroscler Thromb* 2006; 13: 263–4.
4. Shetty C, *et al.* Paradoxical HDL-C reduction during rosiglitazone and fibrate treatment. *Diabet Med* 2007; 24: 94–7.
5. Keidar S, *et al.* High incidence of reduced plasma HDL cholesterol in diabetic patients treated with rosiglitazone and fibrate. *Pharmacoepidemiol Drug Safety* 2007; 16: 1192–4.
6. Venero CV, *et al.* Reduced high-density lipoprotein cholesterol in patients receiving rosiglitazone and fenofibrate. *Am J Med* 2008; 121: e3–e4. Available at: http://download.journals.elsevierhealth.com/pdfs/journals/0002-9343/PIIS0002934308006645.pdf (accessed 23/07/09)

Lipid regulating drugs. The bioavailability of gemfibrozil was reduced by *colestipol*, but was unaffected when gemfibrozil was taken either 2 hours before or 2 hours after colestipol.[1]

For discussion of the interaction between fibrates and *statins*, see p. 1495.3.

1. Forland SC, *et al.* Apparent reduced absorption of gemfibrozil when given with colestipol. *J Clin Pharmacol* 1990; 30: 29–32.

NSAIDs. Acute renal failure due to rhabdomyolysis in a patient has been attributed to an interaction between ciprofibrate and *ibuprofen*.[1] Ibuprofen was believed to have displaced ciprofibrate from protein binding sites. The use of radiological contrast media may also have been a contributory factor.

1. Ramachandran S, *et al.* Acute renal failure due to rhabdomyolysis in presence of concurrent ciprofibrate and ibuprofen treatment. *BMJ* 1997; 314: 1593.

Pharmacokinetics

Bezafibrate is readily absorbed from the gastrointestinal tract. Plasma protein binding is about 95%. The plasma elimination half-life is about 1 to 2 hours. Most of a dose is excreted in the urine, about half as unchanged drug, the remainder as metabolites including 20% as glucuronides. A small proportion (about 3%) of the dose appears in the faeces. Elimination may be increased by forced diuresis. The drug is not dialysable.

References.

1. Abshagen U, *et al.* Disposition pharmacokinetics of bezafibrate in man. *Eur J Clin Pharmacol* 1979; 16: 31–8.
2. Abshagen U, *et al.* Steady-state kinetics of bezafibrate and clofibrate in healthy female volunteers. *Eur J Clin Pharmacol* 1980; 17: 305–8.

The elderly. In a study comparing the pharmacokinetics of bezafibrate in 19 elderly patients with younger healthy subjects,[1] peak plasma concentrations were 1.6 times higher in the elderly group (median 12.1 mg/litre against 7.7 mg/litre) and half-life was increased by 3.8 times (median 6.6 hours against 1.7 hours). The differences could not be attributed solely to diminished renal function in elderly patients. Dosage adjustments in elderly patients should not therefore be based on renal function alone.

1. Neugebauer G, *et al.* Steady-state kinetics of bezafibrate retard in hyperlipidemic geriatric patients. *Klin Wochenschr* 1988; 66: 250–6.

Renal impairment. The half-life of bezafibrate may be prolonged in patients with renal impairment (see under Uses and Administration, p. 1323.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bezacur; Bezalip; Elpi Lip; Nebufurd; *Austria*: Bezacur†; Bezalip; Bezastad; *Belg.*: Cedur; Bulitop; *Braz.*: Cedur; *Canad.*: Bezalip; *Chile*: Nimus; Oralipin; *China*: Abelta (阿贝他); Yi Zhi Te (益之特); *Cz.*: Regadrin B†; *Fin.*: Bezalip; *Fr.*: Befizal; *Ger.*: Befibrat; Bezabeta†; Bezadoc†; Bezagamma†; Cedur†; Lipox†; *Gr.*: Bezachol; Bezalip; Fibrate; Getup; Verbital; *Hong Kong*: Bezalip; *Hung.*: Bezalip; *India*: Beza; Bezalip; Bizalip; *Indon.*: Decrilip; *Israel*: Norlip; *Ital.*: Bezalip; *Jpn*: Bezalip; *Malaysia*: Bezalip; *Mex.*: Befitec; Bexalcor; Bezafisal; Bezalex†; Bezalip†; Bifaren; Bionolip; Colser; Fazebit; Fibroxol; Lesbest; Lipocin; Neptalip; Nivetril; Redalip; Safital; Saprame; Zaf; *Neth.*: Bezalip; *NZ*: Bezalip; Fibalip; *Philipp.*: Bezastad; *Pol.*: Bezamidin†; *Port.*: Bezalip; *Rus.*: Cholesterinorm (Холестеринорм); *S.Afr.*: Bezachole; Bezalip; *Singapore*: Bezalip; Zafibral; *Spain*: Difaterol; Bulitop; *Swed.*: Bezalip; *Switz.*: Cedur; *Thai.*: Bezalip; Bezamil; Evicta; Lipolip†; Polyzalip; Raset; *UAE*: Lipitrol; *UK*: Bezagen; Bezalip Mono; Bezalip; Fibrazate; Zimbacol; *Venez.*: Bezalip.

Pharmacopoeial Preparations

BP 2014: Bezafibrate Tablets; Prolonged-release Bezafibrate Tablets.

Bisoprolol Fumarate

(BANM, USAN, rINNM) ⊗

Bisoprolol Fumarat; Bisoprolol Fumarate de; Bisoprolol fumarato de; Bisoprolol Hemifumarate; Bisoprolol hémifumarate de; Bisoprololfumarat; Bisoprololi Fumaras; Bisoprololi hemifumaras; Bisoprololifumaraatti; CL-297939; EMD-33512 (bisoprolol or bisoprolol fumarate); Fumarato de bisoprolol; Бизопролола Фумарат.

1-[4-(2-Isopropoxyethoxymethyl)phenoxy]-3-isopropylaminopropan-2-ol fumarate.

$(C_{18}H_{31}NO_4)_2C_4H_4O_4$=767.0

CAS — 66722-44-9 (bisoprolol); 66722-45-0 (bisoprolol fumarate); 104344-23-2 (bisoprolol fumarate).

ATC — C07AB07.

ATC Vet — QC07AB07.

UNII — UR59KNS73L.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Bisoprolol Fumarate). A white or almost white, slightly hygroscopic powder. It exhibits polymorphism. Very soluble in water; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Bisoprolol Fumarate). A white crystalline powder. Very soluble in water and in methyl alcohol; freely soluble in alcohol, in chloroform, and in glacial acetic acid; slightly soluble in acetone and in ethyl acetate. Store in airtight containers. Protect from light.

Uses and Administration

Bisoprolol is a cardioselective beta blocker (p. 1316.3). It is reported to be devoid of intrinsic sympathomimetic and membrane-stabilising properties.

Bisoprolol is given as the fumarate in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3). It is also used as an adjunct to standard therapy in patients with stable chronic heart failure (p. 1262.3).

In **hypertension** or **angina pectoris** the usual dose of bisoprolol fumarate is 5 to 10 mg orally as a single daily dose; the maximum recommended dose is 20 mg daily. A reduction in dose may be necessary in patients with hepatic or renal impairment (see p. 1326.1).

In **heart failure** the initial oral dose of bisoprolol fumarate is 1.25 mg once daily. If tolerated, the dose should be doubled after 1 week, and then increased gradually at 1 to 4 week intervals to the maximum dose tolerated; this should not exceed 10 mg once daily.

References.

1. Johns TE, Lopez LM. Bisoprolol: is this just another beta-blocker for hypertension or angina? *Ann Pharmacother* 1995; 29: 403–14.

2. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; 353: 9–13.
3. McGavin JK, Keating GM. Bisoprolol: a review of its use in chronic heart failure. *Drugs* 2002; 62: 2677–96.
4. Rosenberg J, Gustafsson F. Bisoprolol for congestive heart failure. *Expert Opin Pharmacother* 2008; 9: 293–300.

Administration in hepatic or renal impairment. US licensed product information recommends that the initial dose of bisoprolol fumarate for hypertension should be 2.5 mg daily and that the dose should be increased cautiously in patients with severe hepatic impairment or renal impairment (creatinine clearance less than 40 mL/minute). UK licensed product information recommends a maximum dose of 10 mg daily for both angina pectoris and hypertension in patients with severe hepatic impairment or with a creatinine clearance of less than 20 mL/minute.

Bisoprolol is not dialysable.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bisoprolol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Bisoprolol is almost completely absorbed from the gastrointestinal tract and undergoes only minimal first-pass metabolism resulting in an oral bioavailability of about 90%. Peak plasma concentrations occur 2 to 4 hours after oral doses. Bisoprolol is about 30% bound to plasma proteins. It has a plasma elimination half-life of 10 to 12 hours. Bisoprolol is moderately lipid-soluble. It is metabolised in the liver and excreted in urine, about 50% as unchanged drug and 50% as metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Concor; Corbis; Lostaprolol; *Austral.*: Bicard; Bicor; Bispro; *Austria*: Bisocor; Bisostad; Concor; Rivacor; *Belg.*: Bisoprotop†; Bisosandoz†; Docbisopro†; Emconcor; Isoten; *Braz.*: Concardio; Concor; *Canad.*: Monocor†; *Chile*: Concor; *China*: An Shi (安适); Bo Su (博苏); Concor (康可); Luo Ya (洛雅); Rong Ning (荣宁); *Cz.*: Bisoblock†; Bisocard; Bisogamma; Bisogen; Bisprotin; Bivaxol†; Byol†; Concor Cor; Concor; Kordobis†; Rivocor; *Denm.*: Bisoact; Bisocor†; Bisprotin; Cardicor; Emconcor; *Fin.*: Bisomerck†; Bisomyl; Bisoproact; Caraprol; Emconcor; Orloc; *Fr.*: Bisoce; Cardensiel; Cardiocor; Detensiel; *Ger.*: Biso Lich†; Biso-Hennig; Biso-Puren†; Bisobeta; Bisogamma; Bisohexal†; Concor; Jutabis†; *Gr.*: Abitrol; Blocatens; Concor; Pactens; Speridol; *Hong Kong*: Concor; *Hung.*: Bisoblock; Bisocard; Bisogamma; Bisogen†; Concor Cor; Concor; Coviogal; *India*: Bebedol; Bisbeta; Biselect; Bisocar HT; Bisod; Cadrol; Concor; Corbis; *Indon.*: B-Beta; Beta-One; Bipro; Biscor; Concor; Hapsen; Lodoz; Maintate; *Irl.*: Bellimcor; Bisocor; Bisop; Bisopine; Cardicor; Emcolol; Emcor; Emvasc†; Soprol; *Israel*: Bisolol†; Cardiloc; Concor; *Ital.*: Cardicor; Concor; Congescor; Pluscor; Sequacor; *Jpn*: Bisono; Maintate; *Malaysia*: Concor; *Mex.*: Concor; *Neth.*: Bisoblock†; Emcor; *Norw.*: Emconcor; *Philipp.*: Concore; *Pol.*: Antipres; Bicardef; Bisocard; Bisohexal; Bisopromerck; Bisoratio; Concor; Corectin; Coronal; *Port.*: Concor; Libracor†; *Rus.*: Aritel (Арител); Bidop (Бидоп); Biol (Биол); Biprol (Бипрол); Bisocard (Бисокард); Bisogamma (Бисогамма); Concor (Конкор); Corbis (Корбис); Cordinorm (Кордиворм); Coronal (Коронал); Lodoz (Лодоз); Niperten (Нипертен); *S.Afr.*: Adco-Bisocor; Bilocor; Bisohexal; Cardicor; Concor; Ziapro; *Singapore*: Bisohexal; Concor; *Spain*: Emconcor; Euradal; *Swed.*: Bisocard; Bisomerck†; Bisostad; Emconcor; *Switz.*: Bilol; Concor; Rivocor; *Thal.*: Concor; Hypercor; Novacor; *Turk.*: Concor; Soprano; *UK*: Cardicor; Emcor; Vivacor; *Ukr.*: Biprolol (Бипролол); Bisocard (Бисокард); Bisoprol (Бисопрол); Bisostad (Бисостад); Concor (Конкор); Coronal (Коронал); *USA*: Zebeta; *Venez.*: Concor.

Multi-ingredient Preparations. *Arg.*: Concor Plus; Corbis D; Ziac; *Austria*: Bisocombin†; Bisoprolol Comp; Bisoprolol-HCT; Bisostad plus; Concor Plus; Rivacor Plus; *Belg.*: Co-Bisoprolol; Emcoretic; Lodoz; Maxsoten; *Braz.*: Biconcor; *Chile*: Ziac; *Cz.*: Betapres; Lodoz; Tebis Plus H†; *Fin.*: Bisoprolol Comp; Bisostad†; Emconcor Comp; Orloc Comp; *Fr.*: Lodoz; Wytens; *Ger.*: Biso comp†; Biso-Puren comp†; Bisobeta comp; Bisohexal plus†; BisoLich comp†; Bisoplus†; Bisoprolol Comp; Bisoprolol HCT†; Bisoprolol HCTad†; Bisoprolol Plus†; Concor Plus; *Hong Kong*: Lodoz; *Hung.*: Concor Plus; Coviogal Plusz; *India*: Concor-AM; Corbis-H; Lodoz; *Ital.*: Lodoz; *Malaysia*: Lodoz; *Mex.*: Biconcor; *Neth.*: Emcoretic†; *Norw.*: Lodoz; *Philipp.*: Ziac; *Port.*: Concor Plus; *Rus.*: Aritel Plus (Арител Плюс); *S.Afr.*: Ziak; *Singapore*: Lodoz; *Spain*: Emcoretic; *Switz.*: Bilol comp.; Concor Plus; Lodoz; *Thal.*: Lodoz; *Turk.*: Lodoz; *Ukr.*: Alotendin (Алотендин); *USA*: Ziac; *Venez.*: Biconcor; Ziac.

Pharmacopoeial Preparations
BP 2014: Bisoprolol Tablets;
USP 36: Bisoprolol Fumarate and Hydrochlorothiazide Tablets; Bisoprolol Fumarate Tablets.

Bivalirudin *(BAN, USAN, rINN)*

BG-8967; Bivalirudina; Bivalirudine; Bivalirudinum; Bivalirudyna; Hirulog; бивалирудин.

$C_{98}H_{138}N_{24}O_{33}$=2180.3

CAS — 128270-60-0.

ATC — B01AE06.

ATC Vet — QB01AE06.

UNII — TN98EX005G.

Incompatibility. Licensed product information for bivalirudin states that it is incompatible with: alteplase, amiodarone hydrochloride, amphotericin B, chlorpromazine hydrochloride, diazepam, prochlorperazine edisilate, reteplase, streptokinase, and vancomycin hydrochloride. It also states that dobutamine hydrochloride, famotidine, haloperidol lactate, labetalol hydrochloride, lorazepam, and promethazine hydrochloride show concentration-dependent incompatibility with bivalirudin.

Uses and Administration

Bivalirudin, an analogue of the peptide hirudin (p. 1401.2), is a direct thrombin inhibitor with actions similar to Lepirudin, p. 1418.2. It is used as an anticoagulant in patients undergoing percutaneous coronary interventions, including those with, or at risk of, heparin-induced thrombocytopenia. It is also used in patients with acute coronary syndromes in whom early intervention is planned, and has been investigated in patients with acute coronary syndromes treated medically (see Ischaemic Heart Disease, under Uses and Administration of Lepirudin, p. 1418.3).

Some preparations state that bivalirudin is present as the hydrate of the trifluoroacetate salt but doses are given in terms of bivalirudin.

In the management of patients undergoing **planned or primary percutaneous coronary intervention** (PCI), the initial dose of bivalirudin is 750 micrograms/kg by intravenous injection followed immediately by an intravenous infusion of 1.75 mg/kg per hour. In the USA, it is recommended that the activated clotting time is measured 5 minutes after the initial injection and a second injection of 300 micrograms/kg is given if anticoagulation is inadequate. The infusion should be given for the duration of the procedure and may be continued for up to 4 hours afterwards; licensed prescribing information in the UK then allows a reduced dose of 250 micrograms/kg per hour to be infused for a further 4 to 12 hours if necessary, or in the USA 200 micrograms/kg per hour for a further 20 hours.

As part of the management of patients with **acute coronary syndromes**, the initial dose of bivalirudin is 100 micrograms/kg by intravenous injection, followed by an intravenous infusion of 250 micrograms/kg per hour. Again, if measurement of activated clotting time 5 minutes after the initial bolus indicates inadequate anticoagulation, a second bolus of 300 micrograms/kg may be given. In patients managed *medically*, the infusion may be continued for up to 72 hours. For those who proceed to *PCI or coronary artery bypass surgery without cardiopulmonary bypass*, a further intravenous injection of 500 micrograms/kg should be given, and the infusion should be increased to 1.75 mg/kg per hour for the duration of the procedure; after PCI, the infusion may be continued at a dose of 250 micrograms/kg per hour for a further 4 to 12 hours if required. For those who proceed to *coronary artery bypass surgery with cardiopulmonary bypass*, the infusion should be stopped 1 hour before the procedure and the patient should be treated with unfractionated heparin.

The dose of bivalirudin should be reduced in patients with renal impairment (see below).

References.
1. Stone GW, *et al.* ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; 355: 2203–16.
2. Ahrens I, *et al.* Direct thrombin inhibition with bivalirudin as an antithrombotic strategy in general and interventional cardiology. *Expert Opin Drug Metab Toxicol* 2007; 3: 609–20.
3. Harmann F. Safety and efficacy of bivalirudin in acute coronary syndromes. *Curr Pharm Des* 2008; 14: 1191–6.
4. Deeks ED, Curran MP. Bivalirudin: in patients with acute coronary syndromes planned for urgent or early intervention. *Drugs* 2008; 68: 2345–56.
5. Czosnowski QA, *et al.* Bivalirudin for patients with heparin-induced thrombocytopenia undergoing cardiovascular surgery. *Ann Pharmacother* 2008; 42: 1304–9.
6. White HD. Pharmacological and clinical profile of bivalirudin in the treatment of patients with acute coronary syndrome. *Expert Opin Drug Metab Toxicol* 2009; 5: 529–38.
7. Curran MP. Bivalirudin: in patients with ST-segment elevation myocardial infarction. *Drugs* 2010; 70: 909–18.

Administration in renal impairment. The dose of bivalirudin may need to be adjusted in patients with renal impairment and the activated clotting time should be monitored. UK licensed product information recommends the following doses, depending on the glomerular filtration rate (GFR):

- GFR 30 to 59 mL/minute: usual bolus doses (see Uses and Administration, above) but in those undergoing percutaneous coronary intervention (PCI) for any indication the infusion rate should be reduced to 1.4 mg/kg per hour during the procedure
- GFR below 30 mL/minute or dialysis-dependent: contra-indicated

US licensed product information recommends the following doses for those undergoing PCI, based on creatinine clearance (CC):

- CC 30 to 59 mL/minute: usual bolus and infusion doses
- CC below 30 mL/minute: usual bolus doses but infusion rate reduced to 1 mg/kg per hour
- Haemodialysis patients: usual bolus doses but infusion rate reduced to 250 micrograms/kg per hour

For a discussion of the use of direct thrombin inhibitors, including bivalirudin, as alternatives to heparin in patients undergoing haemodialysis or haemofiltration, see Extracorporeal Circuits under Lepirudin, p. 1418.2.

Adverse Effects, Treatment, and Precautions

As for Lepirudin, p. 1419.2.

Interactions

As for Lepirudin, p. 1419.3.

Pharmacokinetics

Bivalirudin is partly metabolised and partly excreted by the kidney. When given intravenously the plasma half-life is about 25 minutes in patients with normal renal function but is prolonged in renal impairment. Bivalirudin does not bind to plasma proteins and is removed by haemodialysis.

References.
1. Robson R, *et al.* Bivalirudin pharmacokinetics and pharmacodynamics: effect of renal function, dose, and gender. *Clin Pharmacol Ther* 2002; 71: 433–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Angiomax; *Austral.*: Angiomax; *Austria*: Angiox; *Belg.*: Angiox; *Canad.*: Angiomax; *Chile*: Angiomax; *Cz.*: Angiox; *Denm.*: Angiox; *Fin.*: Angiox; *Fr.*: Angiox; *Ger.*: Angiox; *Gr.*: Angiox; *Hung.*: Angiox; *India*: Bivaflo; *Irl.*: Angiox; *Israel*: Angiomax; *Ital.*: Angiox; *Neth.*: Angiox; *Norw.*: Angiox; *NZ*: Angiomax; *Pol.*: Angiox; *Port.*: Angiox; *Spain*: Angiox; *Swed.*: Angiox; *Switz.*: Angiox; *UK*: Angiox; *Ukr.*: Angiox (Ангиокс)†; *USA*: Angiomax.

Bopindolol Malonate *(rINNM)* ⊗

Bopindolol Hydrogen Malonate; Bopindolol, Malonate de; Bopindolol, malonato de; Bopindololi Malonas; LT-31-200; Malonato de bopindolol; Бопиндолола Малонат.

(±)-1-(*tert*-Butylamino)-3-[(2-methylindol-4-yl)oxy]propan-2-ol benzoate malonate.

$C_{23}H_{28}N_2O_3C_3H_4O_4$=484.5

CAS — 62658-63-3 (bopindolol); 82857-38-3 (bopindolol malonate).

ATC — C07AA17.

ATC Vet — QC07AA17.

UNII — 53UWR70991.

Profile

Bopindolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to possess some intrinsic sympathomimetic activity.

Bopindolol is given orally as the malonate but doses are expressed in terms of the base; 1.27 mg of bopindolol malonate is equivalent to about 1 mg of base. It is used in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3) in daily doses equivalent to 0.5 to 2 mg of bopindolol.

References.
1. Harron DWG, *et al.* Bopindolol: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1991; 41: 130–49.
2. Nagatomo T, *et al.* Bopindolol: pharmacological basis and clinical implications. *Cardiovasc Drug Rev* 2001; 19: 9–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Sandonorm†; *Gr.*: Sandonorm; *Hung.*: Sandonorm; *Switz.*: Sandonorm†.

Multi-ingredient Preparations. *Switz.*: Sandoretic†.

Bosentan (BAN, USAN, rINN)

Bosentaani; Bosentán; Bosentanio; Bosentanum; Ro-47-0203/029; Бозентан.

p-tert-Butyl-*N*-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]benzenesulfonamide.

$C_{27}H_{29}N_5O_6S$=551.6

CAS — 147536-97-8 (anhydrous bosentan); 157212-55-0 (bosentan monohydrate).

ATC — C02KX01.

ATC Vet — QC02KX01.

UNII — Q326023R30 (bosentan); XUL93R30K2 (anhydrous bosentan).

Uses and Administration

Bosentan is an endothelin receptor antagonist (p. 1245.1) used in the management of pulmonary hypertension (below) and systemic sclerosis (see Scleroderma, below). It has also been investigated in heart failure and in hypertension.

In **pulmonary hypertension**, patients over 12 years of age may be given bosentan orally in an initial dose of 62.5 mg twice daily, increased after 4 weeks to a maintenance dose of 125 mg twice daily. In those with low body-weight (below 40 kg) both the initial and maintenance doses are 62.5 mg twice daily. For the use of bosentan in children, see below.

In **systemic sclerosis** with ongoing digital ulcer disease, bosentan is given in the same doses as for pulmonary hypertension; there are no data on safety or efficacy in patients under 18 years of age.

Use with ritonavir (including ritonavir-boosted HIV-protease inhibitors) increases bosentan plasma concentrations, and US licensed product information for bosentan recommends the following dosage reductions of bosentan in patients taking both drugs together:

- in those who are already taking ritonavir and have been doing so for at least 10 days, start bosentan at an oral dose of 62.5 mg once daily or on alternate days, depending on patient tolerability
- in those who are already taking bosentan, stop bosentan for at least 36 hours before starting ritonavir. After at least 10 days of ritonavir, restart bosentan at a dose of 62.5 mg once daily or on alternate days, depending on patient tolerability

For use in hepatic impairment, see Administration in Hepatic Impairment, below.

References.

1. Dingemanse J, van Giersbergen PLM. Clinical pharmacology of bosentan, a dual endothelin receptor antagonist. *Clin Pharmacokinet* 2004; 43: 1089–1115.
2. Oldfield V, Lyseng-Williamson KA. Bosentan: a review of its use in pulmonary arterial hypertension and systemic sclerosis. *Am J Cardiovasc Drugs* 2006; 6: 189–208.

Administration in children. A short-term study[1] in 19 children with pulmonary hypertension aged 3 to 15 years found that treatment with bosentan resulted in haemodynamic improvement and was well tolerated, and another small study[2] suggested that addition of bosentan allowed epoprostenol dosage to be reduced or stopped. Longer-term studies[3,4] have reported that benefit is maintained and that bosentan may have a role in children with both idiopathic pulmonary hypertension and pulmonary hypertension secondary to heart or lung disease.

Licensed product information in the UK states that in children aged 2 years and above, oral doses greater than 2 mg/kg twice daily are unlikely to increase efficacy. There is limited clinical experience in those aged under 2 years. It notes that the studies cited above used the following doses; these doses are also recommended in the *BNFC*, for children aged 2 to 18 years:

- body-weight 10 to 20 kg: initial dose 31.25 mg once daily, increased to 31.25 mg twice daily after 4 weeks
- body-weight 20 to 40 kg: initial dose 31.25 mg twice daily, increased to 62.5 mg twice daily after 4 weeks
- body-weight over 40 kg and age 12 to 18 years: as for adults (see above)

1. Barst RJ, *et al.* Pharmacokinetics, safety, and efficacy of bosentan in pediatric patients with pulmonary arterial hypertension. *Clin Pharmacol Ther* 2003; 73: 372–82.
2. Ivy DD, *et al.* Weaning and discontinuation of epoprostenol in children with idiopathic pulmonary arterial hypertension receiving concomitant bosentan. *Am J Cardiol* 2004; 93: 943–6.
3. Maiya S, *et al.* Response to bosentan in children with pulmonary hypertension. *Heart* 2006; 92: 664–70.
4. Rosenzweig EB, *et al.* Effects of long-term bosentan in children with pulmonary arterial hypertension. *J Am Coll Cardiol* 2005; 46: 697–704.

Administration in hepatic impairment. Oral bosentan therapy should not be *started* in patients with liver transaminase concentrations more than 3 times the upper limit of normal (ULN). If transaminase concentrations increase *during* treatment, the following modifications are recommended:

- for increases to between 3 and 5 times the ULN, bosentan should be stopped or the dose reduced to the usual initial dose (see Uses and Administration, above). Enzyme concentrations should be monitored every 2 weeks until they return to pretreatment values; therapy may then be continued or reintroduced at the usual initial dose, but aminotransferase concentrations should be checked within 3 days, after a further 2 weeks, and then monthly
- for increases to more than 5 times the ULN up to 8 times the ULN, bosentan should be stopped; reintroduction at the usual initial dose may be considered when concentrations return to pretreatment values
- for increases above 8 times the ULN or if there are symptoms of hepatotoxicity or increases in total bilirubin levels greater than twice the ULN, treatment should be stopped and not reintroduced

Pulmonary hypertension. Pulmonary hypertension (p. 1278.2) is a progressive and incurable disease associated with an increase in pulmonary arterial pressure. Treatment usually involves the use of vasodilators such as calcium-channel blockers, intravenous epoprostenol, or sildenafil, though systemic effects may limit their use. Patients with pulmonary hypertension have raised plasma concentrations of the potent vasoconstrictor endothelin I, and endothelin antagonists such as bosentan are widely used.[1] Studies[2,3] with oral bosentan in patients with mainly functional class III pulmonary arterial hypertension have shown improvement in exercise tolerance and in time to clinical progression; an open study[4] showed sustained benefit with treatment for 1 year or more. However, no effect on mortality has yet been found in randomised studies, although there is some evidence[5,6] that survival may be improved. Some benefit has also been reported with bosentan alone in class II patients.[7] Bosentan has also been tried with other drugs but the role of combination therapy is not clear. When given with epoprostenol[8] there was a non-significant trend towards greater improvement in the group receiving both drugs compared with epoprostenol alone. Bosentan has also been given successfully with sildenafil.[9-11]

There is some evidence that bosentan may be of benefit in pulmonary hypertension associated with congenital heart disease,[12,13] including Eisenmenger syndrome,[13-15] and in pulmonary hypertension associated with HIV infection[16,17] and COPD.[18] Positive results have also been reported[19-21] in chronic thromboembolic pulmonary hypertension.

1. Raja SG, Dreyfus GD. Current status of bosentan for treatment of pulmonary hypertension. *Ann Card Anaesth* 2008; 11: 6–14.
2. Channick RN, *et al.* Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001; 358: 1119–23.
3. Rubin LJ, *et al.* Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; 346: 896–903. Correction. *ibid.*; 1258.
4. Sitbon O, *et al.* Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary arterial hypertension: a 1-year follow-up study. *Chest* 2003; 124: 247–54.
5. McLaughlin VV, *et al.* Survival with first-line bosentan in patients with primary pulmonary hypertension. *Eur Respir J* 2005; 25: 244–9.
6. Sitbon O, *et al.* Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol. *Thorax* 2005; 60: 1025–30.
7. Galiè N, *et al.* Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008; 371: 2093–2100.
8. Humbert M, *et al.* Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004; 24: 353–9.
9. Porhownik NR, *et al.* Addition of sildenafil in patients with pulmonary arterial hypertension with inadequate response to bosentan monotherapy. *Can Respir J* 2008; 15: 427–30.
10. Gruenig E, *et al.* Acute hemodynamic effects of single-dose sildenafil when added to established bosentan therapy in patients with pulmonary arterial hypertension: results of the COMPASS-1 study. *J Clin Pharmacol* 2009; 49: 1343–52.
11. Launay D, *et al.* Long-term outcome of systemic sclerosis-associated pulmonary arterial hypertension treated with bosentan as first-line monotherapy followed or not by the addition of prostanoids or sildenafil. *Rheumatology (Oxford)* 2010; 49: 490–500.
12. Apostolopoulou SC, *et al.* Long-term oral bosentan treatment in patients with pulmonary arterial hypertension related to congenital heart disease: a 2-year study. *Heart* 2007; 93: 350–4.
13. Diller G-P, *et al.* Long-term safety, tolerability and efficacy of bosentan in adults with pulmonary arterial hypertension associated with congenital heart disease. *Heart* 2007; 93: 974–6.
14. Galiè N, *et al.* for the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) Investigators. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation* 2006; 114: 48–54.
15. D'Alto M, *et al.* Long term effects of bosentan treatment in adult patients with pulmonary arterial hypertension related to congenital heart disease (Eisenmenger physiology): safety, tolerability, clinical, and haemodynamic effect. *Heart* 2007; 93: 621–5.
16. Barbaro G, *et al.* Highly active antiretroviral therapy compared with HAART and bosentan in combination in patients with HIV-associated pulmonary hypertension. *Heart* 2006; 92: 1164–6.
17. Degano B, *et al.* Long-term effects of bosentan in patients with HIV-associated pulmonary arterial hypertension. *Eur Respir J* 2009; 33: 92–8.
18. Valerio G, *et al.* Effect of bosentan upon pulmonary hypertension in chronic obstructive pulmonary disease. *Ther Adv Respir Dis* 2009; 3: 15–21.
19. Hughes R, *et al.* Bosentan in inoperable chronic thromboembolic pulmonary hypertension. *Thorax* 2005; 60: 707.
20. Hoeper MM, *et al.* Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2005; 128: 2363–7.
21. Bonderman D, *et al.* Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2005; 128: 2599–2603.

Scleroderma. Bosentan has an established role in pulmonary hypertension secondary to scleroderma (p. 1942.3) or other connective tissue disorders, but may also have additional benefits. Several case reports[1-3] have suggested that treatment with bosentan may be associated with healing of refractory digital ulcers in patients with scleroderma, and a controlled study[4] found that bosentan reduced the incidence of new digital ulcers, although there was no improvement in the healing of existing ulcers. Relatively long-term treatment may need to be given.[5,6]

1. Humbert M, Cabane J. Successful treatment of systemic sclerosis digital ulcers and pulmonary arterial hypertension with endothelin receptor antagonist bosentan. *Rheumatology (Oxford)* 2003; 42: 191–3.
2. Snyder MJ, *et al.* Resolution of severe digital ulceration during a course of bosentan therapy. *Ann Intern Med* 2005; 142: 802–3.
3. Tilton J, *et al.* Successful treatment of systemic sclerosis-related digital ulcers and sarcoidosis with endothelin receptor antagonist (bosentan) therapy. *Br J Dermatol* 2006; 154: 1000–1002.
4. Korn JH, *et al.* Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. *Arthritis Rheum* 2004; 50: 3985–93.
5. García de la Peña-Lefebvre P, *et al.* Long-term experience of bosentan for treating ulcers and healed ulcers in systemic sclerosis patients. *Rheumatology (Oxford)* 2008; 47: 464–6.
6. Tsifetaki N, *et al.* Bosentan for digital ulcers in patients with systemic sclerosis: a prospective 3-year followup study. *J Rheumatol* 2009; 36: 1550–1.

Adverse Effects

Adverse effects reported with bosentan include headache, nasopharyngitis, flushing, oedema, hypotension, dizziness, palpitations, gastrointestinal disturbances, pruritus, rashes, fatigue, muscle cramps, and anaemia. Anaphylaxis and angioedema have been reported rarely. Dose-related increases in liver aminotransferases may also occur, and hepatic cirrhosis and liver failure have been reported.

Bosentan is teratogenic in *animals*; there is also some suggestion that endothelin antagonists may impair testicular function and spermatogenesis.

Effects on the liver. In a postmarketing study,[1] increases in liver aminotransferases to more than 3 times the upper limit of normal occurred in 352 (7.6%) of 4623 patients started on *bosentan* for pulmonary hypertension; treatment was continued or successfully reintroduced after temporary withdrawal in 165 (47%) of these patients. Adverse liver effects may occur less frequently in younger children: postmarketing data[2] showed elevated aminotransferases in 2.7% of children aged under 12 years compared with 7.8% of those aged 12 years and over.

1. Humbert M, *et al.* Results of European post-marketing surveillance of bosentan in pulmonary hypertension. *Eur Respir J* 2007; 30: 338–44.
2. Beghetti M, *et al.* Safety experience with bosentan in 146 children 2–11 years old with pulmonary arterial hypertension: results from the European Postmarketing Surveillance program. *Pediatr Res* 2008; 64: 200–204.

Effects on the skin. Vasculitis was reported[1] in a patient receiving bosentan shortly after the dose was increased to 125 mg twice daily. She was also taking metolazone and acenocoumarol long term, and spironolactone had recently been added. The skin lesions improved slowly over a period of weeks after bosentan was stopped. All other treatment was continued and it was concluded that the lesions were attributable to bosentan alone or to a previously unknown interaction. A pruritic, erythematous drug eruption occurred[2] in a patient 10 days after being given bosentan for systemic sclerosis. The eruption improved after stopping the drug and treatment with corticosteroids, and recurred on rechallenge.

1. Gasser S, *et al.* Severe necrotising leucocytoclastic vasculitis in a patient taking bosentan. *BMJ* 2004; 329: 430.
2. Nagai Y, *et al.* Drug eruption due to bosentan in a patient with systemic sclerosis. *Mod Rheumatol* 2006; 16: 188–90.

Precautions

Bosentan is contra-indicated in patients with moderate to severe hepatic impairment (Child-Pugh Class B or C). Liver-aminotransferase concentrations should be measured before starting therapy, at monthly intervals during therapy, and 2 weeks after any increase in dose; treatment may need to be modified if enzyme concentrations are increased (see Administration in Hepatic Impairment, above).

Haemoglobin concentrations should be monitored every 3 months during therapy, more frequently at the start.

Bosentan should not be given to patients with hypotension. Pulmonary oedema has been reported rarely when vasodilating agents, including endothelin receptor antagonists, have been used in patients with veno-occlusive disease. Therefore, if a patient develops acute pulmonary oedema when starting therapy, the possibility of veno-

occlusive disease should be considered, and the drug discontinued if confirmed.

Although there is no evidence of rebound effects after stopping bosentan, it is recommended that therapy should be withdrawn gradually.

Bosentan and related endothelin receptor antagonists are teratogenic in *rats* and should not be used in pregnancy or in women of child-bearing potential who are not using a reliable method of contraception; hormonal contraceptives alone may not be adequate and additional measures may be required (see Interactions, below).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bosentan as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

Bosentan is metabolised by the cytochrome P450 isoenzymes CYP2C9 and CYP3A4 and is also an inducer of the same isoenzymes. It may also possibly induce CYP2C19. Interactions may therefore occur with other drugs that are either metabolised by, or inhibit, these isoenzymes. Concomitant use of bosentan with both a CYP2C9 inhibitor and a CYP3A4 inhibitor should be avoided. Use with ciclosporin is contra-indicated since plasma concentrations of bosentan are significantly increased (see below). Use with ritonavir also increases bosentan plasma concentrations, and reduced doses of bosentan have been recommended—see Uses and Administration, p. 1327.1. There is an increased risk of hepatotoxicity if bosentan is given with glibenclamide and such use should be avoided; the hypoglycaemic effect of glibenclamide may also be reduced. Bosentan reduces exposure to sildenafil. Bosentan has also reduced the plasma concentrations of some hormonal contraceptives and additional contraceptive measures are advised (see Endothelin Receptor Antagonists, p. 2243.3).

Anticoagulants. For reports of bosentan decreasing the anticoagulant effect of *warfarin*, see Endothelin Receptor Antagonists, p. 1534.1.

Ciclosporin. There appears to be a complex interaction between bosentan and ciclosporin. In a pharmacokinetic study[1] in healthy subjects given both drugs, doses of ciclosporin needed increasing to achieve target trough ciclosporin concentrations; it was calculated that plasma concentrations of ciclosporin would otherwise have been reduced by about half in the presence of bosentan. In addition, plasma concentrations of bosentan were almost doubled by ciclosporin. Licensed product information for bosentan states that plasma concentrations at steady state are 3 to 4 times higher in the presence of ciclosporin and contra-indicates the combination.

1. Binet I, *et al.* Renal hemodynamics and pharmacokinetics of bosentan with and without cyclosporine A. *Kidney Int* 2000; 57: 224–31.

Urological drugs. For a two-way interaction between bosentan and *sildenafil*, see Cardiovascular Drugs under Sildenafil, p. 2366.3.

Pharmacokinetics

Bosentan is absorbed from the gastrointestinal tract with an absolute bioavailability of about 50%. Peak plasma concentrations occur about 3 to 5 hours after an oral dose. It is more than 98% bound to plasma proteins, mainly to albumin. Bosentan is metabolised in the liver by the cytochrome P450 isoenzymes CYP2C9 and CYP3A4 and is an inducer of these enzymes and possibly also of CYP2C19; after multiple dosing, plasma concentrations of bosentan decrease gradually to 50 to 65% of those seen after a single dose. Bosentan has three metabolites, one of which is active. Bosentan is excreted almost entirely as metabolites in the bile; less than 3% of an oral dose is excreted in the urine. The terminal elimination half-life is about 5 hours.

References.

1. Weber C, *et al.* Multiple-dose pharmacokinetics, safety, and tolerability of bosentan, an endothelin receptor antagonist, in healthy male volunteers. *J Clin Pharmacol* 1999; 39: 703–14.
2. van Giersbergen PLM, *et al.* Influence of mild liver impairment on the pharmacokinetics and metabolism of bosentan, a dual endothelin receptor antagonist. *J Clin Pharmacol* 2003; 43: 15–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Tracleer; Usenta†; *Austral.*: Tracleer; *Austria*: Tracleer; *Belg.*: Tracleer; *Braz.*: Tracleer; *Canad.*: Tracleer; *Chile*: Usenta; *China*: Tracleer (全可利); *Cz.*: Tracleer; *Denm.*: Tracleer; *Fin.*: Tracleer; *Fr.*: Tracleer; *Ger.*: Tracleer; *Gr.*: Tracleer; *Hong Kong*: Tracleer; *Hung.*: Tracleer; *Irl.*: Tracleer; *Israel*: Tracleer; *Ital.*: Tracleer; *Malaysia*: Tracleer; *Neth.*: Tracleer; *Norw.*: Tracleer; *NZ*: Tracleer; *Pol.*: Tracleer; *Port.*: Tracleer; *Rus.*: Tracleer (Трацлир); *Singapore*: Tracleer; *Spain*: Tracleer; *Swed.*: Tracleer; *Switz.*: Tracleer; *Thal.*: Tracleer; *Turk.*: Tracleer; *UK*: Tracleer; *USA*: Tracleer.

Bretylium Tosilate *(BAN, rINN)*

ASL-603; Bretilio, tosilato de; Bretylii Tosilas; Bretylii Tosilas; Bretylium, Tosilate de; Bretylium Tosylate (USAN); Bretylio-silat; Bretylinosilaatti; Tosilato de bretilio; Бретилия Тозилат.

(2-Bromobenzyl)ethyldimethylammonium toluene-4-sulphonate.

$C_{11}H_{18}BrN,C_7H_8O_3S$=414.4

CAS — 59-41-6 (bretylium); 61-75-6 (bretylium tosilate).

ATC — C01BD02.

ATC Vet — QC01BD02.

UNII — 78ZP3YR353.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Bretylium Tosilate). A white crystalline powder. M.p. about 98 degrees. It exhibits polymorphism. Freely soluble in water, in alcohol, and in methyl alcohol. A 5% solution in water has a pH of 5.0 to 6.5. Store in airtight containers at a temperature not exceeding 25 degrees. Protect from light.

USP 36: (Bretylium Tosylate). A white, hygroscopic, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; practically insoluble in ether, in ethyl acetate, and in hexane. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Bretylium is a quaternary ammonium compound with class II and class III antiarrhythmic activity (p. 1243.1); it causes an initial release of noradrenaline and then blocks adrenergic transmission by preventing noradrenaline release from adrenergic nerve endings. It suppresses ventricular fibrillation and other ventricular arrhythmias, but its exact mode of action is unknown. It has been given parenterally as the tosilate in the management of ventricular arrhythmias.

Bretylium has also been investigated in complex regional pain syndrome.

References.

1. Bacaner M, Dembo DH. Arrhythmia and acute coronary syndrome suppression and cardiac resuscitation management with bretylium. *Am J Ther* 2009; 16: 534–42.

Adverse Effects and Precautions

The most common adverse effect of bretylium is hypotension, which may be severe. Bretylium may also cause a transient initial increase in blood pressure and heart rate, and a worsening of cardiac arrhythmias due to a release of noradrenaline. Nausea and vomiting may occur particularly during rapid intravenous infusion. Intramuscular injection of bretylium can lead to local tissue necrosis and muscle atrophy. Caution is required in patients with renal impairment, and in patients with severe aortic stenosis or pulmonary hypertension in whom cardiac output may not increase in response to the fall in peripheral resistance produced by bretylium.

Interactions

Bretylium may exacerbate arrhythmias caused by digitalis toxicity and may enhance the effects of sympathomimetics.

Pharmacokinetics

Bretylium is incompletely absorbed from the gastrointestinal tract. It is well absorbed after intramuscular injection. It is not metabolised and is largely excreted unchanged in the urine. The half-life is reported to be between 4 and 17 hours in patients with normal renal function and is prolonged in patients with renal impairment. Bretylium is dialysable.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Singapore*: Bretylate.

Pharmacopoeial Preparations

BP 2014: Bretylium Injection;

USP 36: Bretylium Tosylate in Dextrose Injection; Bretylium Tosylate Injection.

Bucindolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Bucindolol, Chlorhydrate de; Bucindolol, hidrocloruro de; Bucindololi Hydrochloridum; Hidrocloruro de bucindolol; MJ-13105-1; Буциндолола Гидрохлорид.

2-[2-Hydroxy-3-(2-indol-3-yl-1,1-dimethylethylamino)propoxy]benzonitrile hydrochloride.

$C_{22}H_{25}N_3O_2$,HCl=399.9

CAS — 71119-11-4 (bucindolol); 70369-47-0 (bucindolol hydrochloride).

UNII — SH683G4OII.

NOTE. The name Gencaro has been used as a trade mark for bucindolol hydrochloride.

Profile

Bucindolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to possess weak alpha$_1$-blocking activity and direct vasodilating activity; the degree of intrinsic sympathomimetic activity is unclear. Bucindolol hydrochloride has been investigated in the management of hypertension, heart failure, and other cardiac disorders, but development was halted. However, it has been suggested that it may be of benefit in a genetically identifiable subgroup of patients.

References.

1. The Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 2001; 344: 1659–67.
2. Anderson JL, *et al.* Beta-Blocker Evaluation of Survival Trial (BEST) Investigators. Failure of benefit and early hazard of bucindolol for class IV heart failure. *J Card Fail* 2003; 9: 266–77.
3. Ali I, *et al.* Importance of a history of hypertension for the prognosis after acute myocardial infarction—for the Bucindolol Evaluation in Acute myocardial infarction Trial (BEAT) study group. *Clin Cardiol* 2004; 27: 265–9.
4. Bristow MR, *et al.* An α_{2C}-adrenergic receptor polymorphism alters the norepinephrine-lowering effects and therapeutic response of the beta-blocker bucindolol in chronic heart failure. *Circ Heart Fail* 2010; 3: 21–8.

Buflomedil Hydrochloride *(BANM, rINNM)*

Buflomedilihydrokloridi; Buflomédil, Chlorhydrate de; Buflomedil, hidrocloruro de; Buflomedil-hidroklorid; Buflomedil-hydrochlorid; Buflomedilhydrochlorid; Buflomedilhydroklorid; Buflomedili Hydrochloridum; Buflomedilio hidrochloridas; Hidrocloruro de buflomedil; LL-1656; Буфломедила Гидрохлорид.

2′,4′,6′-Trimethoxy-4-(pyrrolidin-1-yl)butyrophenone hydrochloride.

$C_{17}H_{25}NO_4$,HCl=343.8

CAS — 55837-25-7 (buflomedil); 35543-24-9 (buflomedil hydrochloride).

ATC — C04AX20.

ATC Vet — QC04AX20.

UNII — 3J944AFS8S.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Buflomedil Hydrochloride). A white or almost white microcrystalline powder. Freely soluble in water; soluble in alcohol; very slightly soluble in acetone. A 5% solution in water has a pH of 5.0 to 6.5.

Uses and Administration

Buflomedil hydrochloride is a vasodilator that has been used in the treatment of cerebrovascular and peripheral vascular disorders. It has been given orally or by intramuscular or intravenous injection. Serious neurological adverse effects including convulsions and status epilepticus, and cardiovascular effects including severe hypotension and arrhythmias, particularly tachycardia and cardiac arrest, have occurred. These were seen particularly in elderly patients and in patients with renal impairment who did not receive an appropriately reduced dose. Consequently, the EMA recommended the withdrawal of buflomedil in Europe.

References.

1. EMA. European Medicines Agency recommends suspension of all buflomedil-containing medicines (issued 17th November, 2011). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/11/WC500117792.pdf (accessed 02/01/14)
2. Bucolo C, *et al.* Safety profile assessment of buflomedil: an overview of adverse reactions between 1975 and 2011. *Pharmacoepidemiol Drug Safety* 2012; 21: 1190–6.
3. de Backer TLM, Vander Stichele R. Buflomedil for intermittent claudication. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2013 (accessed 02/01/14).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Arteriol; Buflomed; Lofton; *Austria*: Buflohexal†; Buflomed†; Loftyl†; *Belg.*: Loftyl†; *Braz.*: Bufedil; *China*: An Si Tuo Li (安思罗利); Ao Nuo Ya (奥诺娅); Ba Yang Pu Rui (巴阳普瑞); Bu Fu Mai (步复迈); Fonzylane (弗斯兰); Hai Si Xin Da (海斯欣达); Huo Nuo Lin (活诺林); Ikelan (麦道可兰); Jia Er (加尔); Lai Si Duo Wei (莱斯多维); Li Xin Kang (力欣康); Ning Xue Xin (宁雪欣); Qian Tong (前通); Qing Jian (清健); Rui Li Da (瑞立达); Sai Mei Ao (赛美澳); Sai Mu Si (赛姆斯); Sailaile (赛莱乐); Shi Duo Tai (世多泰); Si Jian (斯健); Si Mi Kang (司米康); Xin Zhi Ming (欣智明); Xing Bi De (兴必得); Xu Luo Ling (维络爱); Yisu (意速); *Fr.*: Fonzylane†; *Ger.*: Bufedil†; Buflo-POS†; Buflo-Puren†; Complamin†; Defluina†;

Gr.: Bladiron†; Botamiral†; Buflodil†; Chlorofarm-S†; Cordimedil†; Dialon-T†; Dicasin†; Farmidil†; Flubir†; Gaveril†; Gondofil†; Irrodan†; Loftyl†; Mellrgan†; Odeoxil†; Osramont†; Palimodon†; Penpurin†; Spediol†; Sulodil†; Thiocodin†; Vanogel†; Vardolin†; Zelian†; ***Hong Kong***: Fonzylane†; Irrodan; ***Indon.***: Loftyl; ***Ital.***: Buflan†; Buflocit†; Flomed†; Irrodan†; Loftyl†; ***Neth.***: Loftyl†; ***Pol.***: Buflox†; Buvasodil†; ***Port.***: Loftyl†; ***S. Afr.***: Loftyl; ***Spain***: Loftón†; ***Switz.***: Loftyl†; ***Thai.***: Irrodan†; ***Venez.***: Loftyl.

Multi-ingredient Preparations. *Arg.*: Mimixin.

Bumetanide *(BAN, USAN, rINN)* ⊗

Bumetanid; Bumetanida; Bumetanidas; Bumétanide; Bumetanidi; Bumetanidum; Ro-10-6338; Буметанид.

3-Butylamino-4-phenoxy-5-sulphamoylbenzoic acid.

$C_{17}H_{20}N_2O_5S$=364.4

CAS — 28395-03-1.

ATC — C03CA02.

ATC Vet — QC03CA02.

UNII — 0Y253XUQ5H.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Bumetanide). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol and in acetone; slightly soluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Bumetanide). A practically white powder. Slightly soluble in water; soluble in alkaline solutions. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Although chemically unrelated, bumetanide is a loop diuretic with actions and uses similar to those of furosemide (p. 1387.1). Bumetanide is used in the treatment of oedema associated with heart failure (p. 1262.3) and with renal and hepatic disorders. It is given in high doses in the management of oliguria due to renal failure or insufficiency. Bumetanide has also been used in hypertension (p. 1251.1).

Diuresis starts within about 30 minutes to an hour after an oral dose, reaches a peak at 1 to 2 hours, and lasts for about 4 hours but may be prolonged to 6 hours after high doses; after intravenous injection its effects are evident within a few minutes and last for about 2 hours. As a general guide bumetanide 1 mg produces a diuretic effect similar to furosemide 40 mg although this should not be used for direct substitution at higher doses.

In the treatment of **oedema** the usual oral dose is 1 mg in the morning or early evening; a second dose may be given 6 to 8 hours later if necessary. A dose of 500 micrograms daily may be adequate in some elderly patients.

In refractory oedema higher doses may be necessary. An initial dose of 5 mg daily has been advocated, increased by 5 mg every 12 to 24 hours as required; however other sources have suggested a maximum total dose of 10 mg daily. Twice daily dosing may be preferred at higher doses. For maintenance therapy doses may be given daily or intermittently. In an emergency or when oral therapy cannot be given 0.5 to 1 mg may be given by intramuscular or slow intravenous injection, subsequently adjusted according to response. A dose for pulmonary oedema is 1 to 2 mg by intravenous injection, repeated 20 minutes later if necessary. Alternatively, 2 to 5 mg may be given over 30 to 60 minutes in 500 mL of a suitable infusion fluid.

For doses in children, see below.

In the treatment of **hypertension** bumetanide has been given in oral doses of 0.5 to 1 mg daily, although higher doses have been used.

When very high doses of bumetanide are used careful laboratory control is essential for furosemide (see p. 1387.1; high-dose therapy).

Administration in children. Although unlicensed in the UK for children aged under 12 years, the *BNFC* suggests that bumetanide may be given to children aged from 1 month in the treatment of oedema. An *oral* dose of 15 to 50 micrograms/kg (maximum 2 mg) may be given up to 4 times daily; the maximum daily dose is 5 mg. Alternatively, 25 to 50 micrograms/kg may be given by *intravenous infusion* over 30 to 60 minutes.

Adverse Effects

As for Furosemide, p. 1388.3. Bumetanide may cause muscle pain, particularly at high doses.

Effects on the ears. Early reports suggested that bumetanide might be less ototoxic than furosemide.[1] However, both drugs can cause deafness, especially when given in large doses to patients with renal impairment.

1. Ward A, Heel RC. Bumetanide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use. *Drugs* 1984; 28: 426–64.

Effects on the lungs. Alveolitis, presenting as haemoptysis and steadily increasing dyspnoea in a 79-year-old man, was found to coincide with the use of bumetanide for congestive heart failure.[1] When the diuretic was replaced with furosemide the condition gradually resolved.

1. van Tellingen C. Suspension of disbelief - or the bumetanide paradox. *Neth Heart J* 2007; 15: 31–2.

Effects on the muscles. Bumetanide, particularly in high doses in patients with chronic renal impairment, may cause severe musculoskeletal pain. A curious muscle stiffness distinct from cramp, with tenderness to compression and pain on movement, was noted in 4 patients with end-stage renal failure.[1] The calf muscles were the first to be affected; shoulder girdle and thigh muscle tenderness also occurred in 2 patients, and 1 patient also had neck stiffness. The adverse effect appeared to be dose-related for the individual patients.

1. Barclay JE, Lee HA. Clinical and pharmacokinetic studies on bumetanide in chronic renal failure. *Postgrad Med J* 1975; 51 (suppl 6): 43–6.

Effects on the skin. Bullous pemphigoid developed in a patient about 6 weeks after starting bumetanide.[1] Healing occurred after withdrawal without the need for corticosteroids.

1. Boulinguez S, *et al.* Bullous pemphigoid induced by bumetanide. *Br J Dermatol* 1998; 138: 548–9.

Precautions

Bumetanide's precautions and contra-indications are generally dependent on its effects on fluid and electrolyte balance and are similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1406.1).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bumetanide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Furosemide, p. 1389.3.

Pharmacokinetics

Bumetanide is almost completely and fairly rapidly absorbed from the gastrointestinal tract; the bioavailability is reported to be about 80 to 95%. It has a plasma elimination half-life of about 1 to 2 hours. It is about 95% bound to plasma proteins. About 80% of the dose is excreted in the urine, about 50% as unchanged drug, and 10 to 20% in the faeces.

References to the pharmacokinetics of bumetanide in healthy subjects.

1. Halladay SC, *et al.* Diuretic effect and metabolism of bumetanide in man. *Clin Pharmacol Ther* 1977; 22: 179–87.
2. Pentikäinen PJ, *et al.* Fate of [^{14}C]-bumetanide in man. *Br J Clin Pharmacol* 1977; 4: 39–44.
3. Holazo AA, *et al.* Pharmacokinetics of bumetanide following intravenous, intramuscular, and oral administrations to normal subjects. *J Pharm Sci* 1984; 73: 1108–13.
4. Ward A, Heel RC. Bumetanide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use. *Drugs* 1984; 28: 426–64.
5. McCrindle JL, *et al.* Effect of food on the absorption of frusemide and bumetanide in man. *Br J Clin Pharmacol* 1996; 42: 743–6.

Hepatic impairment. In a study of 8 patients with chronic hepatic disease,[1] the diuretic response to bumetanide 1 mg was impaired but bumetanide excretion rates were normal.

1. Marcantonio LA, *et al.* The pharmacokinetics and pharmacodynamics of the diuretic bumetanide in hepatic and renal disease. *Br J Clin Pharmacol* 1983; 15: 245–52.

Renal impairment. Renal excretion of bumetanide has been shown to be reduced in patients with chronic renal impairment with a subsequent attenuation of diuretic effect.[1-3] The cumulative pharmacodynamic effects of oral and intravenous doses were essentially similar in patients with renal impairment and transition from intravenous to oral maintenance regimens should pose no special problems.[2]

1. Marcantonio LA, *et al.* The pharmacokinetics and pharmacodynamics of the diuretic bumetanide in hepatic and renal disease. *Br J Clin Pharmacol* 1983; 15: 245–52.
2. Lau HSH, *et al.* Kinetics, dynamics, and bioavailability of bumetanide in healthy subjects and patients with chronic renal failure. *Clin Pharmacol Ther* 1986; 39: 635–45.
3. Howlett MR, *et al.* Metabolism of the diuretic bumetanide in healthy subjects and patients with renal impairment. *Eur J Clin Pharmacol* 1990; 38: 583–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Burinex; ***Austria***: Burinex; ***Belg.***: Burinex; ***Braz.***: Burinax; ***Canad.***: Burinex; ***China***: Bai Chang (百畅); Chang Ze (畅泽); Huiyuan (慧源); Lang Qing (朗清); Ni Chang (尼畅); Shu Tong (抒彤); Wei Xin Hong (卫信宏); Xin Di (辛帝); You Bu Ding (优布丁); ***Denm.***: Burinex; ***Fr.***: Burinex; ***Ger.***: Burinex†; ***Gr.***: Burinex; ***Hong Kong***: Burinex; ***Irl.***: Burinex; ***Malaysia***: Burinex; ***Mex.***: Drenural; Miccil; ***Neth.***: Burinex; ***Norw.***: Burinex; ***NZ***: Burinex; ***Philipp.***: Burinex; ***S.Afr.***: Burinex; ***Singapore***: Burinex; ***Spain***: Fordiuran; ***Swed.***: Burinex; ***Switz.***: Burinex†; ***Turk.***: Bumid; ***UK***: Burinex†; ***USA***: Bumex†; ***Venez.***: Bumelex.

Multi-ingredient Preparations. ***Denm.***: Burinex med kaliumklorid†; ***Gr.***: Burinex K; ***Irl.***: Buram†; ***S.Afr.***: Burinex K; ***Singapore***: Burinex K.

Pharmacopoeial Preparations

BP 2014: Bumetanide and Prolonged-release Potassium Tablets; Bumetanide Injection; Bumetanide Oral Solution; Bumetanide Tablets;

USP 36: Bumetanide Injection; Bumetanide Tablets.

Bunazosin Hydrochloride *(rINNM)*

Bunazosina, hidrocloruro de; Bunazosine, Chlorhydrate de; Bunazosini Hydrochloridum; E-643; Hidrocloruro de bunazosina; Буназозина гидрохлорид.

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-butyrylhexahydro-1*H*-1,4-diazepine monohydrochloride.

$C_{19}H_{27}N_5O_3$,HCl=409.9

CAS — 80755-51-7 (bunazosin); 52712-76-2 (bunazosin hydrochloride).

UNII — 18V54TZ7U6.

Pharmacopoeias. In *Jpn*.

Profile

Bunazosin is an alpha$_1$-adrenoceptor blocker (p. 1243.1) with general properties similar to those of prazosin (p. 1473.3). It is given orally as the hydrochloride in the management of hypertension; the usual maintenance dose of bunazosin hydrochloride is 3 to 6 mg daily after food but up to 12 mg daily has been given.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Detantol R (迪坦妥); ***Ger.***: Andante†; ***Indon.***: Detantol†; ***Jpn***: Detantol; ***Thai.***: Detantol†.

Bupranolol Hydrochloride *(rINNM)* ⊗

8-1312; Bupranolol, Chlorhydrate de; Bupranolol, hidrocloruro de; Bupranololi Hydrochloridum; Hidrocloruro de bupranolol; KL-255; Бупранолола гидрохлорид.

1-*tert*-Butylamino-3-(6-chloro-*m*-tolyloxy)propan-2-ol hydrochloride.

$C_{14}H_{22}ClNO_2$,HCl=308.2

CAS — 14556-46-8 (bupranolol); 15148-80-8 (bupranolol hydrochloride).

ATC — C07AA19.

ATC Vet — QC07AA19.

UNII — DTC2G3GDPL.

Pharmacopoeias. In *Jpn*.

Profile

Bupranolol is a beta blocker (p. 1316.3). It is given as the hydrochloride in usual oral doses of 100 to 400 mg daily in the management of cardiovascular disorders.

Bupranolol eye drops have been used in the management of glaucoma.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Betadrenol†.

Multi-ingredient Preparations. ***Austria***: Betamed.

Butizide *(rINN)* ⊗

Buthiazide; (USAN); Buthiazide; Buttsidi; Butizid; Butizida; Butizidum; Isobutylhydrochlorothiazide; Thiabutazide; Бутизид.

6-Chloro-3,4-dihydro-3-isobutyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_{11}H_{16}ClN_3O_4S_2$=353.8

CAS — 2043-38-1.
UNII — W00SSD35VW.

Profile

Butizide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (p. 1403.2). It is used for oedema, including that associated with heart failure (p. 1262.3), and for hypertension (p. 1251.1).

Butizide is given orally, usually with spironolactone; the usual maintenance dose for oedema or hypertension is 5 to 10 mg daily. It has also been given with other antihypertensive drugs.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Aldactone Saltucin; *Indon.*: Aldazide; *Ital.*: Kadiur; *Mex.*: Aldazida; *Philipp.*: Aldazide; *S.Afr.*: Aldazide; *Switz.*: Aldozone†.

Cadralazine *(BAN, rINN)*

Cadralazina; Cadralazinum; CGP-18684/E; ISF-2469; Kadralatsiini; Kadralazin; Кадралазин.

Ethyl 3-[6-[ethyl(2-hydroxypropyl)amino]pyridazin-3-yl]carbazate.

$C_{12}H_{21}N_5O_3$=283.3

CAS — 64241-34-5.
ATC — C02DB04.
ATC Vet — QC02DB04.
UNII — 8T96I3U713.

NOTE. The name Cadral has been used as a trade mark for cadralazine.

Profile

Cadralazine is a vasodilator with actions and uses similar to those of hydralazine (p. 1401.2). It has been used in the management of hypertension.

Reviews.

1. McTavish D, *et al.* Cadralazine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the treatment of hypertension. *Drugs* 1990; 40: 543–60.

Cafedrine Hydrochloride *(BANM, pINNM)*

Cafedrina, hidrocloruro de; Cafédrine, Chlorhydrate de; Cafedrini Hydrochloridum; H-8351; Hidrocloruro de cafedrina; Kafedrin Hydrochloride; Кафедрина Гидрохлорид.

7-[2-(β-Hydroxy-α-methylphenethylamino)ethyl]theophylline hydrochloride.

$C_{18}H_{23}N_5O_3$.HCl=393.9

CAS — 58166-83-9 (cafedrine); 3039-97-2 (cafedrine hydrochloride).
ATC — C01CA21.
ATC Vet — QC01CA21.
UNII — L0N3M6489R.

Profile

Cafedrine hydrochloride is a derivative of theophylline (p. 1229.3), used mainly in preparations with theodrenaline hydrochloride in the treatment of hypotensive states.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Akrinor†; *Fr.*: Praxinor; *Ger.*: Akrinor; *Indon.*: Akrinor; *S.Afr.*: Akrinor.

Calcitonin Gene-related Peptide

CGRP; Péptido relacionado con el gen de la calcitonina; Пептид, Кодируемый Геном Кальцитонина; Генетически Родственный Кальцитонину Пептид.

Profile

Calcitonin gene-related peptide is an endogenous peptide derived from the calcitonin gene. It has vasodilating activity and has been investigated in the management of peripheral vascular disease (Raynaud's syndrome), heart failure, and for ischaemia following neurosurgery for subarachnoid haemorrhage. The endogenous substance may be involved in the pathophysiology of headache and migraine, and antagonists are under investigation in the management of these conditions.

References.

1. Johnston FG, *et al.* Effect of calcitonin-gene-related peptide on postoperative neurological deficits after subarachnoid haemorrhage. *Lancet* 1990; 335: 869–72.
2. Shawkett S, *et al.* Prolonged effect of CGRP in Raynaud's patients: a double-blind randomised comparison with prostacyclin. *Br J Clin Pharmacol* 1991; 32: 209–13.
3. Shekhar YC, *et al.* Effects of prolonged infusion of human alpha calcitonin gene-related peptide on haemodynamics, renal blood flow and hormone levels in congestive heart failure. *Am J Cardiol* 1991; 67: 732–6.
4. European CGRP in Subarachnoid Haemorrhage Study Group. Effect of calcitonin-gene-related peptide in patients with delayed postoperative cerebral ischaemia after aneurysmal subarachnoid haemorrhage. *Lancet* 1992; 339: 831–4.
5. Bunker CB, *et al.* Calcitonin gene-related peptide in treatment of severe peripheral vascular insufficiency in Raynaud's phenomenon. *Lancet* 1993; 342: 80–2.
6. Feuerstein G, *et al.* Clinical perspectives of calcitonin gene related peptide pharmacology. *Can J Physiol Pharmacol* 1995; 73: 1070–4.
7. Gherardini G, *et al.* Venous ulcers: improved healing by iontophoretic administration of calcitonin gene-related peptide and vasoactive intestinal peptide. *Plast Reconstr Surg* 1998; 101: 90–3.
8. Márquez-Rodas I, *et al.* Pathophysiology and therapeutic possibilities of calcitonin gene-related peptide in hypertension. *J Physiol Biochem* 2006; 62: 45–56.
9. Recober A, Russo AF. Calcitonin gene-related peptide: an update on the biology. *Curr Opin Neurol* 2009; 22: 241–6.

Candesartan Cilexetil

(BANM, USAN, rINNM)

Candésartan, Cilexétil de; Candesartán cilexetilo; Candesartani Cilexetilum; CV-11974 (candesartan); H-212/91; Kandesartan Sileksetil; TCV-116; Кандесартана Силексетил.

Cyclohexyl carbonate ester of (±)-1-hydroxyethyl 2-ethoxy-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-7-benzimidazolecarboxylate.

$C_{33}H_{34}N_6O_6$=610.7

CAS — 139481-59-7 (candesartan); 145040-37-5 (candesartan cilexetil).
ATC — C09CA06.
ATC Vet — QC09CA06.
UNII — R85M2X0D68.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Candesartan Cilexetil). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in dehydrated alcohol; freely soluble in dichloromethane.

USP 36: (Candesartan Cilexetil). A white to off-white powder. Practically insoluble in water; sparingly soluble in methyl alcohol. Store in airtight containers at a temperature between 20 degrees and 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Candesartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p. 1422.2). It is used in the management of hypertension (p. 1251.1) and may also be used in heart failure in patients with impaired left ventricular systolic function, either when ACE inhibitors are not tolerated, or in addition to ACE inhibitors, (see under Losartan Potassium, p. 1423.2).

Candesartan is given orally as the ester prodrug candesartan cilexetil. Onset of antihypertensive action occurs about 2 hours after a dose and the maximum effect is achieved within about 4 weeks of starting therapy.

In the management of **hypertension** the usual initial dose of candesartan cilexetil is 8 mg once daily in the UK, or 16 mg once daily in the USA. The dose should be adjusted according to response; the usual maintenance dose is 8 mg once daily, but doses up to 32 mg daily, as a single dose or in 2 divided doses, may be used. Lower initial doses should be considered in patients with intravascular volume depletion; in the UK an initial dose of 4 mg once daily is suggested. Patients with renal or hepatic impairment may also require low initial doses (see below). For doses in children, see Administration in Children, below.

In **heart failure,** candesartan cilexetil is given in an initial dose of 4 mg once daily. The dose should be doubled at intervals of not less than two weeks up to 32 mg once daily if tolerated; blood pressure should be monitored during dose increases.

Reviews.

1. See S, Stirling AL. Candesartan cilexetil: an angiotensin II-receptor blocker. *Am J Health-Syst Pharm* 2000; 57: 739–46.
2. Basthope SE, Jarvis B. Candesartan cilexetil: an update of its use in essential hypertension. *Drugs* 2002; 62: 1253–87.
3. Fenton C, Scott LJ. Candesartan cilexetil: a review of its use in the management of chronic heart failure. *Drugs* 2005; 65: 537–58.
4. McKelvie RS. Candesartan for the management of heart failure: more than an alternative. *Expert Opin Pharmacother* 2006; 7: 1945–56.
5. Meredith PA. Candesartan cilexetil—a review of effects on cardiovascular complications in hypertension and chronic heart failure. *Curr Med Res Opin* 2007; 23: 1693–1705.
6. Mendis B, Page SR. Candesartan: widening indications for this angiotensin II receptor blocker? *Expert Opin Pharmacother* 2009; 10: 1995–2007.

Administration in children. Candesartan cilexetil is used for the treatment of hypertension in children from 1 year of age. It is given in the following oral doses, either as a single daily dose or in 2 divided doses:

- 1 up to 6 years: initially 200 micrograms/kg daily, adjusted according to response to 50 to 400 micrograms/kg daily
- 6 up to 17 years and weighing less than 50 kg: initially 4 to 8 mg daily, adjusted according to response to 2 to 16 mg daily
- 6 up to 17 years and weighing more than 50 kg: initially 8 to 16 mg daily, adjusted according to response to 4 to 32 mg daily

Administration in hepatic impairment. The elimination of candesartan cilexetil is reduced in patients with hepatic impairment. For patients with *hypertension,* an initial oral dose of 4 mg once daily is recommended in the UK in those with mild or moderate impairment. In the USA, no adjustment is considered necessary for patients with mild impairment; an initial oral dose of 8 mg once daily is recommended for those with moderate impairment.

For patients with *heart failure,* no dose adjustments are considered necessary in those with mild to moderate impairment as initial doses are lower for this condition (see Uses and Administration, above).

There is no experience of use in patients with severe hepatic impairment.

Administration in renal impairment. The elimination of candesartan cilexetil is reduced in patients with renal impairment (including patients on haemodialysis[1]) and lower doses may therefore be required.

For patients with *hypertension,* an initial oral dose of 4 mg once daily is recommended in the UK, including for patients on haemodialysis. In the USA, no initial dose adjustment is recommended for renal impairment, although dose reduction may be considered if patients are volume depleted.

For patients with *heart failure,* dose adjustments are not necessary as initial doses are lower for this condition (see Uses and Administration, above).

Candesartan may also have adverse effects on renal function and regular monitoring is advised; treatment may need to be withheld or stopped if renal function deteriorates.

1. Ottosson P, *et al.* Candesartan cilexetil in haemodialysis patients. *Clin Drug Invest* 2003; 23: 545–50.

Diabetic complications. For mention of the potential use of angiotensin II receptor antagonists, including candesartan, in the management of diabetic complications such as retinopathy see under Losartan, p. 1423.1.

Migraine. For reference to the use of angiotensin II receptor antagonists, including candesartan, in the prophylaxis of migraine, see under Losartan, p. 1423.3.

Adverse Effects and Precautions

As for Losartan Potassium, p. 1424.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies candesartan as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

As for Losartan Potassium, p. 1424.3.

Pharmacokinetics

Candesartan cilexetil is an ester prodrug that is hydrolysed to the active form candesartan during absorption from the gastrointestinal tract. The absolute bioavailability for candesartan is about 40% when candesartan cilexetil is given as a solution and about 14% when given as tablets. Peak plasma concentrations of candesartan occur about 3 to 4 hours after oral doses as tablets. Candesartan is more than 99% bound to plasma proteins. It is excreted in urine and bile mainly as unchanged drug with a small amount as inactive metabolites. The terminal elimination half-life is about 9 hours. Candesartan is not removed by haemodialysis.

Reviews.

1. Gleiter CH, Mörike KE. Clinical pharmacokinetics of candesartan. *Clin Pharmacokinet* 2002; 41: 7–17.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Atacand; Dacten; Tiadyl; *Austral.*: Atacand; *Austria*: Atacand; Blopress; *Belg.*: Atacand; *Braz.*: Atacand; Blopress; *Canad.*: Atacand; *Chile*: Atacand; Bilaten; Blopress; Blox; Candex; *China*: Ao Bi Xin (奥必欣); Blopress (必洛斯); Bo Li Gao (搏力高); Da Mai (达迈); Di Zhi Ya (迪之雅); Ni Li An (伲利安); Su Na (苏纳); Wei Er Ya (维尔

亚); Xi Jun Ning (悉君宁); Cz.: Atacand†; Texacand; Xaleec; *Denm.*: Amias; Atacand; Candemox; Candexetil†; *Fin.*: Atacand; Candemox; Candestad; Candexetil; Kandrozid; *Fr.*: Atacand; Kenzen; *Ger.*: Atacand; Blopress; *Gr.*: Atacand; *Hong Kong*: Blopress; *Hung.*: Atacand; *India*: Candelong; Candesar; Candestan; Cantar; Ipsita; *Indon.*: Blopress; *Irl.*: Atacand; Blopress; Candist; Catasart; *Israel*: Atacand; *Ital.*: Blopress; Ratacand; *Jpn*: Blopress; *Malaysia*: Atacand; Blopress; *Mex.*: Atacand; Blopress; *Neth.*: Aldireca; Amias†; Atacand; Blopress; Casarlic; Kairasec; Karbis; Omegacand; Ratacand†; Silardaf; Texacand; *Norw.*: Amias; Atacand; *NZ*: Atacand; Cardosart; *Philipp.*: Blopress; Candelong; Candez; *Pol.*: Atacand; Karbis; *Port.*: Atacand; Blopress; *Rus.*: Atacand (Атаканд); *S.Afr.*: Atacand; *Singapore*: Atacand; *Spain*: Atacand; Blopress; Karbis; Parapres; *Swed.*: Atacand; Candesarstad; Candexetil; *Switz.*: Atacand; Blopress; Cansartan; Pemzek; *Thai.*: Blopress; *Turk.*: Atacand; Ayra; Candexil; Cantab; Tensart; *UK*: Amias; *Ukr.*: Atacand (Атаканд); Candesar (Кандесар); Kasark (Касарк); *USA*: Atacand; Candepressin; *Venez.*: Atacand; Blopress.

Multi-ingredient Preparations. *Arg.*: Atacand D; Atacand Duo; Dacten D; Tiadyl Plus; *Austral.*: Atacand Plus; *Austria*: Atacand Plus; Blopress Plus; *Belg.*: Atacand Plus; *Braz.*: Atacand Comb; Atacand HCT; *Canad.*: Atacand Plus; *Chile*: Atacand Plus; Bilaten-D; Blopress D; Blox-D; Candex-D; *China*: Bokaiqing (波开清); *Cz.*: Atacand Plus†; Texacandozid; Xaleec Combi; *Denm.*: Atacand Zid; Atazid†; Candemox Comp; Candexetil comp; Hytacand; Ratacand Plus; Ratacand Zid†; *Fin.*: Atacand Plus; Candemox Comp; Candestad Comp; Candexetil Comp; *Fr.*: Cokenzen; Hytacand; *Ger.*: Atacand Plus; Blopress Plus; *Gr.*: Atacand Plus; *Hong Kong*: Blopress Plus; *Hung.*: Atacand Plus; *India*: Candelong-H; Candesar-H; *Indon.*: Blopress Plus; *Irl.*: Atacand Plus; Blopress Plus; Candist Plus; Catasart Plus; *Israel*: Atacand Plus; Candesartan Plus; *Ital.*: Blopresid; Ratacand Plus; *Jpn*: Unisia; *Malaysia*: Atacand Plus; *Mex.*: Atacand Plus; Blopress Plus; *Neth.*: Atacand Plus; Blopresid; Cocardax; Omegacand HCT; Texacand HCT; *Norw.*: Atacand Plus; *Philipp.*: Blopress Plus; *Pol.*: Candepres HCT; *Port.*: Blopress Comp; Hytacand; *Rus.*: Atacand Plus (Атаканд Плюс); *S.Afr.*: Atacand Plus; *Singapore*: Atacand Plus; *Spain*: Atacand Plus; Blopress Forte; Blopress Plus; Karbicombi; Parapres Plus; *Swed.*: Atacand Plus; Candemox Comp; *Switz.*: Atacand Plus; Blopress Plus; Cansartan Plus; Co-Candesartan; Pemzek Plus; *Thai.*: Blopress Plus; *Turk.*: Atacand Plus; Ayra Plus; Candexil Plus; Co-Cantab; Tensart Plus; *Ukr.*: Atacand Plus (Атаканд Плюс); Candesar H (Кандесар Н); Kasark H (Касарк Н); Kasark HD (Касарк HD); *USA*: Atacand HCT; Candepressin Plus; *Venez.*: Atacand Plus; Blopress Plus.

Cangrelor Tetrasodium *(BANM, USAN, rINNM)*

AR-C69931MX (cangrelor tetrasodium); AR-C69931XX (cangrelor); Cangrelor tetrasódico; Cangrélor tetrasodique; Cangrelorum tetranatricum; Кангрелор Тетранатрий.

N-[2-(Methylthio)ethyl]-2-[(3,3,3-trifluoropropyl)thio]-5′-adenylic acid monoanhydride with tetrasodium (dichloromethylene)diphosphonate.

$C_{17}H_{21}Cl_2F_3N_5Na_4O_{12}P_3S_2$=864.3

CAS — 163706-06-7 (cangrelor); 163706-36-3 (cangrelor tetrasodium).

UNII — 2144G00Y7W.

Profile

Cangrelor is an adenosine triphosphate analogue, similar to ticagrelor (p. 1511.3). It has a short half-life and is given intravenously. It is under investigation as an antiplatelet drug in the management of acute coronary syndromes but large studies have not shown any benefit over currently available drugs.

References.

1. Harrington RA, *et al.* Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med* 2009; 361: 2318–29.
2. Bhatt DL, *et al.* CHAMPION PLATFORM Investigators. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med* 2009; 361: 2330–41.

Canrenone *(USAN, pINN)* ⊗

Aldadiene; Canrenona; Canrénone; Canrenonum; RP-11614; SC-9376; Канренон.

17-Hydroxy-3-oxo-17α-pregna-4,6-diene-21-carboxylic acid γ-lactone.

$C_{22}H_{28}O_3$=340.5

CAS — 976-71-6.

ATC — C03DA03.

ATC Vet — QC03DA03.

UNII — 78O20X9J0U.

Profile

Canrenone is a potassium-sparing diuretic with properties similar to those of spironolactone (p. 1501.2) and is given orally in the treatment of refractory oedema associated with heart failure (p. 1262.3), renal, or hepatic disease, and in hypertension (p. 1251.1). It is a metabolite of both spironolactone and potassium canrenoate (p. 1472.2). It is given in usual doses of 50 to 200 mg daily. Doses of up to 300 mg daily may be required in some patients.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Luvion.

Captopril *(BAN, USAN, rINN)*

Captoprilum; Kaptoprilli; Kaptopril; Kaptoprilis; SQ-14225; Каптоприл.

1-[(2*S*)-3-Mercapto-2-methylpropionyl]-L-proline.

$C_9H_{15}NO_3S$=217.3

CAS — 62571-86-2.

ATC — C09AA01.

ATC Vet — QC09AA01.

UNII — 9G64RSX1XD.

NOTE. Compounded preparations of captopril may be represented by the following names:

- Co-zidocapt (*BAN*)—captopril 2 parts and hydrochlorothiazide 1 part (w/w).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Captopril). A white or almost white crystalline powder. Soluble in water; freely soluble in dichloromethane and in methyl alcohol. It dissolves in dilute solutions of alkali hydroxides. A 2% solution in water has a pH of 2.0 to 2.6.

USP 36: (Captopril). A white or off-white crystalline powder which may have a characteristic sulfide-like odour. Freely soluble in water, in alcohol, in chloroform, and in methyl alcohol. Store in airtight containers.

Stability. Although captopril itself is relatively stable[1] at temperatures up to 50 degrees, and extemporaneously prepared powders (made by triturating the tablets with lactose) have been reported to be stable for at least 12 weeks at room temperature,[2] aqueous solutions are subject to oxidative degradation, mainly to captopril disulfide,[1] which increases[3] with increase in pH above 4. The manufacturers report that a liquid form of captopril prepared from pulverised tablets in distilled water containing 1 mg/mL retained 96.6% of the original concentration of drug after storage at room temperature for 5 days, but they advise that since it contains no preservative it should be used within 2 days of preparation.[4] Others have reported wide variations in stability depending upon the formulation. In one study[5] the shelf-life of a solution of captopril 1 mg/mL prepared from crushed tablets and tap water was estimated to be 27 days when stored at 5 degrees. However, in another study[6] captopril was much less stable; in sterile water for irrigation captopril was stable for at least 3 days when stored at 5 degrees, but in tap water it disappeared at a much faster rate. Increased stability has been reported after the addition of sodium ascorbate to the solution,[7] and with captopril powder rather than crushed tablets.[8] A 1 mg/mL preparation made with crushed tablets and undiluted syrup has also been reported to be stable for 30 days at 5 degrees and may be more palatable than aqueous formulations.[9]

1. Lund W, Cowe HJ. Stability of dry powder formulations. *Pharm J* 1986; 237: 179–80.
2. Taketomo CK, *et al.* Stability of captopril in powder papers under three storage conditions. *Am J Hosp Pharm* 1990; 47: 1799–1801.
3. Timmins P, *et al.* Factors affecting captopril stability in aqueous solution. *Int J Pharmaceutics* 1982; 11: 329–36.
4. Andrews CD, Essex A. Captopril suspension. *Pharm J* 1986; 237: 734–5.
5. Pereira CM, Tam YK. Stability of captopril in tap water. *Am J Hosp Pharm* 1992; 49: 612–15.
6. Analizi NH, Swenson C. Instability of aqueous captopril solutions. *Am J Hosp Pharm* 1993; 50: 486–8.
7. Nahata MC, *et al.* Stability of captopril in three liquid dosage forms. *Am J Hosp Pharm* 1994; 51: 95–6.
8. Chan DS, *et al.* Degradation of captopril in solutions compounded from tablets and standard powder. *Am J Hosp Pharm* 1994; 51: 1205–7.
9. Lye MYF, *et al.* Effects of ingredients on stability of captopril in extemporaneously prepared oral liquids. *Am J Health-Syst Pharm* 1997; 54: 2483–7.

Uses and Administration

Captopril is a sulfhydryl-containing ACE inhibitor (p. 1282.2). It is used in the management of hypertension (p. 1251.1), in heart failure (p. 1262.3), after myocardial infarction (p. 1257.1), and in diabetic nephropathy (see Kidney Disorders, p. 1284.1).

After oral doses captopril produces a maximum effect within 1 to 2 hours, although the full effect may not develop for several weeks during chronic dosing. The duration of action is dose-dependent and may persist for 6 to 12 hours.

In the treatment of **hypertension** the initial oral dose is 12.5 mg twice daily, increased gradually at intervals of 2 to 4 weeks according to the response. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. An initial dose of 6.25 mg twice daily is recommended if captopril is given in addition to a *diuretic* or to elderly patients; if possible the diuretic should be stopped 2 or 3 days before introducing captopril. The usual maintenance dose is 25 to 50 mg twice daily and should not normally exceed 50 mg three times daily. If hypertension is not satisfactorily controlled at this dosage, addition of a second drug or substitution of an alternative drug should be considered. In the USA higher doses of up to 150 mg three times daily have been suggested for patients with hypertension uncontrolled by lower doses of captopril used with diuretic therapy.

In the treatment of **heart failure** severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus an initial oral dose of 6.25 to 12.5 mg of captopril is given under close medical supervision; the usual maintenance dose is 25 mg two or three times daily, and doses should not normally exceed 50 mg three times daily. Again, in the USA higher doses of up to 150 mg three times daily have been suggested.

After **myocardial infarction**, captopril is used prophylactically in clinically stable patients with symptomatic or asymptomatic left ventricular dysfunction to improve survival, delay the onset of symptomatic heart failure, and reduce recurrent infarction. Captopril is licensed for *acute* treatment starting within 24 hours of the onset of symptoms in patients with stable haemodynamics. A 6.25-mg test dose is given, followed by 12.5 mg after 2 hours, and 25 mg after another 12 hours. If tolerated, a dose of 50 mg twice daily may be started the following day and continued for 4 weeks, before considering adjustment to the maintenance dose for chronic treatment described below.

If not given within 24 hours of the onset of symptoms, *chronic* treatment with captopril may be started within 3 to 16 days post-infarction at an initial dose of 6.25 mg, followed by 12.5 mg three times daily for 2 days, then 25 mg three times daily. The maintenance dose is between 75 and 150 mg daily in 2 or 3 divided doses.

In **diabetic nephropathy** (microalbuminuria greater than 30 mg/day) in type 1 diabetics, 75 to 100 mg of captopril may be given daily, in divided oral doses. Other antihypertensives may be used with captopril if a further reduction in blood pressure is required.

For doses in children, see below.

Doses may need to be reduced in patients with renal impairment (see p. 1332.1).

Administration. Captopril is generally given orally. Sublingual[1] and intravenous[2,3] dosage has also been tried, but these routes are not established.

1. Angeli P, *et al.* Comparison of sublingual captopril and nifedipine in immediate treatment of hypertensive emergencies: a randomized, single-blind clinical trial. *Arch Intern Med* 1991; 151: 678–82.
2. Savi L, *et al.* A new therapy for hypertensive emergencies: intravenous captopril. *Curr Ther Res* 1990; 47: 1073–81.
3. Langes K, *et al.* Efficacy and safety of intravenous captopril in congestive heart failure. *Curr Ther Res* 1993; 53: 167–76.

Administration in children. Experience with captopril in children is limited, but it may be given orally for indications similar to those in adults (see Uses and Administration, above). UK licensed product information suggests an initial dose of 300 micrograms/kg in children and adolescents: half this dose should be given initially to neonates and infants (including premature infants), and children with renal impairment. The dose is adjusted according to response to a maximum of 6 mg/kg daily in 2 or 3 divided doses.

Captopril, given in an initial dose of 250 micrograms/kg daily, increased to up to 2.5 or 3.5 mg/kg daily in 3 divided doses, has also been reported to produce benefit in infants with severe heart failure secondary to congenital defects (mainly manifesting as left-to-right shunt).[1,2]

The following doses of captopril are suggested by the *BNFC* for hypertension, heart failure, or proteinuria in nephritis:

- neonate: test dose, 10 to 50 micrograms/kg (if the neonate is less than 37 weeks postmenstrual age give 10 micrograms/kg) with careful monitoring of blood pressure for 1 to 2 hours; if tolerated, give 10 to 50 micrograms/kg 2 or 3 times daily, increased as necessary to a maximum of 2 mg/kg daily in divided doses (maximum of 300 micrograms/kg daily in divided doses if the neonate is less than 37 weeks postmenstrual age)
- child 1 month to 12 years: test dose, 100 micrograms/kg (maximum 6.25 mg) with careful monitoring of blood pressure for 1 to 2 hours; if tolerated, give 100 to 300 micrograms/kg 2 or 3 times daily, increased as necessary to a maximum of 6 mg/kg daily in divided doses (maximum of 4 mg/kg daily in divided doses in child 1 month to 1 year)
- child 12 years to 18 years: test dose, 100 micrograms/kg or 6.25 mg with careful monitoring of blood pressure for 1 to 2 hours; if tolerated, give 12.5 to 25 mg 2 or 3 times

daily, increased as necessary to a maximum of 150 mg daily in divided doses

The *BNFC* also suggests the same dose in children aged 12 years and over for diabetic nephropathy.

1. Scammell AM, *et al.* Captopril in treatment of infant heart failure: a preliminary report. *Int J Cardiol* 1987; 16: 295–301.
2. Shaw NJ, *et al.* Captopril in heart failure secondary to a left to right shunt. *Arch Dis Child* 1988; 63: 360–3.

Administration in renal impairment. The dose of captopril should be reduced or the dosage interval increased in adults with renal impairment, depending on their creatinine clearance (CC) per 1.73m². The following doses have been suggested:

- CC 21 to 40 mL/minute: initial daily dose 25 mg and maximum daily dose 100 mg
- CC 10 to 20 mL/minute: initial daily dose 12.5 mg and maximum daily dose 75 mg
- CC below 10 mL/minute: initial daily dose 6.25 mg and maximum daily dose 37.5 mg

If a diuretic also needs to be given, a loop diuretic should be chosen rather than a thiazide.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Captopril has been reported to cause false positive results in tests for acetone in urine.

Incidence of adverse effects. Results of postmarketing surveillance[1] in 30 515 hypertensive patients taking captopril showed that 4.9% had their therapy stopped because of adverse effects thought to be due to the drug. The mean initial daily dose was 46 mg; at final evaluation the mean daily dose was 58 mg. The adverse effect most commonly reported was headache (in 1.8%); others included dizziness (1.6%), rashes (1.1%), nausea (1.0%), taste disturbances (0.9%), and cough (0.8%). This study excluded patients with renal impairment but an earlier survey[2] in 6737 patients taking captopril alone or in combination found that rash and dysgeusia were more frequent in patients with renal impairment (occurring in 6.2% and 3.2% respectively of those receiving 150 mg daily or less of captopril) than in those with normal serum creatinine (4.3% and 2.2%). The frequency of both symptoms was somewhat higher in those given higher doses. Symptoms of hypotension occurred in about 5% of patients and were not influenced by dose or renal function. The cumulative frequency of withdrawal due to adverse effects was estimated at 5.8% in this study, which is similar to that in the larger survey. In another postmarketing surveillance study[3] involving more than 60 000 patients, captopril was withdrawn in 8.9% because of adverse effects.

For further reference to some of these adverse effects, see under ACE Inhibitors, p. 1285.2.

1. Schoenberger JA, *et al.* Efficacy, safety, and quality-of-life assessment of captopril antihypertensive therapy in clinical practice. *Arch Intern Med* 1990; 150: 301–6.
2. Jenkins AC, *et al.* Captopril in hypertension: seven years later. *J Cardiovasc Pharmacol* 1985; 7 (suppl 1): S96–S101.
3. Chalmers D, *et al.* Postmarketing surveillance of captopril for hypertension. *Br J Clin Pharmacol* 1992; 34: 215–23.

Breast feeding. Captopril is distributed into breast milk and licensed product information advises that breast feeding should be avoided. However, a study[1] in 12 women found that the concentration of captopril in breast milk was about 1% of maternal blood concentrations, suggesting that the amount ingested by the infant would be very low. No adverse effects were noted in the infants in this study, and the American Academy of Pediatrics considers[2] that captopril is therefore usually compatible with breast feeding.

For advice from UK regulatory authorities against the use of any ACE inhibitor during at least the early weeks of breast feeding see under Precautions of ACE Inhibitors, p. 1287.3.

1. Devlin RG, Fleiss PM. Captopril in human blood and breast milk. *J Clin Pharmacol* 1981; 21: 110–113.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 05/07/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies captopril as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

About 60 to 75% of a dose of captopril is absorbed from the gastrointestinal tract and peak plasma concentrations occur within about an hour. Absorption has been reported to be reduced in the presence of food, but this may not be clinically relevant (see below). Captopril is about 30% bound to plasma proteins. It crosses the placenta and is found in breast milk at about 1% of maternal blood concentrations. It is largely excreted in the urine, 40 to 50% as unchanged drug, the rest as disulfide and other metabolites. The elimination half-life has been reported to be 2 to 3 hours but this is increased in renal impairment. Captopril is removed by haemodialysis.

Reviews.

1. Duchin KL, *et al.* Pharmacokinetics of captopril in healthy subjects and in patients with cardiovascular diseases. *Clin Pharmacokinet* 1988; 14: 241–59.

Absorption. The bioavailability and peak plasma concentrations of captopril have been shown to be reduced by 25 to 55% when given with food in single dose studies[1–4] and with chronic dosing.[5] However, this may not be clinically significant since several studies[3,4,6] indicated that food intake had no effect on the antihypertensive activity of captopril.

1. Williams GM, Sugerman AA. The effect of a meal, at various times relative to drug administration, on the bioavailability of captopril. *J Clin Pharmacol* 1982; 22: 18A.
2. Singhvi SM, *et al.* Effect of food on the bioavailability of captopril in healthy subjects. *J Clin Pharmacol* 1982; 22: 135–40.
3. Mäntylä R, *et al.* Impairment of captopril bioavailability by concomitant food and antacid intake. *Int J Clin Pharmacol Ther Toxicol* 1984; 22: 626–9.
4. Müller HM, *et al.* The influence of food intake on pharmacodynamics and plasma concentration of captopril. *J Hypertens* 1985; 3 (suppl 2): S135–S136.
5. Öhman KP, *et al.* Pharmacokinetics of captopril and its effects on blood pressure during acute and chronic administration and in relation to food intake. *J Cardiovasc Pharmacol* 1985; 7 (suppl 1): S20–S24.
6. Izumi Y, *et al.* Influence of food on the clinical effect of angiotensin I converting enzyme inhibitor (SQ 14225). *Tohoku J Exp Med* 1983; 139: 279–86.

Renal impairment. A study of 9 patients with chronic renal failure undergoing dialysis found that after a single dose of captopril, peak plasma concentrations were 2.5 times higher than in patients with normal renal function, and peak concentrations of its disulfide metabolites were 4 times higher.[1] Peak concentrations occurred later in uraemic patients and the apparent half-life of total captopril was 46 hours in uraemic patients compared with 2.95 hours in patients with normal renal function.

1. Drummer OH, *et al.* The pharmacokinetics of captopril and captopril disulfide conjugates in uraemic patients on maintenance dialysis: comparison with patients with normal renal function. *Eur J Clin Pharmacol* 1987; 32: 267–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Antasten†; *Austral.*: Acenorm; Capoten; Captohexal†; Topace†; Zedace; *Austria*: Capace†; Debax; *Belg.*: Capoten; Capriltop†; Doccaptopri†; *Braz.*: Aorten; Capobal; Capoten; Capotrat; Capotrineo; Capox; Capril; Captolab; Captomed; Captomido; Capton; Captopiril; Captopron; Captotec; Captrizin†; Catoprol†; Ductopril; Hipoten; Normapril; Pressomax†; Prilpressin; Repril; *Canad.*: Apo-Capto; Capoten; Novo-Captoril†; Nu-Capto; *Chile*: Capoten; Properil; *China*: An Ting (安汀); Bang De Mei (邦德美); Capoten (开博通); Kai Pu Lin (开富林); Ya Ning (压宁); *Cz.*: Capoten†; Tensiomin; *Denm.*: Capoten†; Captol; Captovis; *Fin.*: Captomin†; Captostad†; Lopril; *Fr.*: Captolane†; Lopril; *Ger.*: ACE-Hemmer; Adocor†; Capto†; Captobeta; Captodoc†; Captoflux†; Captogamma; Captohexal†; cor tensobon†; Jucapt†; Lopirin†; Tensiomin-Cor†; Tensiomin†; Tensobon†; Tensostad†; *Gr.*: Capoten; Cregar; Ptonavil; Hypotensor; Neo-Ipertas; Normolose; Odupril; Pertacilon; Sancap; *Hong Kong*: Capoten†; Kimafan†; Novo-Captoril†; Ropril†; Tensiomin; *Hung.*: Aceomel; Captogamma†; Tensiomin; *India*: Aceten; Capace; Capotril; *Indon.*: Acepress; Capoten†; Captensin; Casipril†; Dexacap; Farmoten; Forten†; Locap†; Lotensin; Metopril; Otoryl; Praten†; Scantensin; Tenofax†; Tensicap; Tensobon; Vapril; *Irl.*: Aceomel; Capoten; Caprill†; Captor; Geroten†; *Israel*: Aceril; *Ital.*: Acepress†; Capoten; *Malaysia*: Apuzin; Kimafan; *Mex.*: Altiver; Atrisol; Biodezil; Bioxil; Brucap; Bugazon†; Capotena; Captoser; Captral; Cardipril; Catona; Cryopril; Eca Presan; Ecapril; Ecaten; Enlace; Hipertex; Kenolan; Lenpryl; Midrat; Miocap†; Novapress; Ospil; Precaptil†; Prinarten; Proldin; Ranpres; Reductel; Reduprec; Rilten; Romir; Tenca-1; Tensil; Toprifar; Toprilem†; Tropix-HC†; Varaxil; *Norw.*: Capoten†; *NZ*: Capoten; Captohexal†; *Philipp.*: Ace-Bloc; Bloc-Med; Capomed; Capotec; Capoten†; Captogen; Captor; Captril; Cardiovaz; Conamid; Hartylox; Normil; Prelat; Primace; Retensin; Spec-Ace; Tensoril; Unihype; Vasostad; *Port.*: Capoten; Capritin; Carencil; Hipertil†; Hipotensil; Pressil; Prilovase†; Vidapril; *Russ.*: Aceten (Ацетен)†; Angiopril (Ангиоприл); Apo-Capto (Апо-каптo)†; Blocordil (Блокордил); Capopharm (Капофарм); Capoten (Каптен); Rilcapton (Рилкаптон); *S.Afr.*: Aceten†; Adco-Captomax; Capace; Capoten; Captohexal; Cardiace†; Zapto; *Singapore*: Apo-Capto; Catoplin; Dexacap; Epsitron; Kapril; Rilcapton; *Spain*: Capoten; Captosina; Cesplon†; Dilabar†; Tensoprel; *Switz.*: Captosol; Lopirin†; *Thai.*: Capoten†; Capril; Epsitron; Gemzil; Tensiomin; *Turk.*: Kapril; Kaptoril; *UAE*: Captophar; *UK*: Acepril; Capoten; Ecopace; Kaplon; Tensopril†; *USA*: Capoten; *Venez.*: Capoten; Tabulan.

Multi-ingredient Preparations. *Austria*: Capozide; Captohexal Comp†; Captopril-HCT; Co-Captopril; Veracapt; *Braz.*: Capoxi H; Captotec + HCT; Hidropril; Lopril-D; *China*: Kai Fu Te (开富特); *Denm.*: Capozid†; Capthydro; *Fr.*: Captea; Ecazide; *Ger.*: ACE-Hemmer comp; Adocomp†; Capozide†; Capto Comp†; Capto Plus†; Captobeta Comp; Captodoc Comp†; Captogamma HCT; Captohexal Comp†; Captopril Comp†; Captopril HCT†; Captopril Plus†; Cardiagen HCT†; Jutacor comp†; Tensobon comp; *Gr.*: Anastol; Captopress; Captospes+H; Dosturel; Ekzevit; Empirol; Fetylan; Ketazide; Kifarol; Loren-Press; Normolose-H; Pentatec; Piesital; Return; Sancazid; Sedapressin; Superace; Uresan; Zidepril; *India*: Acezide; Angiopril-DU; Capotril-L; *Indon.*: Capozide†; *Irl.*: Capozide; Captor-HCT; Half Capozide; *Ital.*: Acediur; Aceplus; *Mex.*: Capozide; Captral ASA; Co-Captral; *NZ*: Capozide; *Port.*: Lopiretic; *Russ.*: Capozide (Капозид); *S.Afr.*: Capozide†; Captoretic†; Zapto Co; *Spain*: Cesplon Plus†; Dilabar Diu; Ecadiu†; Ecazide; *Switz.*: Capozide†; Captosol comp; Tensobon comp†; *UK*: Acezide; Capozide; Capto-Co; *Ukr.*: Capotiasid (Капотиазид); Captopres (Каптопрес); Normopres (Нормопрес); *USA*: Capozide; *Venez.*: Capozide.

Pharmacopoeial Preparations

BP 2014: Captopril Oral Solution; Captopril Tablets;
USP 36: Captopril and Hydrochlorothiazide Tablets; Captopril Oral Solution; Captopril Oral Suspension; Captopril Tablets.

Carazolol *(BAN, rINN)* ⊗

BM-51052; Carazololum; Каразолол,
1-(Carbazol-4-yloxy)-3-isopropylaminopropan-2-ol.
$C_{18}H_{22}N_2O_2$=298.4
CAS — 57775-29-8.
ATC Vet — QC07AA90.
UNII — 29PW75S82A.

Profile

Carazolol is a beta blocker (p. 1316.3) that is used in veterinary medicine.

Carperitide *(USAN, rINN)* ⊗

Carperitida; Carpéritide; Carperitidum; SUN-4936; Карпептид.
CAS — 89213-87-6.
UNII — GZ8FA500J0.

Profile

Carperitide is a recombinant atrial natriuretic peptide (see p. 1444.1) used in the management of acute heart failure

References.

1. Suwa M, *et al.* Multicenter prospective investigation on efficacy and safety of carperitide for acute heart failure in the 'real world' of therapy. *Circ J* 2005; 69: 283–90.
2. Hata N, *et al.* Effects of carperitide on the long-term prognosis of patients with acute decompensated chronic heart failure: the PROTECT multicenter randomized controlled study. *Circ J* 2008; 72: 1787–93.
3. Nomura F, *et al.* Multicenter prospective investigation on efficacy and safety of carperitide as a first-line drug for acute heart failure syndrome with preserved blood pressure. COMPASS: Carperitide Effects Observed Through Monitoring Dyspnea in Acute Decompensated Heart Failure Study. *Circ J* 2008; 72: 1777–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Hanp.

Carteolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Abbott-43326; Cartéolol, Chlorhydrate de; Carteolol, hidrocloruro de; Carteololhydrochlorid; Carteololi Hydrochloridum; Hidrocloruro de carteolol; Karteolol Hidroklorür; Karteolol-hidroklorid; Karteolol-hydrochlorid; Karteololhydroklorid; Karteololihydrokloridi; Karteololio hidrochloridas; OPC-1085; Карteолола гидрохлорид.
5-(3-*tert*-Butylamino-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one hydrochloride.
$C_{16}H_{24}N_2O_3$,HCl=328.8
CAS — 51781-06-7 (carteolol); 51781-21-6 (carteolol hydrochloride).
ATC — C07AA15; S01ED05.
ATC Vet — QC07AA15; QS01ED05.
UNII — 4797W6I0T4.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Carteolol Hydrochloride). White or almost white crystals or crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane; sparingly soluble in methyl alcohol. A

1% solution in water has a pH of 5.0 to 6.0. Store in airtight containers.

USP 36: (Carteolol Hydrochloride). pH of a 1% solution in water is between 5.0 and 6.0.

Uses and Administration

Carteolol is a non-cardioselective beta blocker (see p. 1316.3). It is reported to possess intrinsic sympathomimetic activity but lacks significant membrane-stabilising activity.

Carteolol is used as the hydrochloride in the management of glaucoma (p. 1999.1), hypertension (p. 1251.1), and some cardiac disorders such as angina pectoris (p. 1254.3) and cardiac arrhythmias (p. 1266.1).

Eye drops containing carteolol hydrochloride 1% or 2% are instilled twice daily to reduce raised intra-ocular pressure in open-angle **glaucoma** and ocular hypertension.

In **hypertension, angina pectoris, and arrhythmias,** carteolol hydrochloride is given orally in a usual dose range of 2.5 to 30 mg daily, adjusted according to response.

The oral dose of carteolol hydrochloride should be reduced in patients with renal impairment (see below).

Reviews.

1. Chrisp P, Sorkin EM. Ocular carteolol: a review of its pharmacological properties, and therapeutic use in glaucoma and ocular hypertension. *Drugs Aging* 1992; **2**: 58–77. Correction. *ibid.* 1994; **4**: 62.
2. Henness S, *et al.* Ocular carteolol: a review of its use in the management of glaucoma and ocular hypertension. *Drugs Aging* 2007; **24**: 509–28.

Administration in renal impairment. The oral dose of carteolol hydrochloride should be reduced in patients with renal impairment. A suggested regimen based on creatine clearance (CC) for patients with hypertension is as follows:

- CC 30 to 80 mL/minute: 10 mg daily
- CC less than 30 mL/minute: use not recommended

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies carteolol as not porphyrinogenic when used as eye drops; it may be used as a drug of first choice and no precautions are needed. A classification is not given for systemic carteolol.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Carteolol is well absorbed from the gastrointestinal tract; peak plasma concentrations occur within 1 to 4 hours of oral doses. The bioavailability is about 84%. It has low lipid solubility. About 20 to 30% is protein bound. The plasma half-life is reported to be 3 to 6 hours. The major route of elimination is renal with 50 to 70% of a dose being excreted unchanged in the urine; carteolol therefore accumulates in patients with renal disease. Major metabolites are 8-hydroxycarteolol and glucuronic acid conjugates of carteolol and 8-hydroxycarteolol. The 8-hydroxycarteolol metabolite is active; its half-life is reported to be 8 to 12 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cartens: Elebloc; Glacout†; Glauteolol; Poenglaucol; Singlauc; Tenoftal; ***Belg.***: Arteoptic; Carteabak; Carteol; ***China***: Mikelan (美开朗); ***Cz.***: Arteoptic; Carteol; ***Fr.***: Carteabak†; Carteol; Mikelan; ***Ger.***: Arteoptic; Endak; ***Gr.***: Cardelol; Carteodose; Fortinol; Glauteol; Napolit; Stobol; Vinitus; Zymoptic; ***Hong Kong***: Arteoptic; ***Hung.***: Fortinol†; ***Irl.***: Teoptic†; ***Israel***: Carteol; ***Ital.***: Carteabak; Carteol; Fortinol; ***Jpn***: Mikelan; ***Neth.***: Arteoptic†; Carteabak; Teoptic; ***Philipp.***: Mikelan; ***Pol.***: Arteoptic; Carteol; ***Port.***: Arteoptic; Carteabak; Physioglau; ***S.Afr.***: Teoptic†; ***Spain***: Arteolol†; Arteoptic; Elebloc; Mikelan; ***Switz.***: Arteoptic; ***Thai.***: Arteoptic; ***Turk.***: Carteol; ***UK***: Teoptic; ***USA***: Cartrol†.

Multi-ingredient Preparations. ***Belg.***: Carteopil†; ***Fr.***: Carpilo†; ***Switz.***: Arteopilo†.

Pharmacopoeial Preparations

BP 2014: Carteolol Eye Drops;
USP 36: Carteolol Hydrochloride Ophthalmic Solution; Carteolol Hydrochloride Tablets.

Carvedilol (BAN, USAN, rINN) ⊗

BM-14190; Carvedilol; Carvedilolum; Karvedilol; Karvediloli; Karvedilolis; Карведилол.

1-Carbazol-4-yloxy-3-[2-(2-methoxyphenoxy)ethylamino]propan-2-ol.

$C_{24}H_{26}N_2O_4$=406.5

CAS — 72956-09-3.

ATC — C07AG02.

ATC Vet — QC07AG02.

UNII — 0K47UL67F2.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Carvedilol). A white or almost white crystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane; practically insoluble in dilute acids.

USP 36: (Carvedilol). A white or nearly white, crystalline powder. Practically insoluble in water and in dilute acids; slightly soluble in alcohol. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Carvedilol is a non-cardioselective beta blocker (p. 1316.3). It has vasodilating properties, which are attributed mainly to its blocking activity at alpha$_1$ receptors; at higher doses calcium-channel blocking activity may contribute. It also has antoxidant properties. Carvedilol is reported to have no intrinsic sympathomimetic activity and only weak membrane-stabilising activity.

Carvedilol is used in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3), and as an adjunct to standard therapy in symptomatic heart failure (p. 1262.3). It is also used to reduce mortality in patients with left ventricular dysfunction after myocardial infarction.

In **hypertension** carvedilol is given in an initial oral dose of 12.5 mg once daily, increased after two days to 25 mg once daily. Alternatively, an initial dose of 6.25 mg is given twice daily, increased after one to two weeks to 12.5 mg twice daily. The dose may be increased further, if necessary, at intervals of at least two weeks, to 50 mg once daily or in divided doses. A dose of 12.5 mg once daily may be adequate for elderly patients.

In **angina pectoris** an initial oral dose of 12.5 mg is given twice daily, increased after two days to 25 mg twice daily.

In **heart failure**, the initial oral dose is 3.125 mg twice daily. It should be taken with food to reduce the risk of hypotension. If tolerated, the dose should be doubled after two weeks to 6.25 mg twice daily and then increased gradually, at intervals of not less than two weeks, to the maximum dose tolerated; this should not exceed 25 mg twice daily in patients with severe heart failure or in those weighing less than 85 kg, or 50 mg twice daily in patients with mild to moderate heart failure weighing more than 85 kg. For doses in children, see below.

In patients with **left ventricular dysfunction after myocardial infarction,** the initial dose is 6.25 mg twice daily, increased after 3 to 10 days, if tolerated, to 12.5 mg twice daily and then to a target dose of 25 mg twice daily. A lower initial dose may be used in symptomatic patients.

A controlled-release preparation containing carvedilol phosphate hemihydrate is available in some countries.

References.

1. Dunn CJ, *et al.* Carvedilol: a reappraisal of its pharmacological properties and therapeutic use in cardiovascular disorders. *Drugs* 1997; **54**: 161–85.
2. Frishman WH. Carvedilol. *N Engl J Med* 1998; **339**: 1759–65.
3. Naccarelli GV, Lukas MA. Carvedilol's antiarrhythmic properties: therapeutic implications in patients with left ventricular dysfunction. *Clin Cardiol* 2005; **28**: 165–73.
4. Carreira RS, *et al.* Carvedilol: just another beta-blocker or a powerful cardioprotector? *Cardiovasc Hematol Disord Drug Targets* 2006; **6**: 257–66.
5. Doughty RN, White HD. Carvedilol: use in chronic heart failure. *Expert Rev Cardiovasc Ther* 2007; **5**: 21–31.
6. Kveiborg B, *et al.* Carvedilol in the treatment of chronic heart failure: lessons from the Carvedilol Or Metoprolol European Trial. *Vasc Health Risk Manag* 2007; **3**: 31–7.
7. Frishman WH, *et al.* Controlled-release carvedilol in the management of systemic hypertension and myocardial dysfunction. *Vasc Health Risk Manag* 2008; **4**: 1387–1400.
8. Stafylas PC, Sarafidis PA. Carvedilol in hypertension treatment. *Vasc Health Risk Manag* 2008; **4**: 23–30.
9. Bakris GL, Weber MA. Appropriate dose transition to a controlled-release formulation of carvedilol in patients with hypertension. *Rev Cardiovasc Med* 2008; **9**: 96–105.
10. Carter NJ, Keating GM. Controlled-release carvedilol. *Am J Cardiovasc Drugs* 2008; **8**: 271–82.
11. Machado V, *et al.* Carvedilol as a protector against the cardiotoxicity induced by anthracyclines (doxorubicin). *Rev Port Cardiol* 2008; **27**: 1277–96.
12. Fonarow GC. Role of carvedilol controlled-release in cardiovascular disease. *Expert Rev Cardiovasc Ther* 2009; **7**: 483–98.
13. Chakraborty S, *et al.* Clinical updates on carvedilol: a first choice beta-blocker in the treatment of cardiovascular diseases. *Expert Opin Drug Metab Toxicol* 2010; **6**: 237–50.

Administration in children. Carvedilol has been used in children with **heart failure**, although experience is limited.[1] Beneficial effects have been reported, including improvement in symptoms and ejection fraction, and delaying the need for heart transplantation, and carvedilol appears to be well tolerated. However, a randomised study[2] in 161 children and adolescents with heart failure found that carvedilol was not significantly better than placebo: clinical improvement occurred in 56% of those taking carvedilol and 56% of those taking placebo, although the study may have been underpowered. A subsequent study[3] in 27 patients with heart failure due to congenital heart disease, about three-quarters of whom were children, found that lower doses and more cautious dose-escalation (increments of 50 to 100 micrograms/kg per month) reduced adverse effects and retained efficacy when compared with the doses used in previous studies.

Carvedilol at an oral dose of about 400 micrograms/kg daily has improved symptoms and left ventricular ejection fraction when added to standard therapy in the management of **dilated cardiomyopathy** in children,[4,5] although up to 6 months of treatment may be required before a significant benefit is seen.[5]

Doses used in paediatric studies have varied, with initial oral doses ranging from 10 to 180 micrograms/kg daily and average oral maintenance doses ranging from 200 to 700 micrograms/kg (maximum 50 mg) daily, usually given in two divided doses. A pharmacokinetic study[6] in 41 children and adolescents aged under 20 years found that, with carvedilol clearance decreasing with increased age, a total oral daily dose of 3 mg/kg in those aged under 2 years, 2 mg/kg in those aged 2 to 11 years, and 1 mg/kg in those aged 12 years and above, were necessary to maintain adequate carvedilol exposure for treatment of heart failure. The authors considered that doses in previous studies may have been too low.

In the UK, the *BNFC* recommends that children aged 2 to 18 years with heart failure may be given an initial oral dose of 50 micrograms/kg (maximum 3.125 mg) twice daily, increased as tolerated, by doubling the dose at intervals of at least 2 weeks, to a maintenance dose of 350 micrograms/kg (maximum 25 mg) twice daily.

1. Greenway SC, Benson LN. The use of carvedilol in pediatric heart failure. *Cardiovasc Hematol Disord Drug Targets* 2006; **6**: 35–42.
2. Shaddy RE, *et al.* Carvedilol for children and adolescents with heart failure: a randomized controlled trial. *JAMA* 2007; **298**: 1171–9.
3. Nishiyama M, *et al.* Efficacy and safety of carvedilol for heart failure in children and patients with congenital heart disease. *Heart Vessels* 2009; **24**: 187–92.
4. Askari H, *et al.* Carvedilol therapy in pediatric patients with dilated cardiomyopathy. *Turk J Pediatr* 2009; **51**: 22–7.
5. Bajcetic M, *et al.* Effects of carvedilol on left ventricular function and oxidative stress in infants and children with idiopathic dilated cardiomyopathy: a 12-month, two-center, open-label study. *Clin Ther* 2008; **30**: 702–14.
6. Albers S, *et al.* Population pharmacokinetics and dose simulation of carvedilol in paediatric patients with congestive heart failure. *Br J Clin Pharmacol* 2008; **65**: 511–22.

Administration in the elderly. Licensed product information for carvedilol recommends an initial dose of 12.5 mg daily for all adults with **hypertension.** A study in 16 elderly hypertensive patients (mean age 70 years) given single doses of 12.5 mg and 25 mg found a high incidence of orthostatic hypotension[1] and the authors suggested that a starting dose lower than 12.5 mg might be necessary in elderly patients.

In contrast, a retrospective study[2] found that standard initial doses for **heart failure** (see Uses and Administration, above) were well tolerated in elderly patients and that the mean achieved dose was similar in those aged under 70 years and those aged 70 years and older, after adjustment for weight. Adverse effects were more common in the older group, but could generally be managed without stopping carvedilol.

1. Krum H, *et al.* Postural hypotension in elderly patients given carvedilol. *BMJ* 1994; **309**: 775–6.
2. Lawless CE, *et al.* Titration of carvedilol in elderly heart failure patients. *Am J Geriatr Cardiol* 2005; **14**: 230–5.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Liver function abnormalities, reversible on stopping treatment with carvedilol, have been reported rarely. Carvedilol is extensively metabolised in the liver and is not recommended in patients with hepatic impairment. Acute renal failure and renal abnormalities have been reported in patients with heart failure who also suffered from diffuse vascular disease and/or renal impairment.

The risk of hypotension may be reduced by taking carvedilol with food to decrease the rate of absorption.

Effects on the liver. Pruritus and elevated serum transaminase concentrations occurred[1] in a man who had been taking carvedilol for 6 months. Liver function tests returned to normal within 3 weeks of stopping carvedilol. However, pruritus recurred when the patient was started on metoprolol about 1 year later.

1. Hagmeyer KO, Stein J. Hepatotoxicity associated with carvedilol. *Ann Pharmacother* 2001; **35**: 1364–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and

the Porphyria Centre Sweden, classifies carvedilol as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Carvedilol is well absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism in the liver; the absolute bioavailability is about 25%. Peak plasma concentrations occur 1 to 2 hours after an oral dose. It has high lipid solubility. Carvedilol is more than 98% bound to plasma proteins. It is extensively metabolised in the liver, primarily by the cytochrome P450 isoenzymes CYP2D6 and CYP2C9, and the metabolites are excreted mainly in the bile. The elimination half-life is about 6 to 10 hours. Carvedilol has been shown to accumulate in breast milk in *animals*.

References.

1. McTavish D, *et al.* Carvedilol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1993; 45: 232–58.
2. Morgan T. Clinical pharmacokinetics and pharmacodynamics of carvedilol. *Clin Pharmacokinet* 1994; 26: 335–46.
3. Tenero D, *et al.* Steady-state pharmacokinetics of carvedilol and its enantiomers in patients with congestive heart failure. *J Clin Pharmacol* 2000; 40: 844–53.
4. Tenero DM, *et al.* Pharmacokinetic properties of a new controlled-release formulation of carvedilol. *Am J Cardiol* 2006; 98: 5L–16L.
5. Packer M, *et al.* 369 Study Group. Pharmacokinetic profile of controlled-release carvedilol in patients with left ventricular dysfunction associated with chronic heart failure or after myocardial infarction. *Am J Cardiol* 2006; 98: 39L–45L.
6. Takekuma Y, *et al.* Evaluation of effects of polymorphism for metabolic enzymes on pharmacokinetics of carvedilol by population pharmacokinetic analysis. *Biol Pharm Bull* 2007; 30: 537–42.
7. Tanwar YS, *et al.* Development and evaluation of carvedilol transdermal patches. *Acta Pharm* 2007; 57: 151–9.
8. Albers S, *et al.* Population pharmacokinetics and dose simulation of carvedilol in paediatric patients with congestive heart failure. *Br J Clin Pharmacol* 2008; 65: 511–22.
9. Horiuchi I, *et al.* Pharmacokinetics of R- and S-carvedilol in routinely treated Japanese patients with heart failure. *Biol Pharm Bull* 2008; 31: 976–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Antibloc; Bidecar; Cardionorm; Carvedil; Corafen; Coritensil; Corubin; Dicarpen; Dilatrend; Duobloc; Filten; Hipoten; Isobloc; Kollosteril; Nexocardil; Pluscor; Rodipal; Rudoxil; Veraten; Vicardol; *Austral.*: Dicarz; Dilasig; Dilatrend; Kredex†; Vedilol; *Austria*: Dilatrend; *Belg.*: Dimitone; Kredex; *Braz.*: Becarve; Cardilol; Carvedilat; Coreg; Cronocor; Divelol; Ictus; Karvil; *Chile*: Betaplex; Blocar; Dicartel; Dilatrend; Dualten; Lodipres; Off-Ten; *China*: Carvidol (辛维络); Dilatrend (达利全); Jin Luo (金络); Kailuo (凯络); Kang Da Xin (康达欣); Ke Wei De (克为德); Luode (络德); Rui Xin Le (瑞欣乐); Shuheng (枢衡); Tuo Er (妥尔); Zhuo Yi (卓异); *Cz.*: Apo-Carve; Atram; Carvedigamma†; Carvesan; Carvetrend†; Coryol; *Dilatrend*; *Talliton*; *Denm.*: Dimitone†; *Fin.*: Cardiol; Carveratio; *Fr.*: Kredex; *Ger.*: CarLich†; Carve-Q†; Carvet†; Carvecard†; Carvedigamma; Dilatrend; Dimetil†; Querto; *Gr.*: Carvedilen; Carvepen; Dilatrend; *Hong Kong*: Dilatrend; Talliton; *Hung.*: Carvedigamma; Carvetrend; Carvol; Coryol; Dilatrend; Talliton; *India*: Caditone; Cadmos; Carca; Cardivas; Carelol; Carloc; Cartab; Carvas; Carvedil; Carvel; Carvetrend; Carvil; Carvimed; Carvipress; Carvizest; Carzec; Caslot; Cevas; Conpres; CVL; Oricar; *Indon.*: Blorec; Carbloxal; Dilbloc; V-Bloc *Irl.*: Biocard; Eucardic; *Israel*: Carvedexxon; *Dimitone†*; *Ital.*: Acarden; Caravel; Carvipress; Colver; Curcix; Dilatrend; Dilocart†; Omeria; Trakor; *Malaysia*: Cardiol; Carvepen; Caslot; Cavel; Dilatrend; *Mex.*: Bloqadre; Dilatrend†; *Neth.*: Carived; Eucardic; *NZ*: Dilatrend; *Philipp.*: Betacard; Cardipres; Carvid; Dilatrend; Karvil; Psicardiol; Vasolexin; Xicard; *Pol.*: Atram; Avedol; Carvedigamma; Carvetrend; Carvilex; Coryol; Dilatrend; Hypoten; Symtrend; Vivacor; *Port.*: Carbetesil†; Coronat; Dilbloc; Dinertone; Vedivril; *Rus.*: Acridilole (Акридилол); Atram (Атрам); Bagodilol (Багодилол); Cardivas (Кардивас); Carvedigamma (Карведигамма); Carvenal (Карвенал); Carvetrend (Карветренд); Carvidil (Карвидил); Coryol (Корил); Dilatrend (Дилатренд); Talliton (Таллитон); Vedicardol (Ведикардол); *S.Afr.*: Carloc; Carvetrend; Dilatrend; Vedibloc; *Singapore*: Carvepen; Dilatrend; *Spain*: Coropres; Normotride; Palacimol†; *Swed.*: Carveratio; Kredex; *Switz.*: Dilatrend; *Thai.*: Caraten; Dilatrend; Tocariol; *Turk.*: Arlec; Calcibor; Carvesan; Carvexal; Coronis; Dilatrend; Kinetra; *UK*: Eucardic†; *Ukr.*: Cardiostad (Кардиостад); Carvedigamma (Карведигамма)†; Carvetrend (Карветренд); Carvidex (Карвидекс); Corvasan (Корвазан); Coryol (Корил); Talliton (Таллитон); *USA*: Coreg; *Venez.*: Carbatil; Carvedil; Coventrol; Dilatrend.

Multi-ingredient Preparations. *Arg.*: Carvedil D; Dilatrend D; Filten D; Gliocarvedil; Isobloc D; *Austria*: Co-Dilatrend.

Pharmacopoeial Preparations
USP 36: Carvedilol Tablets.

Celiprolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Célipróol, Chlorhydrate de; Celiprolol, hidrocloruro de; Celiprololhydrochlorid; Celiprolol-hydrochlorid; Celiprolol-hydroklorid; Celiprololi hydrochloridum; Celiprololio hidrochloridas; Celiprololu chlorowodorek; Hidrocloruro de celiprolol; Seliprololihydrokloridi; Целипролола Гидрохлорид.

3-[3-Acetyl-4-[3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl]-1,1-diethylurea hydrochloride.

$C_{20}H_{33}N_3O_4$,HCl=415.0

CAS — 56980-93-9 (celiprolol); 57470-78-7 (celiprolol hydrochloride).

ATC — C07AB08.

ATC Vet — QC07AB08.

UNII — G1M3398594.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Celiprolol Hydrochloride). A white or very slightly yellow, crystalline powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; soluble in alcohol; very slightly soluble in dichloromethane. Protect from light.

Uses and Administration

Celiprolol is a cardioselective beta blocker (p. 1316.3). It is reported to possess intrinsic sympathomimetic activity and direct vasodilator activity. Celiprolol is used as the hydrochloride in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3). The usual oral dose of celiprolol hydrochloride is 200 to 400 mg once daily before food. Reduced doses may be required in patients with renal impairment (see below).

References.

1. Milne RJ, Buckley MM-T. Celiprolol: an updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in cardiovascular disease. *Drugs* 1991; 41: 941–69.
2. Anonymous. Celiprolol: theory and practice. *Lancet* 1991; 338: 1426–7.
3. Anonymous. Celiprolol—a better beta blocker? *Drug Ther Bull* 1992; 30: 35–6.
4. Kendall MJ, Rajman I. A risk-benefit assessment of celiprolol in the treatment of cardiovascular disease. *Drug Safety* 1994; 10: 220–32.
5. Riddell J. Drugs in focus 18: celiprolol. *Prescribers' J* 1996; 36: 165–8.

Administration in renal impairment. Celiprolol should not be given to patients with a creatinine clearance (CC) of less than 15 mL/minute. Patients with a CC between 15 and 40 mL/minute may be given 100 to 200 mg daily.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Tremor and palpitations associated with intrinsic sympathomimetic activity at $beta_2$ receptors have been reported.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Celiprolol is absorbed from the gastrointestinal tract in a non-linear fashion; the percentage of the dose absorbed increases with increasing dose. The plasma elimination half-life is about 5 to 6 hours. Celiprolol crosses the placenta. It has low lipid solubility and is about 25% bound to plasma proteins. Metabolism is minimal and celiprolol is mainly excreted unchanged in the urine and faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Selectol; *Belg.*: Selectol; *Chile*: Selectol; *China*: Delaien (得米恩); Su Ya (苏亚); *Cz.*: Tenoloc; *Fin.*: Selectol; *Fr.*: Celectol; *Ger.*: Celipro†; Celiprogamma†; Selectol; *Gr.*: Aplonit; Selectol; Versatil; Zilovis; *Hong Kong*: Selectol; *Irl.*: Selectol; *Ital.*: Cordiax; *Jpn*: Selectol; *Neth.*: Dilanorm; *NZ*: Celol; *Pol.*: Celipres; *Rus.*: Celiprol (Целипрол); *Spain*: Cardem; *Switz.*: Selectol; *UK*: Celectol.

Multi-ingredient Preparations. *Austria*: Selecturon.

Pharmacopoeial Preparations
BP 2014: Celiprolol Tablets.

Certoparin Sodium *(BAN, rINN)*

Certoparin; Certoparina sódica; Certoparine Sodique; Certoparinum Natricum; Цертопарин Натрий.

Description. Certoparin sodium is prepared by amyl nitrite degradation of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-*O*-sulfo-2,5-anhydro-D-mannose structure at the reducing end of their chain. The molecular weight of 70% of the components is less than 10 000 and the average molecular weight is about 6000. The degree of sulfation is about 2 to 2.5 per disaccharide unit.

Units

As for Low-molecular-weight Heparins, p. 1426.2.

Uses and Administration

Certoparin sodium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant activity used for the prevention of postoperative venous thromboembolism (p. 1274.1). It is given by subcutaneous injection in a dose of 3000 units 1 to 2 hours before the procedure, followed by 3000 units daily for 7 to 10 days or until the patient is fully ambulant.

References.

1. Kolb G, *et al.* Reduction of venous thromboembolism following prolonged prophylaxis with the low molecular weight heparin certoparin after endoprothetic joint replacement or osteosynthesis of the lower limb in elderly patients. *Thromb Haemost* 2003; 90: 1100–5.
2. Riess H, *et al.* Fixed-dose, body weight-independent subcutaneous low molecular weight heparin certoparin compared with adjusted-dose intravenous unfractionated heparin in patients with proximal deep venous thrombosis. *Thromb Haemost* 2003; 90: 252–9.
3. Diener HC, *et al.* Prophylaxis of thrombotic and embolic events in acute ischemic stroke with the low-molecular-weight heparin certoparin: results of the PROTECT Trial. *Stroke* 2006; 37: 139–44.
4. Tebbe U, *et al.* AFFECT: a prospective, open-label, multicenter trial to evaluate the feasibility and safety of a short-term treatment with subcutaneous certoparin in patients with persistent non-valvular atrial fibrillation. *Clin Res Cardiol* 2008; 97: 389–96.
5. Riess H, *et al.* A randomized, double-blind study of certoparin versus UFH to prevent venous thromboembolic events in acutely ill, non-surgical patients: CERTIFY study. *J Thromb Haemost* 2010; 8: 1209–15.

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p. 1426.3.

Severe bleeding with certoparin may be reduced by the slow intravenous injection of protamine salts; 1 mg of protamine hydrochloride is stated to inhibit the effects of about 80 to 120 units of certoparin sodium.

Interactions

As for Low-molecular-weight Heparins, p. 1427.2.

Pharmacokinetics

Certoparin sodium is rapidly and completely absorbed after subcutaneous injection. Peak plasma activity occurs within 2 to 4 hours. The half-life of anti-factor Xa activity is about 4 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Sandoparin; *Ger.*: Mono-Embolex; *Switz.*: Sandoparine.

Cetiedil Citrate *(USAN, rINNM)*

Cétiédil, Citrate de; Cetiedil, citrato de; Cetiedili Citras; Citrato de cetiedil; Цетиедила Цитрат.

2-(Perhydroazepin-1-yl)ethyl α-cyclohexyl-α-(3-thienyl) acetate dihydrogen citrate monohydrate.

$C_{20}H_{31}NO_2S,C_6H_8O_7,H_2O$=559.7

CAS — 14176-10-4 (cetiedil); 16286-69-4 (anhydrous cetiedil citrate).

ATC — C04AX26.

ATC Vet — QC04AX26.

UNII — IE65P4OE02.

Profile

Cetiedil citrate is a vasodilator with antimuscarinic activity that has been used in the management of peripheral vascular disease.

Chlorothiazide *(BAN, rINN)* ⊗

Chlorothiazid; Chlorothiazidum; Chlorotiazidas; Chlorotiazyd; Clorotiazida; Klooritiatsiid; Klorotiazid; Klortiazid; Хлоротиазид.

6-Chloro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_7H_6ClN_3O_4S_2$=295.7

CAS — 58-94-6.

ATC — C03AA04.

ATC Vet — QC03AA04.

UNII — 7TW477J15H.

Pharmacopoeias. In *US.*

USP 36: (Chlorothiazide). A white or practically white, odourless, crystalline powder. Very slightly soluble in water; practically insoluble in chloroform, in ether, and in benzene; freely soluble in dimethylformamide and dimethyl sulfoxide; slightly soluble in methyl alcohol and in pyridine. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Stability. Alkaline solutions undergo decomposition due to hydrolysis upon standing or heating.

Chlorothiazide Sodium *(BANM, USAN, rINNM)* ⊗

Chlorothiazide Sodique; Clorotiazida sódica; Natrii Chlorothiazidum; Sodium Chlorothiazide; Натрий Хлоротиазид.

$C_7H_5ClN_3NaO_4S_2$=317.7

CAS — 7085-44-1.

ATC — C03AA04.

ATC Vet — QC03AA04.

UNII — SN86FG7N2K.

Pharmacopoeias. *US* includes Chlorothiazide Sodium for Injection.

Incompatibility. The alkaline nature of chlorothiazide in injectable form suggests that incompatibilities with acidic drugs could be expected; US licensed product information states that the injection may be diluted with glucose or sodium chloride solutions.

Uses and Administration

Chlorothiazide is a thiazide diuretic with actions and uses similar to those of hydrochlorothiazide (p. 1403.2). It is used for oedema, including that associated with heart failure (p. 1262.3), and for hypertension (p. 1251.1).

After oral doses of chlorothiazide diuresis usually occurs in about 2 hours, reaches a peak at about 4 hours, and is maintained for 6 to 12 hours.

In the treatment of **oedema** the usual dose of chlorothiazide is 0.5 to 1 g orally once or twice daily; therapy on alternate days or on 3 to 5 days weekly may be adequate.

In the treatment of **hypertension** the recommended initial dose is 0.5 to 1 g daily orally, given as a single or divided dose, although the *American Hospital Formulary Service* have suggested lower initial doses of 125 to 250 mg daily, increased to a maximum of 500 mg daily. US licensed product information states that patients may rarely require up to 2 g daily, given in divided doses.

For the use of chlorothiazide in children, see below.

Chlorothiazide has also been given intravenously as the sodium salt, in doses similar to those given orally. Chlorothiazide sodium 537 mg is equivalent to about 500 mg of chlorothiazide. It is not suitable for subcutaneous or intramuscular injection and extravasation should be avoided. The diuretic effect lasts for up to 2 hours after intravenous injection.

Administration in children. Chlorothiazide may be used in children for the management of *heart failure* or *hypertension*. Usual oral doses are as follows:

- neonates and infants aged 1 to 6 months: 10 to 20 mg/kg twice daily
- age 6 months to 12 years: 10 mg/kg twice daily, to a maximum of 1 g daily
- age 12 to 18 years: 0.25 to 1 g once daily or 125 to 500 mg twice daily

For *diabetes insipidus* in children, the *BNFC* suggests an oral dose of 10 to 20 mg/kg twice daily, to a maximum of 1 g daily.

Chlorothiazide also has a hyperglycaemic effect and has been used in children with *chronic hypoglycaemia* (see under Uses of Glucagon, p. 1554.3). It is usually given with diazoxide and has the added benefit of reducing diazoxide-associated sodium and water retention. The *BNFC* suggests an oral dose of 3 to 5 mg/kg twice daily.

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p. 1404.2. Chlorothiazide sodium injection is alkaline: when giving chlorothiazide by intravenous infusion, care should be taken to ensure that extravasation does not occur.

Breast feeding. Chlorothiazide is distributed into breast milk in small amounts. A single 500-mg oral dose of chlorothiazide was given[1] to 11 women and blood and milk samples taken after 1, 2, and 3 hours; all the samples had concentrations below 1 microgram/mL and it was calculated that an infant would receive no more than 1 mg of drug each day. The American Academy of Pediatrics states that no adverse effects have been seen in infants and therefore considers[2] that chlorothiazide is usually compatible with breast feeding.

1. Werthmann MW, Krees SV. Excretion of chlorothiazide in human breast milk. *J Pediatr* 1972; 81: 781–3.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Interactions

As for Hydrochlorothiazide, p. 1406.1.

Pharmacokinetics

Chlorothiazide is incompletely and variably absorbed from the gastrointestinal tract. It has been estimated to have a plasma half-life of 45 to 120 minutes although the clinical effects may last for up to about 12 hours. It is excreted unchanged in the urine. Chlorothiazide crosses the placental barrier and small amounts are reported to be distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Diurigen; Diuril.

Multi-ingredient Preparations. *Gr.*: Neourizine; *USA*: Aldoclor; Diupres.

Pharmacopoeial Preparations

USP 36: Chlorothiazide Oral Suspension; Chlorothiazide Sodium for Injection; Chlorothiazide Tablets; Methyldopa and Chlorothiazide Tablets; Reserpine and Chlorothiazide Tablets.

Chlortalidone *(BAN, rINN)* ⊗

Chlorotalidon; Chlortalidon; Chlortalidonas; Chlortalidonum; Chlorthalidone (USAN); Chlorthalidone; Clorotalidona; Clortalidona; G-33182; Klooritalidoni; Klortalidon; Klórtalidon; NSC-69200; Хлорталидон.

2-Chloro-5-(1-hydroxy-3-oxoisoindolin-1-yl)benzenesulphonamide.

$C_{14}H_{11}ClN_2O_4S$=338.8

CAS — 77-36-1.

ATC — C03BA04.

ATC Vet — QC03BA04.

UNII — Q0MQD1073Q.

NOTE. Compounded preparations of chlortalidone may be represented by the following names:

- Co-tenidone (*BAN*)—chlortalidone 1 part and atenolol 4 parts (w/w).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Chlortalidone). A white or yellowish-white powder. Very slightly soluble in water; soluble in acetone and in methyl alcohol; practically insoluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides. It exhibits polymorphism.

USP 36: (Chlorthalidone). A white or yellowish-white crystalline powder. Practically insoluble in water, in chloroform, and in ether; slightly soluble in alcohol; soluble in methyl alcohol.

Uses and Administration

Chlortalidone is a diuretic with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1403.2) even though it does not contain a thiazide ring system. It is given orally for hypertension (p. 1251.1), and for oedema, including that associated with heart failure (p. 1262.3). Other indications include diabetes insipidus (p. 2348.2).

Diuresis begins about 2 hours after an oral dose and lasts for 48 to 72 hours.

The usual dose in the treatment of **hypertension** is 25 mg daily, given either alone or with other antihypertensives, increasing to 50 mg daily if necessary.

In the treatment of **oedema** the usual initial dose is 25 to 50 mg daily. In severe cases a daily dose of 100 to 200 mg may be given. If possible lower doses should be used for maintenance; 25 to 50 mg daily or on alternate days may be adequate.

For doses in children, see below.

In **diabetes insipidus** an initial dose of 100 mg twice daily has been used, reduced to a maintenance dose of 50 mg daily.

In the USA, a preparation is available with improved bioavailability; suggested doses range from 15 to 50 mg daily for hypertension and 30 to 120 mg daily for oedema.

References.

1. Taler SJ. Should chlorthalidone be the diuretic of choice for antihypertensive therapy? *Curr Hypertens Rep* 2008; 10: 293–7.
2. Ernst ME, *et al.* All thiazide-like diuretics are not chlorthalidone: putting the ACCOMPLISH study into perspective. *J Clin Hypertens (Greenwich)* 2009; 11: 5–10.
3. Sica DA. Chlorthalidone—a renaissance in use? *Expert Opin Pharmacother* 2009; 10: 2037–9.
4. Massie BM. Prevention of heart failure with chlorthalidone in ALLHAT: placing the results into perspective. *J Clin Hypertens (Greenwich)* 2009; 11: 462–5.
5. Neff KM, Nawarskas JJ. Hydrochlorothiazide versus chlorthalidone in the management of hypertension. *Cardiol Rev* 2010; 18: 51–6.
6. Ernst ME, *et al.* Meta-analysis of dose-response characteristics of hydrochlorothiazide and chlorthalidone: effects on systolic blood pressure and potassium. *Am J Hypertens* 2010; 23: 440–6.

Administration in children. Chlortalidone may be given to children aged from 5 years in the treatment of hypertension, oedema associated with the nephrotic syndrome, stable heart failure, and ascites. The *BNFC* suggests the following oral doses:

- aged 5 to 12 years: usual dose 0.5 to 1 mg/kg on alternate days; maximum dose 1.7 mg/kg on alternate days
- aged over 12 years: usual dose 25 to 50 mg daily. In hypertension, the lower dose is preferred. In heart failure, the dose may be increased to 100 to 200 mg daily if necessary, reduced to the lowest effective dose for maintenance

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p. 1404.2.

Breast feeding. Chlortalidone is distributed into breast milk, but a study[1] in 9 women given a dose of 50 mg daily found that the concentration in milk was only about 5% of that in the blood. However, caution was advised since chlortalidone elimination may be slower in neonates. The American Academy of Pediatrics considers[2] that chlortalidone is usually compatible with breast feeding.

1. Mulley BA, *et al.* Placental transfer of chlorthalidone and its elimination in maternal milk. *Eur J Clin Pharmacol* 1978; 13: 129–31.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Interactions

As for Hydrochlorothiazide, p. 1406.1.

Anticoagulants. For references to the interaction between *warfarin* and chlortalidone, see p. 1533.3.

Pharmacokinetics

Chlortalidone is erratically absorbed from the gastrointestinal tract and bioavailability varies according to the preparation used. It has a prolonged elimination half-life from plasma and blood of 40 to 60 hours and is highly bound to red blood cells; the receptor to which it is bound has been identified as carbonic anhydrase. Chlortalidone is much less strongly bound to plasma proteins. Chlortalidone is mainly excreted unchanged in the urine. It crosses the placental barrier and is distributed into breast milk.

References.

1. Riess W, *et al.* Pharmacokinetic studies with chlorthalidone (Hygroton) in man. *Eur J Clin Pharmacol* 1977; 12: 375–82.
2. Fleuren HLJ, *et al.* Absolute bioavailability of chlorthalidone in man: a cross-over study after intravenous and oral administration. *Eur J Clin Pharmacol* 1979; 15: 35–50.
3. Fleuren HLJ, *et al.* Dose-dependent urinary excretion of chlorthalidone. *Clin Pharmacol Ther* 1979; 25: 806–12.
4. Mulley BA, *et al.* Pharmacokinetics of chlorthalidone: dependence of biological half life on blood carbonic anhydrase levels. *Eur J Clin Pharmacol* 1980; 17: 203–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Euretico; Hygroton; *Austral.*: Hygroton; *Austria*: Hydrosan; *Belg.*: Hygroton; *Braz.*: Clortalil; Clortil; Drenidra; Higromil; Higroton; Neolidona; *Ger.*: Hygroton; *Gr.*: Hygroton; *Hung.*: Hygroton; *India*: Hythalton; Thalizide; *Indon.*: Hygroton; *Israel*: Aquadon†; *Ital.*: Igroton; *Mex.*: Anilid; Bioralin; Hidrona†; Hidropharm; Higroton; Lortal; Sinhidron; Tensoral; *NZ*: Hygroton; *Pol.*: Hygroton; Urandil†; *Port.*: Hygroton; *Rus.*: Oxodoline (Оксодолин); *S.Afr.*: Hygroton; *Spain*: Higrotona; *Switz.*: Hygroton; *Turk.*: Hygroton†; *UK*: Hygroton; *USA*: Hygroton†; Thalitone.

Multi-ingredient Preparations. *Arg.*: Bemplas; Prenoretic; *Austria*: Atenolan comp; Atenolol comp; Polinorm†; Selecturon; Tenoretic; *Belg.*: Logroton; Tenoretic; *Braz.*: Ablok Plus; Angipress CD; Atelidona; Atenorese; Atenoric; Atenuol CRT; Betacard Plus; Diublok; Diupress; Higroton Reserpina; Tenoretic; *Canad.*: Apo-Atenidone; Novo-Atenolthalidone†; Tenoretic; *Cz.*: Amicloton; Neocrystepin†; Tenoretic; *Denm.*: Tenidon; Tenoretic; *Fr.*: Logroton; Tenoretic; Trasitensine†; *Ger.*: Ate Lich comp†; Atehexal comp†; Atel†; Ateno comp†; Atenogamma comp†; Atenolol comp; Diu-Atenolol†; Prelis comp; Teneretic; TRI-Normin; *Gr.*: Apress; Bestocalm; Chlotenor; Hygroton-Reserpine; Merendal; Obosan; Ogerol; Santapertas; Tenoretic; Trasitensin; Typofen; Vagosinol; *Hong Kong*: Target†; Tenoret; Tenoretic; *Hung.*: Blokium Diu; *India*: Atecard-D; Catapres Diu; Clothalton; Tenoclor; Tenoric; *Indon.*: Tenoret†; Tenoretic†; *Irl.*: Atecor CT; Atenetic; Tenoret; Tenoretic; *Ital.*:

Atenigron; Carmian; Clortanol; Diube; Eupres; Igroseles; Igroton-Lopresor; Igroton-Reserpina; Target; Tenoretic; Trandiur; Trasitensin; ***Malaysia***: Apo-Atenidone; Logroton; Pretenol C; Target; Tenoret; Tenoretic; ***Mex.***: Higroton Blok; Higroton-Res; Tenoretic; ***Philipp.***: Tenoretic; ***Port.***: Tenoretic; ***Rus.***: Atehexal Compositum (Атегексал Композитум); Atenolol Compositum (Атенолол Композитум); Tenonorm (Тенонорм); Tenoretic (Теноретик); Tenoric (Тенорик); Tenorox (Тенороис); ***S.Afr.***: Adco-Loten; Tenchlor; Tenoret; Tenoretic; ***Singapore***: Logroton; Pretenol C; Target; Tenoret†; Tenoretic†; ***Spain***: Aldoleo; Blokium Diu; Higrotensin†; Normopresil; Tenoretic; Trasitensin; ***Switz.***: Atedurex; Cardaxen plus; Co-Atenolol; Cotenolol-Neo; Hygroton-Reserpine†; Logroton; Sandoretic†; Slow-Trasitensine; Tenoretic; ***Turk.***: Atexal; Regroton; Tenoretic; ***UK***: AtenixCo; Kalspare; Tenchlor; Tenoret; Tenoretic; Totaretic; ***Ukr.***: Dinorik (Динорик); Tenoric (Тенорик); Tonorma (Тонорма); ***USA***: Clorpres; Demi-Regroton; Edarbyclor; Regroton; Tenoretic; ***Venez.***: Blokiuret; Tenoretic.

Pharmacopoeial Preparations

BP 2014: Chlortalidone Tablets; Co-tenidone Tablets;
USP 36: Atenolol and Chlorthalidone Tablets; Chlorthalidone Tablets; Clonidine Hydrochloride and Chlorthalidone Tablets.

Cibenzoline *(BAN, rINN)*

Cibenzolina; Cibenzolinum; Cifenline (USAN); Ro-22-7796; Ro-22-7796/001 (cibenzoline succinate); UP-339-01; Цибензолин.

(±)-2-(2,2-Diphenylcyclopropyl)-2-imidazoline.

$C_{18}H_{18}N_2$=262.4.

CAS — 53267-01-9 (cibenzoline); 100678-32-8 (cibenzoline succinate).

ATC — C01BG07.

ATC Vet — QC01BG07.

UNII — Z7489237QT.

Uses and Administration

Cibenzoline is a class I antiarrhythmic (p. 1243.1) that has been classified as either Ia or Ic; it also has some class III and class IV properties. It is used in the management of ventricular and supraventricular arrhythmias (p. 1266.1). Cibenzoline is given orally as the succinate or intravenously as a mixture of the base and succinate, but doses for both routes are expressed in terms of the base; 145 mg of cibenzoline succinate is equivalent to about 100 mg of base. The usual oral dose of cibenzoline succinate is the equivalent of 260 to 390 mg cibenzoline daily in divided doses. The usual intravenous dose is the equivalent of about 1 mg/kg cibenzoline base given over 2 to 5 minutes. Dosage should be reduced in the elderly (below), and in renal impairment (below).

Reviews.

1. Harron DW, *et al.* Cibenzoline: a review of its pharmacological properties and therapeutic potential in arrhythmias. *Drugs* 1992; 43: 734–59.

Administration in the elderly. The renal and non-renal clearance of cibenzoline was found to decrease with increasing age in healthy subjects.[1] The mean elimination half-life was 7 hours in the 20- to 30-year age group and 10.5 hours in the 70- to 80-year age group. The reduction in renal clearance was considered to be related to the decrease in creatinine clearance with increasing age. The results suggested that older patients may need lower doses than younger patients to maintain therapeutic plasma-cibenzoline concentrations. Licensed product information recommends a dosage of 130 mg daily in two divided doses in elderly patients.

1. Brazzell RK, *et al.* Age and cibenzoline disposition. *Clin Pharmacol Ther* 1984; 36: 613–19.

Administration in renal impairment. A study[1] in patients with normal or impaired renal function has suggested that in renal impairment initial loading doses of cibenzoline may be equivalent to those used in normal renal function although maintenance doses should be reduced to about two-thirds of normal. Oral doses recommended in licensed product information, based on creatinine clearance (CC), are as follows:

- CC 20 to 40 mL/min: the equivalent of 3 mg/kg daily
- CC 10 to 20 mL/min: the equivalent of 2.5 mg/kg daily

1. Aronoff G, *et al.* Bioavailability and kinetics of cibenzoline in patients with normal and impaired renal function. *J Clin Pharmacol* 1991; 31: 38–44.

Adverse Effects and Precautions

Cibenzoline may cause neurological and gastrointestinal adverse effects including vertigo, tremor, nausea, vomiting, and diarrhoea. Other adverse effects include fatigue, visual disturbances, and hypoglycaemia. It prolongs the QT interval and, like other antiarrhythmics, can cause arrhythmias. It also has a negative inotropic effect and may reduce blood pressure.

Cibenzoline is contra-indicated in patients with heart block and severe heart failure. It should be used with caution in the elderly and in renal impairment, and doses should be reduced.

Effects on the neuromuscular system. Myasthenia-like symptoms have been reported[1-3] in patients with renal impairment taking cibenzoline, including severe respiratory depression in some cases.[2,3]

1. Kasuga A, *et al.* Myasthenia-like syndrome induced by overdosage of cibenzoline. *Intern Med* 1996; 35: 512–14.
2. Similowski T, *et al.* Neuromuscular blockade with acute respiratory failure in a patient receiving cibenzoline. *Thorax* 1997; 52: 582–4.
3. Inada K, *et al.* A case of severe respiratory depression due to cibenzoline overdosage induced by a transient renal dysfunction. *Int J Cardiol* 2002; 82: 177–8.

Hypoglycaemia. Cibenzoline therapy was associated with severe hypoglycaemia in a 67-year-old patient.[1] The plasma-cibenzoline concentration was 1800 nanograms/mL which would probably be considered toxic since the accepted therapeutic trough range is 200 to 600 nanograms/mL. A case-control study[2] also suggested that the risk of hypoglycaemia is increased by cibenzoline.

1. Hilleman DE, *et al.* Cibenzoline-induced hypoglycemia. *Drug Intell Clin Pharm* 1987; 21: 38–40.
2. Takada M, *et al.* The relationship between risk of hypoglycemia and use of cibenzoline and disopyramide. *Eur J Clin Pharmacol* 2000; 56: 335–42.

Interactions

Cibenzoline should not be used with other drugs that prolong the QT interval since the risk of arrhythmias may be increased.

Histamine H_2-antagonists. Increased blood concentrations and prolonged half-lives of cibenzoline occurred in healthy subjects given *cimetidine* but the clinical importance of this was unknown.[1] The interaction did not occur with *ranitidine*.

1. Massarella JW. The effects of cimetidine and ranitidine on the pharmacokinetics of cifenline. *Br J Clin Pharmacol* 1991; 31: 481–3.

Pharmacokinetics

Cibenzoline is well absorbed from the gastrointestinal tract after oral use, with a bioavailability of about 90%. It is about 50 to 60% bound to plasma proteins. About 60% of a dose is excreted unchanged in the urine and the elimination half-life is reported to be about 7 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Cipralan; ***Fr.***: Cipralan; Exacor; ***Jpn***: Cibenol.

Cicletanine *(BAN, USAN, rINN)* ⊗

Ciclétanine; Ciclétanine; Cicletaninum; Win-90000; Циклетанин; (±)-BN-1270; (±)-Cyclétanide.

(±)-3-(*p*-Chlorophenyl)-1,3-dihydro-6-methylfuro[3,4-*c*]pyridin-7-ol.

$C_{14}H_{12}ClNO_2$=261.7.

CAS — 89943-82-8.

ATC — C03BX03.

ATC Vet — QC03BX03.

UNII — CHG7QC509W.

Cicletanine Hydrochloride *(BANM, rINNM)* ⊗

Cicletanina, hidrocloruro de; Cicletanine, Chlorhydrate de; Cicletanini Hydrochloridum; Hidrocloruro de cicletanina; Циклетанина гидрохлорид.

$C_{14}H_{12}ClNO_2$,HCl=298.2.

CAS — 89943-82-8.

ATC — C03BX03.

ATC Vet — QC03BX03.

UNII — T05Y6373OQ.

Profile

Cicletanine hydrochloride is a diuretic with properties similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1403.2). It is used in the treatment of hypertension (p. 1251.1) in a usual oral dose of 50 to 100 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Tenstaten.

Cilazapril *(BAN, USAN, rINN)*

Cilazapril monohydrat; Cilazaprilis; Cilazaprilum; Cilazaprilum Monohydricum; Ro-31-2848 (anhydrous cilazapril); Ro-31-2848/006 (cilazapril monohydrate); Silatsaprilli; Silazapril; Силазаприл.

(1*S*,9*S*)-9-[(*S*)-1-Ethoxycarbonyl-3-phenylpropylamino]-10-oxooctahydropyridazino[1,2-*a*][1,2]diazepine-1-carboxylic acid monohydrate.

$C_{22}H_{31}N_3O_5.H_2O$=435.5.

CAS — 88768-40-5 (anhydrous cilazapril); 92077-78-6 (cilazapril monohydrate).

ATC — C09AA08.

ATC Vet — QC09AA08.

UNII — 8Q9454114Q (anhydrous cilazapril); 19KW7PI29F (cilazapril monohydrate).

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Cilazapril). A white or almost white crystalline powder. Slightly soluble in water; freely soluble in dichloromethane and in methyl alcohol. Protect from light.

Uses and Administration

Cilazapril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1) and heart failure (p. 1262.3).

Cilazapril owes its activity to cilazaprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after about 3 to 7 hours. The haemodynamic action persists for about 24 hours, allowing once-daily dosing. Cilazapril is given orally as the monohydrate, but doses are expressed in terms of the anhydrous substance. Cilazapril 1.04 mg as the monohydrate is equivalent to about 1 mg of anhydrous cilazapril.

In the treatment of **hypertension** the initial dose is 1 mg once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Usual maintenance doses range from 2.5 to 5 mg daily. In the elderly, in patients with mild to moderate renal impairment or with liver cirrhosis, or those taking *diuretics*, a usual initial dose is 500 micrograms daily. If possible the diuretic should be withdrawn 2 to 3 days before cilazapril is started and resumed later if necessary.

In the treatment of **heart failure** severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus therapy should begin with a low dose under close medical supervision. Cilazapril is given in an initial dose of 500 micrograms once daily, increased if tolerated to a usual maintenance dose of 1 to 2.5 mg once daily. The usual maximum dose is 5 mg daily.

Reduced doses may be necessary in patients with renal impairment (see below).

References.

1. Deget F, Brogden RN. Cilazapril: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in cardiovascular disease. *Drugs* 1991; 41: 799–820.

Administration in renal impairment. In patients with a creatinine clearance of 10 to 40 mL/minute, the initial dose of cilazapril is 500 micrograms once daily and the maintenance dose should not exceed 2.5 mg once daily. Cilazapril should be avoided in patients with a creatinine clearance below 10 mL/minute. In patients receiving haemodialysis, cilazapril should be given on the non-dialysis days and the dose should be adjusted according to response.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Licensed product information contra-indicates cilazapril in patients with ascites.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cilazapril as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Cilazapril acts as a prodrug of the diacid cilazaprilat, its active metabolite. After oral dosage and absorption of cilazapril is rapidly metabolised in the liver to cilazaprilat, the bioavailability of which is about 60%. Peak plasma concentrations of cilazaprilat occur within 2 hours of an oral dose of cilazapril. Cilazaprilat is eliminated unchanged in the urine. The effective half-life of cilazaprilat is reported to be 9 hours after once-daily dosing. The elimination of

cilazaprilat is reduced in renal impairment. Both cilazapril and cilazaprilat are removed to a limited extent by haemodialysis.

Reviews.
1. Kelly JG, O'Malley K. Clinical pharmacokinetics of the newer ACE inhibitors: a review. *Clin Pharmacokinet* 1990; 19: 177–96.
2. Kloke HJ, *et al.* Pharmacokinetics and haemodynamic effects of the angiotensin converting enzyme inhibitor cilazapril in hypertensive patients with normal and impaired renal function. *Br J Clin Pharmacol* 1996; 42: 615–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Inhibace; ***Belg.***: Inhibace; ***Braz.***: Vascase; ***Canad.***: Inhibace; ***Chile***: Inhibace; ***China***: Inhibace (一平苏); ***Cz.***: Cazaprol; Inhibace; ***Fr.***: Justor; ***Ger.***: Dynorm; ***Gr.***: Vascase; ***Hong Kong***: Inhibace†; ***Hung.***: Inhibace; ***Irl.***: Vascace; ***Israel***: Cilaril; Vascace†; ***Ital.***: Inibace; Initiss; ***Jpn***: Inhibace; ***Neth.***: Vascase; ***NZ***: Inhibace; Zapril; ***Philipp.***: Vascace; ***Pol.***: Cazaprol; Cilan; Inhibace; Inhibestril; ***Port.***: Inibace; Vascase; ***Rus.***: Inhibace (Ингибейс); ***S.Afr.***: Inhibace; ***Singapore***: Inhibace; ***Spain***: Inhibace; Inocar; ***Swed.***: Inhibace†; ***Switz.***: Inhibace; ***Thai.***: Inhibace; ***Turk.***: Aceprix; Inhibace; ***UK***: Vascace†; ***Venez.***: Inhibace.

Multi-ingredient Preparations. ***Austria***: Inhibace Plus; ***Belg.***: Co-Inhibace; ***Braz.***: Vascase Plus; ***Canad.***: Inhibace Plus; ***Chile***: Inhibace Plus; ***Cz.***: Cazacombi; Inhibace Plus; ***Ger.***: Dynorm Plus; ***Gr.***: Vascase Plus; ***Hung.***: Inhibace Plus; ***Israel***: Cilaril Plus; Cilazapril Plus; Vascace Plus†; ***Ital.***: Inibace Plus; Initiss Plus; ***NZ***: Inhibace Plus; ***Philipp.***: Vascace Plus; ***Pol.***: Cazacombi; Inhibace Plus; ***Port.***: Inibace Plus; Vascase Plus; ***Rus.***: Ampliton (Амплитон); Sonoprel (Сонопрел); ***S.Afr.***: Inhibace Plus; ***Spain***: Inhibace Plus; Inocar Plus; ***Swed.***: Inhibace comp†; ***Switz.***: Inhibace Plus; ***Turk.***: Aceprix Plus; Inhibace Plus.

Cilnidipine *(rINN)*

Cilnidipino; Cilnidipinum; FRC-8653; Цилнидипин.

(±)-(*E*)-Cinnamyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate.

$C_{27}H_{28}N_2O_7$=492.5.

CAS — 132203-70-4.

ATC — C08CA14.

ATC Vet — QC08CA14.

UNII — 97F5AZ1JIP.

Profile

Cilnidipine is a dihydropyridine calcium-channel blocker (p. 1244.2) given orally in the management of hypertension (p. 1251.1). The usual dose is 5 to 10 mg once daily, increased to 20 mg once daily if necessary.

References.
1. Takei K, *et al.* Comparison of the anti-hypertensive effects of the L/N-type calcium channel antagonist cilnidipine, and the L-type calcium channel antagonist amlodipine in hypertensive patients with cerebrovascular disease. *Intern Med* 2009; 48: 1357–61.
2. Takahara A. Cilnidipine: a new generation Ca channel blocker with inhibitory action on sympathetic neurotransmitter release. *Cardiovasc Ther* 2009; 27: 124–39.
3. Abe M, *et al.* Comparison between the antiproteinuric effects of the calcium channel blockers benidipine and cilnidipine in combination with angiotensin receptor blockers in hypertensive patients with chronic kidney disease. *Expert Opin Invest Drugs* 2010; 19: 1027–37.
4. Konoshita T, *et al.* A new-generation N/L-type calcium channel blocker leads to less activation of the renin-angiotensin system compared with conventional L type calcium channel blocker. *J Hypertens* 2010; 28: 2156–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Jiuyue (久悦); Xi Le (西乐); Zhi Xin (致欣); ***India***: Cilacar; ***Jpn***: Atelec; Cinalong†; ***Port.***: Tenvasc.

Cilostazol *(BAN, USAN, pINN)*

Cilostazolum; OPC-21; OPC-13013; Цилостазол.

6-[4-(1-Cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyril.

$C_{20}H_{27}N_5O_2$=369.5.

CAS — 73963-72-1.

ATC — B01AC23; C04AX33.

ATC Vet — QB01AC23.

UNII — N7Z0354068.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Cilostazol). White to off-white crystals. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; freely soluble in chloroform. Store in airtight containers.

Uses and Administration

Cilostazol is a phosphodiesterase type-3 inhibitor with antiplatelet and vasodilating activity. It is used in the management of peripheral vascular disorders (p. 1272.3) and has been tried as an adjunct to coronary stenting in ischaemic heart disease (below) and in other atherothrombotic disorders.

Cilostazol is used to improve walking distance in intermittent claudication; in the EU, it is restricted to second-line use in patients for whom lifestyle changes and other drug treatments are insufficient. The usual dose is 100 mg orally twice daily, at least 30 minutes before or 2 hours after food; doses should be reduced to 50 mg twice daily if given to patients also taking inhibitors of the cytochrome P450 isoenzymes CYP3A4 or CYP2C19. Response to treatment may occur in 2 to 4 weeks, but up to 12 weeks may be required. Patients should be assessed 3 months after starting cilostazol; treatment may need to be withdrawn if there is no clinical improvement.

Reviews.
1. Goto S. Cilostazol: potential mechanism of action for antithrombotic effects accompanied by a low rate of bleeding. *Atheroscler Suppl* 2005; 6: 3–11.
2. Weinraub WS. The vascular effects of cilostazol. *Can J Cardiol* 2006; 22 (suppl B): 56B–60B.
3. Dalainas I. Cilostazol in the management of vascular disease. *Int Angiol* 2007; 26: 1–7.

Ischaemic heart disease. Percutaneous coronary intervention and stenting are widely used in the management of ischaemic heart disease but thrombotic complications and restenosis complicate their use. Antiplatelet drugs (usually aspirin plus a thienopyridine) are given to reduce thrombosis (see Reperfusion and Revascularisation Procedures, p. 1259.2) but generally have little effect on restenosis. Cilostazol has both antiplatelet and antiproliferative actions[1] and there is some evidence that it may reduce the incidence of restenosis,[1-3] particularly with use of bare metal stents. The addition of cilostazol to standard antiplatelet therapy ('triple therapy') appears to be safe[4-6] and may improve outcomes[7] especially in patients at high risk of restenosis including the elderly and those with diabetes mellitus or clopidogrel resistance.[6,8] Further studies are needed to confirm its role, including a possible role in preventing restenosis of peripheral vascular stents (see below).

1. El-Beyrouty C, Spinler SA. Cilostazol for prevention of thrombosis and restenosis after intracoronary stenting. *Ann Pharmacother* 2001; 35: 1108–13.
2. Biondi-Zoccai GGL, *et al.* Systematic review and meta-analysis of randomized clinical trials appraising the impact of cilostazol after percutaneous coronary intervention. *Am Heart J* 2008; 155: 1081–9.
3. Tamhane U, *et al.* Efficacy of cilostazol in reducing restenosis in patients undergoing contemporary stent based PCI: a meta-analysis of randomised controlled trials. *EuroIntervention* 2009; 5: 384–93.
4. Singh I, *et al.* Triple antiplatelet therapy vs. dual antiplatelet therapy in patients undergoing percutaneous coronary intervention: an evidence-based approach to answering a clinical query. *Br J Clin Pharmacol* 2009; 68: 4–13.
5. Jennings DL, Kalus JS. Addition of cilostazol to aspirin and a thienopyridine for prevention of restenosis after coronary artery stenting: a meta-analysis. *J Clin Pharmacol* 2010; 50: 415–21.
6. Rogers KC, *et al.* Use of cilostazol in percutaneous coronary interventions. *Ann Pharmacother* 2012; 46: 839–50.
7. Chen KY, *et al.* Korea Acute Myocardial Infarction Registry Investigators. Triple versus dual antiplatelet therapy in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Circulation* 2009; 119: 3207–14.
8. Park KW, *et al.* Cilostazol attenuates on-treatment platelet reactivity in patients with CYP2C19 loss of function alleles receiving dual antiplatelet therapy: a genetic substudy of the CILON-T randomised controlled trial. *Heart* 2011; 97: 641–7.

Peripheral vascular disease. Intermittent claudication is a major feature of occlusive arterial disease of the lower limbs (p. 1272.3) and is characterised by pain in the legs that develops during exercise and disappears at rest. Many drugs have been used for symptom control, but their efficacy and/or overall place in management remains to be firmly established.

Several randomised, double-blind studies[1] have shown that cilostazol improves walking distances in patients with intermittent claudication, and US guidelines have recommended a trial of cilostazol in all patients with lifestyle-limiting intermittent claudication in the absence of heart failure.[2] However, in the UK, NICE does not favour its use[3] and the EMA has restricted it to second-line treatment after lifestyle changes and other appropriate interventions have failed to provide sufficient improvement.[4] Long-term benefit has not been assessed[1] and, since patients with intermittent claudication are at high risk of other cardiovascular events, appropriate therapy to reduce cardiovascular risk (p. 1246.1) is still required. It has also been investigated[5] for a potential role in preventing restenosis in peripheral vascular stents after endovascular therapy for peripheral vascular disease.

1. Robless P, *et al.* Cilostazol for peripheral arterial disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 19/03/08).
2. Hirsch AT, *et al.* ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). *Circulation* 2006; 113: e463–e654. Available at: http://www.americanheart.org/downloadable/heart/1135028673759PAD_Full%20Text.pdf (accessed 27/06/06)
3. NICE. Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease (TA 223: issued May 2011). Available at: http://www.nice.org.uk/nicemedia/live/13477/54546/54546.pdf (accessed 14/10/13)
4. EMA. Press release: European Medicines Agency recommends restricting use of cilostazol-containing medicines (issued 22nd March, 2013). Available at http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/03/WC500140672.pdf (accessed 28/05/13)
5. Dindyal S, Kyriakides C. A review of cilostazol, a phosphodiesterase inhibitor, and its role in preventing both coronary and peripheral arterial restenosis following endovascular therapy. *Recent Pat Cardiovasc Drug Discov* 2009; 4: 6–14.

Stroke. A review of 3 controlled trials of cilostazol in the secondary prevention of ischaemic stroke in Asian patients suggested cilostazol may be safer and more effective than aspirin in such patients.[1]

1. Ansara AJ, *et al.* Use of cilostazol for secondary stroke prevention: an old dog with new tricks? *Ann Pharmacother* 2012; 46: 394–402.

Adverse Effects and Precautions

Adverse effects of cilostazol include headache, dizziness, palpitations, and diarrhoea; oedema, nausea and vomiting, cardiac arrhythmias, chest pain, rhinitis, ecchymosis, and rashes have also been reported. There is a risk of haemorrhage with cilostazol and patients should report any episode of bleeding or easy bruising; if retinal bleeding occurs, cilostazol should be stopped. Haematological abnormalities including leucopenia, thrombocytopenia, agranulocytosis, and aplastic anaemia have been reported rarely. Cardiovascular toxicity has been reported in *animal* studies of cilostazol, and prolonged oral use of other phosphodiesterase inhibitors (such as amrinone, p. 1305.1) for the treatment of heart failure has been associated with increased mortality. The use of cilostazol in patients with any degree of heart failure is therefore contra-indicated. It is also contra-indicated in patients with a known predisposition to bleeding, including those treated with two or more antiplatelet or anticoagulant drugs. It should not be used in those with a history of severe tachyarrhythmia or ventricular arrhythmias, QT interval prolongation, unstable angina, recent myocardial infarction, or coronary intervention within the previous 6 months. It should also be avoided in patients with severe renal impairment or moderate to severe hepatic impairment and in pregnant or breast-feeding women.

Cilostazol should be avoided or used in reduced doses in patients taking inhibitors of the cytochrome P450 isoenzymes CYP3A4 or CYP2C19 (see Interactions, below).

References.
1. Hiatt WR, *et al.* Long-term safety of cilostazol in patients with peripheral artery disease: the CASTLE study (Cilostazol: a study in long-term effects). *J Vasc Surg* 2008; 47: 330–6.

Interactions

Cilostazol is extensively metabolised to active and inactive metabolites by cytochrome P450 isoenzymes, mainly CYP3A4 and to a lesser extent CYP2C19. Therefore use with other drugs that inhibit or are metabolised by these hepatic enzymes may result in changes in plasma concentrations of either drug and, possibly, adverse effects. Cilostazol should therefore be used with caution in patients taking drugs metabolised by these enzymes; in patients taking enzyme inhibitors it should be avoided or a reduced dose should be considered (see Uses and Administration, above).

The risk of bleeding is increased if cilostazol is given with clopidogrel and aspirin; its use, therefore, is contra-indicated in patients receiving two or more other antiplatelet or anticoagulant drugs.

Pharmacokinetics

Cilostazol is absorbed after oral doses and absorption is increased if taken with a high fat meal. Cilostazol is extensively metabolised in the liver by cytochrome P450 isoenzymes, mainly CYP3A4 and to a lesser extent CYP2C19, to both active and inactive metabolites; these are mainly excreted in the urine (74%) with the remainder in the faeces (20%). The active metabolites have apparent elimination half-lives of 11 to 13 hours. Cilostazol is 95 to 98% protein bound.

References.
1. Woo SK, *et al.* Pharmacokinetic and pharmacodynamic modeling of the antiplatelet and cardiovascular effects of cilostazol in healthy humans. *Clin Pharmacol Ther* 2002; 71: 246–52.
2. Yoo H-D, *et al.* Population pharmacokinetic analysis of cilostazol in healthy subjects with genetic polymorphisms of CYP3A5, CYP2C19 and ABCB1. *Br J Clin Pharmacol* 2010; 69: 27–37.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aclusin; Cibrogan; Cilaal; Cilostal; Cilovas; Licuagen; Pletaal; Policor; Trastocir; Trombonot; Zolplat; *Austral.*: Pletal; *Braz.*: Cebralat; Claudic; Vasativ; Vasogard; *Chile*: Artesol; Ilostal; Kostal†; *China*: Bang Ping (邦平); Pletaal (培达); Si Te Li Pu (斯特里普); Xi Luo (希络); *Fr.*: Pletal†; *Ger.*: Pletal; *Hong Kong*: Pletaal; *India*: Cilodac; Cletus; Pletor; Stilox; Zilast; *Indon.*: Aggravan; Agrezol†; Alista; Antiplat; Citaz; Ilos; Naletal; Pletaal; Qital; Stazol; *Irl.*: Pletal†; *Ital.*: Pletal; *Jpn*: Pletaal; *Malaysia*: Pletaal; *Mex.*: Caudaline; *Philipp.*: Aggravan; Ciletin; Clazol; Pletaal; Trombocil; *Spain*: Ekistol; Pletal; *Swed.*: Pletal; *Thai.*: Cilosol; Pletaal; *Turk.*: Pletal; *UK*: Pletal; *USA*: Pletal.

Multi-ingredient Preparations. *Arg.*: Trastocir Duo.

Pharmacopoeial Preparations
USP 36: Cilostazol Tablets.

Cinepazide Maleate *(BANM, rINNM)*

Cinepazida, maleato de; Cinépazide, Maléate de; Cinepazidi Maleas; Maleato de cinepazida; MD-67350; Цинепазида Малеат.

1-(Pyrrolidin-1-ylcarbonylmethyl)-4-(3,4,5-trimethoxycinnamoyl)piperazine hydrogen maleate.

$C_{22}H_{31}N_3O_8.C_4H_4O_4$=533.6

CAS — 23887-46-9 (cinepazide); 26328-04-1 (cinepazide maleate).

ATC — C04AX27.

ATC Vet — QC04AX27.

UNII — Y3583VA60V.

Profile

Cinepazide maleate is a vasodilator that has been used in peripheral vascular disorders, but has been withdrawn from the market in some countries after reports of agranulocytosis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ke Lin Ao (克林澳).

Ciprofibrate *(BAN, USAN, rINN)*

Ciprofibrat; Ciprofibrate; Ciprofibratas; Ciprofibrato; Ciprofibratum; Siprofibraatti; Win-35833; Ципрофибрат.

2-[4-(2,2-Dichlorocyclopropyl)phenoxy]-2-methylpropionic acid.

$C_{13}H_{14}Cl_2O_3$=289.2

CAS — 52214-84-3.

ATC — C10AB08.

ATC Vet — QC10AB08.

UNII — F8252JGO9S.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Ciprofibrate). A white or slightly yellow, crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol; soluble in toluene. Store in airtight containers. Protect from light.

Uses and Administration

Ciprofibrate, a fibric acid derivative, is a lipid regulating drug with actions on plasma lipids similar to those of bezafibrate (p. 1323.2).

It is used to reduce total cholesterol and triglycerides in the management of hyperlipidaemias (p. 1248.1), including type IIa, type IIb, type III, and type IV hyperlipoproteinaemias. The usual oral dose is 100 mg daily. The dose should be reduced in renal impairment (see below).

Administration in renal impairment. Ciprofibrate is contra-indicated in patients with severe renal impairment. Licensed product information suggests reducing the dose to 100 mg every other day for patients with moderate renal impairment.

Renal clearance of ciprofibrate was reduced and elimination half-life about doubled in patients with severe renal impairment.[1] Mild renal impairment slowed the urinary excretion of ciprofibrate but not its extent. The clearance of ciprofibrate was unaffected by haemodialysis.

1. **Perry N, *et al.*** The influence of renal insufficiency and haemodialysis on the kinetics of ciprofibrate. *Br J Clin Pharmacol* 1989; 28: 675–81.

Adverse Effects and Precautions

As for Bezafibrate, p. 1324.2.

Interactions

As for Bezafibrate, p. 1325.2.

Pharmacokinetics

Ciprofibrate is readily absorbed from the gastrointestinal tract; peak plasma concentrations occur within 1 to 4 hours. Ciprofibrate is highly protein bound. It is excreted in the urine as unchanged drug and as glucuronide conjugates. The elimination half-life varies from about 38 to 86 hours in patients on long-term therapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Estaprol; Fixeril; *Belg.*: Hyperlipen; *Braz.*: Cibrato; Ciprolip; Lipless; Lipneo; Oroxadin; *Chile*: Estaprol; *China*: Modalim (卡比瑞克); *Cz.*: Lipanor; *Fr.*: Lipanor; *Gr.*: Savilen; *Hung.*: Lipanor; *Indon.*: Modalim; *Israel*: Lipanor; *Malaysia*: Modalim; *Mex.*: Oroxadin; *Neth.*: Modalim; *Philipp.*: Modalim; *Pol.*: Lipanor; *Port.*: Fibranin; Lipanor; *Rus.*: Lipanor (Липанор); *Singapore*: Modalim; *Switz.*: Hyperlipen; *UK*: Modalim†; *Venez.*: Hiperlipen.

Clevidipine *(USAN, rINN)*

Clévidipine; Clevidipino; Clevidipinum; H-324/38; Клевидипин.

(Butanoyloxy)methyl methyl (4*RS*)-4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate; (±)-Hydroxymethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate butyrate.

$C_{21}H_{23}Cl_2NO_6$=456.3

CAS — 166432-28-6; 167221-71-8.

ATC — C08CA16.

ATC Vet — QC08CA16.

UNII — 19O2GP387Q.

Uses and Administration

Clevidipine is a dihydropyridine calcium-channel blocker (p. 1244.2); in the USA it is known as clevidipine butyrate. It is used in the management of hypertension (p. 1251.1) as an alternative to oral therapy, and is given by intravenous infusion. The initial dose is 1 to 2 mg/hour, increased if necessary according to the patient's response by doubling the dose, initially every 90 seconds but at longer intervals of 5 to 10 minutes as the desired blood pressure is reached. A dose of 4 to 6 mg/hour is adequate in most patients, with a usual maximum dose of 16 mg/hour; however, up to 32 mg/hour has been required in severe hypertension.

Clevidipine injection has a high lipid content (about 200 mg/mL) and no more than 1 litre should be given in 24 hours.

References.

1. Noviawaty I, *et al.* Drug evaluation of clevidipine for acute hypertension. *Expert Opin Pharmacother* 2008; 9: 2519–29.
2. Aronson S, *et al.* The ECLIPSE trials: comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. *Anesth Analg* 2008; 107: 1110–21.
3. Nguyen HM, *et al.* Clevidipine for the treatment of severe hypertension in adults. *Clin Ther* 2010; 32: 11–23.
4. Ndefo UA, *et al.* Clevidipine: a new intravenous option for the management of acute hypertension. *Am J Health-Syst Pharm* 2010; 67: 351–60.
5. Peacock FW, *et al.* Clevidipine for severe hypertension in acute heart failure: a VELOCITY trial analysis. *Congest Heart Fail* 2010; 16: 55–9.
6. Awad AS, Goldberg ME. Role of clevidipine butyrate in the treatment of acute hypertension in the critical care setting: a review. *Vasc Health Risk Manag* 2010; 6: 457–64.

Administration in children. In a retrospective review,[1] ten children aged from 9 to 18 years and weighing from 26 to 96 kg were given clevidipine either to control hypertension, induce hypotension, or improve distal perfusion. The initial dose was 500 nanograms/kg per minute in 8 patients, and 1 microgram/kg per minute in 2 patients, adjusted by increments of 500 nanograms/kg per minute every 3 to 5 minutes; the highest dose given was 3.5 micrograms/kg per minute. The durations of infusion ranged from 1.5 to 34 hours, and target blood pressures were reached within 10 minutes. Tachycardia required treatment with beta blockers in 2 patients.

1. Towe E, Tobias JD. Preliminary experience with clevidipine in the pediatric population. *J Intensive Care Med* 2010; 25: 349–52.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2). Clevidipine injection is formulated as an emulsion containing soybean oil and egg-yolk phospholipids and should not be used in patients with soy or egg allergies or with defective lipid metabolism.

Interactions

Clevidipine would be expected to have similar pharmacological interactions to other dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2), although published studies are lacking. Clevidipine is reported not to affect cytochrome P450 isoenzymes.

Pharmacokinetics

Clevidipine is rapidly distributed when given intravenously and is metabolised by esterases in the blood and extravascular tissues to the inactive carboxylic acid metabolite. The half-life of the initial phase is about 1 minute and accounts for 85 to 90% of clevidipine elimination; the terminal half-life is about 15 minutes. The metabolite is further metabolised by glucuronidation or oxidation to the pyridine derivative and is eliminated mainly in the urine and faeces, with a terminal half-life of about 9 hours. Clevidipine is more than 99.5% bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Neth.*: Cleviprex; *Switz.*: Cleviprex; *UK*: Cleviprex; *USA*: Cleviprex.

Clinofibrate *(rINN)*

Clinofibrato; Clinofibratum; S-8527; Клинофибрат.

2,2'-[Cyclohexylidenebis(4-phenyleneoxy)]bis[2-methylbutyric acid].

$C_{28}H_{36}O_6$=468.6

CAS — 30299-08-2.

UNII — 0374EZJ8CU.

Pharmacopoeias. In *Jpn.*

Profile

Clinofibrate, a fibric acid derivative (see Bezafibrate, p. 1323.2), is a lipid regulating drug used in the treatment of hyperlipidaemias (p. 1248.1). The usual oral dose is 200 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Lipoclin.

Clofibrate *(BAN, USAN, rINN)*

AY-61.123; Clofibrat; Clofibrato; Clofibratum; Ethyl *p*-Chlorophenoxyisobutyrate; Ethyl Clofibrate; ICI-28257; Klofibraatti; Klofibrat; Klofibrát; Klofibratas; NSC-79389; Клофибрат.

Ethyl 2-(4-chlorophenoxy)-2-methylpropionate.

$C_{12}H_{15}ClO_3$=242.7

CAS — 637-07-0 (clofibrate); 882-09-7 (clofibric acid).

ATC — C10AB01.

ATC Vet — QC10AB01.

UNII — HPN91K7FU3.

NOTE. The name Binograc has been used as a trademark for clofibrate.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Clofibrate). A clear, almost colourless liquid. Very slightly soluble in water; miscible with alcohol.

USP 36: (Clofibrate). A colourless to pale yellow liquid with a characteristic odour. Insoluble in water; soluble in alcohol, in acetone, in chloroform, and in benzene. Store in airtight containers. Protect from light.

Aluminium Clofibrate *(BAN, rINN)*

Alufibrate; Aluminii Clofibras; Aluminium Clofibrate d'; Aluminiumklofibraatti; Aluminiumklofibrat; Aluminum Clofibrate; Clofibrato de aluminio; Алюминия Клофибрат.

Bis[2-(4-chlorophenoxy)-2-methylpropionato]hydroxyaluminium.

$C_{20}H_{21}AlCl_2O_7$=471.3

CAS — 24818-79-9; 14613-01-5.

ATC — C10AB03.

ATC Vet — QC10AB03.

UNII — 56203T2K2X.

Calcium Clofibrate *(rINN)*

Calcii Clofibras; Clofibrate de Calcium; Clofibrato de calcio; Кальция Клофибрат.

$C_{20}H_{20}CaCl_2O_6$=467.4

CAS — 39087-48-4.

UNII — TT85QFR500.

Magnesium Clofibrate (rINN)

Clofibrato de magnesio; Clomag; Magnesii Clofibras; Magnésium, Clofibrate de; UR-112; Магния Клофибрат.

$C_{20}H_{20}Cl_2MgO_6$=451.6

CAS — 14613-30-0.

UNII — YTTSP157PJ.

Profile

Clofibrate, a fibric acid derivative, is a lipid regulating drug with similar properties to bezafibrate (p. 1323.2). It is used to reduce triglycerides and possibly total cholesterol in the management of hyperlipidaemias (p. 1248.1), particularly in patients with hypertriglyceridaemia. Because of the incidence of adverse effects during long-term treatment it should not be used for the prophylaxis of ischaemic heart disease (see Adverse Effects, below). A typical oral daily dose is 0.75 to 1.5 g given in 2 or 3 divided doses, although daily doses of up to 2 g have been used.

The aluminium, calcium, and magnesium salts of clofibrate have also been used.

Adverse effects. Large-scale, long-term studies[1,2] with clofibrate indicated that it was generally well-tolerated but that there was an increased incidence of serious effects, including cholelithiasis, cholecystitis, thromboembolic disorders, and certain cardiac arrhythmias. In one of the studies,[2] an increased mortality rate was unexpectedly found in patients taking clofibrate, producing serious concern over its long-term safety and its use is now generally restricted; the causes of death were spread over a range of malignant and non-malignant disorders.

1. The Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA* 1975; 231: 360–80.
2. Oliver MF, *et al.* A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. *Br Heart J* 1978; 40: 1069–1118.

Neonatal jaundice. Clofibrate has been used in the treatment of jaundice in term infants[1,2] and for prophylaxis in premature infants.[1] In a study[1] involving 93 term infants with jaundice, clofibrate 50 mg/kg as a single oral dose reduced the intensity and duration of jaundice compared with placebo. As a prophylactic measure, clofibrate was shown[1] to reduce the degree of jaundice in premature infants when the plasma concentration of clofibric acid reached 140 micrograms/mL within 24 hours of an oral dose. The dose required to achieve this was estimated to be 100 to 150 mg/kg.

1. Gabilan JC, *et al.* Clofibrate treatment of neonatal jaundice. *Pediatrics* 1990; 86: 647–8.
2. Mohammadzadeh A, *et al.* Effect of clofibrate in jaundiced term newborns. *Indian J Pediatr* 2005; 72: 123–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Elpi†; *Gr.*: Atromid-S; *Hong Kong*: Lipilim†.

Multi-ingredient Preparations. *Braz.*: Lipofacton†.

Pharmacopoeial Preparations
BP 2014: Clofibrate Capsules;
USP 36: Clofibrate Capsules.

Clonidine (BAN, USAN, rINN)

Clonidina; Clonidinum; Klonidiini; Klonidin; ST-155-BS; Клонидин.

2-(2,6-Dichloroanilino)-2-imidazoline; 2,6-Dichloro-*N*-(imidazolidin-2-ylidene)aniline.

$C_9H_9Cl_2N_3$=230.1

CAS — 4205-90-7.

ATC — C02AC01; N02CX02; S01EA04.

ATC Vet — QC02AC01; QN02CX02; QS01EA04.

UNII — MN3L5RMN02.

Pharmacopoeias. In *US*.

USP 36: (Clonidine). A white to almost white, crystalline powder. Freely soluble in alcohol and in methyl alcohol. Store in airtight containers.

Clonidine Hydrochloride (BANM, USAN, rINNM)

Clonidina, hidrocloruro de; Clonidine, chlorhydrate de; Clonidinhydrochlorid; Clonidini Hydrochloridum; Hidroclorúro de clonidina; Klonidiinihydrokloridi; Klonidin-hidroklorid; Klonidin-hydrochlorid; Klonidinhydroklorid; Klonidinio hidrochloridas; Klonidyny chlorowodorek; ST-155; Клонидина Гидрохлорид.

$C_9H_9Cl_2N_3$,HCl=266.6

CAS — 4205-91-8.

ATC — C02AC01; N02CX02; S01EA04.

ATC Vet — QC02AC01; QN02CX02; QS01EA04.

UNII — W76I6XXF06.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Clonidine Hydrochloride). A white or almost white crystalline powder. Soluble in water and in dehydrated alcohol. A 5% solution in water has a pH of 4.0 to 5.0.

USP 36: (Clonidine Hydrochloride). pH of a 5% solution in water is between 3.5 and 5.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Clonidine is an imidazoline antihypertensive that appears to act centrally to reduce sympathetic tone, resulting in a fall in diastolic and systolic blood pressure and a reduction in heart rate. The exact mechanism is unclear; clonidine stimulates alpha$_2$ adrenoceptors and central imidazoline receptors, but it is unknown which receptors mediate which effects. It also acts peripherally, and this peripheral activity may be responsible for the transient increase in blood pressure seen during rapid intravenous injection as well as contributing to the hypotensive effect during chronic use. Peripheral resistance is reduced during continuous treatment. Cardiovascular reflexes remain intact so orthostatic hypotension is uncommon.

Clonidine is used in the management of hypertension (p. 1251.1), including hypertensive crises, although other drugs with fewer adverse effects are now generally preferred. It may be given with a thiazide diuretic, but use with a beta blocker should be avoided where possible. Clonidine has also been used in the prophylactic treatment of migraine or recurrent vascular headaches (but see p. 1340.1) and in the treatment of menopausal flushing. It is used with opioids in the management of cancer pain and has been tried for various other forms of pain (p. 1340.2). It is also used in the management of ADHD (see Hyperactivity p. 1340.1). Other uses of clonidine have included the symptomatic treatment of opioid withdrawal (see under Substance Dependence, p. 1340.3), the diagnosis of phaeochromocytoma (p. 1340.2), and as eye drops in the management of glaucoma (p. 1999.1). It has also been tried in Tourette's syndrome (p. 1341.1) and many other disorders.

Clonidine is used as the hydrochloride. When given orally, its haemodynamic effects appear in about 30 to 60 minutes, reaching a maximum after 2 to 4 hours and lasting up to 8 hours. Tolerance to clonidine has been reported. Withdrawal of clonidine should be gradual because of the risk of rebound hypertension.

In **hypertension**, the usual initial oral dose of clonidine hydrochloride is 50 to 100 micrograms three times daily (or in the USA, 100 micrograms twice daily), increased every second or third day according to response; the usual maintenance dose is 300 to 1200 micrograms daily but doses of 1800 micrograms or more daily may sometimes be required. Modified-release preparations have been used. Clonidine may also be given by transdermal delivery systems that are applied once a week and deliver 100 to 300 micrograms of clonidine base daily at a constant rate.

Clonidine hydrochloride may be given by slow intravenous injection over 10 to 15 minutes in hypertensive crises, usually in doses of 150 to 300 micrograms. The effect usually appears within 10 minutes, but transient hypertension may precede hypotension if the injection is given too rapidly. The hypotensive effect reaches a maximum about 30 to 60 minutes after injection and the duration is about 3 to 7 hours; up to 750 micrograms may be given intravenously over 24 hours. Oral dosage does not produce a sufficiently rapid hypotensive effect for use in emergencies; however, for less urgent reduction of severe hypertension, clonidine has been given orally in an initial dose of 100 to 200 micrograms, followed by 50 to 200 micrograms every hour until blood pressure was controlled or a maximum total dose of 500 to 700 micrograms given.

For doses in children, see below.

In the prophylaxis of **migraine** or recurrent vascular headaches and in the treatment of **menopausal flushing**, an oral dose of 50 micrograms twice daily has been used, increased, if there is no remission after 2 weeks, to 75 micrograms twice daily.

In the management of severe **cancer pain**, clonidine hydrochloride may be given by continuous epidural infusion with an opioid, in an initial dose of 30 micrograms/hour, adjusted according to response.

Administration in children. Although unlicensed for use in children, the *BNFC* suggests that clonidine may be given to treat severe hypertension in children aged 2 years and above in doses according to weight. A suggested initial oral daily dose is 1.5 to 3 micrograms/kg in 3 divided doses, increased gradually if necessary to a maximum daily dose of 25 micrograms/kg (not exceeding 1.2 mg daily) given in divided doses. A slow intravenous injection of 2 to 6 micrograms/kg (maximum of 300 micrograms) may be given as a single dose over 10 to 15 minutes.

See p. 1340.1, p. 1340.3 and p. 1341.1 for details of doses used in ADHD, neonatal abstinence syndrome (Substance Dependence, under Opioid Analgesics), and Tourette's syndrome, respectively.

Anxiety disorders. Clonidine has been tried in various anxiety disorders but evidence of efficacy is limited. A review[1] of its use in panic disorder (p. 1029.1) considered that it might be useful as a last-line anxiolytic in patients unresponsive to standard treatment as occasional success had been obtained in a few patients. There have also been isolated reports of small numbers of patients with post-traumatic stress disorder (p. 1029.2) who have benefited from clonidine.[2]

For mention of clonidine as an adjuvant to sedative drugs in the intensive care unit see p. 1033.1.

1. Puzantian T, Hart LL. Clonidine in panic disorder. *Ann Pharmacother* 1993; 27: 1351–3.
2. Harmon RJ, Riggs PD. Clonidine for posttraumatic stress disorder in preschool children. *J Am Acad Child Adolesc Psychiatry* 1996; 35: 1247–9.

Cardiac arrhythmias. Atrial fibrillation (p. 1266.1) is managed by treatment to slow the increased ventricular responses or by cardioversion. Control of ventricular rate is usually achieved with digoxin, beta blockers, or calcium-channel blockers but clonidine, which reduces sympathetic tone and thus reduces heart rate, has also been tried.[1-3]

1. Roth A, *et al.* Clonidine for patients with rapid atrial fibrillation. *Ann Intern Med* 1992; 116: 388–90.
2. Scardi S, *et al.* Oral clonidine for heart rate control in chronic atrial fibrillation. *Lancet* 1993; 341: 1211–12.
3. Simpson CS, *et al.* Clinical assessment of clonidine in the treatment of new-onset rapid atrial fibrillation: a prospective, randomized clinical trial. *Am Heart J* 2001; 142: e3.

Diarrhoea. Some studies have shown that clonidine possesses antidiarrhoeal properties. Clonidine may stimulate alpha$_2$ adrenoceptors on enterocytes thus promoting fluid and electrolyte absorption and inhibiting anion secretion. It may also modify intestinal motility or rectal sphincter tone.

Most experience with clonidine is in diabetic diarrhoea (see p. 464.1). Oral clonidine 100 to 600 micrograms every 12 hours reduced diabetic diarrhoea in 3 patients with type 1 diabetes[1] and good results have also been reported in such patients when transdermal clonidine was used.[2,3] Benefit has also been reported in patients with symptoms of diabetic gastroparesis in addition to diarrhoea.[3,4] However, oral (but perhaps not transdermal) clonidine may worsen orthostatic hypotension in patients with diabetic diarrhoea and this may limit its usefulness.[5] Clonidine has also been tried in patients with high intestinal output after small bowel transplantation[6] or jejunostomy,[7] and in diarrhoea-predominant irritable bowel syndrome[8] or for the gastrointestinal effects of opioid withdrawal.[9]

1. Pedorak RN, *et al.* Treatment of diabetic diarrhea with clonidine. *Ann Intern Med* 1985; 102: 197–9.
2. Sacerdote A. Topical clonidine for diabetic diarrhea. *Ann Intern Med* 1986; 105: 139.
3. Sacerdote AS. Topical clonidine and diabetic gastroparesis. *Ann Intern Med* 1990; 112: 796.
4. Migliore A, *et al.* Diabetic diarrhea and clonidine. *Ann Intern Med* 1988; 109: 170–1.
5. Ogbonnaya KI, Arem R. Diabetic diarrhea: pathophysiology, diagnosis, and management. *Arch Intern Med* 1990; 150: 262–7.
6. Rovera G, *et al.* The use of clonidine for the treatment of high intestinal output following small bowel transplantation. *Transplant Proc* 1997; 29: 1853–4.
7. Buchman AL, *et al.* Clonidine reduces diarrhea and sodium loss in patients with proximal jejunostomy: a controlled study. *J Parenter Enteral Nutr* 2006; 30: 487–91.
8. Camilleri M, *et al.* A randomized, controlled exploratory study of clonidine in diarrhea-predominant irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2003; 1: 111–21.
9. Ma H, *et al.* The effect of clonidine on gastrointestinal side effects associated with ultra-rapid opioid detoxification. *Anesth Analg* 2003; 96: 1409–12.

Extrapyramidal disorders. There is limited evidence[1] from small studies that clonidine might reduce symptoms of antipsychotic-induced akathisia and tardive dyskinesia (p. 1049.2). However, adverse effects such as sedation and hypotension may limit use.

1. Ahmed I, Takeshita J. Clonidine: a critical review of its role in the treatment of psychiatric disorders. *CNS Drugs* 1996; 6: 53–70.

Growth retardation. Clonidine has been reported to be a stimulant of growth hormone release, presumably as a result of central alpha-adrenergic stimulation, and has been tried in the diagnosis and management of growth retardation (p. 1921.3). It may be given orally as a provocative test for growth hormone deficiency,[1,2] particularly in children,[3] although some consider measurement of circulating somatomedins (insulin-like growth factors; IGFs) to be more useful than provocative tests. A combination of both may be required to confirm diagnosis;[4] guidelines have been suggested.[5] Caution is required when perform-

ing the test in children since severe hypoglycaemia has been reported.[6] Clonidine has also been tried in the treatment of growth retardation, both in children with growth hormone deficiency and in short children without proven deficiency, but results have been contradictory and largely unsatisfactory.[7-9]

1. Gil-Ad I, *et al.* Oral clonidine as a growth hormone stimulation test. *Lancet* 1979; ii: 278–80.
2. Hoffman WH, *et al.* Relationship of plasma clonidine to growth hormone concentrations in children and adolescents. *J Clin Pharmacol* 1989; 29: 538–42.
3. Hindmarsh PC, Swift PGF. An assessment of growth hormone provocation tests. *Arch Dis Child* 1995; 72: 362–8.
4. Cianfarani S, *et al.* Height velocity and IGF-1 assessment in the diagnosis of childhood onset GH insufficiency: do we still need a second GH stimulation test? *Clin Endocrinol (Oxf)* 2002; 57: 161–7.
5. Evans C, Gregory JW. The investigation of short stature: a survey of practice in Wales and suggested practical guidelines. *J Clin Pathol* 2004; 57: 126–30.
6. Huang C, *et al.* Hypoglycemia associated with clonidine testing for growth hormone deficiency. *J Pediatr* 2001; 139: 323–4.
7. Pintor C, *et al.* Clonidine treatment for short stature. *Lancet* 1987; i: 1226–30.
8. Pescovitz OH, Tan E. Lack of benefit of clonidine treatment for short stature in a double-blind, placebo-controlled trial. *Lancet* 1988; ii: 874–7.
9. Allen DB. Effects of nightly clonidine administration on growth velocity in short children without growth hormone deficiency: a double-blind, placebo-controlled study. *J Pediatr* 1993; 122: 32–6.

Hyperactivity. Drug treatment of attention deficit hyperactivity disorder (ADHD, p. 2314.1) is usually begun with a central stimulant; clonidine may be an alternative, either as monotherapy or as an adjunct to stimulant therapy. In the USA, an oral modified-release preparation is available for children and adolescents aged from 6 to 17 years. It is given in an initial dose of 100 micrograms once daily at bedtime, adjusted according to response in weekly increments of 100 micrograms, to a maximum daily dose of 400 micrograms. Daily doses of 200 micrograms and above should be given in two divided doses, split either equally or with the larger dose given at bedtime. When stopping therapy, the dose should be tapered in decrements of 100 micrograms every 3 to 7 days.

A meta-analysis[1] of clonidine used to treat ADHD occurring alone or with other conditions, including tic disorders (see Tourette's Syndrome, p. 1341.1), concluded that clonidine might be a useful second-line treatment but was less effective than stimulants and was associated with many adverse effects. There have been reports[2] of sudden death when clonidine has been used with stimulants, but the role of the drugs in these events is unclear. A study[3] in children with both ADHD and Tourette's syndrome found that clonidine used with methylphenidate was more effective than either drug alone, and only 1 child had evidence of adverse cardiac effects. Others have since reported on the efficacy[4] and safety[5] of clonidine in ADHD, alone or with methylphenidate.

Clonidine has also been tried in the management of children with disturbed behaviour (p. 1030.2).

1. Connor DF, *et al.* A meta-analysis of clonidine for symptoms of attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 1999; 38: 1551–9.
2. Penichet RR. Combining methylphenidate and clonidine: the role of post-marketing surveillance. *J Child Adolesc Psychopharmacol* 1995; 5: 155–6.
3. The Tourette's Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial. *Neurology* 2002; 58: 527–36.
4. Palumbo DR, *et al.* Clonidine for attention-deficit/hyperactivity disorder: I. Efficacy and tolerability outcomes. *J Am Acad Child Adolesc Psychiatry* 2008; 47: 180–8.
5. Daviss WB, *et al.* Clonidine for attention-deficit/hyperactivity disorder: II. ECG changes and adverse events analysis. *J Am Acad Child Adolesc Psychiatry* 2008; 47: 189–98.

Menopausal disorders. Although HRT is the mainstay of treatment for menopausal disorders (p. 2245.1) clonidine has been of some use in countering vasomotor symptoms in patients who cannot use HRT;[1,2] however, some studies have failed to show a reduction in hot flushes. The adverse effects reported in normotensive women, including orthostatic hypotension, may mean that it is best reserved for women who are also hypertensive.

Clonidine has also been tried[3] for hot flushes in women receiving tamoxifen.

1. Young RL, *et al.* Management of menopause when estrogen cannot be used. *Drugs* 1990; 40: 220–30.
2. Lucero MA, McCloskey WW. Alternatives to estrogen for the treatment of hot flashes. *Ann Pharmacother* 1997; 31: 915–17.
3. Pandya KJ, *et al.* Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. *Ann Intern Med* 2000; 132: 788–93.

Migraine. Propranolol is probably the most well established drug for prophylaxis of migraine (p. 670.3). Many other drugs have been used, including clonidine, but a review of clinical studies[1] indicated that it was a poor first choice and seemed unlikely to work even as a last resort. It has been used in patients whose attacks may be precipitated by tyramine-containing foods.

1. Anonymous. Clonidine in migraine prophylaxis—now obsolete. *Drug Ther Bull* 1990; 28: 79–80.

Orthostatic hypotension. Paradoxically, clonidine has produced beneficial effects in a few patients with orthostatic hypotension (p. 1634.3), including that due to autonomic neuropathy[1] and that possibly due to brimonidine and betaxolol eye drops in a hypertensive woman with glaucoma;[2] clonidine improved both the orthostatic hypotension and the supine hypertension.

1. Acott PD, *et al.* Effectiveness of clonidine in congenital orthostatic hypotension. *J Pediatr* 1990; 116: 666–7.
2. Brahmbhatt R, *et al.* Normalization of blood pressure in a patient with severe orthostatic hypotension and supine hypertension using clonidine. *Hypertension* 2001; 37: e24.

Pain. Giving opioids and local anaesthetics by the epidural or intrathecal routes can produce effective analgesia but adverse effects are common. Many other drugs, including clonidine, have been tried by these routes, alone or as adjuncts. Clonidine is thought to produce analgesia by a direct action on alpha$_2$ adrenoceptors in the spinal cord. It has been used in various types of pain, such as postoperative pain (p. 6.1), labour pain (p. 8.3), and the pain associated with cancer (p. 7.1), particularly neuropathic pain (p. 10.1). It has been used alone but is more usually given with local anaesthetics and/or opioids; it has been given by various routes including epidural, intrathecal, intravenous, intramuscular, oral, and transdermal use. An early meta-analysis[1] of postoperative epidural use of clonidine was unable to reach a conclusion owing to the large number of variables. Subsequent systematic reviews considered that addition of clonidine to intermediate-acting local anaesthetics improved their activity in certain peripheral nerve and plexus blocks,[2,3] and that adding clonidine to intrathecal local anaesthetics reduced intra-operative pain, although it increased the risk of hypotension.[4] Adding clonidine to peripheral or plexus blocks seemed to prolong the duration of postoperative analgesia by about 2 hours; it was unclear to what extent the effects of clonidine were dose-responsive.[3] The role and appropriate dosage of clonidine in local anaesthesia remains unclear.[2-4] For further discussion of pain and its management, see p. 4.1. See also Premedication, below.

1. Armand S, *et al.* Meta-analysis of the efficacy of extradural clonidine to relieve postoperative pain: an impossible task. *Br J Anaesth* 1998; 81: 126–34.
2. McCartney CJL, *et al.* Should we add clonidine to local anesthetic for peripheral nerve blockade? A qualitative systematic review of the literature. *Reg Anesth Pain Med* 2007; 32: 330–8.
3. Pöpping DM, *et al.* Clonidine as an adjuvant to local anesthetics for peripheral nerve and plexus blocks: a meta-analysis of randomized trials. *Anesthesiology* 2009; 111: 406–15.
4. Elia N, *et al.* Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials. *Reg Anesth Pain Med* 2008; 33: 159–67.

Phaeochromocytoma. Clonidine acts centrally to suppress catecholamine release and may be used[1] in the diagnosis of phaeochromocytoma (p. 1278.1). Experience gained with the clonidine suppression test and a review of published studies indicated that it is of value in selected patients with moderately elevated plasma and/or urinary catecholamine concentrations.[2]

1. Bravo EL, *et al.* Clonidine-suppression test: a useful aid in the diagnosis of pheochromocytoma. *N Engl J Med* 1981; 305: 623–6.
2. Lenz T, *et al.* Clonidine suppression test revisited. *Blood Pressure* 1998; 7: 153–9.

Premedication. Clonidine has been given pre-operatively for its sedative, anxiolytic and analgesic effects (see also Pain, above), and to provide haemodynamic stability and reduce anaesthetic requirements; it is often given orally, although other routes such as intranasal and intravenous have also been tried. It has often been tried in children,[1] in whom pre-operative use has also been reported to reduce postoperative vomiting[2] (similar results have been reported in adult women[3]); a meta-analysis concluded that it was superior to benzodiazepines in producing sedation at induction, decreasing emergence agitation, and producing early postoperative analgesia, although comparative benefits in reducing postoperative nausea and vomiting were less clear.[4] Clonidine may attenuate the perioperative stress response and has been shown to reduce perioperative oxygen consumption, which is a marker of sympathetic activation.[5] It may also reduce the risk of perioperative myocardial ischaemia.[6]

1. Bergendahl H, *et al.* Clonidine in paediatric anaesthesia: review of the literature and comparison with benzodiazepines for premedication. *Acta Anaesthesiol Scand* 2006; 50: 135–43.
2. Mikawa K, *et al.* Oral clonidine premedication reduces vomiting in children after strabismus surgery. *Can J Anaesth* 1995; 42: 977–81.
3. Oddby-Muhrbeck E, *et al.* Effects of clonidine on postoperative nausea and vomiting in breast cancer surgery. *Anesthesiology* 2002; 96: 1109–14.
4. Dahmani S, *et al.* Premedication with clonidine is superior to benzodiazepines: a meta analysis of published studies. *Acta Anaesthesiol Scand* 2010; 54: 397–402.
5. Taittonen MT, *et al.* Effect of clonidine and dexmedetomidine premedication on perioperative oxygen consumption and haemodynamic state. *Br J Anaesth* 1997; 78: 400–406.
6. Nishina K, *et al.* Efficacy of clonidine for prevention of perioperative myocardial ischemia: a critical appraisal and meta-analysis of the literature. *Anesthesiology* 2002; 96: 323–9.

Restless legs syndrome. Many drugs have been tried for the treatment of restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2). Symptomatic improvement has been reported with clonidine in several case studies[1,2] and small controlled studies,[3] but adverse effects may limit its use.

1. Handwerker JV, Palmer RF. Clonidine in the treatment of "restless leg" syndrome. *N Engl J Med* 1985; 313: 1228–9.
2. Zoe A, *et al.* High-dose clonidine in a case of restless legs syndrome. *Ann Pharmacother* 1994; 28: 878–81.
3. Wagner ML, *et al.* Randomized, double-blind, placebo-controlled study of clonidine in restless legs syndrome. *Sleep* 1996; 19: 52–8.

Shivering. Many drugs, including clonidine, have been tried for the treatment of postoperative shivering (p. 1900.2). Clonidine's central and peripheral effects could both account for its antishivering activity, but some have suggested that it acts by resetting the central threshold temperature for shivering. Several studies[1-3] have suggested that clonidine is effective for the treatment of postoperative shivering. Typical doses of 75 to 150 micrograms intravenously have been used. Clonidine given intraoperatively,[4-7] including to neurosurgical patients after mild hypothermia,[8] has also been reported to reduce the incidence of postoperative shivering. However, studies[9,10] have found nefopam to be superior to clonidine for prevention of postoperative shivering.

1. Joris J, *et al.* Clonidine and ketanserin both are effective treatment for postanesthetic shivering. *Anesthesiology* 1993; 79: 532–9.
2. Capogna G, Celleno D. IV clonidine for post-extradural shivering in parturients: a preliminary study. *Br J Anaesth* 1993; 71: 294–5.
3. Schwarzkopf KRG, *et al.* A comparison between meperidine, clonidine and urapidil in the treatment of postanesthetic shivering. *Anesth Analg* 2001; 92: 257–60.
4. Steinfath M, *et al.* Clonidine administered intraoperatively prevents postoperative shivering. *Br J Clin Pharmacol* 1995; 39: 580P–581P.
5. Vanderstappen I, *et al.* The effect of prophylactic clonidine on postoperative shivering: a large prospective double-blind study. *Anaesthesia* 1996; 51: 351–5.
6. Sia S. I.v. clonidine prevents post-extradural shivering. *Br J Anaesth* 1998; 81: 145–6.
7. Piper SN, *et al.* A comparison of urapidil, clonidine, meperidine and placebo in preventing postanesthetic shivering. *Anesth Analg* 2000; 90: 954–7.
8. Stapelfeldt C, *et al.* Intraoperative clonidine administration to neurosurgical patients. *Anesth Analg* 2005; 100: 226–32.
9. Piper SN, *et al.* A comparison of nefopam and clonidine for the prevention of postanaesthetic shivering: a comparative, double-blind and placebo-controlled dose-ranging study. *Anaesthesia* 2004; 59: 559–64.
10. Bilotta F, *et al.* Nefopam or clonidine in the pharmacologic prevention of shivering in patients undergoing conscious sedation for interventional neuroradiology. *Anaesthesia* 2005; 60: 124–8.

Spasticity. Clonidine, given alone or as an adjunct to baclofen, has been tried in patients with various forms of spasticity (p. 2014.2) including those refractory to baclofen.[1-5]

1. Nance PW, *et al.* Clonidine in spinal cord injury. *Can Med Assoc J* 1985; 133: 41–2.
2. Donovan WH, *et al.* Clonidine effect on spasticity: a clinical trial. *Arch Phys Med Rehabil* 1988; 69: 193–4.
3. Sandford PR, *et al.* Clonidine in the treatment of brainstem spasticity: case report. *Am J Phys Med Rehabil* 1992; 71: 301–3.
4. Middleton JW, *et al.* Intrathecal clonidine and baclofen in the management of spasticity and neuropathic pain following spinal cord injury: a case study. *Arch Phys Med Rehabil* 1996; 77: 824–6.
5. Lubsch L, *et al.* Oral baclofen and clonidine for treatment of spasticity in children. *J Child Neurol* 2006; 21: 1090–2.

Substance dependence. *ALCOHOL* Although drug treatment of alcohol withdrawal (p. 1735.1) is usually with a benzodiazepine, clonidine has shown benefit[1] in mild to moderate withdrawal, although it has no effect on convulsions or delirium tremens and should not be used as sole therapy. It may be considered with a benzodiazepine when opioid withdrawal is also taking place.

1. Mayo-Smith MF, *et al.* Pharmacological management of alcohol withdrawal: a meta-analysis and evidence-based practice guideline. *JAMA* 1997; 278: 144–51.

OPIOID ANALGESICS. Clonidine has been reported to be useful in controlling withdrawal symptoms after abrupt withdrawal of opioids (p. 109.2). However, a systematic review[1] of the use of alpha$_2$-adrenoceptor agonists, including clonidine, concluded that, for gradual withdrawal, they were no more effective than reducing doses of methadone over a period of around 10 days, and patients had more adverse effects and therefore stopped treatment sooner with clonidine. Clonidine is usually given orally in three or four divided doses to a maximum of 1 mg daily.

Clonidine has also been used with naltrexone to shorten the withdrawal syndrome, allowing withdrawal to be achieved within 6 days.[2] Subsequent modification to the regimen allowed 38 of 40 patients addicted to methadone to withdraw completely in 4 to 5 days.[3] Patients required a mean of 2.3 mg of clonidine on the first day which reduced, but did not abolish, symptoms. A further modification was reported allowing opioid withdrawal with minimal drop-out over 2 to 3 days.[4]

Clonidine has also been used in the management of neonatal abstinence syndrome (p. 110.1) in infants born to opioid-addicted mothers maintained on methadone.[5,6] Benefit occurred in 6 of 7 such infants given an initial

clonidine dose of 0.5 to 1 microgram/kg orally, increased over 1 to 2 days to 3 to 5 micrograms/kg daily in divided doses. Total length of treatment ranged from 6 to 17 days. The infant who failed to respond was born to a mother also given haloperidol, desipramine, and theophylline.[6] In another study in 80 infants with neonatal abstinence syndrome,[7] clonidine 1 microgram/kg six times daily shortened treatment duration compared with placebo when given with diluted tincture of opium. However, a systematic review[8] found insufficient evidence to support the use of clonidine in the management of neonatal abstinence syndrome.

1. Gowing L, *et al.* Alpha$_2$-adrenergic agonists for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2009 (accessed 24/09/09).
2. Charney DS, *et al.* Clonidine and naltrexone: a safe, effective, and rapid treatment of abrupt withdrawal from methadone therapy. *Arch Gen Psychiatry* 1982; 39: 1327–32.
3. Charney DS, *et al.* The combined use of clonidine and naltrexone as a rapid, safe, and effective treatment of abrupt withdrawal from methadone. *Am J Psychiatry* 1986; 143: 831–7.
4. Brewer C, *et al.* Opioid withdrawal and naltrexone induction in 48-72 hours with minimal drop-out, using a modification of the naltrexone-clonidine technique. *Br J Psychiatry* 1988; 153: 340–3.
5. Hoder EL, *et al.* Clonidine in neonatal narcotic-abstinence syndrome. *N Engl J Med* 1981; 305: 1284.
6. Hoder EL, *et al.* Clonidine treatment of neonatal narcotic abstinence syndrome. *Psychiatry Res* 1984; 13: 243–51.
7. Agthe AG, *et al.* Clonidine as an adjunct therapy to opioids for neonatal abstinence syndrome: a randomized, controlled trial. *Pediatrics* 2009; 123: e849–e856.
8. Osborn DA, *et al.* Sedatives for opiate withdrawal in newborn infants. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2005 (accessed 03/03/06).

SMOKING. Nicotine dependence may be managed using behavioural or psychological counselling. In addition, nicotine replacement therapy (see Smoking Cessation, p. 2570.2) can help alleviate withdrawal symptoms. Other drugs, including clonidine, have also been tried. A systematic review[1] found clonidine given in doses of 200 to 400 micrograms daily orally or the equivalent transdermally to be effective; however adverse effects limit its usefulness and clonidine should be reserved for second-line treatment under close medical supervision in those who have severe agitation and anxiety when stopping smoking.

Some individual studies have found clonidine to be more effective in women although the authors of the systematic review[1] recommended that these results be interpreted cautiously since some studies also found that women were less successful in giving up smoking unaided than men; treatment with clonidine, however, resulted in similar success rates in both men and women.

1. Gourlay SG, *et al.* Clonidine for smoking cessation. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2004 (accessed 26/09/05).

Tourette's syndrome. Clonidine is one of many drugs that have been tried in the management of Tourette's syndrome (see Tics, p. 1030.1).

Disturbance of monoamine metabolism (including dopamine, noradrenaline, and serotonin) has been implicated in Tourette's syndrome. Clonidine is thought to reduce central noradrenergic activity and may also affect other neurochemical systems, and these properties may account for its beneficial effects in this disorder. Studies of clonidine in Tourette's syndrome have produced mixed results,[1-5] although this may reflect the difficulty in study design for a disease that can vary considerably in severity and presence of comorbid conditions and whose symptoms wax and wane. A retrospective study[6] in juvenile patients given clonidine suggested that those showing improvement in the attention deficit hyperactivity disorder associated with Tourette's syndrome had previously had a longer duration of vocal tics; older children had a better overall response than younger children, who tended to suffer more from clonidine-induced drowsiness. However, no predictors of response could be identified. Nevertheless, clonidine is increasingly favoured for first-line treatment in patients with mild to moderate symptoms, because of a relative lack of serious adverse effects when compared with the commonly used antipsychotics pimozide and haloperidol, although exacerbation of tics and a marked sensation of heat have been reported[7] in one patient. Clonidine has also been reported to successfully control symptoms in some children with Tourette's syndrome unresponsive to haloperidol.[1] The range of oral doses used in these studies was wide, but a typical example[6] was 1.5 to 9.5 micrograms/kg daily (average about 5 micrograms/kg daily) in 53 children aged from 5 to 18 years. Transdermal clonidine has also shown some benefit when given to children at 1 mg weekly (weight under 40 kg), 1.5 mg weekly (weight 40 to 60 kg), or 2 mg weekly (weight over 60 kg).[8]

Clonidine has also been used with stimulants in children with Tourette's syndrome and attention deficit hyperactivity disorder, although there have been concerns about the toxicity of such combinations (see Hyperactivity, p. 1340.1).

1. Cohen DJ, *et al.* Clonidine in Tourette's syndrome. *Lancet* 1979; ii: 551–3.
2. Shapiro AK, *et al.* Treatment of Gilles de la Tourette's syndrome with clonidine and neuroleptics. *Arch Gen Psychiatry* 1983; 40: 1235–40.
3. Leckman JF, *et al.* Short- and long-term treatment of Tourette's syndrome with clonidine: a clinical perspective. *Neurology* 1985; 35: 343–51.
4. Goetz CG, *et al.* Clonidine and Gilles de la Tourette's syndrome: double-blind study using objective rating methods. *Ann Neurol* 1987; 21: 307–10.
5. Leckman JF, *et al.* Clonidine treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 1991; 48: 324–8.
6. Lichter DG, Jackson LA. Predictors of clonidine response in Tourette syndrome: implications and inferences. *J Child Neurol* 1996; 11: 93–7.
7. Kessler AR. Clonidine treatment increases tics in patients with Tourette syndrome: case report. *J Child Neurol* 2001; 16: 380–1.
8. Du Y-S, *et al.* Randomized double-blind multicentre placebo-controlled clinical trial of the clonidine adhesive patch for the treatment of tic disorders. *Aust N Z J Psychiatry* 2008; 42: 807–13.

Adverse Effects and Treatment

Drowsiness, dry mouth, dizziness, and headache are common when starting therapy with clonidine. Constipation is also common, and other adverse effects reported include depression, anxiety, fatigue, nausea, anorexia, parotid pain, sleep disturbances, vivid dreams, impotence and loss of libido, urinary retention or incontinence, orthostatic hypotension, and dry, itching, or burning sensations in the eye. Fluid retention may occur and is usually transient, but may be responsible for a reduction in the hypotensive effect during continued treatment. Clonidine can cause rashes and pruritus, and these are more common with transdermal delivery systems. Bradycardia, including sinus bradycardia with AV block, other ECG disturbances, heart failure, hallucinations, cramp, Raynaud's syndrome, gynaecomastia, and transient abnormalities in liver function tests have been reported less often. Large doses have been associated with initial increases in blood pressure and transient hyperglycaemia, although these do not persist during continued therapy.

Symptoms of overdosage include transient hypertension or profound hypotension, bradycardia, sedation, miosis, respiratory depression, convulsions, and coma. Treatment consists of general supportive measures. An alpha blocker may be given if necessary for hypertension, and atropine may be required for bradycardia and associated hypotension. Cardiac pacing may be needed rarely.

Sudden withdrawal of clonidine may produce rebound hypertension—see Precautions, below.

Effects on the gastrointestinal tract. Constipation is a relatively common adverse effect of clonidine, US licensed product information reporting an incidence of about 10%. Ileus or pseudo-obstruction of the bowel have been reported;[1-3] withdrawal of clonidine was associated with a return of bowel function to normal. Abdominal pain mimicking acute appendicitis occurred in another patient; symptoms recurred on restarting the drug and subsided on withdrawal.[4]

1. Davidov M, *et al.* The antihypertensive effects of an imidazoline compound. *Clin Pharmacol Ther* 1967; 8: 810–16.
2. Bear R, Steer K. Pseudo-obstruction due to clonidine. *BMJ* 1976; 1: 197.
3. Bauer GE, Hellestrand KJ. Pseudo-obstruction due to clonidine. *BMJ* 1976; 1: 769.
4. Mjörndal T, Mellbring G. Abdominal pain associated with clonidine. *BMJ* 1986; 292: 174.

Effects on the heart. Clonidine has been associated with impaired atrioventricular conduction in a few patients,[1,2] although some of these may have had underlying conduction defects and had previously received digitalis, which may have contributed to their condition. Other ECG abnormalities may also occur. Sudden death has been reported in 3 children receiving clonidine and methylphenidate,[3,4] although the significance of these reports has been questioned.[5]

1. Kibler LE, Gazes PC. Effect of clonidine on atrioventricular conduction. *JAMA* 1977; 238: 1930–2.
2. Abiuso P, Abelow G. Atrioventricular dissociation in a patient receiving clonidine. *JAMA* 1978; 240: 108–9.
3. Maloney MJ, Schwam, JS. Clonidine and sudden death. *Pediatrics* 1995; 96: 1176–7.
4. Fenichel RR. Combining methylphenidate and clonidine: the role of post-marketing surveillance. *J Child Adolesc Psychopharmacol* 1995; 5: 155–6.
5. Blackman JA, *et al.* Clonidine and electrocardiograms. *Pediatrics* 1996; 98: 1223–4.

Effects on mental function. There have been occasional reports of disturbed mental state in patients given clonidine.[1-4]

1. Lavin P, Alexander CP. Dementia associated with clonidine therapy. *BMJ* 1975; 1: 628.
2. Enoch MD, Hammad GEM. Acute hallucinosis due to clonidine. *Curr Med Res Opin* 1977; 4: 670–1.
3. Brown MJ, *et al.* Clonidine hallucinations. *Ann Intern Med* 1980; 93: 456–7.
4. Delaney J, *et al.* Clonidine-induced delirium. *Int J Cardiol* 2006; 113: 276–8.

Effects on the skin. Skin reactions have been reported in up to 50% of patients using clonidine transdermal patches.[1] Localised erythema and irritation during early treatment are usually mild, but allergic contact dermatitis may develop.[2-4] Skin reactions may become commoner during prolonged treatment; although only mild skin reactions were seen in a study of transdermal clonidine during 8 to 14 weeks of treatment in 15 patients, severe skin reactions occurred after an average of 20 weeks in 4 of 5 patients who continued treatment.[5] Despite a claim that skin reactions were due to a component in the patch and not to clonidine itself,[6] positive patch tests to clonidine have been obtained.[2,4] Subsequent reaction to oral clonidine in patients who develop skin reactions to the transdermal patch is reported to be rare.[7,8]

1. Carmichael AJ. Skin sensitivity and transdermal drug delivery: a review of the problem. *Drug Safety* 1994; 10: 151–9.
2. Groth H, *et al.* Allergic skin reactions to transdermal clonidine. *Lancet* 1983; ii: 850–1.
3. McMahon FG, Weber MA. Allergic skin reactions to transdermal clonidine. *Lancet* 1983; ii: 851.
4. Boekhorst JC. Allergic contact dermatitis with transdermal clonidine. *Lancet* 1983; ii: 1031–2.
5. Dick JBC, *et al.* Skin reactions to long-term transdermal clonidine. *Lancet* 1987; i: 516.
6. Anonymous. Transdermal clonidine sensitiser identified? *Pharm J* 1984; 233: 16.
7. Bigby M. Transdermal clonidine dermatitis. *JAMA* 1987; 258: 1819.
8. Burris JF. Transdermal clonidine dermatitis. *JAMA* 1987; 258: 1819–20.

PEMPHIGOID. Anogenital cicatricial pemphigoid has been reported[1] in a patient receiving long-term clonidine therapy.

1. van Joost T, *et al.* Drug-induced anogenital cicatricial pemphigoid. *Br J Dermatol* 1980; 102: 715–18.

Hypersensitivity. See Effects on the Skin, above.

Overdosage. Analysis by the UK National Poisons Information Service[1] of poisoning by clonidine in 133 children and 37 adults between 1976 and 1977 revealed that there were no deaths but clinical features were often severe. Supportive measures were usually adequate but atropine was often needed for severe and persistent bradycardia. Forced diuresis was not advised because hypotension could be enhanced and there was no evidence that excretion of clonidine was increased. More recently, death has been reported[2] in a 23-month old child.

Direct medical evaluation has been recommended[3] for children who have ingested the following amounts: 100 micrograms or more in those aged 4 years and under; more than 200 micrograms in those aged 5 to 8 years; and 400 micrograms or more in older children; 4 hours may be long enough to detect full onset of symptoms. However, others[4] believe that medical evaluation is indicated in any child who has unintentionally ingested more than a weight-appropriate therapeutic dose.

Although naloxone has been suggested as an antidote for clonidine overdose, no reversal of the hypotensive effects of clonidine 300 micrograms was noted in 6 hypertensive subjects given naloxone by intravenous infusion.[5] In a retrospective analysis of 47 children with clonidine poisoning, only 3 of 19 given naloxone showed definite improvement;[6] it was concluded that naloxone is at best an inconsistent antidote for clonidine poisoning.

Severe symptoms of overdosage have also been reported after the ingestion of clonidine transdermal patches,[7] and after probable subcutaneous injection during filling of an epidural pump reservoir.[8]

1. Stein B, Volans GN. Dixarit overdose: the problem of attractive tablets. *BMJ* 1978; 2: 667–8.
2. Klein-Schwartz W. Trends and toxic effects from pediatric clonidine exposures. *Arch Pediatr Adolesc Med* 2002; 156: 392–6.
3. Spiller HA, *et al.* Toxic clonidine ingestion in children. *J Pediatr* 2005; 146: 263–6.
4. Langhan M, Chan GM. Clonidine exposures, not toxicity. *J Pediatr* 2006; 148: 565.
5. Rogers JF, Cubeddu LX. Naloxone does not antagonise the antihypertensive effect of clonidine in essential hypertension. *Clin Pharmacol Ther* 1983; 34: 68–73.
6. Wiley JF, *et al.* Clonidine poisoning in young children. *J Pediatr* 1990; 116: 654–8.
7. Raber JH, *et al.* Clonidine patch ingestion in an adult. *Ann Pharmacother* 1993; 27: 719–22. Correction. *Ibid.*; 1143.
8. Frye CB, Vance MA. Hypertensive crisis and myocardial infarction following massive clonidine overdose. *Ann Pharmacother* 2000; 34: 611–15.

Precautions

Clonidine should be used with caution in patients with cerebrovascular disease, ischaemic heart disease including myocardial infarction, renal impairment, occlusive peripheral vascular disorders such as Raynaud's disease, or those with a history of depression.

Clonidine causes drowsiness and patients should not drive or operate machinery where loss of attention could be dangerous.

Systemic effects also occur after epidural use and patients should be closely monitored, particularly during the first few days of therapy.

Intravenous injections of clonidine should be given slowly to avoid a possible transient pressor effect especially in patients already taking other antihypertensives such as guanethidine or reserpine.

Withdrawal of clonidine antihypertensive therapy should be gradual as stopping suddenly may cause rebound hypertension, sometimes severe. Symptoms of increased catecholamine release such as agitation, sweating, tachycardia, headache, and nausea may also occur. Beta blockers can exacerbate the rebound hypertension and if both are being used, clonidine should not be stopped until several days after the withdrawal of the beta blocker. Patients should be warned of the risk of missing a dose or stopping the drug without consulting their doctor and should carry a reserve supply.

Although hypotension may occur during anaesthesia in clonidine-treated patients clonidine should not be withdrawn; indeed, if necessary it should be given intravenously during the operation to avoid the risk of rebound hypertension.

Abuse. Despite its central effects and ability to cause a form of physical dependence, WHO rated the likelihood of abuse as very low.[1] However, clonidine may potentiate the psychoactive effects of morphine and abuse has been reported.[2]

1. WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser 775* 1989. Available at: http://libdoc.who.int/trs/WHO_TRS_775.pdf (accessed 19/08/08)
2. Sullivan JT, *et al.* Does clonidine alter the abuse potential of morphine? *Clin Pharmacol Ther* 1995; 57: 163.

Diabetes mellitus. The effects of clonidine on carbohydrate metabolism appear to be variable. Some studies suggest that it does not affect carbohydrate metabolism in diabetic[1] or non-diabetic hypertensive patients,[2] although there has been a report of a diabetic patient in whom clonidine was associated with elevated fasting blood-glucose values,[3] and increased insulin requirements were noted in a diabetic child treated with clonidine for tics.[4] Conversely, clonidine was associated with severe hypoglycaemia in children when used as a provocative test for growth hormone deficiency (see Growth Retardation, p. 1339.3). However, a study in 10 diabetic hypertensive patients found that although clonidine impaired response to an acute glucose load, it did not significantly affect diabetic control over a 10-week period.[5] Problems may arise when clonidine is given to diabetics with autonomic neuropathy: both severe orthostatic hypotension[6] and paradoxical hypertension[7] have been reported.

For discussion of the use of clonidine in diabetic diarrhoea see p. 1339.3.

1. Nilsson-Ehle P, *et al.* Lipoproteins and metabolic control in hypertensive type II diabetics treated with clonidine. *Acta Med Scand* 1988; 224: 131–4.
2. Mollich MB, *et al.* Effects of antihypertensive medications on carbohydrate metabolism. *Curr Ther Res* 1986; 39: 398–407.
3. Okada S, *et al.* Effect of clonidine on insulin secretion: a case report. *J Int Med Res* 1986; 14: 299–302.
4. Mimouni-Bloch A, Mimouni M. Clonidine-induced hyperglycemia in a young diabetic girl. *Ann Pharmacother* 1993; 27: 980.
5. Guthrie GP, *et al.* Clonidine in patients with diabetes and mild hypertension. *Clin Pharmacol Ther* 1983; 34: 713–17.
6. Moffat B. Postural hypotension induced by clonidine in insulin dependent diabetes. *BMJ* 1985; 290: 822.
7. Young E, *et al.* Paradoxical hypertension from clonidine. *Ann Intern Med* 1984; 101: 282–3.

ECT. Maximal ECT stimuli were unsuccessful in producing seizures in 4 of 7 treatment attempts in a 66-year-old patient receiving clonidine.[1] It was suggested that clonidine may elevate the seizure threshold.

1. Elliott RL. Case report of a potential interaction between clonidine and electroconvulsive therapy. *Am J Psychiatry* 1983; 140: 1237–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clonidine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The hypotensive effect of clonidine may be enhanced by diuretics, other antihypertensives, and drugs that cause hypotension. However, beta blockers may exacerbate rebound hypertension after clonidine withdrawal (see Precautions, p. 1341.3); and tricyclic antidepressants may antagonise the hypotensive effect. The sedative effect of clonidine may be enhanced by CNS depressants.

Antidepressants. Although tricyclic antidepressants commonly cause orthostatic hypotension, they may antagonise the hypotensive effects of clonidine. Blood pressure control was lost in 4 of 5 hypertensive patients taking clonidine and a diuretic when they were given *desipramine* 75 mg daily.[1] Increase in blood pressure generally occurred in the second week of treatment, but 1 patient had a dramatic rise in blood pressure within 24 hours of starting treatment. The mechanism is thought to be due to a central interaction between clonidine and the tricyclic antidepressant, although a peripheral effect cannot be completely excluded.[2] Loss of blood pressure control also occurred in a patient receiving guanfacine, another alpha$_2$-adrenoceptor agonist, when *amitriptyline* was given.[3] The reaction recurred with *imipramine*. However, in another study clonidine was given to 11 patients taking amitriptyline or imipramine, and 10 achieved good blood pressure control, although 4 developed an acute rise in blood pressure when methyldopa or guanethidine was added.[4] *Maprotiline*[5] or *mianserin*[6] do not appear to interact with clonidine.

There have been reports[7,8] of hypertensive crisis when the tetracyclic antidepressant *mirtazapine* was given with clonidine. Clonidine exerts an effect at central alpha$_2$ receptors; mirtazapine is an antagonist at these receptors and may displace clonidine at high doses.

1. Briant RH, *et al.* Interaction between clonidine and desipramine in man. *BMJ* 1973; 1: 522–3.
2. van Spanning HW, van Zwieten PA. The interference of tricyclic antidepressants with the central hypotensive effect of clonidine. *Eur J Pharmacol* 1973; 24: 402–4.
3. Buckley M, Peely J. Antagonism of antihypertensive effect of guanfacine by tricyclic antidepressants. *Lancet* 1991; 337: 1173–4.
4. Raftos J, *et al.* Clonidine in the treatment of severe hypertension. *Med J Aust* 1973; 1: 786–93.
5. Gundert-Remy U, *et al.* Lack of interaction between the tetracyclic antidepressant maprotiline and the centrally acting antihypertensive drug clonidine. *Eur J Clin Pharmacol* 1983; 25: 595–9.
6. Elliott HL, *et al.* Absence of an effect of mianserin on the actions of clonidine or methyldopa in hypertensive patients. *Eur J Clin Pharmacol* 1983; 24: 15–19.
7. Abo-Zena RA, *et al.* Hypertensive urgency induced by an interaction of mirtazapine and clonidine. *Pharmacotherapy* 2000; 20: 476–8.
8. Troncoso AL, Gill T. Hypertensive urgency with clonidine and mirtazepine. *Psychosomatics* 2004; 45: 449–50.

Antipsychotics. Acute, severe hypotension occurred in 2 agitated hypertensive patients after use of clonidine with either *chlorpromazine* or *haloperidol*. Both patients had mitral insufficiency.[1]

1. Fruncillo RJ, *et al.* Severe hypotension associated with concurrent clonidine and antipsychotic medication. *Am J Psychiatry* 1985; 142: 274.

Dopaminergic antiparkinsonian drugs. For a report of the inhibition of the therapeutic effect of *levodopa* by clonidine, see Antihypertensives, p. 907.2.

Histamine. For the effect of clonidine on histamine given exogenously, see p. 2525.3.

Immunosuppressants. For a report of clonidine increasing whole blood-*ciclosporin* concentrations, see p. 1958.1.

Pharmacokinetics

Clonidine is well absorbed from the gastrointestinal tract, and peak plasma concentrations occur about 3 to 5 hours after an oral dose. It is about 20 to 40% protein bound. About 50% of a dose is metabolised in the liver. It is excreted in the urine as unchanged drug and metabolites, 40 to 60% of an oral dose being excreted in 24 hours as unchanged drug; about 20% of a dose is excreted in the faeces, probably via enterohepatic circulation. The elimination half-life has been variously reported to range between 6 and 24 hours, extended to up to 41 hours in patients with renal impairment. Clonidine crosses the placenta and is distributed into breast milk.

It is absorbed through the skin; absorption is reported to be better from the chest or arm than from the thigh. Therapeutic plasma concentrations are achieved 2 or 3 days after application of a transdermal patch and are roughly equivalent to trough concentrations achieved after oral dosage. Therapeutic plasma concentrations are maintained for about 8 hours after removal of the delivery system and then decline slowly over several days.

Reviews.

1. Lowenthal DT, *et al.* Clinical pharmacokinetics of clonidine. *Clin Pharmacokinet* 1988; 14: 287–310.
2. Potts AL, *et al.* Clonidine disposition in children: a population analysis. *Paediatr Anaesth* 2007; 17: 924–33.

Pregnancy. A study in 5 pregnant women treated with clonidine for pre-eclampsia[1] reported an average ratio of cord- to plasma-concentrations of 0.87, indicating placental transfer of clonidine. Similar ratios were seen in another study[2] in 17 women given clonidine in mid or late pregnancy. The oral clearance of clonidine was found to increase during pregnancy (although renal clearance appeared to remain unchanged), and higher or more frequent dosing might thus be needed.

1. Boutroy MJ, *et al.* Clonidine placental transfer and neonatal adaption. *Early Hum Dev* 1988; 17: 275–86.
2. Buchanan ML, *et al.* Clonidine pharmacokinetics in pregnancy. *Drug Metab Dispos* 2009; 37: 702–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Clonidural; *Austral.*: Catapres; *Austria*: Catapresan; Isoglaucon; *Belg.*: Catapressan; Dixarit; *Braz.*: Atensina; *Canad.*: Catapres; Dixarit; *Chile*: Catapresan; *China*: Run Rui (润瑞); *Cz.*: Aruclonin; Catapresan†; *Denm.*: Catapresan; Dixarit; *Fin.*: Catapresan; *Fr.*: Catapressan; *Ger.*: Catapresan; Clonid-Ophtal; Clonistada†; Dispaclonidin†; Haemiton†; Isoglaucon; Paracefan; *Gr.*: Catapres; Catapresan; *Hong Kong*: Dixarit†; *Hung.*: Aruclonin†; *India*: Arkamin; Catapres; Cloneon; *Indon.*: Catapres; *Irl.*: Catapres; Dixarit; *Israel*: Clonnirit; Normopresan; *Ital.*: Catapresan; Isoglaucon; *Jpn*: Catapres; *Mex.*: Catapresan; Epiclodina; *Neth.*: Catapresan; Dixarit; *Norw.*: Catapresan; *NZ*: Catapres; Dixarit; *Philipp.*: Catapin; Catapres; Melzin; *Pol.*: Iporel; *Port.*: Catapresan; Edolglau; *Rus.*: Clophelin (Клофелин); Haemiton (Гемитон)†; *S.Afr.*: Dixarit; Menograine; *Singapore*: Dixarit; *Spain*: Catapresan; Isoglaucon†; *Swed.*: Catapresan; *Switz.*: Catapresan; *Thai.*: Catapres†; Hypodine; *UK*: Catapres; Dixarit; *Ukr.*: Clophelin (Клофелин); *USA*: Catapres; Duraclon; Jenloga; Kapvay; Nexiclon†; *Venez.*: Catapresan; Lowpres; Naclodin; Velaril.

Multi-ingredient Preparations. *Arg.*: Bemplas; Pertenso; *India*: Arkamin-R; Catapres Diu; Clothalton; *Rus.*: Proxofeline (Проксофелин); *USA*: Clorpres.

Pharmacopoeial Preparations

BP 2014: Clonidine Injection; Clonidine Tablets;
USP 36: Clonidine Hydrochloride and Chlorthalidone Tablets; Clonidine Hydrochloride Tablets; Clonidine Transdermal System.

Clopamide *(BAN, USAN, rINN)* ⊗

Clopamid; Clopamida; Clopamidum; DT-327; Klopamid; Klopamidi; Клопамид.

4-Chloro-*N*-(2,6-dimethylpiperidino)-3-sulphamoylbenzamide; *cis*-3-(Aminosulphonyl)-4-chloro-*N*-(2,6-dimethyl-1-piperidinyl)benzamide.

$C_{14}H_{20}ClN_3O_3S$=345.8

CAS — 636-54-4.

ATC — C03BA03.

ATC Vet — QC03BA03.

UNII — 17S83WON0I.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Clopamide). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Slightly soluble in water and in anhydrous alcohol; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Profile

Clopamide is a diuretic with properties similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1403.2) even though it does not contain a thiazide ring system. It is used for oedema, including that associated with heart failure (p. 1262.3), and for hypertension (p. 1251.1).

Diuresis starts in 1 to 2 hours after an oral dose, reaches a maximum in about 3 to 6 hours, and lasts for up to 24 hours.

In the treatment of oedema a usual oral maintenance dose has been 10 to 20 mg daily or on alternate days. For hypertension doses of 5 to 10 mg daily, either alone, or with other antihypertensives have been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hung.*: Brinaldix; *India*: Brinaldix.

Multi-ingredient Preparations. *Austria*: Brinerdin; *Belg.*: Viskaldix; *Braz.*: Viskaldix; *Chile*: Viskaldix; *Cz.*: Crystepin†; *Fr.*: Viskaldix; *Ger.*: Briserin N; Viskaldix†; *Gr.*: Viskaldix; *Hung.*: Viskaldix; *Irl.*: Viskaldix†; *Ital.*: Brinerdina; *Malaysia*: Viskaldix; *Neth.*: Viskaldix†; *Philipp.*: Viskaldix; *Pol.*: Normatens; *Rus.*: Brinerdin (Бринердин); Crystepin (Кристепин); Normatens (Норматенс); Viskaldix (Вискалдикс); *S.Afr.*: Brinerdin; *Switz.*: Brinerdine; Viskaldix; *Thai.*: Bedin; Brinerdin; Briscotin†; *UK*: Viskaldix; *Ukr.*: Normatens (Норматенс).

Clopidogrel Bisulfate

(BANM, USAN, rINNM)

Bisulfato de clopidogrel; Clopidogrel, Bisulfate de; Clopidogrel, bisulfato de; Clopidogrel Bisulphate; Clopidogrel Hydrogen Sulphate; Clopidogreli Bisulfas; PCR-4099 (clopidogrel); SR-25990C; Клопидогрела бисульфат.

Methyl (*S*)-2-chlorophenyl(4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-5-yl)acetate bisulphate; Methyl (+)-(*S*)-α-(o-chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-acetate sulphate.

$C_{16}H_{16}ClNO_2S.H_2SO_4$=419.9

CAS — 113665-84-2 (clopidogrel); 94188-84-8 (clopidogrel); 120202-66-6 (clopidogrel bisulfate).

ATC — B01AC04.

ATC Vet — QB01AC04.

UNII — 0B179HTP27.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Clopidogrel Hydrogen Sulfate). A white or almost white powder. It exhibits polymorphism. Freely

soluble in water and in methyl alcohol; practically insoluble in cyclohexane. Protect from light.

USP 36: (Clopidogrel Bisulfate). A white to off-white powder.

Uses and Administration

Clopidogrel is a thienopyridine antiplatelet drug used in thromboembolic disorders. An analogue of ticlopidine (p. 1512.1), it is a platelet $P2Y_{12}$-receptor antagonist that acts by inhibiting adenosine diphosphate-mediated platelet aggregation. It is given prophylactically as an alternative to aspirin in patients with chronic occlusive peripheral arterial disease (p. 1272.3) or other atherosclerotic complications increasing the risk of thromboembolic disorders such as myocardial infarction (p. 1257.1), peripheral arterial thromboembolism (p. 1273.3), and stroke (p. 1269.2). Clopidogrel is also used with aspirin in acute coronary syndromes, including acute myocardial infarction and unstable angina (p. 1254.3), and in coronary stenting (see Reperfusion and Revascularisation Procedures, below).

Clopidogrel is given orally as the besilate, bisulfate, or the hydrochloride but doses are expressed in terms of the base; 75 mg of the base is equivalent to:

- 111.86 mg of clopidogrel besilate
- 97.86 mg of clopidogrel bisulfate
- 83.50 mg of clopidogrel hydrochloride

For the **prophylaxis of thromboembolic events**, the usual dose of clopidogrel is 75 mg once daily.

In the management of **acute ST-elevation myocardial infarction**, clopidogrel is used with aspirin as an adjunct in medically-treated patients. It is given in a dose of 75 mg once daily; patients under 75 years of age may be given a loading dose of 300 mg. Treatment should be continued for at least 4 weeks.

In the management of **unstable angina** and **non-Q-wave myocardial infarction**, clopidogrel is used with aspirin as an adjunct to either medical or interventional treatment, including coronary stenting. A single loading dose of 300 mg is given, followed by 75 mg once daily.

Reviews.

1. Sharis PJ, *et al.* The antiplatelet effects of ticlopidine and clopidogrel. *Ann Intern Med* 1998; 129: 394–405.
2. Jarvis B, Simpson K. Clopidogrel: a review of its use in the prevention of atherothrombosis. *Drugs* 2000; 60: 347–77.
3. Solet DJ, *et al.* The role of adenosine 5'-diphosphate receptor blockade in patients with cardiovascular disease. *Am J Med* 2001; 111: 45–53.
4. Zambahari R, *et al.* Clinical use of clopidogrel in acute coronary syndrome. *Int J Clin Pract* 2007; 61: 473–81.
5. Eshaghian S, *et al.* Role of clopidogrel in managing atherothrombotic cardiovascular disease. *Ann Intern Med* 2007; 146: 434–41.
6. Plosker GL, Lyseng-Williamson KA. Clopidogrel: a review of its use in the prevention of thrombosis. *Drugs* 2007; 67: 613–46.

Administration in children. Clopidogrel is not licensed for paediatric use in either the UK or the USA, although it has been given to small numbers of patients.

A retrospective study[1] of the use of clopidogrel in 15 children aged from 6 weeks to 16 years, 14 of whom had congenital heart disease, found that it was safe and effective; nearly all of the children were also taking aspirin and/or anticoagulants, and severe bleeding was reported in only 1 of them. The usual dose ranged from 1 to 3 mg/kg once daily, although a dose of 6 mg/kg daily was tolerated when given in error to 1 patient. However, another retrospective study[2] in similar children found that daily doses of 0.5 to 1 mg/kg were associated with an increased risk of bleeding complications, and the dose was subsequently reduced to 200 to 300 micrograms/kg. Younger children in particular may require lower doses; a randomised study[3] in children aged 0 to 24 months found that a dose of 200 micrograms/kg daily produced a similar antiplatelet effect to a 75-mg dose in adults.

A cohort study[4] of the use of clopidogrel alone or with aspirin in 17 children aged 1.5 to 17 years with arterial ischaemic stroke found that a daily dose of 0.5 to 2.4 mg/kg (target dose 1 mg/kg) was well tolerated, although subdural haematomas developed in 2 patients who were also taking aspirin.

1. Pinkelstein Y, *et al.* Clopidogrel use in children. *J Pediatr* 2005; 147: 657–61.
2. Mertens L, *et al.* Safety and efficacy of clopidogrel in children with heart disease. *J Pediatr* 2008; 153: 61–4.
3. Li JS, *et al.* Dosing of clopidogrel for platelet inhibition in infants and young children: primary results of the Platelet Inhibition in Children On cLOpidogrel (PICOLO) trial. *Circulation* 2008; 117: 553–9.
4. Soman T, *et al.* The risks and safety of clopidogrel in pediatric arterial ischemic stroke. *Stroke* 2006; 37: 1120–2.

Atherosclerotic disorders. The use of aspirin to reduce the risk of cardiovascular events in patients with atherosclerotic vascular disorders is well established. Clopidogrel may have a role as an alternative. The CAPRIE study[1] compared clopidogrel with aspirin in 19 185 patients at risk of ischaemic events, and found that clopidogrel reduced the risk of ischaemic stroke, myocardial infarction, or death from vascular causes to a greater extent than aspirin, although the absolute difference was small.

In acute coronary syndromes, clopidogrel may provide benefit when used in addition to aspirin. In patients with *unstable angina or non-ST elevation myocardial infarction*, the CURE study[2] found that the risk of cardiovascular death, myocardial infarction, or stroke was lower in patients treated with clopidogrel and aspirin, compared with those receiving aspirin alone. Clopidogrel was given in a loading dose of 300 mg, started within 24 hours of the onset of symptoms, followed by 75 mg daily for 3 to 12 months.

Similar results have been reported in patients with acute *ST-elevation myocardial infarction*. Clopidogrel given with aspirin and thrombolytic therapy improved the patency of the affected artery and reduced the incidence of ischaemic complications at 30 days,[3] while a further study[4] found that addition of clopidogrel to aspirin and standard therapy (including thrombolytics in over half of the patients) also reduced early mortality.

Use of clopidogrel with aspirin has also been studied in *ischaemic stroke* but any benefit appears to be outweighed by an increased risk of bleeding. In the MATCH study,[5] adding aspirin to clopidogrel did not reduce the incidence of vascular events compared with clopidogrel alone, but the risk of major or life-threatening bleeding was increased. However, clopidogrel alone appears to have similar efficacy and safety to aspirin with dipyridamole.[6]

In the CHARISMA study in patients with *stable atherosclerotic disease or multiple risk factors*, addition of clopidogrel to aspirin had no significant effect on the incidence of cardiovascular events, but the risk of moderate to severe bleeding was increased.[7,8]

1. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; 348: 1329–39.
2. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; 345: 494–502. Correction. *ibid.*; 1716.
3. Sabatine MS, *et al.* for the CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; 352: 1179–89.
4. COMMIT (CLOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005; 366: 1607–21.
5. Diener H-C, *et al.* Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004; 364: 331–7.
6. Sacco RL, *et al.* PRoFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008; 359: 1238–51.
7. Bhatt DL, *et al.* CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006; 354: 1706–17.
8. Berger PB, *et al.* CHARISMA Investigators. Bleeding complications with dual antiplatelet therapy among patients with stable vascular disease or risk factors for vascular disease: results from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. *Circulation* 2010; 121: 2575–83.

Reperfusion and revascularisation procedures. Percutaneous coronary intervention (PCI) has an established role in the management of both acute and stable coronary disease (see p. 1259.2). Adjunctive antiplatelet therapy is given to reduce the risk of thrombosis, both during and after the procedure; a regimen of clopidogrel with aspirin improves outcomes[1] and is now generally recommended,[2,3] particularly if coronary stents are used. Although ticlopidine with aspirin was used initially in patients receiving stents, clopidogrel appears to be as effective as ticlopidine[4,5] but has a lower risk of haematological toxicity and is now generally preferred. A randomised study (CLASSICS)[6] found that, in patients given long-term aspirin, clopidogrel in a dose of 75 mg daily for 28 days, with or without a 300-mg loading dose, was as effective as ticlopidine; it was also better tolerated.

Pretreatment with clopidogrel appears to be most effective, but the increased bleeding risk may be of concern if emergency surgery is required. Use of a 300-mg loading dose shortly before the procedure appears to be safe, but efficacy may be reduced if it is given less than 6 hours before the intervention, and there is some evidence that it needs to be given at least 15 hours before.[7] A higher dose of 600 mg may be effective if given at least 2 hours before PCI,[8,9] and has been recommended in patients undergoing PCI for non-ST elevation acute coronary syndromes.[2]

The duration of combination therapy depends on the clinical situation. For patients given bare-metal stents, clopidogrel in a dose of 75 mg daily is usually given with aspirin for 2 to 4 weeks, and aspirin is then continued indefinitely. In patients with drug-eluting stents, the risk of occlusion persists for longer and combination therapy is usually recommended for at least 3 to 6 months; there is some evidence[10-12] that extending the duration further may provide additional benefit, and treatment for 12 months or longer has been suggested.[3] See also under Withdrawal, p. 1344.1. Prolonged combination therapy may also be of benefit in patients undergoing PCI for unstable angina, whether or not they receive stents.[1]

1. Mehta SR, *et al.* Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; 358: 527–33.
2. Harrington RA, *et al.* Antithrombotic therapy for non-ST-elevation acute coronary syndromes: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133 (suppl): 670S–707S.
3. Becker RC, *et al.* The primary and secondary prevention of coronary artery disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133 (suppl): 776S–814S.
4. Mishkel GJ, *et al.* Clopidogrel as adjunctive antiplatelet therapy during coronary stenting. *J Am Coll Cardiol* 1999; 34: 1884–90.
5. Berger PB. Clopidogrel versus ticlopidine after intracoronary stent placement. *J Am Coll Cardiol* 1999; 34: 1891–4.
6. Bertrand ME, *et al.* Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS). *Circulation* 2000; 102: 624–9.
7. Steinhubl SR, *et al.* The CREDO Investigators. Optimal timing for the initiation of pre-treatment with 300 mg clopidogrel before percutaneous coronary intervention. *J Am Coll Cardiol* 2006; 47: 939–43.
8. Longstreth KL, Wertz JR. High-dose clopidogrel loading in percutaneous coronary intervention. *Ann Pharmacother* 2005; 39: 918–22.
9. Hochholzer W, *et al.* Time dependence of platelet inhibition after a 600-mg loading dose of clopidogrel in a large, unselected cohort of candidates for percutaneous coronary intervention. *Circulation* 2005; 111: 2560–4.
10. Zimarino M, *et al.* Optimal duration of antiplatelet therapy in recipients of coronary drug-eluting stents. *Drugs* 2005; 65: 725–32.
11. Steinhubl SR, *et al.* Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; 288: 2411–20. Correction. *ibid.* 2003; 289: 987.
12. Eisenstein EL, *et al.* Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA* 2007; 297: 159–68.

Adverse Effects and Precautions

As for Ticlopidine, p. 1512.2.

The incidence of adverse effects, particularly blood dyscrasias, is lower with clopidogrel, although fatalities have been reported (see Effects on the Blood, p. 1512.3). Routine blood counts are not necessary, although they should be performed promptly when clinical signs suggest blood dyscrasias. Other adverse effects, reported rarely, include serum sickness, interstitial pneumonitis, erythema multiforme, Stevens-Johnson syndrome, lichen planus, and myalgia.

Consideration should be given to stopping clopidogrel 5 to 7 days before elective surgery (but see Withdrawal, p. 1344.1).

Effects on the blood. For reports of blood dyscrasias associated with clopidogrel therapy see under Adverse Effects of Ticlopidine, p. 1512.3.

Effects on taste. Loss of taste occurred in 2 patients 6 to 8 weeks after starting treatment with clopidogrel, but recovered fully when clopidogrel was withdrawn.[1] Rechallenge in 1 of the patients led to recurrence of the taste loss, which persisted when treatment was stopped.

1. Golka K, *et al.* Reversible ageusia as an effect of clopidogrel treatment. *Lancet* 2000; 355: 465–6.

Hypersensitivity. Clopidogrel has been associated with hypersensitivity reactions including angioedema.[1] There have also been reports[2-5] of a hypersensitivity syndrome comprising fever, rash, and varying additional symptoms. Successful desensitisation protocols have been described.[6,7]

1. Fischer TC, *et al.* Clopidogrel-associated angioedema. *Am J Med* 2003; 114: 77–8.
2. Sarrot-Reynauld F, *et al.* Severe hypersensitivity associated with clopidogrel. *Ann Intern Med* 2001; 135: 305–6.
3. Phillips EJ, *et al.* Serum sickness-like reaction associated with clopidogrel. *Br J Clin Pharmacol* 2003; 56: 583.
4. Wolf I, *et al.* Clopidogrel-induced systemic inflammatory response syndrome. *Mayo Clin Proc* 2003; 78: 618–20.
5. Doogue MP, *et al.* Clopidogrel hypersensitivity syndrome with rash, fever, and neutropenia. *Mayo Clin Proc* 2005; 80: 1368–70.
6. von Tiehl KF, *et al.* Clopidogrel desensitization after drug-eluting stent placement. *J Am Coll Cardiol* 2007; 50: 2039–43.
7. Oppedijk B, *et al.* Rapid oral desensitisation procedure in clopidogrel hypersensitivity. *Neth Heart J* 2008; 16: 21–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clopidogrel as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Resistance. Results from platelet aggregation studies suggest that there is considerable variation in response to clopidogrel, although the clinical relevance of a low response (clopidogrel resistance) is unclear.[1,2] There is some evidence that the risk of cardiovascular events is higher in patients with clopidogrel resistance,[3] but this is not established. A study[4] using loading doses of clopidogrel based on platelet monitoring reported improved outcomes after percutaneous coronary intervention. Factors that may contribute to clopidogrel resistance include drug interac-

tions; conditions such as diabetes mellitus[5] or acute coronary syndromes, which appear to attenuate response;[6] and genetic variation in platelet sensitivity or clopidogrel metabolism.[1,2] A genetic polymorphism in the cytochrome P450 isoenzyme CYP2C19, which is involved in formation of the active metabolite, has been shown to affect the pharmacokinetics and pharmacodynamics of clopidogrel,[7,8] and studies[9-12] have suggested that patients with the reduced function polymorphism are at higher risk for clinical events. However, causality has not been established, and alternative theories have been discussed.[13,14] Screening for genetic polymorphisms and monitoring residual platelet aggregation have been suggested to identify resistant individuals and guide dosing,[15-17] although the clinical benefits require confirmation.

1. Nguyen TA, *et al.* Resistance to clopidogrel: a review of the evidence. *J Am Coll Cardiol* 2005; 45: 1157–64.
2. Angiolillo DJ, *et al.* Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *J Am Coll Cardiol* 2007; 49: 1505–16.
3. Geisler T, *et al.* Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation. *Eur Heart J* 2006; 27: 2420–5.
4. Bonello L, *et al.* Adjusted clopidogrel loading doses according to vasodilator-stimulated phosphoprotein phosphorylation index decrease rate of major adverse cardiovascular events in patients with clopidogrel resistance: a multicenter randomized prospective study. *J Am Coll Cardiol* 2008; 51: 1404–11.
5. Geisler T, *et al.* Platelet response to clopidogrel is attenuated in diabetic patients undergoing coronary stent implantation. *Diabetes Care* 2007; 30: 372–4.
6. Geisler T, *et al.* Residual platelet activity is increased in clopidogrel- and ASA-treated patients with coronary stenting for acute coronary syndromes compared with stable coronary artery disease. *Heart* 2008; 94: 743–7.
7. Brandt JT, *et al.* Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *J Thromb Haemost* 2007; 5: 2429–36.
8. Kim KA, *et al.* The effect of CYP2C19 polymorphism on the pharmacokinetics and pharmacodynamics of clopidogrel: a possible mechanism for clopidogrel resistance. *Clin Pharmacol Ther* 2008; 84: 236–42.
9. Mega JL, *et al.* Cytochrome P-450 polymorphisms and response to clopidogrel. *N Engl J Med* 2009; 360: 354–62.
10. Simon T, *et al.* French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009; 360: 363–75.
11. Collet J-P, *et al.* Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet* 2009; 373: 309–17.
12. Shuldiner AR, *et al.* Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA* 2009; 302: 849–57.
13. Ford NF. Clopidogrel resistance: pharmacokinetic or pharmacogenetic? *J Clin Pharmacol* 2009; 49: 506–12.
14. Momary KM, *et al.* Genetic causes of clopidogrel nonresponsiveness: which ones really count? *Pharmacotherapy* 2010; 30: 265–74.
15. Bonello L, *et al.* Emergence of the concept of platelet reactivity monitoring of response to thienopyridines. *Heart* 2009; 95: 1214–19.
16. Kulczkowski W, *et al.* Interindividual variability in the response to oral antiplatelet drugs: a position paper of the Working Group on antiplatelet drugs resistance appointed by the Section of Cardiovascular Interventions of the Polish Cardiac Society, endorsed by the Working Group on Thrombosis of the European Society of Cardiology. *Eur Heart J* 2009; 30: 426–35.
17. Gladding P, *et al.* Pharmacogenetic testing for clopidogrel using the rapid INFINITI analyzer: a dose-escalation study. *JACC Cardiovasc Interv* 2009; 2: 1095–1101.

Withdrawal. In patients given dual antiplatelet therapy after implantation of drug-eluting stents, there is some evidence that the incidence of late in-stent thrombosis increases after withdrawal of clopidogrel,[1] even after prolonged courses.[2] The optimum duration of dual antiplatelet therapy remains to be established, but it has been suggested[2] that it should be continued indefinitely in patients at low risk of bleeding. Although withdrawal of clopidogrel before planned surgery is usually recommended, it may be preferable to assess each patient individually and only stop clopidogrel in those for whom the risk of bleeding outweighs the risk of an acute coronary event.[3] Similar considerations apply in patients undergoing endoscopy.[4]

1. Ho PM, *et al.* Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. *JAMA* 2008; 299: 532–9.
2. Bhatt SR, Hauser TH. Very late stent thrombosis after dual antiplatelet therapy discontinuation in a patient with a history of acute stent thrombosis. *Ann Pharmacother* 2008; 42: 708–12.
3. Chassot P-G, *et al.* Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. *Br J Anaesth* 2007; 99: 316–28.
4. Veitch AM, *et al.* Guidelines for the management of anticoagulant and antiplatelet therapy in patients undergoing endoscopic procedures. *Gut* 2008; 57: 1322–9.

Interactions

Clopidogrel should be used with caution in patients receiving other drugs that increase the risk of bleeding, including anticoagulants, other antiplatelets, and NSAIDs. Drugs that inhibit the activity of cytochrome P450 isoenzymes involved in the metabolism of clopidogrel may reduce its antiplatelet effect. Clopidogrel may inhibit the isoenzyme CYP2C9 and interactions with drugs metabolised by this isoenzyme are theoretically possible; it may also inhibit CYP2B6 (see Bupropion, below).

Anticoagulants. Use of clopidogrel with oral anticoagulants increases the risk of haemorrhagic events,[1] particularly if patients are also taking aspirin,[2] and the risks and benefits of treatment should be assessed for each individual.

1. Johnson SG, *et al.* Outcomes associated with combined antiplatelet and anticoagulant therapy. *Chest* 2008; 133: 948–54.
2. Hermosillo AJ, Spinler SA. Aspirin, clopidogrel, and warfarin: is the combination appropriate and effective or inappropriate and too dangerous? *Ann Pharmacother* 2008; 42: 790–805.

Antifungals. A study[1] in healthy subjects found that *ketoconazole* decreased the plasma concentration of the active metabolite of clopidogrel; platelet inhibitory action was also reduced.

1. Farid NA, *et al.* Cytochrome P450 3A inhibition by ketoconazole affects prasugrel and clopidogrel pharmacokinetics and pharmacodynamics differently. *Clin Pharmacol Ther* 2007; 81: 735–41.

Bupropion. A study[1] in healthy subjects found that clopidogrel reduced the conversion of bupropion to its active metabolite, suggesting that clopidogrel inhibits the cytochrome P450 isoenzyme CYP2B6.

1. Turpeinen M, *et al.* Effect of clopidogrel and ciclopidine on cytochrome P450 2B6 activity as measured by bupropion hydroxylation. *Clin Pharmacol Ther* 2005; 77: 553–9.

Ciclosporin. For reports of rhabdomyolysis developing in patients when given clopidogrel in addition to ciclosporin and a statin, see Statins, below.

Proton pump inhibitors. Proton pump inhibitors (PPIs) are recommended to reduce the risk of gastrointestinal bleeding in patients taking aspirin for cardiovascular indications.[1] However, clopidogrel is metabolised to an active metabolite by the cytochrome P450 isoenzyme CYP2C19, and PPIs, which exhibit competitive inhibition of CYP2C19 to varying degrees, may reduce its antiplatelet effect if patients are taking clopidogrel as well as aspirin, or are given a PPI with clopidogrel alone. A randomised study[2] in patients given aspirin and clopidogrel after coronary stenting suggested that addition of *omeprazole* reduced the antiplatelet effect of clopidogrel, and a small pharmacokinetic study[3] in healthy subjects taking clopidogrel with *lansoprazole* found a similar effect. Epidemiological studies[4-6] in patients taking clopidogrel for cardiovascular indications have also shown an increase in cardiovascular events in those taking PPIs as well; in one of the studies[5] it was suggested that this did not apply to patients taking *pantoprazole*, but it is unclear whether the difference between pantoprazole and other PPIs was significant, and others have reported a higher incidence of cardiovascular events in clopidogrel-treated patients taking pantoprazole than with other PPIs.[7] Since pantoprazole is thought to have a lower affinity for the cytochrome[5] it has been suggested that other mechanisms may also be involved.[7,8] A meta-analysis[9] of 23 studies concluded that the data on cardiovascular outcomes and overall mortality was conflicting and inconsistent, and study quality often poor, and that clinicians should consider the potential gastrointestinal harm from clopidogrel before witholding PPIs.

The MHRA in the UK,[10] the EMEA,[11] and the FDA[12] discourage the use of clopidogrel with either *omeprazole* or *esomeprazole*, but no longer consider there to be sufficient grounds to extend the warning across all PPIs.

1. Bhatt DL, *et al.* ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* 2008; 118: 1894–1909.
2. Gilard M, *et al.* Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol* 2008; 51: 256–60.
3. Small DS, *et al.* Effects of the proton pump inhibitor lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel. *J Clin Pharmacol* 2008; 48: 475–84.
4. Pezalla E, *et al.* Initial assessment of clinical impact of a drug interaction between clopidogrel and proton pump inhibitors. *J Am Coll Cardiol* 2008; 52: 1038–9.
5. Juurlink DN, *et al.* A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ* 2009; 180: 713–18.
6. Ho PM, *et al.* Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009; 301: 937–44.
7. MHRA/CHM. Clopidogrel and proton pump inhibitors: interaction. *Drug Safety Update* 2009; 2 (12): 2–3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0517716&RevisionSelectionMethod=LatestReleased (accessed 16/08/10)
8. EMEA. Public statement on possible interaction between clopidogrel and proton pump inhibitors (issued 29th May 2009). Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/Plavix/32895609en.pdf (accessed 16/08/10)
9. Kwok CS, Loke YK. Meta-analysis: the effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel. *Aliment Pharmacol Ther* 2010; 31: 810–23.
10. MHRA/CHM. Clopidogrel and proton pump inhibitors: interaction—updated advice. *Drug Safety Update* 2010; 3 (9): 4–5. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON076503&RevisionSelectionMethod=LatestReleased (accessed 09/06/10)
11. EMEA. Interaction between clopidogrel and proton-pump inhibitors: CHMP updates warning for clopidogrel-containing medicines (issued 17th March 2010). Available at: http://www.ema.europa.eu/humandocs/PDFs/EPAR/Plavix/17494810en.pdf (accessed 09/06/10)
12. FDA. Follow-Up to the January 26, 2009, Early Communication about an Ongoing Safety Review of Clopidogrel Bisulfate (marketed as Plavix) and Omeprazole (marketed as Prilosec and Prilosec OTC) (issued 17th November 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190784.htm (accessed 09/06/10)

Statins. There have been reports of rhabdomyolysis developing in patients when given clopidogrel in addition to ciclosporin and a statin (atorvastatin,[1,2] lovastatin,[3] or simvastatin[3]). Rhabdomyolysis is a recognised adverse effect when ciclosporin and statins are used together (see Immunosuppressants under Interactions of Simvastatin, p. 1495.3), but the patients in these reports had previously received the combination without incident and developed rhabdomyolysis 1 to 3 weeks after clopidogrel was started. It has been suggested[2] that the mechanism is a three way interaction involving competition for binding sites on the cytochrome P450 isoenzyme CYP3A4 between statins and clopidogrel, exacerbated by ciclosporin-mediated enzyme inhibition.

Although it has been suggested that statins may decrease the antiplatelet effect of clopidogrel, evidence for such an interaction has been conflicting;[4] short-term clinical follow-up[5] of around 1000 patients has suggested no adverse outcome from using this drug combination.

1. Anon. Clopidogrel (Plavix): suspected drug interaction with atorvastatin (Lipitor) and cyclosporine resulting in rhabdomyolysis. *Can Adverse React News* 2005; 15 (Apr): 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n2_e.pdf (accessed 01/09/05)
2. Burton JR, *et al.* Clopidogrel-precipitated rhabdomyolysis in a stable heart transplant patient. *Ann Pharmacother* 2007; 41: 133–7.
3. Uber PA, *et al.* Clopidogrel and rhabdomyolysis after heart transplantation. *J Heart Lung Transplant* 2003; 22: 107–8.
4. Tafreshi MJ, *et al.* Combination of clopidogrel and statins: a hypothetical interaction or therapeutic dilemma? *Pharmacotherapy* 2006; 26: 388–94.
5. Geisler T, *et al.* Statins do not adversely affect post-interventional residual platelet aggregation and outcomes in patients undergoing coronary stenting treated by dual antiplatelet therapy. *Eur Heart J* 2008; 29: 1635–43.

Pharmacokinetics

Clopidogrel is rapidly but incompletely absorbed after oral doses; absorption appears to be at least 50%. It is a prodrug and is extensively metabolised in the liver, mainly to the inactive carboxylic acid derivative; metabolism is mediated by cytochrome P450 isoenzymes including CYP3A4 and CYP2B6, CYP1A2, CYP1A1, and CYP2C19. The active metabolite appears to be a thiol derivative; it has been identified *in vitro* but appears to be too unstable to be isolated from plasma. Clopidogrel and the carboxylic acid derivative are highly protein bound. Clopidogrel and its metabolites are excreted in urine and in faeces; about 50% of an oral dose is recovered from the urine and about 46% from the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Antiplaq; Ariclopin; Clodian; Iscover; Klopik; Nabratin; Nadenel; Nefazan; Plavix; Pleyar; Troken; *Austral.*: Clovix; Iscover; Piax; Plavix; *Austria*: Clogombix; Clogrelhexal; Cloroden; Grepid; Plavix; *Belg.*: Plavix; *Braz.*: Clopido-Gran; Clopidror; Iscover; Lopigrel; Plagrel; Plaquevix; Plavix; *Canad.*: Plavix; *Chile*: Agreplat; Artevil; Clentel; Eurogrel; Iskimil; Plavix; Ravalgen; Sildecross; *China*: Plavix (波立维); Talcom (赛嘉); *Cz.*: Agrelex; Carder; Clopidostad; Clopigamma; Clopithan; Cloroden; Defrozyp; Egitromb; Grepid; Hemafluid; Iscover; Kloptimar; Lofradyk; Lopigalel; Nofardom; Perclod†; Picturlop; Platarex; Plavix; Plavocorin; Sarovex; Sudroc; Teclop; Tessyron; Trogran; Trombex; Tuxedon; Vatoud; Zopya; Zylagren; Zylit; *Denm.*: Biriklopi†; Clohys; Clonoren†; Clopidonorm; Clopitom; Cloricard; Derichem; Glopenel; Grepid; Iscover†; Janogrel; Klandryn†; Klepisal; Klodigan; Kloptimar; Pelidren†; Platarex†; Plavix; Plegrin†; Redras; Relidop; Roclas; Sidoklop; Sudroc; *Fin.*: Cloricard; Plavix; *Fr.*: Plavix; *Ger.*: Clopidocard†; Clopidocor†; Clopidolut; Clopigamma; Iscover; Plavix; *Gr.*: Bidogrel; Carder; Clodel; Clodelib; Clopidosyn; Cloricard; Cloroden; Cloromboz; Clovelen; Clovix; Dapixol; Darxa; Dasogrel-S; Diclop; Espelio; Globel; Glopenel; Greligen; Grepid; Heart-Free; Iscover; Larvin; Niaclop; Novigrel; Optigrel; Plasiver; Platel; Plavelate; Plavidosa; Plavix; Plavogrel; Sanvix; Tansix; Throimper; Unplaque; Zystol; *Hong Kong*: Clopistad; Clopivas; Clopivid; Lopirel; Plavix; *Hung.*: Atrombin; Clopidep; Clopigamma; Clopithan; Egitromb; Kardogrel; Kerberan; Lopigalel; Nofardom; Plagrel; Plavix; Trombex; Tuxedon; *India*: Aclotil; Adplatt; Antiban; Antiplar; Aplatin; Aptogrel; Blothin; C-Grel; Caplor; Carpigrel; Cenoza; Ceruvin; Cidogrel; Class; Clavix; Clodrel; Cloflow; Clofre; Clolyse; Clopact; Clopi; Clopicard; Clopid; Clopigrel; Clopikare; Clopilet; Clopirad; Clopitab; Clopivas; Clopizide; Cloplat; Clopod; Cloprez; Clotsafe; Deplatt; Glory; Grelet; Klov; Noklot; Noplaq; Nugrel; Orawis; Plavix; *Indon.*: Artepid; Clogin; Clopisan; Clotix; Copidrel; CPG; Pidovix; Placta; Pladel; Pladogrel; Plavix; Vaclo; *Irl.*: Clodel; Grepid; Iscover; Plavix; Zopya; Zylagren; Zylit; *Israel*: Clood; Clopid; Clopidexcel; Plavix; *Ital.*: Plavix; Vatoud; *Jpn*: Plavix;

Malaysia: Ceruvin; Clopivid; Kogrel; Plavix; ***Mex.***: Iscover; Plavix; ***Neth.***: Clopidocor†; Grepid; Iscover; Plavix; Plegrin†; Vatoud; Zopya†; Zylagren; Zyllt; ***Norw.***: Plavix; ***NZ***: Plavix; ***Philipp.***: Antiplar; Atheros; Cardogrel; Clomex; Clopida; Clopido; Clopimet; Clopivaz; Clopix; Cloplat; Clotiz; Clovax; Clovix; Deplatt; Dogrel; Hemaflow; Klopide; Noklot; Norplat; Plagerine; Platexan; Plavihex; Plavix; Plogrel; Syclopid; Trombix; Vivelon; ***Pol.***: Agregex; Areplex; Carder; Clogrel; Clopidim; Clopidix; Clopinovo; Egitromb; Grepid; Iscover; Klepisal; Miflexin; Plavix; Plavocorin; Sudroc; Tessyron; Trogran; Trombex; Zopya; Zylagren; Zyllt; ***Port.***: Atlabicio; DuoCover; DuoPlavin; Grepid; Hemopass; Ketapi; Plavix; Rasec†; Sades†; Satoxi; Ticofarma†; Vasagrin; Vastec; Zopya; Zylagren; Zyllt; ***Rus.***: Agregal (Агрегаль); Clopilet (Клопилет); Detromb (Детромб); Egitromb (Эгитромб); Listab (Листаб); Lopirel (Лопирел); Plagril (Плагрил); Plavix (Плавикс); Plogrel (Плогрель); Troken (Трокен); Zillt (Зилт); Zyllt (Зилт); ***S.Afr.***: Clopivas; Mistro; Plagrol; Plavix; ***Singapore***: Deplatt; Placta; Plagril; Plavix; ***Spain***: Agrelan; Arapamin; Iscover; Maboclop; Plavix; Vatoud; Zyllt; ***Swed.***: Cloriocard; Grepid; Plavix; ***Switz.***: Clogrel†; Clopidrax; Plavix; ***Thai.***: Apolets; Ceruvin; Pidogen†; Plavix; ***Turk.***: Atervix; Clopra; Diloxol; Diporel; Karum; Klopis; Opirel; Pingel; Planor; Plavix; ***UK***: Grepid; Plavix; ***Ukr.***: Areplex (Апеплекс)†; Aterocard (Атерокард); Atrogrel (Атрогрел); Cardogrel (Кардогрель); Clopix (Клопикс); Lopigrol (Лопигрол); Lopirel (Лопирел); Pingel (Пингель); Plagril (Плагрил); Plavix (Плавикс); Reodar (Реодар); Reomax (Реомакс); Tessiron (Тессирон); Trombonet (Тромбонет); Zilt (Зилт); ***USA***: Plavix; ***Venez.***: Plavix.

Multi-ingredient Preparations. ***Arg.***: Nefazan Compuesto; ***Austral.***: CoPlavix; DuoCover; ***Fr.***: DuoPlavin; ***Ger.***: DuoCover; DuoPlavin; ***Gr.***: DuoCover; DuoPlavin; ***India***: Antiban-ASP; Asicom Plus; C-Grel Plus; Caplor-AS; Cenoza A; Ceruvin-A; Cidogrel-A; Clasprin; Class-A; Clavix-AS; Clodrel Forte; Clodrel Plus; Clofre AS; Clopact A; Clopid-AS; Clopigrel-A; Clopirad-A; Clopisa; Clopitab-A; Clopivas AP; Clopizide-A; Clopod-A; Cloprez-A; Clouds; Complatt; Deplatt-A; Deplatt-CV; Dospin; Ecosprin Gold; Grelet-A; Kabitrol; Myogrel-AP; Noklot Plus; Noklot-CV; Nugrel Plus; ***Irl.***: DuoCover; DuoPlavin; ***Israel***: CoPlavix; ***Ital.***: DuoPlavin; ***Neth.***: DuoCover; DuoPlavin; ***Pol.***: DuoCover; DuoPlavin; ***Singapore***: CoPlavix; ***Spain***: DuoPlavin; ***Switz.***: DuoPlavin; ***Thai.***: CoPlavix; ***Ukr.***: Clopix Forte (Клопикс Форте).

Pharmacopoeial Preparations
USP 36: Clopidogrel Tablets.

Cloricromen *(rINN)*

Cloricromène; Cloricromeno; Cloricromenum; Клорикромен.

Ethyl ([8-chloro-3-[2-(diethylamino)ethyl]-4-methyl-2-oxo-2*H*-1-benzopyran-7-yl]oxy)acetate.

$C_{20}H_{26}ClNO_5$=395.9

CAS — 68206-94-0.

ATC — B01AC02.

ATC Vet — QB01AC02.

UNII — B9454PE93C.

Profile

Cloricromen is an antiplatelet drug with vasodilating activity and is used in thromboembolic disorders (p. 1273.2). It is given as the hydrochloride in arterial vascular disorders where there is a risk of thrombosis. It may be given orally in a dose of 100 mg two or three times daily or intravenously in a dose of 30 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Proendotel.

Colesevelam Hydrochloride

(BANM, USAN, rINNM)

Colésevélam, Chlorhydrate de; Colesevelam, hidrocloruro de; Colesevelami Hydrochloridum; GT31-104HB; Hidrocloruro de colesevelam; Колезевелама Гидрохлорид.

Allylamine polymer with epichlorohydrin (1-chloro-2,3-epoxypropane), α-(6-(allylamino)hexyl]trimethylammonium chloride and *N*-allyldecylamine, hydrochloride.

$(C_3H_7N)_m(C_3H_5ClO)_n(C_{12}H_{27}ClN_2)_o(C_{13}H_{27}N)_p.xHCl$

CAS — 182815-44-7.

ATC — C10AC04.

ATC Vet — QC10AC04.

UNII — P4SG24W15Q.

Uses and Administration

Colesevelam hydrochloride is a nonabsorbable hydrogel. It binds bile acids in the intestine and has actions similar to those of colestyramine (p. 1346.1). It is used for the treatment of hypercholesterolaemia (see Hyperlipidaemias, p. 1248.1), particularly type IIa hyperlipoproteinaemia, either alone or with a statin and/or ezetimibe. It may also be used as an adjunct to improve glycaemic control in type 2 diabetes mellitus (p. 459.1). The usual oral dose is 3.75 g daily, as a single dose or in two divided doses, with meals. When used as monotherapy for hypercholesterolaemia, the dose may be increased to 4.375 g daily if required. When used with a statin and/or ezetimibe, the dose is 2.5 to 3.75 g daily.

For use in children, see below.

References.
1. Davidson MH, *et al.* Colesevelam hydrochloride (Cholestagel): a new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. *Arch Intern Med* 1999; **159**: 1893–1900.
2. Aldridge MA, Ito MK. Colesevelam hydrochloride: a novel bile acid-binding resin. *Ann Pharmacother* 2001; **35**: 898–907.
3. Steinmetz KL. Colesevelam hydrochloride. *Am J Health-Syst Pharm* 2002; **59**: 932–9.
4. Bays H, Jones PH. Colesevelam hydrochloride: reducing atherosclerotic coronary heart disease risk factors. *Vasc Health Risk Manag* 2007; **3**: 733–42.
5. Florentin M, *et al.* Colesevelam hydrochloride in clinical practice: a new approach in the treatment of hypercholesterolaemia. *Curr Med Res Opin* 2008; **24**: 995–1009.
6. Corsini A, *et al.* Colesevelam hydrochloride: usefulness of a specifically engineered bile acid sequestrant for lowering LDL-cholesterol. *Eur J Cardiovasc Prev Rehabil* 2009; **16**: 1–9.
7. Sonnett TE, *et al.* Colesevelam hydrochloride for the treatment of type 2 diabetes mellitus. *Clin Ther* 2009; **31**: 245–59.
8. Goldfine AB, Fonseca VA. The use of colesevelam HCl in patients with type 2 diabetes mellitus: combining glucose- and lipid-lowering effects. *Postgrad Med* 2009; **121** (suppl 1): 13–18.
9. Handelsman Y. The role of colesevelam HCl in type 2 diabetes mellitus therapy. *Postgrad Med* 2009; **121** (suppl 1): 19–24.

Administration in children. US licensed product information allows the use of colesevelam hydrochloride to treat heterozygous familial hypercholesterolaemia in boys and postmenarchal girls from 10 years of age. It is given either alone or with a statin in an oral dose of 3.75 g daily, as a single dose or in 2 divided doses.

Adverse Effects and Precautions

As for Colestyramine, p. 1346.3.

Interactions

Colesevelam, like colestyramine (see p. 1347.1), has the potential to interfere with the absorption of other drugs; those with a narrow therapeutic range should be given at least 1 hour before or 4 hours after colesevelam unless there is known to be no interaction.

References.
1. Donovan JM, *et al.* Drug interactions with colesevelam hydrochloride, a novel, potent lipid-lowering agent. *Cardiovasc Drugs Ther* 2000; **14**: 681–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Cholestagel; ***Canad.***: Lodalis; ***Cz.***: Cholestagel; ***Denm.***: Cholestagel; ***Ger.***: Cholestagel; ***Gr.***: Cholestagel; ***Irl.***: Cholestagel; ***Israel***: Cholestagel; ***Neth.***: Cholestagel; ***Norw.***: Cholestagel; ***Pol.***: Cholestagel; ***Port.***: Cholestagel; ***Spain***: Cholestagel; ***Swed.***: Cholestagel; ***UK***: Cholestagel; ***USA***: Welchol.

Colestilan *(rINN)*

Colestilan Chloride (USAN); Colestilanum; Colestimide; MCI-196; Колестилан.

2-Methylimidazole polymer with 1-chloro-2,3-epoxypropane.

$(C_4H_8N_2.C_3H_5ClO)_n$

CAS — 95522-45-5.

Uses and Administration

Colestilan is a bile-acid binding and phosphate adsorbing anion exchange resin. It is a lipid regulating drug with similar properties to colestyramine (p. 1346.1) and is used to reduce cholesterol in the management of hyperlipidaemias (p. 1248.1). Colestilan is also used as a phosphate binder in the treatment of hyperphosphataemia (p. 1778.3).

In hyperlipidaemias, colestilan is given orally in a usual dose of 1.5 g twice daily with food.

For the treatment of hyperphosphataemia in patients with severe renal impairment receiving haemodialysis or peritoneal dialysis, colestilan is given orally, with food, at a starting dose of 6 to 9 g daily in 3 divided doses. The dose should then be adjusted, according to serum-phosphorus concentration, and may be increased in steps of 3 g every 2 to 3 weeks. A maximum of 15 g daily has been given.

It is also under investigation in diabetes mellitus.

References.
1. Kurihara S, *et al.* Effect of MCI-196 (colestilan) as a phosphate binder on hyperphosphataemia in haemodialysis patients: a double-blind, placebo-controlled, short-term trial. *Nephrol Dial Transplant* 2005; **20**: 424–30.
2. Yamakawa T, *et al.* Effect of colestimide therapy for glycemic control in type 2 diabetes mellitus with hypercholesterolemia. *Endocr J* 2007; **54**: 53–8.
3. Tanisi M, *et al.* Treatment of nonalcoholic steatohepatitis with colestimide. *Hepatol Res* 2009; **39**: 685–93.
4. Locatelli F, *et al.* Effect of MCI-196 on serum phosphate and cholesterol levels in haemodialysis patients with hyperphosphataemia: a double-blind, randomized, placebo-controlled study. *Nephrol Dial Transplant* 2010; **25**: 574–81.
5. Kondo K, Kadowaki T. Colestilan monotherapy significantly improves glycaemic control and LDL cholesterol levels in patients with type 2 diabetes: a randomized double-blind placebo-controlled study. *Diabetes Obes Metab* 2010; **12**: 246–51.

Adverse Effects and Precautions

As for Colestyramine, p. 1346.3 and p. 1347.1. Hypocalcaemia and decreased appetite are common with colestilan. Serious gastrointestinal haemorrhage has occurred uncommonly. Other uncommon effects include dizziness, hypotension, musculoskeletal pain, and raised hepatic enzymes. There have been rare cases of intestinal obstruction and colestilan is contra-indicated in patients with bowel obstruction.

Interactions

As for Colestyramine (p. 1347.1); other drugs should be given at least 1 hour before or 3 hours after colestilan.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Cholebine; ***UK***: BindRen.

Colestipol Hydrochloride

(BANM, USAN, rINNM)

Colestipol, chlorhydrate de; Colestipol, hidrocloruro de; Colestipol Hydrochloridum; Hidrocloruro de colestipol; Kolestipol Hidroklorür; U-26597A; Колестипола Гидрохлорид.

CAS — 26658-42-4 (colestipol); 50925-79-6 (colestipol); 37296-80-3 (colestipol hydrochloride).

ATC — C10AC02.

ATC Vet — QC10AC02.

UNII — X7D10K905G.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Colestipol Hydrochloride). A copolymer of diethylenetriamine and epichlorohydrin (1-chloro-2,3-epoxypropane). Each g binds not less than 1.1 mEq and not more than 1.7 mEq of sodium cholate, calculated as the cholate binding capacity and with reference to the dried substance. Yellow to orange hygroscopic beads. Swells but does not dissolve in water and in dilute solutions of acids or alkalis. Practically insoluble in alcohol and in dichloromethane. The supernatant of a 10% w/w suspension in water has a pH of 6.0 to 7.5. Store in airtight containers.

USP 36: (Colestipol Hydrochloride). A basic anion-exchange resin. It is the hydrochloride of a copolymer of diethylenetriamine and epichlorohydrin (1-chloro-2,3-epoxypropane). Each g binds not less than 1.1 mEq and not more than 1.6 mEq of sodium cholate, calculated as cholate binding capacity. Yellow to orange beads. Swells but does not dissolve in water or dilute aqueous solutions of acids or alkalis. Insoluble in common organic solvents. The supernatant of a 10% w/w suspension in water has a pH of 6.0 to 7.5. Store in airtight containers.

Uses and Administration

Colestipol hydrochloride is a bile-acid binding resin and lipid regulating drug with actions similar to those of colestyramine (p. 1346.1). It is used to reduce cholesterol in the treatment of hyperlipidaemias (p. 1248.1), particularly type IIa hyperlipoproteinaemia.

Colestipol hydrochloride is available as granules and is given orally as a suspension in water or a flavoured vehicle. The initial dose is 5 g daily or twice daily, increasing gradually at intervals of 1 to 2 months to up to 30 g daily in a single dose or two divided doses as necessary.

Colestipol hydrochloride is also available as tablets; doses range from 2 to 16 g daily.

Adverse Effects and Precautions

As for Colestyramine, p. 1346.3.

Effects on thyroid function. Reductions in total serum-thyroxine and thyroxine-binding globulin concentrations were found during routine monitoring of thyroid function in patients receiving colestipol and nicotinic acid, but were considered to be benign.[1] This effect has been used thera-

peutically in patients with hyperthyroidism (see under Uses of Colestyramine, below).

1. Cashin-Hemphill L, *et al.* Alterations in serum thyroid hormonal indices with colestipol-niacin therapy. *Ann Intern Med* 1987; 107: 324–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies colestipol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Colestyramine, p. 1347.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Colestid; *Belg.*: Colestid; *Canad.*: Colestid; *Denm.*: Lestid; *Fin.*: Lestid†; *Gr.*: Lestid; *Israel*: Colestid; *Norw.*: Lestid; *NZ*: Colestid; *Port.*: Colestid; *Spain*: Colestid; *Swed.*: Lestid; *Switz.*: Colestid; *UK*: Colestid; *USA*: Colestid.

Pharmacopoeial Preparations
BP 2014: Colestipol Granules;
USP 36: Colestipol Hydrochloride for Oral Suspension; Colestipol Hydrochloride Tablets.

Colestyramine *(BAN, rINN)*

Cholestyramine; Cholestyramine Resin; Colestiramina; Colestyramin; Colestyraminum; Divistyramine; Kolestiramin; Kolestiraminas; Kolestyramiini; Kolestyramin; Kolestyramina; МК-135; Колестирамин.

CAS — 11041-12-6.
ATC — C10AC01.
ATC Vet — QC10AC01.
UNII — 4B33BGK082.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Colestyramine). A strongly basic anion-exchange resin in the chloride form, consisting of styrene-divinylbenzene copolymer with quaternary ammonium groups. Each g exchanges not less than 1.8 g and not more than 2.2 g of sodium glycocholate, calculated with reference to the dried material. A white or almost white, fine, hygroscopic powder. Insoluble in water, in alcohol, and in dichloromethane. A 1% suspension in water has a pH of 4.0 to 6.0 after standing for 10 minutes. Store in airtight containers.

USP 36: (Cholestyramine Resin). A strongly basic anion-exchange resin containing quaternary ammonium functional groups which are attached to a styrene-divinylbenzene copolymer. Each g exchanges not less than 1.8 g and not more than 2.2 g of sodium glycocholate, calculated on the dried basis. It is used in the chloride form. A white to buff-coloured, hygroscopic, fine powder, odourless or has not more than a slight amine-like odour. It loses not more than 12% of its weight on drying. Insoluble in water, in alcohol, in chloroform, and in ether. A 1% slurry in water has a pH of 4.0 to 6.0. Store in airtight containers.

Uses and Administration

Colestyramine is a bile-acid binding resin and lipid regulating drug. It is used to reduce cholesterol in the treatment of hyperlipidaemias (p. 1248.1), particularly type IIa hyperlipoproteinaemia, and for the primary prevention of ischaemic heart disease (see Cardiovascular Risk Reduction, p. 1246.1) in middle-aged men with primary hypercholesterolaemia. Colestyramine is also used for the relief of diarrhoea associated with ileal resection, Crohn's disease, vagotomy, diabetic vagal neuropathy, and radiation, and to relieve the pruritus associated with the deposition in dermal tissue of excess bile acids in patients with partial biliary obstruction or primary biliary cirrhosis.

Colestyramine is not absorbed from the gastrointestinal tract and binds with bile acids in the intestine to form an insoluble complex that is excreted in the faeces. The normal reabsorption of bile acids is thus prevented and this leads to an increased oxidation of cholesterol to bile acids to replace those partially removed from the enterohepatic circulation, and an increased synthesis of low-density lipoprotein (LDL)-cholesterol receptors on hepatocytes. The overall effect is a reduction of total plasma-cholesterol concentration, mainly by lowering LDL-cholesterol; this may be accompanied by moderate increases in plasma triglyceride and high-density lipoprotein (HDL)-cholesterol concentrations. Since the uses of colestyramine are based upon the removal of intestinal bile acids it is unlikely that a response will be achieved in patients with complete biliary obstruction.

Colestyramine may be introduced gradually over 3 to 4 weeks to minimise gastrointestinal effects: the *BNF* suggests an initial dose of 4 g, increased by 4 g at weekly intervals.

In hyperlipidaemias and diarrhoea the usual oral dose is 12 to 24 g daily, given either as a single dose or in up to 4 divided doses. Dosage should be adjusted according to the patient's response and may be increased to 36 g daily if necessary. Lower doses may be adequate in some forms of hyperlipidaemia.

In pruritus doses of 4 to 8 g daily are usually sufficient.

For the use of colestyramine in children, see below.

Colestyramine should be given as a suspension in water or a flavoured vehicle.

General references.
1. Insull W. Clinical utility of bile acid sequestrants in the treatment of dyslipidemia: a scientific review. *South Med J* 2006; 99: 257–73.

Administration in children. Colestyramine has been used in children and small studies[1,2] have found that it is effective in familial hypercholesterolaemia with no adverse effects on physical growth when taken long-term;[2] however, compliance may be a problem.[1]

For *hypercholesterolaemia*, the *BNFC* gives the usual oral dose for children aged 6 to 12 years as 4 g once daily, increased to 4 g up to 3 times daily according to response. Children aged 12 to 18 years may be given the usual adult dose (see above). Alternatively, licensed doses are calculated from body-weight, either as a percentage of the adult (70 kg) dose, or as a dose of 240 mg/kg daily in divided doses.

For *pruritus* or *diarrhoea*, the *BNFC* recommends the following oral doses based on age:

- 1 month to 1 year: initially 1 g once daily, adjusted according to response to a maximum dose of 9 g daily in 2 to 4 divided doses
- 1 to 6 years: initially 2 g once daily, adjusted according to response to a maximum dose of 18 g daily in 2 to 4 divided doses
- 6 to 12 years: initially 4 g once daily, adjusted according to response to a maximum dose of 24 g daily in 2 to 4 divided doses
- 12 to 18 years: initially 4 to 8 g once daily, adjusted according to response to a maximum dose of 36 g daily in 2 to 4 divided doses

1. West RJ, Lloyd JK. Long-term follow-up of children with familial hypercholesterolaemia treated with cholestyramine. *Lancet* 1980; ii: 873–5.
2. Tonstad S, *et al.* Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial hypercholesterolemia. *J Pediatr* 1996; 129: 42–9.

Antibiotic-associated colitis. Colestyramine binds *Clostridium difficile* toxins and there are a few reports of use as an alternative, or as an adjunct, to vancomycin or metronidazole in patients with diarrhoea associated with *C. difficile* toxins after antibacterial therapy (p. 183.1). However, evidence of benefit is limited and in general its use is not recommended.

Biliary disorders. Colestyramine is used to relieve diarrhoea (p. 1808.2) associated with bile acid malabsorption and to manage pruritus and hypercholesterolaemia in patients with primary biliary cirrhosis (p. 2638.3). It has been used for pruritus in cholestasis of pregnancy,[1] although such use has been associated with severe fetal intracranial haemorrhage.[2] Beneficial responses have been reported with colestyramine in the management of congenital nonobstructive nonhaemolytic hyperbilirubinaemia (Crigler-Najjar disease)[3,4] and in sclerosing cholangitis.[5]

1. Jenkins JK, Boothby LA. Treatment of itching associated with intrahepatic cholestasis of pregnancy. *Ann Pharmacother* 2002; 36: 1462–5.
2. Sadler LC, *et al.* Severe fetal intracranial haemorrhage during treatment with cholestyramine for intrahepatic cholestasis of pregnancy. *Br J Obstet Gynaecol* 1995; 102: 169–70.
3. Arrowsmith WA, *et al.* Comparison of treatments for congenital nonobstructive nonhaemolytic hyperbilirubinaemia. *Arch Dis Child* 1975; 50: 197–201.
4. Odièvre M, *et al.* Case of congenital nonobstructive, nonhaemolytic jaundice: successful long-term phototherapy at home. *Arch Dis Child* 1978; 53: 81–2.
5. Polter DE, *et al.* Beneficial effect of cholestyramine in sclerosing cholangitis. *Gastroenterology* 1980; 79: 326–33.

Diabetes mellitus. Bile acids may have a role in modulating carbohydrate metabolism and small studies have shown that bile-acid binding resins such as colestyramine reduce blood glucose.[1] Their role in type 2 diabetes mellitus (p. 459.1) is under investigation: colesevelam (p. 1345.1) may be used as an adjunct to standard therapy to improve glycaemic control.

1. Staels B, Kuipers F. Bile acid sequestrants and the treatment of type 2 diabetes mellitus. *Drugs* 2007; 67: 1383–92.

Diarrhoea. In addition to its use in diarrhoea (p. 1808.2) associated with biliary disorders (above), colestyramine has been investigated in the management of diarrhoea and faecal incontinence from other causes.[1–4] See also Antibiotic-associated Colitis, above.

1. Baert D, *et al.* Chronic diarrhoea in non collagenous microscopic colitis: therapeutic effect of cholestyramine. *Acta Clin Belg* 2004; 59: 258–62.
2. Balagani R, *et al.* Cholestyramine improves tropical-related diarrhea. *Am J Ther* 2006; 13: 281–2.
3. Flieger D, *et al.* Phase II clinical trial for prevention of delayed diarrhea with cholestyramine/levofloxacin in the second-line treatment with irinotecan biweekly in patients with metastatic colorectal carcinoma. *Oncology* 2007; 72: 10–16.
4. Remes-Troche JM, *et al.* Cholestyramine—a useful adjunct for the treatment of patients with fecal incontinence. *Int J Colorectal Dis* 2008; 23: 189–94.

Hyperthyroidism. Bile-acid binding resins also bind thyroid hormones and may interfere with their enterohepatic circulation. Reduced serum-thyroxine concentrations have occurred in patients given bile-acid binding resins for hyperlipidaemias (see Effects on Thyroid Function under Colestipol, p. 1345.3) and both colestyramine[1–3] and colestipol[4] have been tried as adjunctive treatment for hyperthyroidism (p. 2332.2). Colestyramine has also been used in thyroxine overdose.[5,6]

1. Mercado M, *et al.* Treatment of hyperthyroidism with a combination of methimazole and cholestyramine. *J Clin Endocrinol Metab* 1996; 81: 3191–3.
2. Tsai W-C, *et al.* The effect of combination therapy with propylthiouracil and cholestyramine in the treatment of Graves' hyperthyroidism. *Clin Endocrinol (Oxf)* 2005; 62: 521–4.
3. Kaykhaei MA, *et al.* Low doses of cholestyramine in the treatment of hyperthyroidism. *Endocrine* 2008; 34: 52–5.
4. Hagag P, *et al.* Role of colestipol in the treatment of hyperthyroidism. *J Endocrinol Invest* 1998; 21: 725–31.
5. Shakir KMM, *et al.* The use of bile acid sequestrants to lower serum thyroid hormones in iatrogenic hyperthyroidism. *Ann Intern Med* 1993; 118: 112–13.
6. de Luis DA, *et al.* Light symptoms following a high-dose intentional L-thyroxine ingestion treated with cholestyramine. *Horm Res* 2002; 57: 61–3.

Adverse Effects

The most common adverse effect of colestyramine is constipation; faecal impaction may develop and haemorrhoids may be aggravated. Other gastrointestinal adverse effects include abdominal discomfort or pain, heartburn, flatulence, nausea, vomiting, and diarrhoea.

Colestyramine in high doses may cause steatorrhoea by interfering with the absorption of fats from the gastrointestinal tract and therefore decreased absorption of fat-soluble vitamins, such as vitamins A, D, E, and K, may occur. Chronic use of colestyramine may thus result in an increased bleeding tendency due to hypoprothrombinaemia associated with vitamin K deficiency; it also has a potential to cause osteoporosis due to impaired calcium and vitamin D absorption. Colestyramine may increase plasma-triglyceride concentrations, see Uses and Administration, above.

Colestyramine is the chloride form of an anion-exchange resin and prolonged use may produce hyperchloraemic acidosis, particularly in children.

Skin rashes and pruritus of the tongue, skin, and perianal region have occasionally occurred.

Reviews.
1. Jacobson TA, *et al.* Safety considerations with gastrointestinally active lipid-lowering drugs. *Am J Cardiol* 2007; 99 (Issue 6 suppl 1): 47C–55C.

Incidence of adverse effects. Results of the Lipid Research Clinics Coronary Primary Prevention Trial[1] involving 3806 men given colestyramine or placebo for an average of 7.4 years showed that gastrointestinal adverse effects occurred frequently in both groups but especially in the colestyramine group. In the first year 68% of the colestyramine group had at least 1 gastrointestinal adverse effect compared with 43% of the placebo group; by the seventh year the incidence had fallen to 29% and 26% respectively. Constipation and heartburn, especially, were more frequent in the colestyramine group, which also reported more abdominal pain, belching or bloating, gas, and nausea. These adverse effects were usually not severe and could be dealt with by standard clinical means.

The incidence of malignant neoplasms was similar in the 2 groups although there were differences in incidence at some sites. In particular, there were 21 cases of malignancy in the gastrointestinal tract (8 fatal) in the colestyramine group compared with 11 cases (1 fatal) in the placebo group. Rare cancers of the buccal cavity or pharynx were more common with colestyramine; during the study[1] there were 6 cases in the colestyramine group and none in the placebo group, and after follow-up[2] for a further 6 years and reassessment of the original diagnoses the incidences were 8 and 2, respectively. However, there was no clear dose relationship, and cigarette smoking may have been a confounder.[2] Colorectal malignancies were similar in the 2 groups, although at follow-up more non-malignant colorectal neoplasms had occurred in the colestyramine group.[2]

1. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. *JAMA* 1984; 251: 351–64.
2. The Lipid Research Clinics Investigators. The Lipid Research Clinic Coronary Primary Prevention Trial: results of 6 years of post-trial follow up. *Arch Intern Med* 1992; 152: 1399–1410.

Precautions

Colestyramine powder should be given as a suspension in water or a flavoured vehicle to minimise the risk of oesophageal obstruction.

Colestyramine should not be used in patients with complete biliary obstruction as it is unlikely to be effective.

Because of the risk of vitamin deficiencies, supplements of vitamins A, D, E, and K should be considered during prolonged therapy with colestyramine; if given orally they need to be in a water-miscible form. Parenteral supplementation, particularly of vitamin K for hypoprothrombinaemia, may be necessary if a deficiency becomes established. Reduced serum-folate concentrations have also been reported in children with familial hypercholesterolaemia and supplementation with folic acid should be considered in such circumstances.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies colestyramine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

Colestyramine may delay or reduce the absorption of other drugs, particularly acidic drugs. Enterohepatic circulation may be reduced. Delayed or reduced absorption of thiazide diuretics, propranolol, digoxin and related glycosides, loperamide, phenylbutazone, barbiturates, oestrogens, progestogens, thyroid hormones, warfarin, deferasirox, and some antibacterials, has either been reported or may be expected. It is therefore recommended that other drugs should be taken at least 1 hour before, or 4 to 6 hours after, the use of colestyramine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Questran; *Austral.*: Questran; *Austria*: Quantalan; *Belg.*: Questran; *Braz.*: Questran; *Canad.*: Novo-Cholamine; Olestyr; *Cz.*: Questran†; Vasosan; *Denm.*: Questran; *Fin.*: Questran; *Fr.*: Questran; *Ger.*: Colestyr†; Lipocol; Quantalan; Vasosan; *Gr.*: Questran; *Hong Kong*: Questran†; *Indon.*: Questran†; *Irl.*: Questran; *Mex.*: Questran; *Neth.*: Questran; *Norw.*: Questran; *NZ*: Questran; *Pol.*: Vasosan; *Port.*: Quantalan; *S.Afr.*: Questran; *Singapore*: Resincolestiramina; *Spain*: Efensol; Resincolestiramina; *Swed.*: Questran; *Switz.*: Ipocol; Quantalan; *Thai.*: Questran; Resincolestiramina; *Turk.*: Kolestran; *UK*: Questran; *USA*: Locholest; Prevalite; Questran.

Pharmacopoeial Preparations
BP 2014: Colestyramine Oral Powder;
USP 36: Cholestyramine for Oral Suspension.

Colextran Hydrochloride *(rINNM)*

Colextran, Chlorhydrate de; Colextrán, hidrocloruro de; Colextrani Hydrochloridum; DEAE-dextran Hydrochloride; Detaxtran Hydrochloride; Diethylaminoethyl-dextran Hydrochloride; Hidrocloruro de colextrán; Колекстрана гидрохлорид.

Dextran 2-(diethylamino)ethyl ether hydrochloride.

CAS — 9015-73-0 (colextran); 9064-91-9 (colextran hydrochloride).
ATC — C10AC03.
ATC Vet — QC10AC03.
UNII — B5AMG1WQ9L.

Profile

Colextran hydrochloride, an anion-exchange resin that binds bile acids in the intestine, is a lipid regulating drug used in the treatment of hyperlipidaemias (p. 1248.1). It is given in a usual dose of 2 to 3 g daily orally in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Pulsar; Rationale; *Spain*: Dexide.

Cyclandelate *(BAN, rINN)*

BS-572; Ciclandelato; Cyclandelate; Cyclandelatum; Cyklandelat; Syklandelaatti; Цикланделат.

3,3,5-Trimethylcyclohexyl mandelate.

$C_{17}H_{24}O_3$=276.4

CAS — 456-59-7.
ATC — C04AX01.
ATC Vet — QC04AX01.
UNII — 4139C1O4Y2.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Cyclandelate). A white crystalline powder. M.p. about 58 degrees. Practically insoluble in water; very soluble in alcohol, in acetonitrile, and in ether. Store in airtight containers below 40 degrees, preferably between 15 degrees and 30 degrees. Protect from light.

Profile

Cyclandelate is a vasodilator used in the management of cerebrovascular (p. 1269.2) and peripheral vascular disorders (p. 1272.3). It is given orally in an initial dosage of up to 2 g daily in divided doses; a usual maintenance dose is 0.8 to 1.2 g daily.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cyclandelate as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Cyclophilin; Cyclospasmol; *India*: Cyclasyn; Cyclospasmol; Martispasmol.

Cyclopenthiazide *(BAN, USAN, rINN)* ⊗

Ciclopentiazida; Cyclopenthiaz; Cyclopenthiazidum; Ciklopentiazid; NSC-107679; Su-8341; Syklopentiatsidi; Циклопентиазид.

6-Chloro-3-cyclopentylmethyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_{13}H_{18}ClN_3O_4S_2$=379.9

CAS — 742-20-1.
ATC — C03AA07.
ATC Vet — QC03AA07.
UNII — VX4S2N85F5.

NOTE. Compounded preparations of cyclopenthiazide may be represented by the following names:

- Co-prenozide (*BAN*)—cyclopenthiazide 1 part and oxprenolol hydrochloride 640 parts (w/w).

Pharmacopoeias. In *Br.*

BP 2014: (Cyclopenthiazide). A white, odourless or almost odourless powder. Practically insoluble in water; soluble in alcohol and in acetone; practically insoluble in chloroform; very slightly soluble in ether.

Profile

Cyclopenthiazide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (p. 1403.2). It is given orally for hypertension (p. 1251.1), and for oedema, including that associated with heart failure (p. 1262.3).

Diuresis is induced in 1 to 3 hours after an oral dose, reaches a peak in 4 to 8 hours, and lasts up to about 12 hours.

In the treatment of hypertension the usual dose is 250 to 500 micrograms daily either alone, or with other antihypertensives. In the treatment of oedema the usual initial dose is 250 to 500 micrograms daily; up to 1 mg daily may be given in heart failure but higher doses rarely achieve any further benefit. The dose should be reduced to the lowest effective dose for maintenance.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Navidrex.

Multi-ingredient Preparations. *Hong Kong*: Navispare; *S.Afr.*: Lenurex-K†; *UK*: Navispare; Trasidrex†.

Pharmacopoeial Preparations
BP 2014: Cyclopenthiazide Tablets.

Dabigatran *(BAN, USAN, rINN)*

BIBR-953; BIBR-953ZW; Dabigatrán; Dabigatranum; Дабигатран.

N-{[2-[(*p*-Amidinoanilino)methyl]-1-methyl-5-benzimidazol-yl]carbonyl}-*N*-2-pyridyl-β-alanine.

$C_{25}H_{25}N_7O_3$=471.5

CAS — 211914-51-1.
ATC — B01AE07.
ATC Vet — QB01AE07.
UNII — IOVM4M70GC.

Dabigatran Etexilate *(BAN, USAN, rINN)*

BIBR-1048; BIBR-1048/BSA951; Dabigatran Etexilate; Dabigatrán etexilato; Dabigatranetexilat; Dabigatranum Etexilatum; Etexilato de dabigatrana; Дабигатран Этексилат.

Ethyl 3-{[2-({4-[[(hexyloxy)carbonyl]amino]iminomethyl}phenyl)amino]methyl}-1-methyl-1*H*-benzimidazol-5-yl]carbonyl}(pyridin-2-yl)amino)propanoate.

$C_{34}H_{41}N_7O_5$=627.7

CAS — 211915-06-9.
ATC — B01AE07.
ATC Vet — QB01AE07.
UNII — 2E18WX195X.

Dabigatran Etexilate Mesilate *(rINNM)*

BIBR-1048MS; Dabigatran Etexilate, Mésilate de; Dabigatran Etexilate Mesylate (USAN); Dabigatrani Etexilati Mesilas; Mesilato de dabigatrán etexilato; Дабигатрана Этексилата Мезилат.

$C_{35}H_{45}N_7O_8S$=723.8

CAS — 593282-20-3.
ATC — B01AE07.
ATC Vet — QB01AE07.
UNII — SC7NUW5IIT.

Uses and Administration

Dabigatran is a direct thrombin inhibitor given orally as the mesilate of the prodrug dabigatran etexilate; doses are expressed in terms of the equivalent amount of dabigatran etexilate.

It is used for the prophylaxis of venous thromboembolism (p. 1274.1) in patients undergoing elective orthopaedic surgery, and for the prevention of stroke and systemic embolisation in patients with non-valvular atrial fibrillation (see Cardiac Arrhythmias, p. 1266.1).

In **orthopaedic** patients, the usual initial dose is 110 mg given within 1 to 4 hours of the completion of surgery, followed by 220 mg once daily. A reduced dose of 150 mg once daily should be given if taken with *amiodarone*, *quinidine*, or *verapamil*; (where this is necessary, the 2 drugs should be taken at the same time). Treatment should be continued for a total of 10 days after knee replacement and 28 to 35 days after hip replacement.

In patients with **atrial fibrillation** the usual dose is 150 mg twice daily. A reduced dose of 110 mg twice daily should be given if taken at the same time as verapamil. This dose may also be considered for patients at increased risk of bleeding.

Appropriate dosage for use in the elderly and in patients with renal impairment is discussed on p. 1348.1. For advice on switching to an alternative anticoagulant, see Administration, below.

References.

1. Wolowacz SE, *et al.* Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty: a meta-analysis. *Thromb Haemost* 2009; **101**: 77–85.
2. Schulman S, *et al.* RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009; **361**: 2342–52.
3. Siddiqui FM, Qureshi AI. Dabigatran etexilate, a new oral direct thrombin inhibitor, for stroke prevention in patients with atrial fibrillation. *Expert Opin Pharmacother* 2010; **11**: 1403–11.
4. Friedman RJ, *et al.* RE-MOBILIZE, RE-MODEL, RE-NOVATE Steering Committees. Dabigatran versus enoxaparin for prevention of venous thromboembolism after hip or knee arthroplasty: a pooled analysis of three trials. *Thromb Res* 2010; **126**: 175–82.
5. Garnock-Jones KP. Dabigatran etexilate: a review of its use in the prevention of stroke and systemic embolism in patients with atrial fibrillation. *Am J Cardiovasc Drugs* 2011; **11**: 57–72.
6. Hankey GJ, Eikelboom JW. Dabigatran etexilate: a new oral thrombin inhibitor. *Circulation* 2011; **123**: 1436–50.
7. Schulman S, Majeed A. A benefit-risk assessment of dabigatran in the prevention of venous thromboembolism in orthopaedic surgery. *Drug Safety* 2011; **34**: 449–63.
8. Blommel ML, Blommel AL. Dabigatran etexilate: a novel oral direct thrombin inhibitor. *Am J Health-Syst Pharm* 2011; **68**: 1506–19.
9. Bovio JA, *et al.* Dabigatran etexilate: a novel oral thrombin inhibitor for thromboembolic disease. *Ann Pharmacother* 2011; **45**: 603–14.
10. Burness CB, McKeage K. Dabigatran etexilate: a review of its use for the prevention of venous thromboembolism after total hip or knee replacement surgery. *Drugs* 2012; **72**: 963–86.

Administration. If patients receiving dabigatran therapy must be switched to another anticoagulant, the following regimens have been suggested based on creatinine clearance (CC).

In patients with atrial fibrillation, parenteral anticoagulants may be started 12 hours after the last dose of dabigatran; or after 24 hours in patients with CC < 30 mL/minute.

Warfarin should be *started*:

- CC more than 50 mL/minute: 3 days *before stopping* dabigatran
- CC 30 to 50 mL/minute: 2 days *before stopping* dabigatran
- CC 15 to 30 mL/minute: 1 day *before stopping* dabigatran
- CC less than 15 mL/minute: no recommendation can be made

In patients receiving short-term dabigatran after orthopaedic surgery, it is suggested that a period of 24 hours should elapse after the last dose of dabigatran before starting a parenteral anticoagulant.

Administration in the elderly. There is limited clinical experience with dabigatran in patients over the age of 75 years but plasma concentrations appear to be higher in older subjects[1] and dose reduction should be considered.

For **orthopaedic** patients, UK licensed product information recommends an initial oral dose of 75 mg of dabigatran etexilate (as the mesilate) given within 1 to 4 hours of the completion of surgery, followed by 150 mg once daily for a total of 10 days after knee replacement and 28 to 35 days after hip replacement. For patients with **atrial fibrillation**, those aged 80 years and over should be given a dose of 110 mg twice daily. This dose may also be considered in those who are aged from 75 to 80 years and at a high risk of bleeding.

1. Stangier J, *et al.* Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. *Clin Pharmacokinet* 2008; 47: 47–59.

Administration in renal impairment. Dabigatran is excreted mainly by the kidneys but only limited clinical experience with its use in renal impairment has been published.[1]

UK licensed product information has recommended reduced doses in patients with creatinine clearance (CC) between 30 and 50 mL/minute (moderate impairment). In **orthopaedic** patients, the initial oral dose should be the equivalent of 75 mg of dabigatran etexilate given within 1 to 4 hours of the completion of surgery, followed by 150 mg once daily for a total of 10 days after knee replacement and 28 to 35 days after hip replacement. A maximum daily dose of 75 mg should be considered in those with moderate renal impairment who are also taking *verapamil*. In patients with **atrial fibrillation**, a reduced dose of 110 mg twice daily should be considered in patients with moderate renal impairment and an increased risk of bleeding; otherwise the normal dose may be given. UK information contra-indicates dabigatran in all patients with a CC below 30 mL/minute.

US licensed product information (where the sole indication is for atrial fibrillation) recommends a reduced dose of 75 mg twice daily in patients with a CC of 15 to 30 mL/minute (severe impairment); this reduced dose should also be considered for patients with a CC of 30 to 50 mL/minute (moderate impairment) who are taking either systemic *ketoconazole* or *dronedarone* with dabigatran. No dosing recommendations are made for CC below 15 mL/minute or for patients on dialysis.

1. Stangier J, *et al.* Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet* 2010; 49: 259–68.

Adverse Effects and Treatment

The most common adverse effect with dabigatran is bleeding. Gastrointestinal disturbances such as dyspepsia, nausea, and diarrhoea are also common. Raised liver enzyme values have been reported. There is no antidote to dabigatran. If haemorrhagic complications occur treatment should be stopped; surgical haemostasis or blood volume replacement may be considered.

Effects on the liver. Jaundice, fatigue, and anorexia, with raised liver enzyme values indicating mild hepatic dysfunction, developed in a 71-year-old man about 1 month after starting dabigatran. He recovered within 2 weeks after stopping the drug.[1] Isolated cases of severe hepatitis have also occurred.

1. Rochwerg B, *et al.* Dabigatran-induced acute hepatitis. *Clin Appl Thromb Hemost* 2012; 18: 549–50.

Overdosage. There is no antidote to dabigatran etexilate. Management of bleeding may include delaying or stopping the drug, local compression, and surgical haemostasis. Oral activated charcoal may be considered if the patient presents within 1 to 2 hours. Infusion of fresh frozen plasma could be appropriate, depending on associated coagulopathies, but it will not reverse the anticoagulant effects of dabigatran specifically. Although it has been suggested that other blood components might be tried in life-threatening bleeding, this is generally based on *animal* studies; these treatments include recombinant factor VIIa [eptacog alfa (activated)] and prothrombin complex concentrates (activated or non-activated).[1] In a study of 12 healthy subjects, however, a single dose of a non-activated prothrombin complex concentrate did not reverse the effects of dabigatran on blood coagulation tests.[2] Nevertheless, the use of a prothrombin complex concentrate with fresh frozen plasma was reported to decrease the activated partial thromboplastin time (aPTT) and stabilise haemoglobin concentrations in a case of dabigatran-induced gastrointestinal bleeding.[3]

Dabigatran is removed by haemodialysis.[1]

In an emergency, the most useful indicators of bleeding risk are thrombin time (TT) and activated partial thromboplastin time (APTT), although APTT is less sensitive at supratherapeutic dabigatran levels. Prothrombin time is relatively insensitive to dabigatran, and the international normalised ratio (INR) should not be used. The ecarin clotting time is highly sensitive to the anticoagulant effects of dabigatran but a test is not readily available for clinical use.[1]

1. van Ryn J, *et al.* Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 2010; 103: 1116–27.
2. Berrettenberg BS, *et al.* Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011; 124: 1573–9.
3. Dumkow LE, *et al.* Reversal of dabigatran-induced bleeding with a prothrombin complex concentrate and fresh frozen plasma. *Am J Health-Syst Pharm* 2012; 69: 1646–50.

Precautions

Dabigatran should not be used in patients with clinically significant bleeding or who are at high risk for bleeding. It is contra-indicated in patients with mechanical prosthetic heart valves because of an increased risk of both thromboembolism and major bleeding. US licensed product information also warns that dabigatran is not recommended for thromboembolic prophylaxis in atrial fibrillation in patients with other forms of valvular heart disease or with a bioprosthetic heart valve, because information is lacking. In patients already taking dabigatran, treatment should generally be stopped 1 to 2 days before surgery or invasive procedures; longer withdrawal intervals may be needed before major surgery, spinal puncture or catheter placement, and in patients with renal impairment.

It may be best used with caution in patients with hepatic impairment and should be used in reduced doses or avoided in patients with renal impairment (see Administration in Renal Impairment under Uses and Administration, above).

The elderly. Elderly patients may be at increased risk of bleeding from dabigatran, particularly those with impaired renal function or low body-weight.[1-5] See Administration in the Elderly (above) for recommended dose reductions.

1. Legrand M, *et al.* The use of dabigatran in elderly patients. *Arch Intern Med* 2011; 171: 1285–6.
2. Harper P, *et al.* Bleeding risk with dabigatran in the frail elderly. *N Engl J Med* 2012; 366: 864–6.
3. Wychowski MK, Koulides PA. Dabigatran-induced gastrointestinal bleeding in an elderly patient with moderate renal impairment. *Ann Pharmacother* 2012; 46: e10.
4. Béné J, *et al.* Rectal bleeding and hemostatic disorders induced by dabigatran etexilate in 2 elderly patients. *Ann Pharmacother* 2012; 46: e14.
5. Freshour JE, *et al.* Epistaxis associated with dabigatran in an elderly patient with reduced creatinine clearance. *Am J Health-Syst Pharm* 2012; 69: 1184–6.

Interactions

Dabigatran should not be given with other drugs that affect coagulation, such as anticoagulants and thrombolytics. It should be used with caution, if at all, with antiplatelet drugs, NSAIDs, SSRIs, or serotonin and noradrenaline reuptake inhibitors (SNRIs), since the risk of bleeding may be increased. Dabigatran is a substrate for the efflux transporter P-glycoprotein and interactions may occur with drugs that affect P-glycoprotein function, although advice given in UK and US licensed product information varies. In the UK, recommendations vary slightly between the two indications:

- use with P-glycoprotein inducers (such as rifampicin, St John's wort, carbamazepine, and phenytoin) should be avoided in all patients
- the strong P-glycoprotein inhibitors ciclosporin, dronedarone, itraconazole, systemic ketoconazole, and tacrolimus are contra-indicated in all patients
- when taken with verapamil the dose of dabigatran should be reduced in all patients
- when taken with amiodarone or quinidine the dose of dabigatran should be reduced in orthopaedic patients, but not in atrial fibrillation patients (although caution is required)
- use with clarithromycin requires caution in all patients
- use with ticagrelor requires caution in all patients because of both its antiplatelet effect and P-glycoprotein inhibition

(For details of dosage reductions, see Uses and Administration, p. 1347.3).

In the USA (where the sole indication is atrial fibrillation), licensed product information also advises that the concomitant use of dabigatran and P-glycoprotein inducers such as rifampicin should generally be avoided. Dosage adjustments of dabigatran are not considered necessary when given with amiodarone, quinidine, clarithromycin, ketoconazole, or verapamil in patients with normal renal function, although a reduced dose may be necessary for use with ketoconazole or dronedarone in patients with moderate renal impairment (see Administration in Renal Impairment, above). However, in those with severe renal impairment (creatinine clearance < 30 mL/minute) US licensed product information advises that concomitant use with P-glycoprotein inhibitors should be avoided.

Pharmacokinetics

When given orally, dabigatran etexilate is rapidly and completely hydrolysed to its active metabolite, dabigatran, by an esterase-catalysed reaction. The absolute oral bioavailability of dabigatran when given as dabigatran etexilate is about 3 to 7%. Oral bioavailability of dabigatran etexilate from both the UK and US proprietary products may be increased by up to 75% if the pellets are taken without the capsule shell. Peak plasma concentrations of dabigatran occur within 0.5 to 2 hours after an oral dose. Food delays the time to peak concentrations but the bioavailability is not affected. Dabigatran has low plasma-protein binding (about 35%). It is metabolised to a limited extent to active acylglucuronide conjugates; about 80 to 85% of a dose is excreted in the urine, mainly as unchanged dabigatran. The terminal plasma half-life is about 12 to 17 hours. Dabigatran is removed by dialysis.

Reviews.

1. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clin Pharmacokinet* 2008; 47: 285–95.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Pradaxa; *Austral.*: Pradaxa; *Austria*: Pradaxa; *Belg.*: Pradaxa; *Braz.*: Pradaxa; *Canad.*: Pradax; *Chile*: Pradaxa; *Cz.*: Pradaxa; *Denm.*: Pradaxa; *Fr.*: Pradaxa; *Ger.*: Pradaxa; *Gr.*: Pradaxa; *Hong Kong*: Pradaxa; *Hung.*: Pradaxa; *Indon.*: Pradaxa; *Irl.*: Pradaxa; *Israel*: Pradaxa; *Ital.*: Pradaxa; *Jpn*: Prazaxa; *Malaysia*: Pradaxa; *Neth.*: Pradaxa; *Norw.*: Pradaxa; *NZ*: Pradaxa; *Philipp.*: Pradaxa; *Pol.*: Pradaxa; *Port.*: Pradaxa; *Rus.*: Pradaxa (Прадакса); *Singapore*: Pradaxa; *Spain*: Pradaxa; *Swed.*: Pradaxa; *Switz.*: Pradaxa; *Thai.*: Pradaxa; *UK*: Pradaxa; *Ukr.*: Pradaxa (Прадакса); *USA*: Pradaxa.

Dalteparin Sodium *(BAN, USAN, rINN)*

Dalteparininatrium; Dalteparin-Natrium; Dalteparin sodná sůl; Dalteparin Sodyum; Dalteparina sódica; Daltéparine sodique; Dalteparinnatrium; Dalteparin-nátrium; Dalteparino natrio druska; Dalteparinum Natricum; Dalteparyna sodowa; Kabi-2165; Tedelparin Sodium; Дальтепарин Натрий.

CAS — 9041-08-1.
ATC — B01AB04.
ATC Vet — QB01AB04.
UNII — 12M44VTJ7B.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dalteparin Sodium). The sodium salt of a low-molecular-mass heparin that is obtained by nitrous acid depolymerisation of heparin from porcine intestinal mucosa. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-*O*-sulfo-2,5-anhydro-D-mannitol structure at the reducing end of their chain. The mass-average relative molecular mass ranges between 5600 and 6400, with a characteristic value of about 6000. The mass percentage of chains lower than 3000 is not more than 13.0% and the mass percentage of chains higher than 8000 ranges between 15.0% and 25.0%. The degree of sulfation is 2.0 to 2.5 per disaccharide unit.

The potency is not less than 110 units and not more than 210 units of anti-factor Xa activity per mg with reference to the dried substance, and the ratio of anti-factor Xa activity to anti-factor IIa activity is between 1.9 and 3.2.

Stability. The anti-Xa activity of dalteparin remained stable for 4 weeks[1] when diluted by a factor of 10 in preservative-free normal saline and stored in syringes at 4 degrees.

1. Goldenberg NA, *et al.* Anti-Xa stability of diluted dalteparin for pediatric use. *Ann Pharmacother* 2008; 42: 511–15.

Units

As for Low-molecular-weight Heparins, p. 1426.2.

Uses and Administration

Dalteparin sodium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant properties. It is used in the treatment and prophylaxis of venous thromboembolism (p. 1274.1) and to prevent clotting during extracorporeal circulation. It is also used in the management of unstable angina (p. 1254.3).

Dalteparin is given by subcutaneous or intravenous injection. Doses are expressed in terms of units of anti-factor Xa activity.

For *prophylaxis* of **venous thromboembolism** during surgical procedures, dalteparin is usually started pre-operatively.

- For patients at moderate risk of thrombosis 2500 units of dalteparin sodium are given by subcutaneous injection 1 to 2 hours before the procedure, followed by 2500 units once daily for 5 to 7 days or until the patient is fully ambulant.
- For patients at high risk, such as those undergoing orthopaedic surgery, 2500 units are given 1 to 2 hours before and 8 to 12 hours after the procedure followed by 5000 units daily. Alternatively, 5000 units may be given the evening before surgery followed by 5000 units each subsequent evening for 5 to 10 days, or up to 5 weeks after hip replacement surgery.
- A further option in patients undergoing hip replacement surgery is to omit the pre-operative dose; treatment is begun with a dose of 2500 units given 4 to 8 hours postoperatively followed by 5000 units daily.
- For prophylaxis in medical patients, a dose of 5000 units once daily may be given for 14 days or longer.

In the *treatment* of established deep-vein thrombosis, pulmonary embolism, or both, dalteparin sodium is given subcutaneously in a dose of 200 units/kg daily. This may be given as a single dose, or in pregnant patients and those at higher risk of bleeding complications, in two divided doses. The maximum recommended dose is 18 000 units daily. (In pregnant patients, early-pregnancy body-weight should be used.)

Patients with symptomatic venous thromboembolism and cancer may be given 200 units/kg subcutaneously once daily for 30 days, followed by 150 units/kg once daily for up to 5 months. Again, the maximum recommended dose is 18 000 units daily. In those who develop chemotherapy-induced thrombocytopenia, the total daily dose of dalteparin should be reduced by 2500 units while platelet counts are below 100 000 cells/mm^3; treatment should be temporarily stopped if platelet counts are below 50 000 cells/mm^3.

For prevention of clotting in the extracorporeal circulation during **haemodialysis** or **haemofiltration** in adults with chronic renal impairment an intravenous injection of dalteparin sodium 30 to 40 units/kg is followed by an intravenous infusion of 10 to 15 units/kg per hour. A single injection of 5000 units may be given for a haemodialysis or haemofiltration session lasting less than 4 hours. The dose of dalteparin sodium should be reduced in patients at high risk of bleeding complications or who are in acute renal failure; in such patients an intravenous injection of 5 to 10 units/kg is followed by an infusion of 4 to 5 units/kg per hour.

In the management of **unstable angina**, dalteparin sodium is given subcutaneously in a dose of 120 units/kg every 12 hours; the maximum dose is 10 000 units every 12 hours. Treatment is continued for 5 to 8 days and low-dose aspirin should also be given. For patients who require treatment for longer than 8 days while awaiting a revascularisation procedure, a dose of 5000 units (7500 units in men weighing 70 kg or over and women weighing 80 kg or over) may be given every 12 hours for up to 45 days until the procedure is performed.

For administration in children, see below.

References.

1. Dunn CJ, Sorkin EM. Dalteparin sodium: a review of its pharmacology and clinical use in the prevention and treatment of thromboembolic disorders. *Drugs* 1996; 52: 276–305.
2. Howard PA. Dalteparin: a low-molecular-weight heparin. *Ann Pharmacother* 1997; 31: 192–203.
3. Dunn CJ, Jarvis B. Dalteparin: an update of its pharmacological properties and clinical efficacy in the prophylaxis and treatment of thromboembolic disease. *Drugs* 2000; 60: 203–37.
4. Pineo GF, Hull RD. Dalteparin: pharmacological properties and clinical efficacy in the prophylaxis and treatment of thromboembolic diseases. *Eur J Med Res* 2004; 9: 215–24.
5. Bick RL. Cancer-associated thrombosis: focus on extended therapy with dalteparin. *J Support Oncol* 2006; 4: 115–20.
6. Linkins LA. Management of venous thromboembolism in patients with cancer: role of dalteparin. *Vasc Health Risk Manag* 2008; 4: 279–87.

Administration in children. Although unlicensed in the UK for use in children, the *BNFC* suggests that dalteparin may be given to neonates and children aged up to 12 years in the following subcutaneous doses:

- for the *prophylaxis* of venous thromboembolism, 100 units/kg once daily
- for the *treatment* of venous thromboembolism, 100 units/kg twice daily

Those aged 12 years and over may be given the usual adult doses (see p. 1348.3).

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p. 1426.3.

Severe bleeding with dalteparin may be reduced by the slow intravenous injection of protamine sulfate; 1 mg of protamine sulfate is stated to inhibit the effects of about 100 units of dalteparin sodium.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dalteparin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/10/11)

Interactions

As for Low-molecular-weight Heparins, p. 1427.2.

Pharmacokinetics

Dalteparin is almost completely absorbed after subcutaneous doses, with a bioavailability of about 87%. Peak plasma activity occurs in about 4 hours. The terminal half-life is about 2 hours after intravenous injection and 3 to 5 hours after subcutaneous injection. Dalteparin is excreted via the kidneys and the half-life is prolonged in patients with renal impairment.

Renal impairment. Dalteparin may accumulate in patients with renal impairment, although possibly to a lesser extent than with other low-molecular-weight heparins. In small studies, dalteparin appeared to accumulate when given to patients with severe renal impairment at therapeutic,[1] but not prophylactic,[2] doses; however, there was considerable variation, and any dose adjustment would need to be individualised, based on anti-factor Xa activity.[1]

1. Schmid P, *et al.* Study of bioaccumulation of dalteparin at a therapeutic dose in patients with renal insufficiency. *J Thromb Haemost* 2009; 7: 1629–32.
2. Schmid P, *et al.* Study of bioaccumulation of dalteparin at a prophylactic dose in patients with various degrees of impaired renal function. *J Thromb Haemost* 2009; 7: 552–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ligofragmin; *Austral.*: Fragmin; *Austria*: Fragmin; *Belg.*: Fragmin; *Braz.*: Fragmin; *Canad.*: Fragmin; *Chile*: Fragmin; *China*: Fragmin (法安明); *Cz.*: Fragmin; *Denm.*: Fragmin; *Fin.*: Fragmin; *Fr.*: Fragmine; *Ger.*: Fragmin; *Gr.*: Fragmin; *Hong Kong*: Fragmin; *Hung.*: Fragmin; *India*: Dalpin; Daltehep; Fragmin; *Israel*: Fragmin; *Ital.*: Fragmin; *Mex.*: Fragmin; *Neth.*: Fragmin; *Norw.*: Fragmin; *NZ*: Fragmin; *Philipp.*: Eurodal; Fragmin†; *Pol.*: Fragmin; *Port.*: Fragmin; *Rus.*: Fragmin (Фрагмин); *S.Afr.*: Fragmin; *Singapore*: Fragmin; *Spain*: Fragmin; *Swed.*: Fragmin; *Switz.*: Fragmin; *Turk.*: Fragmin; *UK*: Fragmin; *Ukr.*: Fragmin (Фрагмин); *USA*: Fragmin; *Venez.*: Fragmin.

Pharmacopoeial Preparations

BP 2014: Dalteparin Sodium Injection.

Danaparoid Sodium *(BAN, USAN, rINN)*

Danaparoid-Natrium; Danaparoid sodná sůl; Danaparoid sodowy; Danaparoide sódico; Danaparoide sodique; Danaparoidum Natricum; Lomoparan; Org-10172; Данапароид Натрий.

CAS — 83513-48-8.

ATC — B01AB09.

ATC Vet — QB01AB09.

UNII — 5004UU3156.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Danaparoid Sodium). A preparation containing the sodium salts of a mixture of sulfated glycosaminoglycans present in porcine tissues. It is prepared from the intestinal mucosa of pigs and the major constituents are suleparoid (heparan sulfate) (p. 1507.2) and dermatan sulfate (p. 1350.3). It has a potency of 11.0 to 17.0 anti-factor Xa units per milligram, calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 7.0. Store in airtight containers.

Uses and Administration

Danaparoid sodium is a low-molecular-weight heparinoid. It is an anticoagulant and, like heparin (p. 1397.1), enhances the action of antithrombin III. Like low-molecular-weight heparins (p. 1426.1) it has a higher ratio of anti-factor Xa to anti-factor IIa (antithrombin) activity than heparin, but is reported to be a much more selective inhibitor of factor Xa than the low-molecular-weight heparins. It was therefore hoped that danaparoid might be associated with a low incidence of bleeding complications, although this has not been established.

Danaparoid sodium is used in the prophylaxis of venous thromboembolism (p. 1274.1) in patients undergoing surgery. It may be used as an anticoagulant for prophylaxis or treatment in patients with heparin-induced thrombocytopenia providing there is no cross-reactivity. Danaparoid has been investigated in acute ischaemic stroke.

Doses of danaparoid sodium are expressed in terms of units of anti-factor Xa activity. In the prophylaxis of **venous thromboembolism** it is given by subcutaneous injection in a dose of 750 units twice daily for 7 to 10 days. The first dose should be given 1 to 4 hours before surgery.

For patients with **heparin-induced thrombocytopenia** requiring anticoagulation, danaparoid sodium is given intravenously. The initial bolus dose is 2500 units (or 1250 units for patients weighing less than 55 kg, or 3750 units for patients weighing more than 90 kg) followed by an infusion of 400 units/hour for 2 hours, then 300 units/hour for 2 hours, then 200 units/hour for 5 days. Monitoring of plasma anti-factor Xa activity is recommended for patients with renal impairment, or those weighing more than 90 kg. For administration in children, see below.

References.

1. Skoutakis VA. Danaparoid in the prevention of thromboembolic complications. *Ann Pharmacother* 1997; 31: 876–87.
2. Wilde MI, Markham A. Danaparoid: a review of its pharmacology and clinical use in the management of heparin-induced thrombocytopenia. *Drugs* 1997; 54: 903–24.
3. Ibbotson T, Perry CM. Danaparoid: a review of its use in thromboembolic and coagulation disorders. *Drugs* 2002; 62: 2283–2314.
4. Magnani HN, Gallus A. Heparin-induced thrombocytopenia (HIT): a report of 1,478 clinical outcomes of patients treated with danaparoid (Orgaran) from 1982 to mid-2004. *Thromb Haemost* 2006; 95: 967–81.
5. Schindewolf M, *et al.* Danaparoid in der Schwangerschaft bei Heparinunverträglichkeit–Einsatz in 59 Fällen. *Hamostaseologie* 2007; 27: 89–97.
6. Magnani HN. An analysis of clinical outcomes of 91 pregnancies in 83 women treated with danaparoid (Orgaran). *Thromb Res* 2010; 125: 297–302.
7. Magnani HN. A review of 122 published outcomes of danaparoid anticoagulation for intermittent haemodialysis. *Thromb Res* 2010; 125: e171–e176.

Administration in children. Although unlicensed in the UK for use in children, the *BNFC* suggests that danaparoid may be given to treat venous thromboembolism in neonates and children aged up to 16 years with heparin-induced thrombocytopenia as an initial intravenous injection of 30 units/kg (to a maximum of 1250 units for those weighing under 55 kg, or 2500 units for those over 55 kg), followed by an intravenous infusion of 1.2 to 2 units/kg per hour, adjusted according to coagulation activity.

Adverse Effects and Treatment

Haemorrhage may occur after use of danaparoid sodium (although there is a possible decreased risk of bleeding complications compared with heparin this has not been definitely established). Liver enzymes may be transiently elevated. Other adverse effects include hypersensitivity reactions, thrombocytopenia, and pain at the site of injection.

Protamine sulfate only partially neutralises the anticoagulant effect of danaparoid sodium and cannot be relied on to reverse bleeding associated with overdosage.

Precautions

As for Heparin, p. 1399.3.

Danaparoid sodium should not be given to patients who have developed thrombocytopenia with heparin if they show cross-reactivity in an *in-vitro* test.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies danaparoid as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/10/11)

Pharmacokinetics

After subcutaneous dosage danaparoid sodium is well absorbed and peak anti-factor Xa activity occurs in about 4 to 5 hours. The elimination half-lives of anti-factor Xa and anti-factor IIa (antithrombin) activities are about 25 and 7 hours, respectively. Danaparoid sodium is excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Orgaran; *Austria*: Orgaran; *Belg.*: Orgaran; *Canad.*: Orgaran; *Fr.*: Orgaran; *Ger.*: Orgaran; *Gr.*: Orgaran; *Irl.*: Orgaran; *Neth.*: Orgaran; *NZ*: Orgaran†; *Port.*: Orgaran; *Swed.*: Orgaran; *Switz.*: Orgaran; *UK*: Orgaran.

Debrisoquine Sulfate *(BANM, rINNM)*

Debrisoquin Sulfate (USAN); Debrisoquina; sulfato de; Débrisoquine, Sulfate de; Debrisoquine Sulphate; Debriso-

quini Sulfas; Isocaramidine Sulfate; Ro-5-3307/1; Sulfato de debrisoquina; Дебризохина Сульфат.
1,2,3,4-Tetrahydroisoquinoline-2-carboxamidine sulfate.
$(C_{10}H_{13}N_3O)_2H_2SO_4$=448.5
CAS — 1131-64-2 (debrisoquine); 581-88-4 (debrisoquine sulfate).
ATC — C02CC04.
ATC Vet — QC02CC04.
UNII — Q94064N9NW.

Pharmacopoeias. In *Br.*

BP 2014: (Debrisoquine Sulfate). A white, odourless or almost odourless, crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol; practically insoluble in chloroform and in ether. A 3% solution in water has a pH of 5.3 to 6.8. Protect from light.

Uses and Administration

Debrisoquine is an antihypertensive with actions and uses similar to those of guanethidine (p. 1395.2), but it causes less depletion of noradrenaline stores. When given orally, debrisoquine acts within about 4 to 10 hours and has effects lasting for 9 to 24 hours. It has been used in the management of hypertension (p. 1251.1), but has largely been superseded by other drugs.

For reference to the use of debrisoquine in identifying metabolic phenotypes, see Genetic Polymorphism, below.

Adverse Effects, Treatment, and Precautions

As for Guanethidine Monosulfate, p. 1395.3.

Diarrhoea is rare with debrisoquine sulfate. Treatment should not be stopped abruptly as this may lead to rebound hypertension.

The metabolism of debrisoquine is subject to genetic polymorphism and non-metabolisers may show a marked response to doses that have little or no effect in metabolisers.

Interactions

As for Guanethidine Monosulfate, p. 1396.1.

Pharmacokinetics

Debrisoquine is rapidly absorbed from the gastrointestinal tract. The major metabolite is 4-hydroxydebrisoquine; metabolism is subject to genetic polymorphism.

A study[1] in 15 hypertensive patients and 4 healthy subjects indicated that debrisoquine undergoes pre-systemic metabolism to 4-hydroxydebrisoquine, but the mechanism appears to be saturable and increases in the dose of debrisoquine could therefore produce disproportionate decreases in blood pressure. The estimated half-life of elimination for debrisoquine and 4-hydroxydebrisoquine ranged from 11.5 to 26 hours and from 5.8 to 14.5 hours respectively.

1. Silas JH, *et al.* The disposition of debrisoquine in hypertensive patients. *Br J Clin Pharmacol* 1978; 5: 27–34.

Genetic polymorphism. Debrisoquine, along with sparteine and several other drugs, is a substrate for the cytochrome P450 isoenzyme CYP2D6, a polymorphic enzyme coded by a gene mapped to chromosome 22. Patients homozygous for the mutant allele are termed *poor metabolisers* and express little or no active enzyme. The prevalence of the poor-metaboliser phenotype is about 5% in most Caucasian populations, while studies in other genetic groups have indicated a range of about 2 to 10% although in some groups, such as the Japanese, poor metabolisers have yet to be identified. Poor metabolisers of debrisoquine are unable to 4-hydroxylate the drug adequately to its inactive metabolite and are thus prone to excessive hypotension. Many other drugs are metabolised by the same enzyme, but the clinical consequences of polymorphism in patients taking them depends on the relative activity and toxicity of parent drug and metabolite, and the availability and relative importance of other routes of metabolism. Phenotype has been determined by giving a drug that is metabolised by this enzyme and assaying parent drug and metabolite in urine collected over a defined period of time, but DNA-based tests may represent a more convenient and safer alternative.

References.

1. *Relling MV.* Polymorphic drug metabolism. *Clin Pharm* 1989; 8: 852–63.
2. Zanger UM, *et al.* Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. *Naunyn Schmiedebergs Arch Pharmacol* 2004; 369: 23–37.
3. Llerena A, *et al.* Pharmacogenetics of debrisoquine and its use as a marker for CYP2D6 hydroxylation capacity. *Pharmacogenomics* 2009; 10: 17–28.

Defibrotide *(BAN, rINN)*

Defibrotida; Défibrotide; Defibrotidum; Дефибротид.
CAS — 83712-60-1.
ATC — B01AX01.
ATC Vet — QB01AX01.
UNII — 438HCF2X0M.

Profile

Defibrotide consists of polydeoxyribonucleotides from bovine lung; the molecular weights range between 45 000 and 55 000. Preparations derived from porcine tissues and with a lower molecular weight range are also used. Defibrotide has antithrombotic and fibrinolytic properties, although its mechanism of action is uncertain; it appears to increase levels of prostaglandin E_2 and prostacyclin, to alter platelet activity, and to increase tissue plasminogen activator function at the same time as decreasing activity of tissue plasminogen activator inhibitor. It is used in the management of thromboembolic disorders. Oral and parenteral formulations have been used in typical doses of 800 mg daily.

Defibrotide is being investigated for use in the treatment of hepatic veno-occlusive disease and thrombotic thrombocytopenic purpura.

References.

1. Palmer KJ, Goa KL. Defibrotide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in vascular disorders. *Drugs* 1993; 45: 259–94.
2. Richardson PG, *et al.* Treatment of severe veno-occlusive disease with defibrotide: compassionate use results in response without significant toxicity in a high-risk population. *Blood* 1998; 92: 737–44.
3. Pogliani EM, *et al.* Defibrotide in recurrent thrombotic thrombocytopenic purpura. *Clin Appl Thromb Hemost* 2000; 6: 69–70.
4. Chopra R, *et al.* Defibrotide for the treatment of hepatic veno-occlusive disease: results of the European compassionate-use study. *Br J Haematol* 2000; 111: 1122–9.
5. Corti P, *et al.* Defibrotide as a promising treatment for thrombotic thrombocytopenic purpura in patients undergoing bone marrow transplantation. *Bone Marrow Transplant* 2002; 29: 542–3.
6. Richardson PG, *et al.* Multi-institutional use of defibrotide in 88 patients after stem cell transplantation with severe veno-occlusive disease and multisystem organ failure: response without significant toxicity in a high-risk population and factors predictive of outcome. *Blood* 2002; 100: 4337–43.
7. Kornblum N, *et al.* Defibrotide, a polydisperse mixture of single-stranded phosphodiester oligonucleotides with lifesaving activity in severe hepatic veno-occlusive disease: clinical outcomes and potential mechanisms of action. *Oligonucleotides* 2006; 16: 105–14.
8. Ho VT, *et al.* Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: update on defibrotide and other current investigational therapies. *Bone Marrow Transplant* 2008; 41: 229–37.
9. Qureshi A, *et al.* Defibrotide in the prevention and treatment of veno-occlusive disease in autologous and allogeneic stem cell transplantation in children. *Pediatr Blood Cancer* 2008; 50: 831–2.
10. Morabito F, *et al.* Insights into defibrotide: an updated review. *Expert Opin Biol Ther* 2009; 9: 763–72.

Adverse effects. Anaphylaxis was reported[1] in a patient given defibrotide for chronic venous insufficiency. A positive skin-prick test confirmed a type 1 hypersensitivity reaction.

1. Artesani MC. Anaphylactic shock to defibrotide. *Allergy* 2006; 61: 1022.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Noravid; *Ital.*: Noravid†; Procidide†.

Delapril Hydrochloride *(USAN, rINNM)*

Alindapril Hydrochloride; CV-3317; Délapril, Chlorhydrate de; Delapril, hidrocloruro de; Delaprili Hydrochloridum; Hidrocloruro de delapril; Indalapril Hydrochloride; REV-6000A; Делаприла Гидрохлорид.
Ethyl (*S*)-2-[[(*S*)-1-(carboxymethyl-2-indanylcarbamoyl)ethyl]amino]-4-phenylbutyrate hydrochloride.
$C_{26}H_{32}N_2O_5$,HCl=489.0
CAS — 83435-66-9 (delapril); 83435-67-0 (delapril hydrochloride).
ATC — C09AA12.
ATC Vet — QC09AA12.
UNII — 2SMM3M5ZMH.

Profile

Delapril is an ACE inhibitor (p. 1282.2). It is converted in the body to two metabolites to which it owes its activity. It is given orally as the hydrochloride in the treatment of hypertension (p. 1251.1), in usual maintenance doses of 30 to 60 mg daily in two divided doses.

Reviews.

1. McCormack PL, Keating GM. Delapril/manidipine. *Drugs* 2006; 66: 961–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Delacard; *Ital.*: Delaket; *Jpn*: Adecut; *Philipp.*: Cupressin; *Singapore*: Cupressin†; *Spain*: Beniod; Trinordiol; *Thai.*: Cupressin; *Turk.*: Delaket.

Multi-ingredient Preparations. *Austria*: Delapride†; Vivace†; *Braz.*: Hipertil; *Ger.*: Vivace; *Gr.*: Dinapres; Vivace; *Ital.*: Delapride; Dinapres; *Spain*: Bimade; Vivace; *Turk.*: Delapride.

Denopamine *(rINN)*

Denopamina; Dénopamine; Denopaminum; TA-064; Денопамин.
(-)-(*R*)-α-[[(3,4-Dimethoxyphenethyl)amino]methyl]-*p*-hydroxybenzyl alcohol.
$C_{18}H_{23}NO_4$=317.4
CAS — 71771-90-9.
UNII — V5F60UPD8P.

NOTE. The name Herpamine has been used as a trademark for denopamine.

Profile

Denopamine is a sympathomimetic (p. 1507.3) with mainly beta-adrenergic activity selective to $beta_1$ receptors. It acts as a partial agonist and is used orally in the treatment of heart failure at a daily dose of 15 to 30 mg in 3 divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Kalgut.

Dermatan Sulfate

Chondroitin Sulfate B; Dermataanisulfaatti; Dermatan solfato; Dermatán, sulfato de; Dermatan Sulphate; LMW-DS (depolymerised dermatan sulfate); MF-701; OP-370 (depolymerised dermatan sulfate); Sulfat dermată; Дерматан Сульфат; Дерматансульфат.
CAS — 24967-94-0.
ATC — B01AX04.
ATC Vet — QB01AX04.

Dermatan Sulfate Sodium

Chondroitin Sulfate B Sodium; Dermatan Sulphate Sodium; Дерматана Сульфат Натрия.
CAS — 54328-33-5.
ATC — B01AX04.
ATC Vet — QB01AX04.

Profile

Dermatan sulfate is a naturally occurring glycosaminoglycan used as an anticoagulant for prophylaxis of venous thromboembolism (p. 1274.1). It is given as the sodium salt in a dose of 100 to 300 mg daily by intramuscular injection. The dose may be increased to 300 mg twice daily in patients at high risk of thromboembolism, such as those undergoing major orthopaedic surgery.

Dermatan sulfate is a component of sulodexide (p. 1507.3) and its sodium salt is a component of danaparoid sodium (p. 1349.2).

Dermatan sulfate has been investigated for the treatment of venous thromboembolism, heparin-induced thrombocytopenia, and to prevent clotting during haemodialysis. Low-molecular-weight (depolymerised) dermatan sulfate has also been studied.

References.

1. Dawes J, *et al.* The pharmacokinetics of dermatan sulphate MF701 in healthy human volunteers. *Br J Clin Pharmacol* 1991; 32: 361–6.
2. Gianese P, *et al.* The pharmacokinetics and pharmacodynamics of dermatan sulphate MF701 during haemodialysis for chronic renal failure. *Br J Clin Pharmacol* 1993; 35: 335–9.
3. Miglioli M, *et al.* Bioavailability of Desmin, a low molecular weight dermatan sulfate, after subcutaneous administration to healthy volunteers. *Int J Clin Lab Res* 1997; 27: 195–8.
4. Nenci GG. Dermatan sulphate as an antithrombotic drug. *Pathophysiol Haemost Thromb* 2002; 32: 303–7.
5. Yamada S, Sugahara K. Potential therapeutic application of chondroitin sulfate/dermatan sulfate. *Curr Drug Discov Technol* 2008; 5: 289–301.
6. Vitale C, *et al.* Effects of dermatan sulfate for anticoagulation in continuous renal replacement therapy. *J Nephrol* 2008; 21: 205–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Mistral; *Port.*: Venorix.

Deserpidine *(BAN, rINN)*

Canescine; Deserpidiini; Deserpidin; Deserpidina; Déserpidine; Deserpidinum; 11-Desmethoxyreserpine; Raunormine; Recanescine; Дезерпидин.
Methyl 11-demethoxy-O-(3,4,5-trimethoxybenzoyl)reserpate.
$C_{32}H_{38}N_2O_8$=578.7
CAS — 131-01-1.

ATC — C02AA05.
ATC Vet — QC02AA05.
UNII — 9016E3VB47.

Profile

Deserpidine is an ester alkaloid isolated from the root of *Rauwolfia canescens*. It has properties similar to those described under reserpine (p. 1485.3) and has been used in the treatment of hypertension and psychoses.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *China*: Enduronyl (降压乐).

Desirudin *(BAN, USAN, rINN)*

CGP-39393; Desirudiini; Desirudina; Désirudine; Desirudinum; Desirudyna; Desulphatohirudin; Дезирудин.
63-Desulfohirudin (*Hirudo medicinalis* isoform HV1).
$C_{287}H_{440}N_{80}O_{110}S_6$=6963.5
CAS — 120993-53-5.
ATC — B01AE01.
ATC Vet — QB01AE01.
UNII — U0JZ726775.

Uses and Administration

Desirudin is a recombinant hirudin (p. 1401.2) that is a direct inhibitor of thrombin with actions similar to Lepirudin, p. 1418.2. It is used as an anticoagulant for the prevention of postoperative venous thromboembolism (p. 1274.1) in patients undergoing orthopaedic surgery. It has been investigated in arterial thromboembolic disorders such as myocardial infarction and unstable angina, and as an adjunct in angioplasty procedures (see Ischaemic Heart Disease, under Uses and Administration of Lepirudin, p. 1418.3).

In the prevention of venous thromboembolism, desirudin is given subcutaneously in a dose of 15 mg twice daily, the first dose 5 to 15 minutes before surgery, but after induction of regional block anaesthesia, if used. Treatment is continued until the patient is fully ambulant, usually for 9 to a maximum of 12 days.

Response to desirudin should be monitored using activated partial thromboplastin time (APTT) in patients with hepatic or renal impairment, or increased risk of bleeding. Doses may need to be reduced in patients with renal impairment (see below).

References.
1. Matheson AJ, Goa KL. Desirudin: a review of its use in the management of thrombotic disorders. *Drugs* 2000; 60: 679–700.

Administration in renal impairment. The dose of desirudin should be reduced in patients with renal impairment, depending on creatinine clearance (CC) and activated partial thromboplastin time (APTT), which should be measured daily. US licensed product information recommends the following subcutaneous doses:

- CC 31 to 60 mL/minute per 1.73 m^2, initial dose 5 mg every 12 hours, subsequently adjusted according to APTT
- CC below 31 mL/minute per 1.73 m^2, initial dose 1.7 mg every 12 hours, subsequently adjusted according to APTT

However, a study[1] of pharmacokinetic data from patients with moderate renal impairment (CC 31 to 60 mL/minute) suggested that in fact standard doses of 15 mg twice daily subcutaneously without additional monitoring of APTT would be appropriate in this group.

1. Nafziger AN, Bertino JS. Desirudin dosing and monitoring in moderate renal impairment. *J Clin Pharmacol* 2010; 50: 614–22.

Adverse Effects and Precautions

As for Lepirudin, p. 1419.2.

Teratogenicity has been seen in *animals*.

Interactions

As for Lepirudin, p. 1419.3.

Pharmacokinetics

Peak plasma concentrations of desirudin occur 1 to 3 hours after subcutaneous injection. Desirudin is metabolised and excreted by the kidney, and 40 to 50% of a dose is excreted unchanged in the urine. After subcutaneous or intravenous injection the terminal elimination half-life of desirudin is 2 to 3 hours.

References.
1. Lefèvre G, *et al.* Effect of renal impairment on the pharmacokinetics and pharmacodynamics of desirudin. *Clin Pharmacol Ther* 1997; 62: 50–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Revasc†; *Austria*: Revasc; *Cz.*: Revasc; *Fr.*: Revasc†; *Ger.*: Revasc; *Gr.*: Revasc; *Irl.*: Revasc; *Neth.*: Revasc; *NZ*: Revasc†; *Pol.*: Revasc; *Port.*: Revasc; *Spain*: Revasc; *USA*: Iprivask.

Deslanoside *(BAN, rINN)*

Deacetyl-lanatoside C; Desacetyl-lanatoside C; Deslanosid; Deslanosídeo; Deslanosidi; Deslanósido; Deslanosidum; Deslanozidas; Dezlanozid; Дезланозид.
3-[(*O*-β-D-Glucopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12,14-dihydroxy-3β,5β,12β-card-20(22)-enolide.
$C_{47}H_{74}O_{19}$=943.1
CAS — 17598-65-1.
ATC — C01AA07.
ATC Vet — QC01AA07.
UNII — YGY317RK75.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Deslanoside). A white or almost white, crystalline or finely crystalline hygroscopic powder. Practically insoluble in water; very slightly soluble in alcohol. In an atmosphere of low relative humidity, it loses water. Store in airtight, glass containers at a temperature below 10 degrees. Protect from light.

USP 36: (Deslanoside). Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Deslanoside, a cardiac glycoside with positive inotropic activity, is a derivative of lanatoside C. It has the general properties of digoxin (p. 1353.3) and has been used similarly in the management of some cardiac arrhythmias and in heart failure.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Cedilanide; Deslanol.

Pharmacopoeial Preparations
USP 36: Deslanoside Injection.

Desmoteplase *(USAN, rINN)*

bat-PA; Bat Plasminogen Activator; Desmoteplasa; Desmotéplase; Desmoteplasum; ds-PA; rDSPA alpha-1; SH-576; Десмотеплаз.
Plasminogen activator (*Desmodus rotundus* isoform α1 protein moiety reduced).
CAS — 145737-38-8.
UNII — T36L245S3T.

Profile

Desmoteplase is a recombinant form of a plasminogen activator originally isolated from the saliva of the vampire bat *Desmodus rotundus* (Desmodontinae). It converts fibrin-bound plasminogen to the active form plasmin, resulting in fibrinolysis and dissolution of clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p. 1124.3. Desmoteplase is a highly fibrin-specific thrombolytic (see p. 1245.3) with a relatively long terminal half-life. It is under investigation in the management of stroke (p. 1269.2), particularly in patients treated more than 3 hours after onset.

References.
1. Hacke W, *et al.* The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke* 2005; 36: 66–73.
2. Furlan AJ, *et al.* Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS): evidence of safety and efficacy 3 to 9 hours after stroke onset. *Stroke* 2006; 37: 1227–31.
3. Hacke W, *et al.* Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion-diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomised, double-blind, placebo-controlled study. *Lancet Neurol* 2009; 8: 141–50.
4. Tebbe U, *et al.* Desmoteplase in acute massive pulmonary thromboembolism. *Thromb Haemost* 2009; 101: 557–62.
5. Paciaroni M, *et al.* Desmoteplase. *Expert Opin Biol Ther* 2009; 9: 773–8.

Detajmium Bitartrate *(rINN)*

Bitartrato de detajmio; Detajmii Bitartras; Détajmium, Bitartrate de; Детаймия битартрат.
4-[3-(Diethylamino)-2-hydroxypropyl]ajmalinium, hydrogen tartrate monohydrate.
$C_{31}H_{47}N_3O_9.H_2O$=623.7
CAS — 53862-81-0.
UNII — 916D9H1058.

Profile

Detajmium is a class I antiarrhythmic (p. 1243.1). It has been given orally as the bitartrate, in the treatment of supraventricular and ventricular arrhythmias (p. 1266.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Tachmalcor†; *Ger.*: Tachmalcor†.

Diazoxide *(BAN, USAN, rINN)*

Diatoksidi; Diazoksidas; Diazoksit; Diazoxid; Diazóxido; Diazoxidum; NSC-64198; Sch-6783; SRG-95213; Диазоксид.
7-Chloro-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide.
$C_8H_7ClN_2O_2S$=230.7
CAS — 364-98-7.
ATC — C02DA01; V03AH01.
ATC Vet — QC02DA01; QV03AH01.
UNII — O5CB12L4FN.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Diazoxide). A white or almost white, fine or crystalline powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in dimethylformamide; very soluble in dilute solutions of alkali hydroxides.

USP 36: (Diazoxide). White or cream-white crystals or crystalline powder. Practically insoluble to sparingly soluble in water and in most organic solvents; freely soluble in dimethylformamide; very soluble in strong alkaline solutions. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Diazoxide increases the concentration of glucose in the plasma; it inhibits the secretion of insulin by the beta cells of the pancreas, and may increase the hepatic output of glucose. When given intravenously, it produces a fall in blood pressure by a vasodilator effect on the arterioles and a reduction in peripheral resistance. Diazoxide is closely related structurally to the thiazide diuretics, but has an antidiuretic action and thus produces fluid and electrolyte retention; it may be given with a diuretic to reduce fluid retention.

Diazoxide is used orally in the management of intractable hypoglycaemia (see under Glucagon, p. 1554.3) and intravenously in the management of hypertensive crises (p. 1251.1), particularly when first-line drugs such as sodium nitroprusside are ineffective or unsuitable. Diazoxide is not suitable for the chronic treatment of hypertension because of its severe adverse effects.

In **hypoglycaemia**, the initial dose is 3 to 5 mg/kg daily in 2 or 3 divided oral doses, then adjusted according to response. Usual maintenance doses are from 3 to 8 mg/kg daily but total doses of up to 10 to 15 mg/kg daily have been given to adults with refractory hypoglycaemia, as with insulinoma (see Neuroendocrine Tumours, p. 716.3). The hyperglycaemic effect normally begins within 1 hour of a dose and lasts for up to 8 hours.

In **hypertensive crises**, a bolus intravenous injection of 1 to 3 mg/kg is given within 30 seconds, up to a maximum dose of 150 mg, and repeated after 5 to 15 minutes if required.

For doses in children, see below.

Reduced doses may be necessary in patients with renal impairment.

Administration in children. Diazoxide may be given to neonates, infants, and children in the treatment of intractable hypoglycaemia, and for hypertensive emergencies and resistant hypertension.

In **hypoglycaemia**, diazoxide may be given orally or by intravenous injection in the following doses according to age:

- neonates: initially 5 mg/kg twice daily, adjusted according to response to a usual maintenance dose of 1.5 to 3 mg/kg two or three times daily, although up to 7 mg/kg three times daily may be required in some cases
- children aged 1 month and above: initially 1.7 mg/kg three times daily, adjusted according to response to a usual maintenance dose of 1.5 to 3 mg/kg two or three times daily, although up to 5 mg/kg three times daily may be required in some cases

Diazoxide may be given to neonates and children in the treatment of resistant **hypertension** in an initial oral dose of 1.7 mg/kg three times daily, adjusted according to response to a usual daily maximum of 15 mg/kg. It may be

given to those aged 1 month and over in the treatment of **hypertensive emergencies** in an initial intravenous injection of 1 to 3 mg/kg (maximum 150 mg) as a single dose, repeated after 5 to 15 minutes until blood pressure is controlled. A maximum of 4 doses may be given every 24 hours.

Adverse Effects

In addition to inappropriate hypotension and hyperglycaemia (which includes ketoacidosis and hyperosmolar nonketotic coma), adverse effects often include oedema due to salt and water retention, which may precipitate heart failure. Other adverse effects include: dysgeusia, nausea, anorexia, and other gastrointestinal disturbances; mild hyperuricaemia; extrapyramidal symptoms; eosinophilia and thrombocytopenia; dyspnoea; hypertrichosis; and headache, dizziness, tinnitus, and blurred vision. Hypersensitivity has occurred, manifesting as rashes, leucopenia, and fever.

During intravenous therapy, particularly after large bolus injections, adverse effects may be associated with too rapid a reduction in blood pressure and include: coronary ischaemia leading to angina, cardiac arrhythmias, marked ECG changes, tachycardia, palpitations, and bradycardia; cerebral ischaemia leading to confusion, convulsions, loss of consciousness, and neurological deficit; renal impairment; and symptoms of vasodilatation.

Diazoxide may cause a burning sensation in the injected vein; extravasation of the alkaline solution is painful.

Effects on the blood. A 26-year-old man with hypertension developed reversible haemolytic anaemia when treated with diazoxide orally on 3 separate occasions.[1]

1. Best RA, Clink HM. Haemolysis associated with diazoxide, used for the control of hypertension. *Postgrad Med J* 1975; 51: 402–4.

Effects on the hair. *Hirsutism* and *hypertrichosis* are different types of excessive hair growth, but the terms have often been used interchangeably. Hirsutism is androgen-related whereas hypertrichosis is thought to be independent of hormone stimulation. Hypertrichosis is acknowledged to be a frequent adverse effect of diazoxide in children receiving long-term treatment for idiopathic hypoglycaemia.[1] Two such children had unusually deep (low-pitched) voices as well as marked hypertrichosis.[2] A woman on continuous diazoxide therapy who developed so-called hirsutism without signs of virilisation had raised serum concentrations of androgens.[3]

Alopecia has been reported[4] in 4 infants born to mothers who had been on long-term treatment with diazoxide during pregnancy; the condition was still present to some extent when the infants were last seen at the ages of 5 months to 1 year.

1. Burton JL, *et al.* Hypertrichosis due to diazoxide. *Br J Dermatol* 1975; 93: 707–11.
2. West RJ. Side effects of diazoxide. *BMJ* 1978; 2: 506.
3. Hallengren B, Hökfelt B. Increase of serum androgens during diazoxide treatment. *Lancet* 1984; ii: 1044–5.
4. Milner RDG, Chouksey SK. Effects of fetal exposure to diazoxide in man. *Arch Dis Child* 1972; 47: 537–43.

Extrapyramidal effects. In a study[1] of 100 hypertensive patients receiving diazoxide, the incidence of extrapyramidal symptoms was 15%.

1. Pohl JEF. Development and management of extrapyramidal symptoms in hypertensive patients treated with diazoxide. *Am Heart J* 1975; 89: 401–2.

Pancreatitis. Ten patients with severe hypertension and renal failure were treated with diazoxide in a last attempt to avert nephrectomy; 1 patient developed acute pancreatitis and another diabetic ketoacidosis.[1] Both patients recovered from these effects when diazoxide was withdrawn.

1. De Broe M, *et al.* Oral diazoxide for malignant hypertension. *Lancet* 1972; i: 1397.

Voice changes. See Effects on the Hair, above.

Treatment of Adverse Effects

Treatment is largely symptomatic. Severe hyperglycaemia may be corrected by giving insulin: less severe hyperglycaemia may respond to oral hypoglycaemics. Hypotension may be managed with intravenous fluids. Severe hypotension may require sympathomimetics. Antiparkinsonian drugs, such as procyclidine, have been given to control extrapyramidal effects while a diuretic may be required for salt and water retention. Diazoxide can be removed from the body by dialysis but recovery is relatively low owing to extensive protein binding.

Precautions

Diazoxide should be used with care in patients with impaired cardiac or cerebral circulation and in patients with aortic coarctation, arteriovenous shunt, heart failure, or other cardiac disorders in which an increase in cardiac output could be detrimental. During prolonged therapy blood-glucose concentrations and blood pressure should be monitored and the blood should be examined regularly for signs of leucopenia and thrombocytopenia; in children, bone and psychological maturation, and growth, should be regularly assessed. Caution is necessary in patients with renal impairment.

If given during labour, diazoxide may cause cessation of uterine contractions and delay delivery unless oxytocin is also given.

Pregnancy. Transplacental transfer of diazoxide was considered[1] to be responsible for an inappropriately low plasma-insulin concentration in an infant whose mother had received a dose of 150 mg daily for 47 days before delivery. For reference to alopecia in neonates whose mothers had received diazoxide during pregnancy, see Effects on the Hair under Adverse Effects, above.

For reports of sedation, hypotonia, and apnoea among infants born to mothers given both diazoxide and clomethiazole for the treatment of toxaemia of pregnancy, see Precautions, Pregnancy, in Clomethiazole Edisilate, p. 1055.1. Diazoxide is nonetheless one of the drugs that has been used for hypertensive emergencies in pregnancy (see Hypertension, p. 1251.1) and a study found that miniboluses of diazoxide 15 mg intravenously successfully reduced blood pressure and were well tolerated.[2]

1. Smith MJ, *et al.* Neonatal hyperglycaemia after prolonged maternal treatment with diazoxide. *BMJ* 1982; 284: 1234.
2. Hennessy A, *et al.* A randomised comparison of hydralazine and miniboluses diazoxide for hypertensive emergencies in pregnancy: the PIVOT trial. *Aust N Z J Obstet Gynaecol* 2007; 47: 279–85.

Interactions

The hyperglycaemic, hyperuricaemic, and hypotensive actions of diazoxide may be enhanced by diuretics. Use of diazoxide with other antihypertensives or vasodilators may lead to increased risk of hypotension.

Chlorpromazine. Chlorpromazine was reported[1] to enhance the hyperglycaemic effect of diazoxide in a 2-year-old child.

1. Aynsley-Green A, Illig R. Enhancement by chlorpromazine of hyperglycaemic action of diazoxide. *Lancet* 1975; ii: 658–9.

Phenytoin. For the effect of diazoxide on serum-phenytoin concentrations, see Antihypertensives, p. 543.3.

Pharmacokinetics

Diazoxide is readily absorbed from the gastrointestinal tract and more than 90% bound to plasma proteins, although protein binding is decreased in uraemic patients. Its plasma half-life has been estimated to range from about 20 to 45 hours but values of up to 60 hours have been reported. The half-life is reported to be prolonged in renal impairment and shorter for children. The plasma half-life greatly exceeds the duration of vascular activity. Diazoxide is partly metabolised in the liver and is excreted in the urine both unchanged and in the form of metabolites; only small amounts are recovered from the faeces. It crosses the placenta and the blood-brain barrier.

Children. In 4 children with hypoglycaemia the plasma half-life of diazoxide was 9.5 to 24 hours, which is considerably shorter than that in adults.[1]

1. Pruitt AW, *et al.* Disposition of diazoxide in children. *Clin Pharmacol Ther* 1973; 14: 73–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Proglicem; *Braz.*: Tensuril; *Canad.*: Proglycem; *Fr.*: Proglicem; *Ger.*: Proglicem; *Gr.*: Budemine; Proglicem; *Ital.*: Proglicem; *Jpn*: Aroglycem; *Mex.*: Sefulken; *Neth.*: Proglicem; *Singapore*: Proglicem; *Switz.*: Proglicem; *UK*: Eudemine; Eudemine; *USA*: Hyperstat†; Proglycem.

Pharmacopoeial Preparations
BP 2014: Diazoxide Injection; Diazoxide Tablets;
USP 36: Diazoxide Capsules; Diazoxide Injection; Diazoxide Oral Suspension.

Dicoumarol *(rINN)*

Bishydroxycoumarin; Dicoumarin; Dicoumarolum; Dicumarol (USAN); Dicumarolo; Dikumarol; Dikumarolis; Melitoxin; Дикумарол

3,3'-Methylenebis(4-hydroxycoumarin).

$C_{19}H_{12}O_6$=336.3

CAS — 66-76-2.

ATC — B01AA01.

ATC Vet — QB01AA01.

UNII — 7QID3E78G7.

Pharmacopoeias. In *Int.*

Profile

Dicoumarol is an oral coumarin anticoagulant with actions similar to those of warfarin (p. 1527.1). It has been used in the management of thromboembolic disorders, but because of its unpredictable response and high incidence of gastrointestinal effects it has been largely replaced by warfarin.

Digitalis Leaf

Digit. Fol.; Digit. Leaf; Digital, hoja de; Digitale Pourpre; Digitale Pourprée, Feuille de; Digitalisenlehti; Digitalis; Digitalis Folium; Digitalis Purpureae Folium; Digitalisblad; Digitalis-purpurea-Blätter; Feuille de Digitale; Fingerhutblatt; Folha de Dedaleira; Foxglove Leaf; Hoja de Digital; Lišt náprstníku červeného; Piros gyűszűviráglevél; Rusmen-lapai.

ATC — C01AA03.

ATC Vet — QC01AA03.

*ATC Herb — HC01AA5002 (*Digitalis purpurea *leaf).*

UNII — F1T8QT9U8B.

NOTE. The term 'digitalis' is often used to describe the entire class of cardiac glycosides.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Digitalis Leaf). The dried leaf of *Digitalis purpurea*. It contains not less than 0.3% of cardenolic glycosides, expressed as digitoxin, and calculated with reference to the drug dried at 100 degrees to 105 degrees. Protect from light and moisture.

USP 36: (Digitalis). The dried leaf of *Digitalis purpurea* (Scrophulariaceae). The potency is such that, when assayed as directed, 100 mg is equivalent to not less than 1 USP unit. Store in containers that protect it from absorbing moisture.

Profile

Digitalis leaf contains several cardiac glycosides with positive inotropic activity, including digitoxin, gitoxin, and gitaloxin. It has the general properties described under digoxin (p. 1353.3) and has been used similarly in the management of heart failure. However, when treatment with a cardiac glycoside is required a single glycoside is preferred to digitalis, and digoxin or digitoxin are most commonly used.

Digitalis is used in herbal medicine.

Homoeopathy

Digitalis leaf has been used in homoeopathic medicines under the following names: Digitalis; Digitalis purpurea; Dig. pur.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Augentropfen Stulln†; *Ger.*: Augentropfen Stulln Mono; Unguentum lymphaticum†; *Switz.*: Augentonicum; Collypan; *Venez.*: Linfoderm.

Homoeopathic Preparations. *Austria*: Cora; Corasan; Pumpan; *Canad.*: Headache & Migraine L77; Headache & Migraine; *Fr.*: Abbe Chaupitre no 20†; Abbe Chaupitre no 82†; Boripharm No 23; Boripharm No 31; Phapax; Vinicard†; *Ger.*: Conva-cyl Ho-Len-Complex; Derivatio H; Derivatio; Habstal-Cor N; Lowe-Komplex Nr 13; Phonix Silybum spag; Phonix Solidago spag; Phonix Urtica-Arsenicum spag; *Neth.*: Phonix Solidago comp; *Rus.*: Pumpan (Пумпан); *Ukr.*: Pumpan (Пумпан).

Pharmacopoeial Preparations
USP 36: Digitalis Capsules; Digitalis Tablets.

Digitalis Lanata Leaf

Austrian Digitalis; Austrian Foxglove; Digitalis lanata, hoja de; Digitalis Lanatae Folium; Woolly Foxglove Leaf.

CAS — 17575-20-1 (lanatoside A).

*ATC Herb — HC01AA5001 (*Digitalis lanata: *leaf).*

UNII — R80JPF49ZY.

Profile

Digitalis lanata leaf consists of the dried leaves of the woolly foxglove, *Digitalis lanata* (Scrophulariaceae), containing about 1 to 1.4% of a mixture of cardioactive glycosides, including digoxin, digitoxin, acetyldigoxin, acetyldigitoxin, lanatoside A, and deslanoside.

Digitalis lanata leaf is used as a source for the manufacture of digoxin and other glycosides.

There have been reports[1] of toxicity after ingestion of dietary supplements contaminated with *Digitalis lanata*.

1. Slifman NR, *et al.* Contamination of botanical dietary supplements by *Digitalis lanata*. *N Engl J Med* 1998; 339: 806–11.

Digitoxin (BAN, rINN)

Digitaline Cristallisée; Digitoksiini; Digitoksinas; Digitoksyna; Digitoxina; Digitoxine; Digitoxinum; Digitoxoside; Dijitoksin; Дигитоксин.

3β-[(*O*-2,6-Dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-14β-hydroxy-5β-card-20(22)-enolide.

$C_{41}H_{64}O_{13}$=765.0

CAS — 71-63-6.

ATC — C01AA04.

ATC Vet — QC01AA04.

UNII — E90NZP2L9U.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Digitoxin). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; freely soluble in a mixture of equal volumes of chloroform and methyl alcohol. Protect from light.

USP 36: (Digitoxin). A cardiotonic glycoside obtained from *Digitalis purpurea*, *Digitalis lanata* (Scrophulariaceae), or other suitable species of *Digitalis*. A white or pale buff-coloured, odourless, microcrystalline powder. Practically insoluble in water; soluble 1 in 150 of alcohol and 1 in 40 of chloroform; very slightly soluble in ether. Store in airtight containers.

Adsorption. Binding to an in-line intravenous filter containing a cellulose ester membrane accounted for a reduction[1] in digitoxin concentration of up to 25% from solutions of digitoxin 200 micrograms in 50 mL of glucose 5% or sodium chloride 0.9%. Pretreatment of the filter with a polymer coating reduced adsorption by about half.[2]

Digitoxin was found to be adsorbed onto glass and plastic in substantial amounts from simple aqueous solutions but not from solutions in 30% alcohol, or in plasma, or urine.[3]

1. Butler LD, *et al.* Effect of inline filtration on the potency of low-dose drugs. *Am J Hosp Pharm* 1980; 37: 935–41.
2. Kanke M, *et al.* Binding of selected drugs to a "treated" inline filter. *Am J Hosp Pharm* 1983; 40: 1323–8.
3. Molin L, *et al.* Solubility, partition, and adsorption of digitalis glycosides. *Acta Pharm Suec* 1983; 20: 129–44.

Uses and Administration

Digitoxin is a cardiac glycoside with positive inotropic activity. It has actions similar to those of digoxin (below) and is used in the management of some cardiac arrhythmias (p. 1266.1) and in heart failure (p. 1262.3).

Digitoxin is the most potent of the digitalis glycosides and is the most cumulative in action. The onset of its action is slower than that of the other cardiac glycosides and it may therefore be less suitable than digoxin for rapid digitalisation; after oral doses its effects may be evident in about 2 hours and its full effects in about 12 hours. Its effects persist for about 3 weeks.

As described under digoxin, dosage should be carefully adjusted to the needs of the individual patient. Steady-state therapeutic plasma concentrations of digitoxin may range from 10 to 35 nanograms/mL; higher values may be associated with toxicity. In adults 1 to 1.5 mg has been given orally in divided doses over 24 hours for rapid digitalisation, while for slow digitalisation an oral dose of 200 micrograms twice daily for 4 days has been given. The usual maintenance dose is 100 to 200 micrograms daily, but 100 micrograms on alternate days may be adequate. Digitoxin may also be given by slow intravenous injection when vomiting or other conditions prevent oral use; maintenance doses of 70 to 100 micrograms daily have been used. It has also been given intramuscularly but injections may be irritant.

Administration in children. Children were found to have a greater volume of distribution of digitoxin than adults and a shorter mean half-life, although individual variation was considerable. The increase in total clearance in children compared with adults was attributed to greater metabolic clearance. Single digitalisation doses of 20 micrograms/kg were well tolerated.[1]

1. Larsen A, Storstein L. Digitoxin kinetics and renal excretion in children. *Clin Pharmacol Ther* 1983; 33: 717–26.

Administration in the elderly. Digitoxin half-life, apparent volume of distribution, and clearance were not found to differ in elderly subjects compared with young adults after intravenous injection in a single-dose study. The long half-life may make once weekly dosing possible in poorly compliant patients.[1]

1. Donovan MA, *et al.* The effect of age on digitoxin pharmacokinetics. *Br J Clin Pharmacol* 1981; 11: 401–2.

Administration in renal disease. The pharmacokinetics of digitoxin were changed significantly in 5 patients with nephrotic syndrome. The apparent volume of distribution of digitoxin was increased and protein binding decreased. Such patients should be maintained at lower serum-digitoxin concentrations than other patients but will need larger doses because of the shortened serum half-life and the increased renal excretion of digitoxin and its cardioactive metabolites.[1]

1. Storstein L. Studies on digitalis VII: influence of nephrotic syndrome on protein binding, pharmacokinetics, and renal excretion of digitoxin and cardioactive metabolites. *Clin Pharmacol Ther* 1976; 20: 158–66.

Malignant neoplasms. There has been some interest in the potential anticancer activity of digitoxin and related compounds.

References.

1. Haux J. Digitoxin is a potential anticancer agent for several types of cancer. *Med Hypotheses* 1999; 53: 543–8.
2. Haux J, *et al.* Digitoxin medication and cancer: case control and internal dose-response studies. *BMC Cancer* 2001; 1: 11.
3. Johansson S, *et al.* Cytotoxicity of digitoxin and related cardiac glycosides in human tumor cells. *Anticancer Drugs* 2001; 12: 475–83.
4. López-Lázaro M, *et al.* Digitoxin inhibits the growth of cancer cell lines at concentrations commonly found in cardiac patients. *J Nat Prod* 2005; 68: 1642–5.
5. López-Lázaro M. Digitoxin as an anticancer agent with selectivity for cancer cells: possible mechanisms involved. *Expert Opin Ther Targets* 2007; 11: 1043–53.

Adverse Effects, Treatment, and Precautions

As for Digoxin, p. 1354.3. Toxicity may be more prolonged after withdrawal of digitoxin because of the longer half-life.

References.

1. Lely AH van Enter CHJ. Large-scale digitoxin intoxication. *BMJ* 1970; 3: 737–40.
2. Gilfrich H-J, *et al.* Treatment of massive digitoxin overdose by charcoal haemoperfusion and cholestyramine. *Lancet* 1978; 1: 505.
3. Pond S, *et al.* Treatment of digitoxin overdose with oral activated charcoal. *Lancet* 1981; II: 1177–8.
4. Kurowski V, *et al.* Treatment of a patient with severe digitoxin intoxication by Fab fragments of anti-digitalis antibodies. *Intensive Care Med* 1992; 18: 439–42.
5. Schmitt K, *et al.* Massive digitoxin intoxication treated with digoxin-specific antibodies in a child. *Pediatr Cardiol* 1994; 15: 48–9.
6. Lehmann G, *et al.* Digitoxin intoxication in a 79-year-old patient: a description of a case and review of the literature. *Int J Cardiol* 2000; 75: 109–13.
7. Hippius M, *et al.* Adverse drug reaction monitoring—digitoxin overdosage in the elderly. *Int J Clin Pharmacol Ther* 2001; 39: 336–43.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies digitoxin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Digoxin, p. 1356.1. Since digitoxin is significantly metabolised in the liver it may be affected by drugs that induce microsomal enzymes, including rifampicin (see below) and antiepileptics such as phenobarbital.

Antibacterials. Acute heart failure has been reported in a patient taking digitoxin when treatment with *rifampicin* and isoniazid was started; plasma-digitoxin concentrations fell from a pretreatment steady-state value of 27 nanograms/mL to 10 nanograms/mL. The reduction in the digitoxin concentration was attributed to induction of digitoxin metabolism by rifampicin.[1]

Digitoxin toxicity has been described in 2 patients after addition of *azithromycin* to their therapy.[2]

1. Boman G, *et al.* Acute cardiac failure during treatment with digitoxin—an interaction with rifampicin. *Br J Clin Pharmacol* 1980; 10: 89–90.
2. Thalhammer F, *et al.* Azithromycin-related toxic effects of digitoxin. *Br J Clin Pharmacol* 1998; 45: 91–2.

Antineoplastics. A mean overall increase of 109% was seen in digitoxin clearance in 5 patients also given *aminoglutethimide*. The interaction was attributed to the induction of hepatic enzymes by aminoglutethimide.[1]

1. Lønning PE, *et al.* Effect of aminoglutethimide on antipyrine, theophylline, and digitoxin disposition in breast cancer. *Clin Pharmacol Ther* 1984; 36: 796–802.

Calcium-channel blockers. Steady-state plasma concentrations of digitoxin increased by an average of 35% over 2 to 3 weeks in 8 of 10 patients when *verapamil* 240 mg daily was added to their therapy. Total body clearance and extra-renal clearance of digitoxin were reduced by 27% and 29% respectively although renal excretion was unchanged. Plasma-digitoxin concentrations increased by a mean of 21% in 5 of 10 patients treated with *diltiazem* but were not increased by *nifedipine*.[1]

1. Kuhlman J. Effects of verapamil, diltiazem, and nifedipine on plasma levels and renal excretion of digitoxin. *Clin Pharmacol Ther* 1985; 38: 667–73.

Diuretics. *Spironolactone* has been reported to decrease the half-life and the urinary elimination of unchanged digitoxin when given for at least 10 days to 8 patients on oral maintenance digitoxin therapy.[1] However, increased digitoxin half-life has been reported[2] in 3 healthy subjects when spironolactone was added to digitoxin therapy. The interaction was judged to be of minor clinical importance.

1. Wirth KE, *et al.* Metabolism of digitoxin in man and its modification by spironolactone. *Eur J Clin Pharmacol* 1976; 9: 345–54.
2. Carruthers SG, Dujovne CA. Cholestyramine and spironolactone and their combination in digitoxin elimination. *Clin Pharmacol Ther* 1980; 27: 184–7.

Pharmacokinetics

Digitoxin is readily and completely absorbed from the gastrointestinal tract. Therapeutic plasma concentrations may range from 10 to 35 nanograms/mL but there is considerable interindividual variation. Digitoxin is more than 90% bound to plasma proteins. It is very slowly eliminated from the body and is metabolised in the liver. Most metabolites are inactive; the major active metabolite is digoxin. Enterohepatic recycling occurs and digitoxin is excreted in the urine, mainly as metabolites. It is also excreted in the faeces and this route becomes significant in renal impairment. Digitoxin has an elimination half-life of up to 7 days or more. The half-life is generally unchanged in renal impairment.

The pharmacokinetics of digitoxin may be affected by age and by concurrent diseases (see under Uses and Administration, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Digimerck; *Braz.*: Digitaline; *Ger.*: Digimed†; Digimerck; *Gr.*: Digitaline; *Hung.*: Digimerck; *USA*: Crystodigin.

Multi-ingredient Preparations. *China*: Stulln (旌图伦); Stulln (旌图伦).

Pharmacopoeial Preparations

BP 2014: Digitoxin Tablets;

USP 36: Digitoxin Injection; Digitoxin Tablets.

Digoxin (BAN, rINN)

Digoksiini; Digoksin; Digoksinas; Digoksyna; Digoxina; Digoxine; Digoxinum; Digoxosidum; Дигоксин.

3β-[(*O*-2,6-Dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14β-dihydroxy-5β-card-20(22)-enolide.

$C_{41}H_{64}O_{14}$=780.9

CAS — 20830-75-5.

ATC — C01AA05.

ATC Vet — QC01AA05.

UNII — 73K4184T59.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Digoxin). A white or almost white powder or colourless crystals. Practically insoluble in water; slightly soluble in alcohol; soluble in a mixture of equal volumes of dichloromethane and methyl alcohol. Protect from light.

USP 36: (Digoxin). A cardiotonic glycoside obtained from the leaves of *Digitalis lanata* (Scrophulariaceae). Clear to white, odourless, crystals, or a white, odourless, crystalline powder. Practically insoluble in water and in ether; slightly soluble in diluted alcohol and in chloroform; freely soluble in pyridine. Store in airtight containers.

Uses and Administration

Digoxin is a cardiac glycoside used in the management of supraventricular arrhythmias, particularly atrial fibrillation (p. 1266.1), and in heart failure (p. 1262.3).

The principal actions of digoxin are an increase in the force of myocardial contraction (positive inotropic activity) and a reduction in the conductivity of the heart, particularly in conduction through the atrioventricular (AV) node. Digoxin also has a direct action on vascular smooth muscle and indirect effects mediated mainly by the autonomic nervous system, and particularly by an increase in vagal activity. There are also reflex alterations in autonomic activity due to the effects on the circulation. Overall, these actions result in positive inotropic effects, negative chronotropic effects, and decreased AV nodal activity.

Cardiac arrhythmias. In atrial arrhythmias digoxin's actions cause a decrease in the conduction velocity through the AV node and an increase in the effective refractory

period, thus reducing ventricular rate. In addition there is a decrease in the refractory period of the cardiac muscle and depression of the sinus node partly in response to the increase in vagal activity.

Digoxin is thus given to slow the increased ventricular rate that occurs in response to *atrial fibrillation*, although other drugs may be preferred; treatment is usually long term. In patients with the Wolff-Parkinson-White syndrome and atrial fibrillation, digoxin can cause rapid ventricular rates, and possibly ventricular fibrillation, and should be avoided. In *atrial flutter*, the ventricular rate is normally more difficult to control with digoxin. Drug therapy is not the preferred method of treatment, but treatment with digoxin may restore sinus rhythm, or it may convert the flutter to fibrillation and sinus rhythm may then be induced by subsequent withdrawal of digoxin. Digoxin may be given to relieve an attack of *paroxysmal supraventricular tachycardia* and has also been given to prevent further attacks.

Heart failure. Digoxin and other cardiac glycosides directly inhibit the activity of the enzyme sodium-potassium adenosine triphosphatase (Na/K-ATPase), which is required for the active transport of sodium from myocardial cells. The result is a gradual increase in the intracellular sodium concentration and a decrease in the intracellular potassium concentration. The increased concentration of sodium inside the cells leads, by stimulation of sodium-calcium exchange, to an increase in the intracellular calcium concentration with enhancement of mechanical contractile activity and an increased inotropic effect.

When used in heart failure the increased force of myocardial contraction results in increased cardiac output, decreased end-systolic volume, decreased heart size, and decreased end-diastolic pressure and volume. Increased blood flow through the kidneys results in diuresis with a reduction in oedema and blood volume. The decrease in pulmonary venous pressure relieves dyspnoea and orthopnoea. Digoxin may thus provide symptomatic improvement in patients with heart failure and is mainly used for adjunctive therapy.

Dosage. When given orally, digoxin may take effect within about 2 hours and the maximum effect may be reached in about 6 hours. Initially a loading dose may be given to digitalise the patient, although this may not be necessary in, for example, mild heart failure.

Dosage should be carefully adjusted to the needs of the individual patient. Factors that may be considered include the patient's age, lean body-mass, renal status, thyroid status, electrolyte balance, degree of tissue oxygenation, and the nature of the underlying cardiac or pulmonary disease. Bearing in mind the above factors, steady-state plasma-digoxin concentrations (in a sample taken at least 6 hours after a dose) of 0.5 to 2 nanograms/mL are generally considered acceptable, although concentrations at the lower end of the range may be more appropriate in patients with heart failure. For reference to therapeutic drug monitoring, see below.

If rapid digitalisation is required then a loading dose is given to allow for the large volume of distribution. A total *oral* loading dose of 750 to 1500 micrograms of digoxin may be given during the initial 24-hour period, either as a single dose, or where there is less urgency or greater risk of toxicity, in divided doses at 6-hourly intervals. Alternatively, a total oral loading dose of 10 to 15 micrograms/kg may be given in divided doses (50% initially, then 25% portions given 6 to 8 hourly). A less rapid digitalisation may be achieved with an oral loading dose of 250 to 750 micrograms daily for 1 week. If the loading dose is not necessary, it may be omitted and treatment started with the maintenance dose. The usual oral maintenance dose of digoxin is 125 to 250 micrograms daily, but may range from 62.5 to 500 micrograms daily. Steady-state plasma concentrations occur within 1 to 3 weeks, depending on renal function.

In urgent cases, provided that the patient has not received cardiac glycosides during the previous 2 weeks, digoxin may initially be given *intravenously*. It generally produces a definite effect on the heart rate within 30 minutes, reaching a maximum within about 5 hours. A total loading dose of 500 to 1000 micrograms, or 8 to 12 micrograms/kg is used; the loading dose is given in divided doses (50% initially, then smaller portions given 4 to 8 hourly), with each infused over 5 to 20 minutes. Maintenance treatment is then usually given orally. Oral doses are typically around one-third higher than intravenous doses, due to the lower bioavailability of oral formulations. Digoxin has also been given intramuscularly but this route is not generally recommended since such injections may be painful and tissue damage has been reported. Digoxin should not be given subcutaneously as intense local irritation may occur.

For doses in children, see below.

For administration in elderly patients or in those with renal impairment, see below.

General reviews on the actions and uses of digoxin and the other cardiac glycosides.

1. Opie LH. Digitalis and sympathomimetic stimulants. *Lancet* 1980; i: 912–18.
2. Taggart AJ, McDevitt DG. Digitalis: its place in modern therapy. *Drugs* 1980; 20: 398–404.
3. Chamberlain DA. Digitalis: where are we now? *Br Heart J* 1985; 54: 227–33.
4. Doherty JE. Clinical use of digitalis glycosides: an update. *Cardiology* 1985; 72: 225–54.
5. Smith TW. Digitalis: mechanisms of action and clinical use. *N Engl J Med* 1988; 318: 358–65.
6. Hampton JR. Digoxin. *Br J Hosp Med* 1997; 58: 321–3.
7. Riaz K, Parker AD. Digoxin use in congestive heart failure: current status. *Drugs* 1998; 55: 747–58.
8. Campbell TJ, MacDonald PS. Digoxin in heart failure and cardiac arrhythmias. *Med J Aust* 2003; 179: 98–102.
9. Gheorghiade M, *et al.* Digoxin for the treatment of chronic and acute heart failure syndromes. *Acute Card Care* 2009; 11: 83–7.
10. Master J, Schweitzer P. Is there a role for digoxin in atrial fibrillation without heart failure? *Cardiol J* 2009; 16: 483–6.

Administration in children. Digoxin is given to neonates, infants, and children in the treatment of supraventricular tachycardias such as atrial fibrillation. It may also be used to treat heart failure, particularly when the response to diuretics and ACE inhibitors has been inadequate.

In comparison with adults, neonates have immature renal function and require lower doses proportional to body-weight, while infants and young children require proportionally higher doses. Daily maintenance doses in those aged under 10 years may be given as a single dose or 2 divided doses. Children aged over 10 years may be given adult doses (see p. 1353.3).

It is usually given orally, but may be given by intravenous infusion if necessary. The *BNFC* recommends the following doses according to age and body-weight:

- neonate under 1.5 kg: initially 25 micrograms/kg orally, or 20 micrograms/kg intravenously, in 3 divided doses for 24 hours, then 4 to 6 micrograms/kg daily
- neonate of 1.5 to 2.5 kg: initially 30 micrograms/kg orally or intravenously in 3 divided doses for 24 hours, then 4 to 6 micrograms/kg daily
- neonate over 2.5 kg: initially 45 micrograms/kg orally, or 35 micrograms/kg intravenously, in 3 divided doses for 24 hours, then 10 micrograms/kg daily
- child aged 1 month to 2 years: initially 45 micrograms/kg orally, or 35 micrograms/kg intravenously, in 3 divided doses for 24 hours, then 10 micrograms/kg daily
- child aged 2 to 5 years: initially 35 micrograms/kg orally or intravenously in 3 divided doses for 24 hours, then 10 micrograms/kg daily
- child aged 5 to 10 years: initially 25 micrograms/kg (maximum 750 micrograms orally or 500 micrograms intravenously) in 3 divided doses for 24 hours, then 6 micrograms/kg (maximum 250 micrograms) daily

Administration in the elderly. The volume of distribution of digoxin and the elimination half-life increase with age.[1] Therefore there are problems in giving digoxin to elderly patients since steady-state plasma concentrations may not be reached for up to 2 weeks. Fears of toxicity have led some practitioners to use a fixed 'geriatric' dose of 62.5 micrograms daily. However, such a dose can produce subtherapeutic concentrations.[2] The routine use of very low doses of digoxin in the elderly is inappropriate and dosage should be individualised.

1. McMurray J, McDevitt DG. Treatment of heart failure in the elderly. *Br Med Bull* 1990; 46: 202–29.
2. Nolan L, *et al.* The need for reassessment of digoxin prescribing for the elderly. *Br J Clin Pharmacol* 1989; 27: 367–70.

Administration in renal impairment. The pharmacokinetics of cardiac glycosides in patients with renal impairment have been reviewed.[1] The rate but not the extent of digoxin absorption is reduced in renal impairment but this is unlikely to be clinically important. Plasma-protein binding may also be reduced but since digoxin is poorly bound to these proteins and has a large apparent volume of distribution this also is unlikely to be important. The apparent volume of distribution is reduced by one-third to one-half and the loading dose of digoxin should therefore be reduced; an oral loading dose of 10 micrograms/kg is suggested (but see also under Therapeutic Drug Monitoring, below). Non-renal clearance of digoxin is unaffected or only slightly reduced but renal clearance is reduced, the extent being closely related to creatinine clearance. The elimination half-life of digoxin is prolonged and it therefore takes longer to reach steady state and longer for toxicity to resolve. Because of the reduction in renal clearance of digoxin, maintenance doses must be reduced in line with renal function. Serum-digoxin concentration should be monitored although the presence of digoxin-like immunoreactive substances may make interpretation difficult. In addition, the presence of hyperkalaemia in patients with renal impairment may reduce sensitivity to the effects of digoxin.[2]

Since digoxin has such a large distribution volume, procedures such as peritoneal dialysis and haemodialysis remove only very small amounts of drug from the body and no dosage supplement is needed.

1. Aronson JK. Clinical pharmacokinetics of cardiac glycosides in patients with renal dysfunction. *Clin Pharmacokinet* 1983; 8: 155–78.
2. Marzke GR, Frye RF. Drug administration in patients with renal insufficiency: minimising renal and extrarenal toxicity. *Drug Safety* 1997; 16: 205–31.

Therapeutic drug monitoring. Digoxin has a narrow therapeutic index. It is generally considered that plasma-digoxin concentrations required for a therapeutic effect are usually between 0.5 and 2.0 nanograms/mL,[1-3] although some studies[4-6] have suggested that concentrations of 0.5 to 0.9 nanograms/mL are adequate for heart failure; concentrations at the upper end of the range may be associated with worse outcomes.[5,6] The factor for converting nanograms/mL to nanomoles/litre is 1.28.

Digoxin dosage can be calculated in uncomplicated cases by considering the patient's weight, renal function, and clinical status. Therapeutic drug monitoring is *not* considered to be necessary in patients with a satisfactory clinical response to conventional doses in the absence of signs or symptoms of toxicity.[1,2] Measurement of plasma-digoxin concentrations is useful if poor compliance is suspected, if response is poor or there is a deterioration in response without apparent reason, if renal function is fluctuating, when it is unknown if a cardiac glycoside has been previously taken, during drug interactions, and to confirm clinical toxicity.[1,3,7] A plasma concentration should never be considered in isolation and should be used with other patient data as an important component in clinical decision making. This is particularly important in the diagnosis of digoxin toxicity since signs and symptoms of toxicity may be difficult to distinguish from the underlying disease and can occur within the usual therapeutic range.

Several factors may influence the response to digoxin and thus the interpretation of digoxin assays. These include renal impairment, extremes of age, thyroid disease, patient compliance, drug interactions, and electrolyte disturbances.[1-3,7] Variations in the bioavailability of different digoxin preparations have also caused problems. Renal impairment and hypokalaemia are two of the most important factors affecting dosage of digoxin and whenever plasma-digoxin concentrations are assayed renal function and plasma potassium should also be measured. A dosing nomogram has been proposed[8] relating dose in patients with heart failure to renal function and either height or ideal body weight: for most patients with moderate or severe renal impairment (creatinine clearance below 60 mL/minute) an oral dose of 125 micrograms every other day was considered sufficient. The interpretation of digoxin assays is further confounded by the presence of digoxin-like immunoreactive substances in patients with renal or hepatic impairment, in pregnant women, and in neonates. Blood samples for digoxin assay should be taken at least 6 hours after a dose to allow for distribution.[1,3,7] In addition, reported assay values for the same sample may vary widely enough between laboratories to mandate different clinical management.[9]

The usefulness of plasma-digoxin concentrations in the diagnosis of toxicity in children is unclear. For children older than 12 months the adult guidelines can probably be followed, and for younger children the trend for increased risk of toxicity at increased plasma-digoxin concentrations appears to hold but the threshold for toxicity may be higher, especially in children less than 3 months old.[1]

1. Aronson JK. Indications for the measurement of plasma digoxin concentrations. *Drugs* 1983; 26: 230–42.
2. Lee TR, Smith TW. Serum digoxin concentration and diagnosis of digitalis toxicity: current concepts. *Clin Pharmacokinet* 1983; 8: 279–85.
3. Aronson JK, Hardman M. Digoxin. *BMJ* 1992; 305: 1149–52.
4. Adams KF, *et al.* Clinical benefits of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol* 2002; 39: 946–53.
5. Rathore SS, *et al.* Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003; 289: 871–8.
6. Adams KF, *et al.* Relationship of serum digoxin concentration to mortality and morbidity in women in the Digitalis Investigation Group trial: a retrospective analysis. *J Am Coll Cardiol* 2005; 46: 497–504.
7. Brodie MJ, Feely J. Practical clinical pharmacology: therapeutic drug monitoring and clinical trials. *BMJ* 1988; 296: 1110–14.
8. Bauman JL, *et al.* A method of determining the dose of digoxin for heart failure in the modern era. *Arch Intern Med* 2006; 166: 2539–45.
9. Rogers NM, *et al.* Frequently discordant results from therapeutic drug monitoring for digoxin: clinical confusion for the prescriber. *Intern Med J* 2010; 40: 52–6.

Adverse Effects

Digoxin and the other cardiac glycosides commonly produce adverse effects because the margin between the therapeutic and toxic doses is small; plasma concentrations of digoxin in excess of 2 nanograms/mL are considered to be an indication that the patient is at special risk although there is considerable interindividual variation. There have been many fatalities, particularly due to cardiotoxicity.

Nausea, vomiting, and anorexia may be among the earliest symptoms of digoxin toxicity or overdosage; diarrhoea and abdominal pain may occur. Certain neurological effects are also common symptoms of digoxin

overdosage and include headache, facial pain, fatigue, weakness, dizziness, drowsiness, disorientation, mental confusion, bad dreams and more rarely delirium, acute psychoses, and hallucinations. Convulsions have been reported. Visual disturbances including blurred vision may occur; colour vision may be affected with objects appearing yellow or, less frequently, green, red, brown, blue, or white. Hypersensitivity reactions are rare; thrombocytopenia has been reported. The cardiac glycosides may have some oestrogenic activity and occasionally cause gynaecomastia at therapeutic doses.

Rapid intravenous injection of digoxin may cause vasoconstriction and transient hypertension. Intramuscular or subcutaneous injection can cause local irritation.

The most serious adverse effects are those on the heart. Toxic doses may cause or aggravate heart failure. Supraventricular or ventricular arrhythmias and defects of conduction are common and may be an early indication of excessive dosage, particularly in children. In general the incidence and severity of arrhythmias is related to the severity of the underlying heart disease. Almost any arrhythmia may ensue, but particular note should be made of supraventricular tachycardia, especially AV junctional tachycardia and atrial tachycardia with block. Ventricular arrhythmias including extrasystoles, sinoatrial block, sinus bradycardia, and AV block may also occur.

Hypokalaemia predisposes to digoxin toxicity; adverse reactions to digoxin may be precipitated if hypokalaemia occurs, for example after prolonged use of diuretics. Hyperkalaemia occurs in acute digoxin overdosage.

As digoxin has a shorter half-life than digitalis or digitoxin any toxic effects will tend to resolve more rapidly.

General references to digitalis toxicity.

1. Pentel PR, Salerno DM. Cardiac drug toxicity: digitalis glycosides and calcium-channel and β -blocking agents. *Med J Aust* 1990; **152**: 88–94.
2. Wells TG, *et al.* Age-related differences in digoxin toxicity and its treatment. *Drug Safety* 1992; **7**: 135–51.
3. Johnston GD. Adverse reaction profile: digoxin. *Prescribers' J* 1993; **33**: 29–35.
4. Kernan WN, *et al.* Incidence of hospitalization for digitalis toxicity among elderly Americans. *Am J Med* 1994; **96**: 426–31.
5. Li-Saw-Hee FL, Lip GYH. How safe is digoxin? *Adverse Drug React Bull* 1998; (Feb): 715–18.
6. Gitteiman MA, *et al.* Acute pediatric digoxin ingestion. *Pediatr Emerg Care* 1999; **15**: 359–62.
7. López-Gómez D, *et al.* Intoxicación grave por digoxina: utilización exitosa del tratamiento clásico. *Rev Esp Cardiol* 2000; **53**: 471–2.
8. Ma G, *et al.* Electrocardiographic manifestations: digitalis toxicity. *J Emerg Med* 2001; **20**: 145–52.
9. Demiryürek AT, Demiryürek S. Cardiotoxicity of digitalis glycosides: roles of autonomic pathways, autacoids and ion channels. *Auton Autacoid Pharmacol* 2005; **25**: 35–52.
10. Bauman JL, *et al.* Mechanisms, manifestations, and management of digoxin toxicity in the modern era. *Am J Cardiovasc Drugs* 2006; **6**: 77–86.
11. Haynes K, *et al.* Declining public health burden of digoxin toxicity from 1991 to 2004. *Clin Pharmacol Ther* 2008; **84**: 90–4.

Effects on the blood. Thrombocytopenia has been reported[1] in a small number of patients taking digoxin. An association between several cardiovascular drugs, including digitalis glycosides (digoxin and acetyldigoxin), and agranulocytosis was also found in an international study[2] although again the incidence was low.

1. George JN, *et al.* Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med* 1998; **129**: 886–90.
2. Kelly JP, *et al.* Risks of agranulocytosis and aplastic anemia in relation to the use of cardiovascular drugs: the international agranulocytosis and aplastic anemia study. *Clin Pharmacol Ther* 1991; **49**: 330–41.

Effects in the elderly. Elderly patients may be particularly susceptible to digoxin toxicity, even at therapeutic plasma concentrations.[1] Adverse effects reported in elderly patients with toxic plasma-digoxin concentrations have included chorea,[2] profuse watery diarrhoea,[3] and dysphagia with dysphonia.[4]

1. Miura T, *et al.* Effect of aging on the incidence of digoxin toxicity. *Ann Pharmacother* 2000; **34**: 427–32.
2. Mulder LJMM, *et al.* Generalised chorea due to digoxin toxicity. *BMJ* 1988; **296**: 1262.
3. Andrews PA, Wilkinson PR. Diarrhoea as a side effect of digoxin. *BMJ* 1990; **301**: 1398.
4. Cordeiro MF, Arnold KG. Digoxin toxicity presenting as dysphagia and dysphonia. *BMJ* 1991; **302**: 1025.

Hypersensitivity. Hypersensitivity reactions to cardiac glycosides are rare but skin reactions have been reported. An 86-year-old man developed a generalised, pruritic, erythematous rash after digoxin was given intravenously.[1] The rash recurred on rechallenge with digoxin tablets.

1. Martin SJ, Shah D. Cutaneous hypersensitivity reaction to digoxin. *JAMA* 1994; **271**: 1905.

Treatment of Adverse Effects

In *acute poisoning* with cardiac glycosides such as digoxin, repeated doses of activated charcoal may be given to reduce absorption and enterohepatic recycling if the patient presents within 1 to 2 hours of ingestion. Binding resins such as colestyramine and colestipol have also been used. Gastric lavage has also been tried. Attempts to remove cardiac glycosides by haemodialysis or peritoneal dialysis have generally been ineffective and the value of haemoperfusion is controversial.

For the treatment of *chronic poisoning* temporary withdrawal of digoxin or other cardiac glycosides may be all that is necessary, with subsequent doses adjusted according to the needs of the patient.

Cardiotoxicity in acute or chronic poisoning should be treated under ECG control and serum electrolytes should be regularly monitored and imbalances corrected. Progressive hyperkalaemia can occur with massive overdose and is fatal unless reversed; soluble insulin with glucose, or if the hyperkalaemia is refractory, dialysis may be tried. Any antiarrhythmic treatment for cardiac glycoside toxicity should be determined by the specific arrhythmia present (see p. 1266.1). Atropine is given intravenously to correct bradycardia and in patients with heart block. Pacing may be necessary if atropine is not effective.

Digoxin-specific antibody fragments (p. 1549.1) may be used to treat acute and chronic digoxin, or digitoxin overdoses, but are generally restricted to the treatment of severe intoxication in which conventional treatment is ineffective. Successful treatment of lanatoside C poisoning has also been reported.

References.

1. Allen NM, Dunham GD. Treatment of digitalis intoxication with emphasis on the clinical use of digoxin immune Fab. *DICP Ann Pharmacother* 1990; **24**: 991–8.
2. Dick M, *et al.* Digitalis intoxication recognition and management. *J Clin Pharmacol* 1991; **31**: 444–7.
3. Critchley JAJH, Critchley LAH. Digoxin toxicity in chronic renal failure: treatment by multiple dose activated charcoal intestinal dialysis. *Hum Exp Toxicol* 1997; **16**: 733–5.
4. Kirrane BM, *et al.* Inconsistent approach to the treatment of chronic digoxin toxicity in the United States. *Hum Exp Toxicol* 2009; **28**: 285–92.
5. Bilbault P, *et al.* Emergency step-by-step specific immunotherapy in severe digoxin poisoning: an observational cohort study. *Eur J Emerg Med* 2009; **16**: 145–9.
6. Bateman DN. Digoxin-specific antibody fragments: how much and when? *Toxicol Rev* 2004; **23**: 135–43.

Precautions

Digoxin is generally contra-indicated in patients with hypertrophic obstructive cardiomyopathy unless there is severe cardiac failure, since the outflow obstruction may be worsened. It is also contra-indicated in patients with the Wolff-Parkinson-White syndrome or other evidence of an accessory pathway, especially if it is accompanied by atrial fibrillation, since ventricular tachycardia or fibrillation may be precipitated. Although digoxin is used to treat supraventricular arrhythmias it is not an appropriate form of therapy for any *ventricular* arrhythmia.

Digoxin toxicity is common and may result from raised plasma concentrations or an increase in sensitivity to digoxin. Almost any deterioration in the condition of the heart or circulation may increase the sensitivity to digoxin and it should be used with caution in all patients with cardiovascular disease. Early signs of digoxin toxicity should be watched for and the heart rate should generally be maintained above 60 beats per minute. Toxicity may result from giving loading doses too rapidly and from accumulation of maintenance doses as well as from acute poisoning. Even with intravenous doses a response may take several hours, and persistence of tachycardia is therefore not a reason to exceed the recommended intravenous dose.

Digoxin should be used with caution in partial heart block since complete heart block may be induced; it should also be used with care in sinus node disorders. Caution is also required in acute myocarditis (such as rheumatic carditis), in acute myocardial infarction, in advanced heart failure, and in severe pulmonary disease, due to the increased myocardial sensitivity. Digoxin may also enhance the occurrence of arrhythmias in patients undergoing cardioversion and should be withdrawn 1 to 2 days before such procedures if possible. If cardioversion is essential and digoxin has already been given, low energy shocks must be used.

Electrolyte imbalances may affect the sensitivity to digoxin, as may thyroid dysfunction. The effects of digoxin are enhanced by hypokalaemia, hypomagnesaemia, hypercalcaemia, hypoxia, and hypothyroidism and doses may need to be reduced until these conditions are corrected. Resistance to the effects of digoxin may occur in hyperthyroidism. Digoxin should be given with care, and possibly in reduced dosage, to patients who have received it or other cardiac glycosides within the previous 2 to 3 weeks.

Digoxin doses should generally be reduced and plasma-digoxin concentrations monitored in patients with renal impairment, in the elderly, and in premature infants (see Uses and Administration, p. 1353.3).

Breast feeding. Studies[1,2] have shown that digoxin is distributed into breast milk, although the amount was considered too small to have an effect on the child. No adverse effects have been seen in breast-feeding infants whose mothers were receiving digoxin, and the American Academy of Pediatrics considers[3] that it is therefore usually compatible with breast feeding.

1. Levy M, *et al.* Excretion of drugs in human milk. *N Engl J Med* 1997; **297**: 789.
2. Chan V, *et al.* Transfer of digoxin across the placenta and into breast milk. *Br J Obstet Gynaecol* 1978; **85**: 605–9.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *Ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Gastrointestinal disorders. Absorption from tablets of digoxin may be decreased due to inadequate dissolution in patients with malabsorption syndromes or small bowel resections and it has been recommended that liquid dosage forms of digoxin should be used in the latter case.[1] However, only 40 to 60% of a digoxin dose given as elixir was absorbed in a patient with a small bowel resection[2] compared with about 80% in patients with normal gastrointestinal function, suggesting a need for slightly increased oral maintenance doses of digoxin in patients with resections. In a further patient with a similar resection[3] a therapeutic plasma-digoxin concentration was not achieved with any oral formulation.

1. Kumer KP, *et al.* Perspectives on digoxin absorption from small bowel resections. *Drug Intell Clin Pharm* 1983; **17**: 121–3.
2. Verticaden SJ, *et al.* Digoxin absorption in a patient with short-bowel syndrome. *Clin Pharm* 1986; **5**: 62–4.
3. Ehrenpreis ED, *et al.* Malabsorption of digoxin tablets, gel caps, and elixir in a patient with an end jejunostomy. *Ann Pharmacother* 1994; **28**: 1239–40.

Heart surgery. Patients undergoing cardiac surgery appear to have increased sensitivity to digoxin toxicity and thus an increased risk of arrhythmias.[1] Digoxin has been found[2] to be no better than placebo in preventing postoperative arrhythmias after coronary artery bypass surgery, and actually induced supraventricular arrhythmias in 2 patients. Arrhythmias compatible with digoxin intoxication have occurred postoperatively[1] although serum-digoxin concentrations ranged from 0 to 2.8 nanograms/mL; therefore, the arrhythmias may have been due to either the surgical procedures or to increased sensitivity to digoxin.

1. Rose MR, *et al.* Arrhythmias following cardiac surgery: relation to serum digoxin levels. *Am Heart J* 1975; **89**: 288–94.
2. Weiner B, *et al.* Digoxin prophylaxis following coronary artery bypass surgery. *Clin Pharm* 1986; **5**: 55–8.

Interference with digoxin assays. The presence of endogenous digoxin-like substances in neonates, and in patients with liver or kidney dysfunction, may be responsible for elevated values or false-positive results in some plasma-digoxin assays.[1] Some patients may have antibodies that react with the assay system and produce falsely elevated values.[2]

Some drugs may also interfere with plasma-digoxin assays; these include prednisolone[1] and ginseng.[3] Raised serum-digoxin concentrations (but without signs of digoxin toxicity) were noted in an elderly man after the use of Siberian ginseng (*Eleutherococcus senticosus*). However, concentrations remained high even when digoxin was discontinued and returned to the therapeutic range only after the ginseng was stopped. Siberian ginseng contains eleutherosides, which are chemically related to cardiac glycosides such as digoxin, and the assay may have measured these compounds, or their derivatives, as well as digoxin. Although it has been suggested that this reaction may have been due to the substitution of the unrelated cardiotoxic herb *Periploca sepium*,[4] both ginseng and Siberian ginseng have been shown to interfere with some digoxin assays *in vitro* and *in vivo*.[5] Spironolactone may interfere with digoxin assays but may also produce changes in digoxin concentrations (see Diuretics under Interactions, p. 1357.2).

1. Yosselson-Superstine S. Drug interferences with plasma assays in therapeutic drug monitoring. *Clin Pharmacokinet* 1984; **9**: 67–89.
2. Liendo C, *et al.* A new interference in some digoxin assays: anti-murine heterophilic antibodies. *Clin Pharmacol Ther* 1996; **60**: 593–8.
3. McRae S. Elevated serum digoxin levels in a patient taking digoxin and Siberian ginseng. *Can Med Assoc J* 1996; **155**: 293–5.
4. Awang DVC. Siberian ginseng toxicity may be case of mistaken identity. *Can Med Assoc J* 1996; **155**: 1237.
5. Dasgupta A, *et al.* Effect of Asian and Siberian ginseng on serum digoxin measurement by five digoxin immunoassays: significant variation in digoxin-like immunoreactivity among commercial ginsengs. *Am J Clin Pathol* 2003; **119**: 298–303.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies digoxin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pregnancy. There is considerable evidence that digoxin crosses the placenta freely with serum-digoxin concentrations at term similar in the newborn and mother. No significant adverse effects attributed to digoxin have been

noted in the fetus or neonate although adverse fetal effects, including fetal death, have been reported in mothers with digitalis toxicity. Some concern has been expressed that maternal digitalis therapy may occasionally cause low birth-weights in infants of mothers with heart disease, but the underlying disease might also be important.[1] The presence of endogenous digoxin-like immunoreactive substances in the serum of pregnant women and neonates could make the interpretation of digoxin assays difficult. In one study,[2] high concentrations of endogenous digoxin-like immunoreactivity in cord blood suggested that it might be synthesised during delivery, in which case the placental transfer of digoxin might be overestimated.

1. Rotmensch HH, *et al.* Management of cardiac arrhythmias during pregnancy: current concepts. *Drugs* 1987; 33: 623–33.
2. Lupoglazoff JM, *et al.* Endogenous digoxin-like immunoreactivity during pregnancy and at birth. *Br J Clin Pharmacol* 1993; 35: 251–4.

Interactions

There may be interactions between digoxin and drugs that alter its absorption, interfere with its excretion, or have additive effects on the myocardium. Drugs that cause electrolyte disturbances increase the risk of toxicity from cardiac glycosides. Thiazides and loop *diuretics* cause hypokalaemia and also hypomagnesaemia which may lead to cardiac arrhythmias. Other causes of hypokalaemia include treatment with *corticosteroids*, *beta$_2$ agonists* (such as salbutamol), *amphotericin B*, *sodium polystyrene sulfonate*, *carbenoxolone*, and dialysis. Hypercalcaemia may also increase toxicity and intravenous use of *calcium salts* is best avoided in patients taking cardiac glycosides. Serum-digoxin concentrations may be significantly increased by *quinidine*, *amiodarone*, *dronedarone* and *propafenone* and reduction of digoxin dosage may be required. Other antiarrhythmics may have additive effects on the myocardium increasing the likelihood of adverse effects; *beta blockers* may potentiate bradycardia due to digoxin. *Calcium-channel blockers* may increase digoxin concentrations.

Digoxin is a substrate for P-glycoprotein and interactions may occur with drugs that affect P-glycoprotein function (see Metabolism and Excretion under Pharmacokinetics, p. 1358.3).

Reviews of drug interactions occurring with digoxin.

1. Rodin SM, Johnson BF. Pharmacokinetic interactions with digoxin. *Clin Pharmacokinet* 1988; 15: 227–44.
2. Magnani B, Malini PL. Cardiac glycosides: drug interactions of clinical significance. *Drug Safety* 1995; 12: 97–109.

ACE inhibitors. Although increased serum-digoxin concentrations have been reported in patients with severe chronic heart failure given *captopril*,[1] other studies have failed to confirm this effect.[2,3] Studies with various other ACE inhibitors have also failed to show any significant effect on serum-digoxin concentrations. However, ACE inhibitors may cause a deterioration in renal function and this could lead to an increase in serum-digoxin concentration due to impaired digoxin excretion.[4]

1. Cleland JGF, *et al.* Interaction of digoxin and captopril. *Br J Clin Pharmacol* 1984; 17: 214P.
2. Magelli C, *et al.* Lack of effect of captopril on serum digoxin in congestive heart failure. *Eur J Clin Pharmacol* 1989; 36: 99–100.
3. Rossi GP, *et al.* Effect of acute captopril administration on digoxin pharmacokinetics in normal subjects. *Curr Ther Res* 1989; 46: 439–44.
4. Mignat C, Unger T. ACE inhibitors: drug interactions of clinical significance. *Drug Safety* 1995; 12: 334–47.

Alpha blockers. *Prazosin*[1] has been reported to increase the mean plasma-digoxin concentration in patients receiving a maintenance dose of digoxin.

1. Çopur S, *et al.* Effects of oral prazosin on total plasma digoxin levels. *Fundam Clin Pharmacol* 1988; 2: 13–17.

Angiotensin II receptor antagonists. In a study[1] in healthy subjects, *telmisartan* increased peak serum-digoxin concentrations but trough concentrations were unaffected and it was suggested that the effect was unlikely to be clinically significant. No interaction was found when digoxin was given with *losartan*[2] or with *eprosartan*[3] in healthy subjects.

1. Stangier J, *et al.* The effect of telmisartan on the steady-state pharmacokinetics of digoxin in healthy male volunteers. *J Clin Pharmacol* 2000; 40: 1373–9.
2. de Smet M, *et al.* Effect of multiple doses of losartan on the pharmacokinetics of single doses of digoxin in healthy volunteers. *Br J Clin Pharmacol* 1995; 40: 571–5.
3. Martin DE, *et al.* Lack of effect of eprosartan on the single dose pharmacokinetics of orally administered digoxin in healthy male volunteers. *Br J Clin Pharmacol* 1997; 43: 661–4.

Antiarrhythmics. *AMIODARONE.* An interaction between digoxin and amiodarone resulting in increased plasma-digoxin concentrations has been reported[1–5] on several occasions; the concentration may be doubled.[5] An increase in serum-digoxin concentrations of 68 to 800% has been reported[2] during amiodarone therapy in children. The interaction does not appear to be due to a reduction in urinary excretion alone[3,4] and seems to be dose-related. It has been recommended[1,6] that the initial dose of digoxin should be halved when amiodarone is given.

1. Moysey JO, *et al.* Amiodarone increases plasma digoxin concentrations. *BMJ* 1981; 282: 272.
2. Koren G, *et al.* Digoxin toxicity associated with amiodarone therapy in children. *J Pediatr* 1984; 104: 467–70.
3. Douste-Blazy F, *et al.* Influence of amiodarone on plasma and urine digoxin concentrations. *Lancet* 1984; i: 903.
4. Mingardi G. Amiodarone and plasma digoxin levels. *Lancet* 1984; i: 1338.
5. Johnston A, *et al.* The digoxin-amiodarone interaction. *Br J Clin Pharmacol* 1987; 24: 253P.
6. Naccarelli GV, *et al.* Adverse effects of amiodarone: pathogenesis, incidence and management. *Med Toxicol Adverse Drug Exp* 1989; 4: 246–53.

DISOPYRAMIDE. Disopyramide appears to have no clinically significant effect on the pharmacokinetics of digoxin in healthy subjects[1,2] but has been reported to modify the cardiovascular effects of digoxin.[1]

1. Elliott HL, *et al.* Pharmacodynamic and pharmacokinetic evaluation of the interaction between digoxin and disopyramide. *Br J Clin Pharmacol* 1982; 14: 141P.
2. Risler T, *et al.* On the interaction between digoxin and disopyramide. *Clin Pharmacol Ther* 1983; 34: 176–80.

DRONEDARONE. Increased serum digoxin concentrations and an increased incidence of gastrointestinal disorders have been reported when dronedarone was given with digoxin. Dronedarone inhibits the P-glycoprotein transport system resulting in a 2.5-fold increase in digoxin exposure, therefore the dose of digoxin should be reduced by about 50% when dronedarone therapy is started in patients already taking digoxin; if appropriate, digoxin treatment should be stopped.

Digoxin may potentiate the electrophysiologic effects of dronedarone such as decreased AV node conduction.

FLECAINIDE. Giving flecainide 200 mg twice daily to 15 healthy subjects taking digoxin caused a mean increase of 24% in predose digoxin concentrations and of 13% in digoxin concentrations 6 hours after the digoxin dose.[1] It was considered that in most cases these increases in plasma-digoxin concentrations would not present a clinical problem, but that patients with higher plasma-digoxin concentrations or atrioventricular nodal dysfunction should be monitored.

1. Weeks CE, *et al.* The effect of flecainide acetate, a new antiarrhythmic, on plasma digoxin levels. *J Clin Pharmacol* 1986; 26: 27–31.

PROPAFENONE. Increased serum-digoxin concentrations have been reported when propafenone is also given.[1–4] There is considerable interindividual variation in the extent of the interaction; increases in serum-digoxin concentrations of up to 254% have been reported. If digoxin and propafenone are given together, the dose of digoxin should be reduced and serum-digoxin concentration should be monitored.

1. Nolan PE, *et al.* Effects of coadministration of propafenone on the pharmacokinetics of digoxin in healthy volunteer subjects. *J Clin Pharmacol* 1989; 29: 46–52.
2. Calvo MV, *et al.* Interaction between digoxin and propafenone. *Ther Drug Monit* 1989; 11: 10–15.
3. Zalzstein E, *et al.* Interaction between digoxin and propafenone in children. *J Pediatr* 1990; 116: 310–12.
4. Bigot M-C, *et al.* Serum digoxin levels related to plasma propafenone levels during concomitant treatment. *J Clin Pharmacol* 1991; 31: 521–6.

QUINIDINE. Quinidine causes an increase in serum-digoxin concentration in almost all patients given the two drugs together.[1–3] The serum-digoxin concentration may be increased by up to 500% but is usually approximately doubled.[1] Signs and symptoms of digoxin toxicity may occur although some workers[4] have suggested that these may be accounted for by an additive effect of the 2 drugs rather than by the effect on serum-digoxin concentration. The exact mechanism of interaction is not clear but a substantial decrease in the renal and nonrenal clearance of digoxin has been found.[5] The distribution volume of digoxin may also be reduced[2] reflecting impaired tissue binding, and there is increased systemic availability.[1] It is generally recommended that the dose of digoxin is halved in digitalised patients who are to be given quinidine.[2] Subsequently, serum-digoxin concentrations should be monitored, especially during the first 1 to 2 weeks after which the new steady-state digoxin concentration should be achieved.[2]

1. Bigger JT, Leahey EB. Quinidine and digoxin: an important interaction. *Drugs* 1982; 24: 229–39.
2. Pedersen KE. Digoxin interactions: the influence of quinidine and verapamil on the pharmacokinetics and receptor binding of digitalis glycosides. *Acta Med Scand* 1985; 697 (suppl): 1–40.
3. Mordel A, *et al.* Quinidine enhances digitalis toxicity at therapeutic serum digoxin levels. *Clin Pharmacol Ther* 1993; 53: 457–62.
4. Walker AM, *et al.* Drug toxicity in patients receiving digoxin and quinidine. *Am Heart J* 1983; 105: 1025–8.
5. Hedman A, *et al.* Interactions in the renal and biliary elimination of digoxin: stereoselective difference between quinine and quinidine. *Clin Pharmacol Ther* 1990; 47: 20–6.

VERAPAMIL. For a discussion on the interaction between digoxin and verapamil, see under Calcium-channel Blockers, p. 1357.2.

Antibacterials. About 10% of patients receiving digoxin may metabolise 40% or more of the drug to cardio-inactive metabolites.[1] Gut flora contribute greatly to this process, and the use of antibacterials such as *erythromycin* or *tetracycline* in these patients appears to reduce this metabolic process resulting in higher serum concentrations.[2] Digoxin toxicity has been reported in digitalised patients given erythromycin,[3,4] *azithromycin*,[5] *clarithromycin*,[6–8] and *roxithromycin*.[9] A Canadian population-based case-control study investigating the risk of digoxin toxicity associated with concomitant macrolide treatment found that the increase in risk was highest with clarithromycin (almost 15-fold) and was less marked with erythromycin or *azithromycin* (about a fourfold increase in risk).[10] It has been postulated[5,11] that the macrolide antibacterials may also inhibit P-glycoprotein-mediated renal tubular secretion of digoxin. Oral *neomycin* may reduce serum-digoxin concentrations by reducing digoxin absorption.

Rifampicin may reduce serum-digitoxin concentrations by inducing its metabolism (see p. 1353.2) although a study[12] in healthy subjects suggested that this reduction might rather be due to induction of intestinal P-glycoprotein. Digoxin is mainly excreted unchanged in the urine but rifampicin increased digoxin dose requirements substantially in 2 patients dependent on dialysis.[13] When rifampicin was stopped digoxin requirements fell by about 50%.

1. Doherty JE. A digoxin-antibiotic drug interaction. *N Engl J Med* 1981; 305: 827–8.
2. Lindenbaum J, *et al.* Inactivation of digoxin by the gut flora: reversal by antibiotic therapy. *N Engl J Med* 1981; 305: 789–94.
3. Maxwell DL, *et al.* Digoxin toxicity due to interaction of digoxin with erythromycin. *BMJ* 1989; 298: 572.
4. Morton MR, Cooper JW. Erythromycin-induced digoxin toxicity. *Di J Ann Pharmacother* 1989; 23: 668–70.
5. Ten Eick AP, *et al.* Possible drug interaction between digoxin and azithromycin in a young child. *Clin Drug Invest* 2000; 20: 61–64.
6. Mldoneck SR, Etingin OR. Clarithromycin-related toxic effects of digoxin. *N Engl J Med* 1995; 333: 1505.
7. Nawarskas JJ, *et al.* Digoxin toxicity secondary to clarithromycin therapy. *Ann Pharmacother* 1997; 31: 864–6.
8. Laberge P, Martineau P. Clarithromycin-induced digoxin intoxication. *Ann Pharmacother* 1997; 31: 999–1002.
9. Corallo CB, Rogers IR. Roxithromycin-induced digoxin toxicity. *Med J Aust* 1996; 165: 433–4.
10. Gomes T, *et al.* Macrolide-induced digoxin toxicity: a population-based study. *Clin Pharmacol Ther* 2009; 86: 383–6.
11. Wakasugi H, *et al.* Effect of clarithromycin on renal excretion of digoxin: interaction with P-glycoprotein. *Clin Pharmacol Ther* 1998; 64: 123–8.
12. Greiner B, *et al.* The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin. *J Clin Invest* 1999; 104: 147–53.
13. Gault H, *et al.* Digoxin-rifampin interaction. *Clin Pharmacol Ther* 198-; 39: 750–4.

Antidepressants. In a study[1] in healthy subjects, use of digoxin with an extract of *St John's wort* for 10 days resulted in a significant decrease in the plasma-digoxin concentration. It was suggested that the interaction might be due to induction of the P-glycoprotein transporter. In a study[2] in healthy male subjects, *nefazodone* increased steady-state plasma-digoxin concentrations by about 30% but no adverse or clinical effects were associated with the increase. However, due to the narrow therapeutic range of digoxin, it was suggested that plasma-digoxin concentrations should be monitored in patients also given nefazodone. Similar recommendations have been made for *trazodone*.

Digoxin toxicity developed in a patient shortly after starting *paroxetine* and was associated with increased serum-digoxin concentrations.[3] However, the role of paroxetine in the reaction has been queried.[4,5]

1. Johne A, *et al.* Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (Hypericum perforatum). *Clin Pharmacol Ther* 1999; 66: 338–45.
2. Dockens RC, *et al.* Assessment of pharmacokinetic and pharmacodynamic drug interactions between nefazodone and digoxin in healthy male volunteers. *J Clin Pharmacol* 1996; 36: 160–7.
3. Yasui-Furukori N, Kaneko S. Digitalis intoxication induced by paroxetine co-administration. *Lancet* 2006; 367: 788.
4. Bateman DN, *et al.* Digitalis intoxication induced by paroxetine co-administration. *Lancet* 2006; 368: 1962–3.
5. Hallberg P, Melhus H. Digitalis intoxication induced by paroxetine co-administration. *Lancet* 2006; 368: 1963.

Antidiabetics. Subtherapeutic plasma-digoxin concentrations were noted in a diabetic woman receiving *acarbose* and digoxin.[1] The plasma concentration of digoxin increased to a therapeutic level when acarbose was stopped. A study[2] in healthy subjects suggested that the interaction was due to inhibition of the absorption of digoxin by acarbose.

Canagliflozin may cause a minor increase in digoxin exposure.

1. Serrano JS, *et al.* A possible interaction of potential clinical interest between digoxin and acarbose. *Clin Pharmacol Ther* 1996; 60: 589–92.
2. Miura T, *et al.* Impairment of absorption of digoxin by acarbose. *J Clin Pharmacol* 1998; 38: 654–7.

Antiepileptics. *Phenytoin* caused a marked decrease in steady-state serum-digoxin concentrations when given with digoxin and acetyldigoxin to 6 healthy subjects for 7 days.[1] Total digoxin clearance was increased by an average of 27% and elimination half-life was reduced by an average of 30%. This interaction may be more likely with digitoxin, since digitoxin is more dependent on the liver for elimination.

A brief report of an open study[2] in 12 subjects indicated a slight but significant decrease in digoxin bioavailability when *topiramate* was also given, although half-life and renal clearance of digoxin did not appear to be affected.

1. Rameis H. On the interaction between phenytoin and digoxin. *Eur J Clin Pharmacol* 1985; 29: 49–53.
2. Liao S, Palmer M. Digoxin and topiramate drug interaction study in male volunteers. *Pharm Res* 1993; 10 (suppl): S405.

Antifungals. Two men given *itraconazole* while receiving digoxin developed signs and symptoms of digoxin toxicity and elevated serum-digoxin concentrations.[1,2] A further case report[3] suggested that the interaction was due to a reduction in the renal clearance of digoxin when itraconazole was given.

Additive adverse effects due to hypokalaemia may occur when digoxin is given with *amphotericin B*.

1. Rex J. Itraconazole–digoxin interaction. *Ann Intern Med* 1992; 116: 525.
2. Alderman CP, Jerrmann HPA. Digoxin–itraconazole interaction. *Med J Aust* 1993; 159: 838–9.
3. Alderman CP, Allcroft PD. Digoxin-itraconazole interaction: possible mechanisms. *Ann Pharmacother* 1997; 31: 438–40.

Antimalarials. In 6 subjects given *quinine sulfate*, total body clearance of digoxin after an intravenous dose was decreased by 26%, mainly through a reduction in nonrenal clearance.[1] Increased urinary excretion of digoxin was consistent with alterations in the nonrenal clearance of digoxin and might be due to changes in the metabolism or biliary secretion of digoxin. Quinine increased the mean elimination half-life of digoxin from 34.2 to 51.8 hours but did not consistently change the volume of distribution.

An increase in the plasma-digoxin concentration, but without symptoms of toxicity, was noted in 2 women given *hydroxychloroquine* (for rheumatoid arthritis) in addition to long-term digoxin therapy.[2]

1. Wandell M, *et al.* Effect of quinine on digoxin kinetics. *Clin Pharmacol Ther* 1980; 28: 425–30.
2. Leden I. Digoxin–hydroxychloroquine interaction? *Acta Med Scand* 1982; 211: 411–12.

Antineoplastics. A study[1] in patients undergoing antineoplastic therapy found that the absorption of digoxin from tablets was reduced by an average of 46.5%, whereas that of digoxin from liquid-filled capsules was not significantly changed. Another study[2] in similar patients found that the steady-state concentration of digoxin after giving acetyldigoxin was reduced, but that digitoxin concentrations were maintained. It was suggested that the interaction was due to reduced absorption of digitalis glycosides through the damaged gastrointestinal mucosa and that liquid-filled capsules or digitoxin might be preferred in these patients.

Licensed product information for *lenalidomide* states that it may increase plasma exposure of digoxin and recommends that digoxin concentrations should be monitored.

1. Bjornsson TD, *et al.* Effects of high-dose cancer chemotherapy on the absorption of digoxin in two different formulations. *Clin Pharmacol Ther* 1986; 39: 25–8.
2. Kuhlmann J. Inhibition of digoxin absorption but not of digitoxin during cytostatic drug therapy. *Arzneimittelforschung* 1982; 32: 698–704.

Antithyroid drugs. Reduced peak serum-digoxin concentrations were noted in 9 of 10 healthy subjects after a single oral dose of *carbimazole* although conversely in the tenth subject digoxin concentrations rose.[1] Caution is also needed since changes in thyroid function may independently affect sensitivity to digoxin (see Precautions, p. 1355.2).

1. Rao BR, *et al.* Influence of carbimazole on serum levels and haemodynamic effects of digoxin. *Clin Drug Invest* 1997; 13: 350–4.

Antivirals. A woman stabilised on digoxin and tolerating lamivudine, indinavir and stavudine for HIV infection, developed symptoms of digoxin toxicity 3 days after *ritonavir* was added to her treatment.[1] It was suggested that the interaction might be due to inhibition of the P-glycoprotein transporter system by ritonavir. A pharmacokinetic study[2] showing significant inhibition of renal digoxin clearance by ritonavir seemed to support this hypothesis.

1. Phillips EJ, *et al.* Digoxin toxicity and ritonavir: a drug interaction mediated through p-glycoprotein? *AIDS* 2003; 17: 1577–8.
2. Ding R, *et al.* Substantial pharmacokinetic interaction between digoxin and ritonavir in healthy volunteers. *Clin Pharmacol Ther* 2004; 76: 73–84.

Benzodiazepines. Raised serum-digoxin concentrations have been reported in patients also taking *diazepam*[1] or *alprazolam*.[2,3] The clearance of digoxin was reduced by these benzodiazepines.

1. Castillo-Ferrando JR, *et al.* Digoxin levels and diazepam. *Lancet* 1980; ii: 368.
2. Tollefson G, *et al.* Alprazolam-related digoxin toxicity. *Am J Psychiatry* 1984; 141: 1612–14.
3. Guven R, *et al.* Age-related digoxin-alprazolam interaction. *Clin Pharmacol Ther* 1993; 54: 42–4.

Beta$_2$ agonists. A single intravenous[1,2] or oral[3] dose of *salbutamol* has been reported to decrease steady-state serum-digoxin concentrations by up to 16% and 22% respectively in healthy subjects. Although salbutamol had no significant effect on the concentration of digoxin in skeletal muscle, it was considered that increased binding to skeletal muscle could explain the interaction. Beta$_2$ agonists such as salbutamol can also cause hypokalaemia which may increase susceptibility to digoxin-induced arrhythmias.

1. Edner M, Jogestrand T. Effect of salbutamol on digoxin concentration in serum and skeletal muscle. *Eur J Clin Pharmacol* 1989; 36: 235–8.
2. Edner M, *et al.* Effect of salbutamol on digoxin pharmacokinetics. *Eur J Clin Pharmacol* 1992; 42: 197–201.
3. Edner M, Jogestrand T. Oral salbutamol decreases serum digoxin concentration. *Eur J Clin Pharmacol* 1990; 38: 195–7.

Beta blockers. Beta blockers may increase the risk of heart block and bradycardia with digoxin. In addition, *carvedilol* has been reported[1-3] to increase plasma concentrations of digoxin, although the effect is generally small and probably not clinically significant. However, a study[4] in 8 children (aged 2 weeks to 7.8 years) found that the clearance of digoxin was about halved by carvedilol and 2 of the children developed digoxin toxicity. An increase in digoxin bioavailability has also been reported with *talinolol*.[5]

1. Grunden JW, *et al.* Augmented digoxin concentrations with carvedilol dosing in mild-moderate heart failure. *Am J Ther* 1994; 1: 157–161.
2. Wermeling DP, *et al.* Effects of long-term oral carvedilol on the steady-state pharmacokinetics of oral digoxin in patients with mild to moderate hypertension. *Pharmacotherapy* 1994; 14: 600–6.
3. De Mey C, *et al.* Carvedilol increases the systemic bioavailability of oral digoxin. *Br J Clin Pharmacol* 1990; 29: 486–90.
4. Ratnapalan S, *et al.* Digoxin-carvedilol interactions in children. *J Pediatr* 2003; 142: 572–4.
5. Westphal K, *et al.* Oral bioavailability of digoxin is enhanced by talinolol: evidence for involvement of intestinal P-glycoprotein. *Clin Pharmacol Ther* 2000; 68: 6–12.

Calcium-channel blockers. Studies on interactions between digoxin and calcium-channel blockers appear to show that *verapamil* increases plasma-digoxin concentrations[1-3] by up to 70%. The effect of *nifedipine* is not as clear. Although it has been reported[1] to produce a 45% increase in plasma-digoxin concentrations, other studies[4,5] have reported little or no increase and the interaction is unlikely to be of clinical significance for most patients. Studies on the interaction between digoxin or metildigoxin and *diltiazem* have also produced conflicting results. Increases in plasma-digoxin concentrations of 20% and up to 59% have been reported[6,7] and an increase in metildigoxin concentrations[7] of up to 51%. However, other studies[8,9] have shown no diltiazem-induced change in digoxin pharmacokinetics or plasma concentration. *Bepridil*,[10] *gallopamil*,[1] *nisoldipine*,[11] and *nitrendipine*[12] have all been reported to increase plasma-digoxin concentrations. Bepridil increased the concentration by 34% and it was recommended that patients given this combination be monitored carefully. *Felodipine*[13,14] and *isradipine*[3] have both been reported to increase peak serum-digoxin concentrations, but steady-state digoxin concentrations were not affected and the interactions were unlikely to be of clinical relevance.

The mechanism of interaction between calcium-channel blockers and digoxin is not completely understood but appears to be related to decreased renal and nonrenal clearance of digoxin. The pharmacodynamic effects of digoxin and calcium-channel blockers may also be additive.

1. Belz GG, *et al.* Interaction between digoxin and calcium antagonists and antiarrhythmic drugs. *Clin Pharmacol Ther* 1983; 33: 410–17.
2. Pedersen KE, *et al.* Influence of verapamil on the inotropism and pharmacokinetics of digoxin. *Eur J Clin Pharmacol* 1983; 25: 199–206.
3. Rodin SM, *et al.* Comparative effects of verapamil and isradipine on steady-state digoxin kinetics. *Clin Pharmacol Ther* 1988; 43: 668–72.
4. Schwartz JB, Migliore PJ. Effect of nifedipine on serum digoxin concentration and renal digoxin clearance. *Clin Pharmacol Ther* 1984; 36: 19–24.
5. Kleinbloesem CH, *et al.* Interactions between digoxin and nifedipine at steady state in patients with atrial fibrillation. *Ther Drug Monit* 1985; 7: 372–6.
6. Rameis H, *et al.* The diltiazem-digoxin interaction. *Clin Pharmacol Ther* 1984; 36: 183–9.
7. Oyama Y, *et al.* Digoxin-diltiazem interaction. *Am J Cardiol* 1984; 53: 1480–1.
8. Beltrami TR, *et al.* Lack of effects of diltiazem on digoxin pharmacokinetics. *J Clin Pharmacol* 1985; 25: 390–2.
9. Elkayam U, *et al.* Effect of diltiazem on renal clearance and serum concentration of digoxin in patients with cardiac disease. *Am J Cardiol* 1985; 55: 1393–5.
10. Belz GG, *et al.* Digoxin and bepridil: pharmacokinetic and pharmacodynamic interactions. *Clin Pharmacol Ther* 1986; 39: 65–71.
11. Kirch W, *et al.* Influence of nisoldipine on haemodynamic effects and plasma levels of digoxin. *Br J Clin Pharmacol* 1986; 22: 155–9.
12. Kirch W, *et al.* Nitrendipine increases digoxin plasma levels dose dependently. *J Clin Pharmacol* 1986; 26: 553.
13. Rehnqvist N, *et al.* Pharmacokinetics of felodipine and effect on digoxin plasma levels in patients with heart failure. *Drugs* 1987; 34 (suppl 3): 33–42.
14. Dunselman PHJM, *et al.* Digoxin-felodipine interaction in patients with congestive heart failure. *Eur J Clin Pharmacol* 1988; 35: 461–5.

Diuretics. *Amiloride* increased renal clearance of digoxin and reduced the extrarenal digoxin clearance in 6 healthy subjects after a single intravenous dose of digoxin.[1] Amiloride also inhibited the digoxin-induced positive inotropic effect, but the clinical implications in cardiac patients are unknown. A further study[2] failed to confirm this effect.

Spironolactone and its metabolites have been reported to interfere with serum-digoxin determinations by radioimmunoassay or fluorescence-polarisation immunoassay resulting in falsely elevated measurements.[3,4] The interference with digoxin assays is neither consistent nor predictable and falsely low readings have also been reported.[5] Serum-digoxin concentrations should be interpreted with caution when digoxin is given with spironolactone or *canrenoate*, especially since spironolactone has also been reported to decrease digoxin clearance by a median of 26% resulting in a true increase in the serum-digoxin concentration.[6]

Diuretic therapy with *triamterene* in association with a thiazide or loop diuretic increased the mean serum-digoxin concentration; this interaction was considered unlikely to be of clinical importance, except perhaps in patients with renal impairment.[7]

1. Waldorff S, *et al.* Amiloride-induced changes in digoxin dynamics and kinetics: abolition of digoxin-induced inotropism with amiloride. *Clin Pharmacol Ther* 1981; 30: 172–6.
2. Richter JP, *et al.* The acute effects of amiloride and potassium canrenoate on digoxin-induced positive inotropism in healthy volunteers. *Eur J Clin Pharmacol* 1993; 45: 195–6.
3. Paladino JA, *et al.* Influence of spironolactone on serum digoxin concentration. *JAMA* 1984; 251: 470–1.
4. Foukaridis GN. Influence of spironolactone and its metabolite canrenone on serum digoxin assays. *Ther Drug Monit* 1990; 12: 82–4.
5. Steimer W, *et al.* Intoxication due to negative canrenone interference in digoxin drug monitoring. *Lancet* 1999; 354: 1176–7.
6. Waldorff S, *et al.* Spironolactone-induced changes in digoxin kinetics. *Clin Pharmacol Ther* 1978; 24: 162–7.
7. Impivaara O, Ilsalo E. Serum digoxin concentrations in a representative digoxin-consuming adult population. *Eur J Clin Pharmacol* 1985; 27: 627–32.

Gastrointestinal drugs. Some gastrointestinal drugs can affect the absorption of digoxin by binding to it or by changing gastrointestinal motility. The problem has often been related to the bioavailability of the digoxin formulation and appears to be less important with currently used preparations. Some *antacids*,[1,2] particularly liquid formulations, and *adsorbents*[1] such as kaolin-pectin, can reduce the absorption of digoxin from the gastrointestinal tract and doses should probably be separated by at least 2 hours. *Activated charcoal*, and *ion-exchange resins* such as colestyramine and colestipol, also reduce digoxin absorption. *Sucralfate*[3] may also reduce the absorption of digoxin.

Omeprazole, and possibly other gastric acid inhibitors, may reduce the gastrointestinal metabolism and enhance the absorption of unchanged digoxin,[4] resulting in small increases in digoxin plasma concentrations that are unlikely to be clinically significant in most patients,[5] although toxicity was reported in a woman whose digoxin concentration increased from 1.1 nanograms/mL to 3.9 nanograms/mL one month after starting omeprazole.[6]

Drugs that increase gastrointestinal motility can reduce the absorption of digoxin, especially if digoxin is given as a slowly dissolving formulation. Reduced absorption of digoxin has occurred when digoxin and *metoclopramide* have been given together,[7] and a similar effect has been reported with *cisapride*[8] and *tegaserod*.[9] Conversely, *anticholinergics* reduce motility, and propantheline has increased digoxin absorption.

Sulfasalazine has been found to impair the absorption of digoxin and to reduce the serum-digoxin concentration,[10] but the mechanism is unclear.

1. Rodin SM, Johnson BF. Pharmacokinetic interactions with digoxin. *Clin Pharmacokinet* 1988; 15: 227–44.
2. Gugler R, Allgayer H. Effects of antacids on the clinical pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1990; 18: 210–19.
3. Rey AM, Gums JG. Altered absorption of digoxin, sustained-release quinidine, and warfarin with sucralfate administration. *DICP Ann Pharmacother* 1991; 25: 745–6.
4. Cohen AF, *et al.* Influence of gastric acidity on the bioavailability of digoxin. *Ann Intern Med* 1991; 115: 540–5.
5. Oosterhuis B, *et al.* Minor effect of multiple dose omeprazole on the pharmacokinetics of digoxin after a single oral dose. *Br J Clin Pharmacol* 1991; 32: 569–72.
6. Kiley CA, *et al.* Omeprazole-associated digoxin toxicity. *South Med J* 2007; 100: 400–2.
7. Johnson BF, *et al.* Effect of metoclopramide on digoxin absorption from tablets and capsules. *Clin Pharmacol Ther* 1984; 36: 724–30.
8. Kubler PA, *et al.* Possible interaction between cisapride and digoxin. *Ann Pharmacother* 2001; 35: 127–8.
9. Zhou H, *et al.* The effects of tegaserod (HTF 919) on the pharmacokinetics and pharmacodynamics of digoxin in healthy subjects. *J Clin Pharmacol* 2001; 41: 1131–9.
10. Juhl RP, *et al.* Effect of sulfasalazine on digoxin bioavailability. *Clin Pharmacol Ther* 1976; 20: 387–94.

Ginseng. Varieties of ginseng may interfere with plasma-digoxin assays (see under Precautions, p. 1355.3).

Immunosuppressants. Increased serum-digoxin concentrations with symptoms of toxicity have been reported in patients when *ciclosporin* was added to their digoxin therapy.[1,2]

1. Dorian P, *et al.* Digoxin-cyclosporine interaction: severe digitalis toxicity after cyclosporine treatment. *Clin Invest Med* 1988; 11: 108–12.

2. Robieux I, *et al.* The effects of cardiac transplantation and cyclosporine therapy on digoxin pharmacokinetics. *J Clin Pharmacol* 1992; 32: 338–43.

Lipid regulating drugs. Small increases in plasma-digoxin concentrations have been reported with some *statins*, although the clinical significance is not clear. *Atorvastatin* at doses of 80 mg, but not of 10 mg, has been shown[1] to increase plasma-digoxin concentrations by about 20%. This may be due to the inhibition of P-glycoprotein-mediated secretion of digoxin in the intestine by atorvastatin.

1. Boyd RA, *et al.* Atorvastatin coadministration may increase digoxin concentrations by inhibition of intestinal P-glycoprotein-mediated secretion. *J Clin Pharmacol* 2000; 40: 91–98.

Neuromuscular blockers. *Pancuronium* or *suxamethonium* may interact with digitalis glycosides resulting in an increased incidence of arrhythmias; the interaction is more likely with pancuronium.[1]

1. Bartolone RS, Rao TLK. Dysrhythmias following muscle relaxant administration in patients receiving digitalis. *Anesthesiology* 1983; 58: 567–9.

NSAIDs. An increase in serum-digoxin concentration has been reported with *aspirin, ibuprofen, indometacin, fenbufen,* and *diclofenac.*[1] Potentially toxic serum-digoxin concentrations occurred in preterm infants[2] with patent ductus arteriosus receiving digoxin when given indometacin orally in a mean total dose of 320 micrograms/kg; it was recommended that the dose of digoxin should be halved initially if indometacin is also given. (For the possible effect of digoxin on indometacin see Half-life, under Pharmacokinetics of Indometacin, p. 74.1.) Lack of increase in serum-digoxin concentrations has also been reported with aspirin or indometacin, as well as with *ketoprofen,* and *tiaprofenic acid,*[1] and also with *etoricoxib*[3] and *rofecoxib,*[4] but some of these studies were in healthy subjects and it is advised that digoxin therapy be monitored carefully whenever any NSAID is started or stopped in digitalised patients.

1. Verbeeck RK. Pharmacokinetic drug interactions with nonsteroidal anti-inflammatory drugs. *Clin Pharmacokinet* 1990; 19: 44–66.
2. Koren G, *et al.* Effects of indomethacin on digoxin pharmacokinetics in preterm infants. *Pediatr Pharmacol* 1984; 4: 25–30.
3. Schwartz JI, *et al.* Evaluation of the pharmacokinetics of digoxin in healthy subjects receiving etoricoxib. *Br J Clin Pharmacol* 2008; 66: 811–17.
4. Schwartz JI, *et al.* Effect of rofecoxib on the pharmacokinetics of digoxin in healthy volunteers. *J Clin Pharmacol* 2001; 41: 107–112.

Penicillamine. Digoxin concentrations can be reduced by penicillamine. One manufacturer of penicillamine (*Alliance, UK*) recommends that digoxin should not be given within 2 hours of penicillamine, as oral absorption of digoxin may be reduced. However, serum-digoxin concentrations were reduced when an oral dose of penicillamine was given either 2 or 16 hours after an oral dose of digoxin, or 2 hours after an intravenous dose,[1] indicating that the interaction is not entirely related to reduced oral absorption of digoxin. Reductions in the serum-digoxin concentration were also noted in children on oral digoxin given oral penicillamine.[2]

1. Moezzi B, *et al.* The effect of penicillamine on serum digoxin levels. *Jpn Heart J* 1978; 19: 366–75.
2. Moezzi B, *et al.* Reversal of digoxin-induced changes in erythrocyte electrolyte concentrations by penicillamine in children. *Jpn Heart J* 1980; 21: 335–9.

Urological drugs. *Mirabegron,* a beta$_3$-adrenoceptor agonist, was reported to increase the peak plasma concentration and AUC of digoxin by 29 and 27%, respectively; therefore the lowest initial dose of digoxin should be given to patients who are starting concomitant therapy and serum-digoxin concentrations monitored.

Vasopressin receptor antagonists. The vasopressin receptor antagonists *conivaptan* and *tolvaptan* can reduce the clearance, and subsequently increase concentrations, of digoxin.

Pharmacokinetics

The absorption of digoxin from the gastrointestinal tract is variable depending upon the formulation used. About 70% of a dose is absorbed from tablets which comply with BP or USP specifications, 80% is absorbed from an elixir, and over 90% is absorbed from liquid-filled soft gelatin capsules. The generally accepted therapeutic plasma concentration range is 0.5 to 2.0 nanograms/mL but there is considerable interindividual variation. Digoxin has a large volume of distribution and is widely distributed in tissues, including the heart, brain, erythrocytes, and skeletal muscle. The concentration of digoxin in the myocardium is considerably higher than in plasma. From 20 to 30% is bound to plasma proteins. Digoxin has been detected in CSF and breast milk; it also crosses the placenta. It has an elimination half-life of 1.5 to 2 days.

Digoxin is mainly excreted unchanged in the urine by glomerular filtration and tubular secretion; reabsorption also occurs. Extensive metabolism has been reported in a minority of patients (see under Metabolism and Excretion, below). Excretion of digoxin is proportional to the glomerular filtration rate. After intravenous injection 50 to 70% of the dose is excreted unchanged. Digoxin is not removed from the body by dialysis, and only small amounts are removed by exchange transfusion and during cardiopulmonary bypass.

Reviews of the clinical pharmacokinetics of digoxin.

1. Iisalo E. Clinical pharmacokinetics of digoxin. *Clin Pharmacokinet* 1977; 2: 1–16.
2. Aronson JK. Clinical pharmacokinetics of digoxin 1980. *Clin Pharmacokinet* 1980; 5: 137–49.
3. Mooradian AD. Digitalis: an update of clinical pharmacokinetics, therapeutic monitoring techniques and treatment recommendations. *Clin Pharmacokinet* 1988; 15: 165–79.

Absorption. Studies in 6 healthy subjects found that food decreased the rate but not the extent of absorption of digoxin.[1]

1. Johnson BF, *et al.* Effect of a standard breakfast on digoxin absorption in normal subjects. *Clin Pharmacol Ther* 1978; 23: 315–19.

Bioavailability. Large variations in the content, disintegration, and dissolution of solid dosage forms of digoxin preparations have led to large variations in plasma concentrations from different proprietary preparations. Other factors involved in varying bioavailability include the pharmaceutical formulation and presentation (capsules, solution, or tablets), particle size, and biological factors. Serious problems occurred in the UK[1] in 1972 and in Israel[2] in 1975 after changes in the manufacturing procedure for *Lanoxin* led to a twofold increase in bioavailability.

1. Anonymous. Therapeutic non-equivalence. *BMJ* 1972; 3: 599–600.
2. Danon A, *et al.* An outbreak of digoxin intoxication. *Clin Pharmacol Ther* 1977; 21: 643–6.

Distribution and protein binding. Digoxin has been reported to be 5 to 60% bound to plasma proteins,[1] depending partly on the method of measurement, but the figure is usually around 20%. Protein binding is reduced in patients undergoing haemodialysis; mean reductions of about 8 and 10% have been reported.[1,2] Injection of heparin has produced a similar reduction.[2]

Digoxin is widely distributed to tissues and serum-digoxin concentrations have been reported to be increased during immobilisation[3] and decreased during exercise[4,5] due to changes in binding to tissues such as skeletal muscle.

1. Storstein L. Studies on digitalis V: the influence of impaired renal function, hemodialysis, and drug interaction on serum protein binding of digitoxin and digoxin. *Clin Pharmacol Ther* 1976; 20: 6–14.
2. Storstein L, Janssen H. Studies on digitalis VI: the effect of heparin on serum protein binding of digitoxin and digoxin. *Clin Pharmacol Ther* 1976; 20: 15–23.
3. Pedersen KE, *et al.* Effects of physical activity and immobilization on plasma digoxin concentration and renal digoxin clearance. *Clin Pharmacol Ther* 1983; 34: 303–8.
4. Joreteg T, Jogestrand T. Physical exercise and digoxin binding to skeletal muscle: relation to exercise intensity. *Eur J Clin Pharmacol* 1983; 25: 585–8.
5. Joreteg T, Jogestrand T. Physical exercise and binding of digoxin to skeletal muscle—effect of muscle activation frequency. *Eur J Clin Pharmacol* 1984; 27: 567–70.

The elderly. For references to alterations in the pharmacokinetics of digoxin in the elderly, see under Uses and Administration, p. 1354.2.

Infants and neonates. Digoxin has been widely used in the treatment of cardiac disorders in neonates and infants and its pharmacokinetics in this age group have been reviewed.[1,2] In full-term neonates or infants, 80 to 90% of a dose of digoxin given orally in liquid form is absorbed, with peak plasma concentrations occurring within 30 to 120 minutes. The rate of absorption may be slower in preterm and low birth-weight infants, with peak concentrations at 90 to 180 minutes, and may be significantly reduced in severe heart failure and in malabsorption syndromes. After digoxin is given intravenously there is a rapid distribution phase with an apparent half-life of 20 to 40 minutes followed by a slower exponential decay of plasma concentrations. In full-term neonates, digoxin has an apparent volume of distribution of 6 to 10 litres/kg. Low birth-weight infants have a volume of distribution of 4.3 to 5.7 litres/kg while in older infants the volume may range from 10 to 22 litres/kg which is 1.5 to 2 times reported adult values. This large volume of distribution in full-term neonates and infants is thought to be due to increased tissue binding, a larger extracellular fluid volume, and slightly lower plasma protein binding.

The apparent plasma half-life in healthy and sick neonates is generally very long and may range from 20 to 70 hours in full-term neonates or from 40 to 180 hours in preterm neonates. Digoxin is eliminated at a considerably faster rate in infants than in neonates and, in parallel with maturation of kidney function, a marked increase in clearance rate is usually seen between the second and third month of life. The large apparent volume of distribution, higher clearance values, and greater concentrations of digoxin in the myocardial tissue and red cells of infants might justify the traditional assumption that infants tolerate digoxin better than adults and that higher doses are consequently needed in infants. However, studies have shown that in infants, as in adults, toxic signs become evident at plasma-digoxin concentrations above 3 nanograms/mL and that the therapeutic range may be 1.5 to 2 nanograms/mL.

1. Morselli PL, *et al.* Clinical pharmacokinetics in newborns and infants: age-related differences and therapeutic implications. *Clin Pharmacokinet* 1980; 5: 485–527.
2. Besunder JB, *et al.* Principles of drug biodisposition in the neonate: a critical evaluation of the pharmacokinetic-pharmacodynamic interface. *Clin Pharmacokinet* 1988; 14: 189–216 (part I) and 261–86 (part II).

Metabolism and excretion. Although digoxin is reported to be excreted mainly unchanged in the urine there is evidence to suggest that metabolism may sometimes be extensive. Metabolites that have been detected in the urine include digoxigenin, dihydrodigoxigenin, the mono- and bisdigitoxosides of digoxigenin, and dihydrodigoxin. Digoxigenin mono- and bisdigitoxosides are known to be cardioactive whereas dihydrodigoxin is probably much less active than digoxin.[1]

In about 10% of patients there is considerable reduction to cardio-inactive metabolites, chiefly dihydrodigoxin, and 40% or more of a dose may be excreted in the urine as dihydrodigoxin.[2-4] Bacterial flora in the gastrointestinal tract appear to be responsible for this metabolism and antibacterials can reduce the process. Oral digoxin formulations with a high bioavailability are mostly absorbed in the stomach and upper small intestine and little digoxin is available in the lower intestine for bacterial degradation to dihydrodigoxin.[4]

The excretion of digoxin is thought to be mediated by the efflux pump, P-glycoprotein,[5] which transports its substrates out of the cell. This may be the basis for some interactions hitherto poorly understood,[6] although the hypothesis has been questioned.[7]

1. Iisalo E. Clinical pharmacokinetics of digoxin. *Clin Pharmacokinet* 1977; 2: 1–16.
2. Doherty JE. A digoxin-antibiotic drug interaction. *N Engl J Med* 1981; 305: 827–8.
3. Rund DG, *et al.* Decreased digoxin cardioinactive-reduced metabolite after administration of an encapsulated liquid concentrate. *Clin Pharmacol Ther* 1983; 34: 738–43.
4. Lofts F, *et al.* Digoxin metabolism to reduced products: clinical significance. *Br J Clin Pharmacol* 1986; 21: 600P.
5. Tanigawara Y. Role of P-glycoprotein in drug disposition. *Ther Drug Monit* 2000; 22: 137–40.
6. Pronin MF. P-glycoprotein: a defense mechanism limiting oral bioavailability and CNS accumulation of drugs. *Int J Clin Pharmacol Ther* 2000; 38: 69–74.
7. Chiou WL, *et al.* A comprehensive account on the role of efflux transporters in the gastrointestinal absorption of 13 commonly used substrate drugs in humans. *Int J Clin Pharmacol Ther* 2001; 39: 93–101.

Renal impairment. For references to alterations in the pharmacokinetics of digoxin in patients with renal impairment, see under Uses and Administration, p. 1354.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cardiogoxin; Digocard-G; Lanicor; Lanoxin; ***Austral.***: Lanoxin; Sigmaxin; ***Belg.***: Lanoxin; ***Braz.***: Cardcor; Cardionil; Cimecard; Digitax†; Digobal; Digoxen; Digoxil; Valoxin; ***Canad.***: Lanoxin; Toloxin; ***China***: Ke Li (可力); ***Fr.***: Hemigoxine Nativelle; ***Ger.***: Digacin; Lanicor; Lenoxin; ***Gr.***: Lanoxin; ***Hong Kong***: Lanoxin†; ***India***: Digitran; Digosyp; Digox; Dixin; Geoxin; Lanoxin; ***Indon.***: Fargoxin; Lanoxin; ***Irl.***: Lanoxin; ***Israel***: Lanoxin; ***Ital.***: Eudigox; Lanoxin; ***Jpn***: Digosin; ***Malaysia***: Lanoxin; ***Mex.***: Bioxalyt; Lanoxin; Mapluxin; Valvulan; ***Neth.***: Lanoxin; ***Norw.***: Lanoxin; ***NZ***: Lanoxin; ***Philipp.***: Cardioxin; Lanox; Lanoxin; ***Port.***: Lanoxin; ***S.Afr.***: Lanoxin; Purgoxin; ***Singapore***: Lanoxin; ***Spain***: Lanacordin; ***Swed.***: Lanoxin; ***Thai.***: Cardial; Grexin; Lanoxin; Toloxin; ***UK***: Lanoxin; ***USA***: Lanoxin; ***Venez.***: Lanicor.

Pharmacopoeial Preparations

BP 2014: Digoxin Injection; Digoxin Tablets; Paediatric Digoxin Injection; Paediatric Digoxin Oral Solution;
USP 36: Digoxin Elixir; Digoxin Injection; Digoxin Tablets.

Dihydralazine Sulfate *(BANM, rINNM)*

Dihidralazina, sulfato de; Dihidralazino sulfatas, hidratuotas; Dihidralazin-szulfát-hidrát; Dihydralatsiinisulfaatti, hydratoitu; Dihydralazine, Sulfate de; Dihydralazine (sulfate de) hydraté; Dihydralazine Sulphate; Dihydralazini Sulfas; Dihydralazini sulfas hydricus; Dihydralazin-sulfát; Dihydralazinsulfat, hydratiserat; Dihydralazinum Sulfuricum; Dihydralazyny siarczan; Dihydrallazine Sulphate; Sulfato de dihidralazina; Дигидралазина Сульфат.

Phthalazine-1,4-diyldihydrazine sulfate hemipentahydrate.

$C_8H_{10}N_6.H_2SO_4.2\frac{1}{2}H_2O$=333.3

CAS — 484-23-1 (dihydralazine); 7327-87-9 (dihydralazine sulfate).

ATC — C02DB01.
ATC Vet — QC02DB01.
UNII — 1C281W91NK.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Dihydralazine Sulfate, Hydrated). A white or slightly yellow crystalline powder. Slightly soluble in water; practically insoluble in dehydrated alcohol. It dissolves in dilute mineral acids.

Profile

Dihydralazine is a vasodilator with actions and uses similar to those of hydralazine (p. 1401.2). It is given orally as the sulfate. Dihydralazine sulfate hemipentahydrate 14.45 mg is equivalent to about 12.5 mg of anhydrous dihydralazine sulfate. In hypertension (p. 1251.1) the usual initial dose is the equivalent of 12.5 mg of anhydrous dihydralazine sulfate twice daily and the maximum recommended dose is 50 mg twice daily. Higher doses have been used in the management of heart failure.

Other salts of dihydralazine that have been used in oral preparations include the hydrochloride and the tartrate. The mesilate is given by injection.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dihydralazine as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Nepresol†; *Fr.*: Nepressol; *Ger.*: Depressan†; Nepresol; *Gr.*: Nepresol; *Hung.*: Depressan; *India*: Apresol; Nepresol; *Thai.*: Nepresol†.

Multi-ingredient Preparations. *China*: Fufang Lixueping (复方利血平); No 0 (0号); *Ger.*: Triniton†; *India*: Adelphane-Esidrex; Adelphane; Beptazine-H†; Beptazine†; Genophane; *Indon.*: Dellasidrex†; *Rus.*: Adelphane-Esidrex (Адельфан-эзидрекс); Triresid K (Трирезид К)†; *Turk.*: Adelphan-Esidrex†; Adelphan†; *Ukr.*: Adelphane-Esidrex (Адельфан-Эзидрекс).

Di-isopropylammonium Dichloroacetate

Diisopropilamina, dicloroacetato de; Di-isopropylamine Dichloroacetate; Di-isopropylamine Dichloroethanoate; DIPA-DCA.

$C_6H_{17}Cl_2NO_2$=230.1

CAS — 660-27-5.

UNII — BA6QDP0R4E.

Profile

Di-isopropylammonium dichloroacetate is a vasodilator that has been given in peripheral and cerebral vascular disorders. Preparations containing it have sometimes been described as 'pangamic acid' (p. 2582.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Bo Lang (博朗); Ke Rui Te (克瑞特); Ya Pu Yi (雅普宜); *Israel*: Kit For Tc-99 Labeled DIPA; *Mex.*: Ditrei.

Multi-ingredient Preparations. *China*: Compound Diisopropylamine Dichloroacetate (复方二氯醋酸二异丙胺); Er Qi (尔琪); *Spain*: Vitaber A E.

Dilazep Hydrochloride *(rINNM)*

Asta C-4898; Dilazep, Chlorhydrate de; Dilazep, hidrocloruro de; Dilazepi Hydrochloridum; Hidrocloruro de dilazep; Дилазепа Гидрохлорид.

Perhydro-1,4-diazepin-1,4-diylbis(trimethylene 3,4,5-trimethoxybenzoate) dihydrochloride.

$C_{31}H_{44}N_2O_{10}$,2HCl=677.6

CAS — 35898-87-4 (dilazep); 20153-98-4 (dilazep hydrochloride).

ATC — C01DX10.

ATC Vet — QC01DX10.

Pharmacopoeias. *Jpn* includes the monohydrate.

Profile

Dilazep hydrochloride is an oral vasodilator that is used in ischaemic heart disease at a dose of 50 mg three times daily, and in the treatment of proteinuria at a dose of 100 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Cornelian; *Jpn*: Comelian.

Diltiazem Hydrochloride

(BANM, USAN, rINNM)

CRD-401; Diltiatseemihydrokloridi; Diltiazem, chlorhydrate de; Diltiazem, hidrocloruro de; Diltiazem Hidroklorür; Diltiazem hydrochlorid; Diltiazem-hidroklorid; Diltiazemhydrochlorid; Diltiazemhydroklorid; Diltiazemi Hydrochloridum; Diltiazemo hidrochloridas; Diltiazemu chlorowodorek; Hidrocloruro de diltiazem; Latiazem Hydrochloride; MK-793 (diltiazem malate); Дилтиазема Гидрохлорид.

(+)-*cis*-3-Acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one hydrochloride; (2*S*,3*S*)-5-(2-Dimethylaminoethyl)-2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepin-3-yl acetate hydrochloride.

$C_{22}H_{26}N_2O_4S$,HCl=451.0

CAS — 42399-41-7 (diltiazem); 33286-22-5 (diltiazem hydrochloride); 144604-00-2 (diltiazem malate).

ATC — C08DB01.

ATC Vet — QC08DB01.

UNII — OLH94387TE.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Diltiazem Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water, in dichloromethane, and in methyl alcohol; slightly soluble in dehydrated alcohol. The pH of a 1% solution in water is 4.3 to 5.3. Store in airtight containers. Protect from light.

USP 36: (Diltiazem Hydrochloride). A white, odourless, crystalline powder, or small crystals. Freely soluble in water, in chloroform, in formic acid, and in methyl alcohol; sparingly soluble in dehydrated alcohol; insoluble in ether. Store in airtight containers. Protect from light.

Uses and Administration

Diltiazem is a benzothiazepine calcium-channel blocker (p. 1244.2) and class IV antiarrhythmic (p. 1243.1). It is a peripheral and coronary vasodilator with limited negative inotropic activity but its vasodilator properties are less marked than those of the dihydropyridine calcium-channel blocker nifedipine (p. 1447.2). Unlike nifedipine, diltiazem inhibits cardiac conduction, particularly at the sino-atrial and atrioventricular nodes.

Diltiazem hydrochloride is given orally in the management of angina pectoris (p. 1254.3) and hypertension (p. 1251.1). In some countries it is available for intravenous use in the treatment of various cardiac arrhythmias (atrial fibrillation or flutter and paroxysmal supraventricular tachycardia) (p. 1266.1). It has also been used topically in the management of anal fissure (see below).

The variety of formulations means that dosage is dependent on the preparation used. Reduced doses may be required in the elderly or those with renal or hepatic impairment (see below).

In **angina pectoris** an initial dose is 60 mg orally three times daily (or 30 mg four times daily in the USA), increased if necessary to 360 mg daily; up to 480 mg daily has sometimes been given. Formulations suitable for once- or twice-daily use may be given in doses of 120 to 480 mg daily; up to 540 mg daily has been used.

In **hypertension** diltiazem hydrochloride may be given as modified-release capsules or tablets. Depending on the formulation, an initial dose is 90 to 120 mg twice daily, increased as required to a maximum of 360 mg daily. Formulations suitable for once-daily dosage may be given in similar daily doses, although up to 540 mg daily has been given.

In **cardiac arrhythmias** an initial dose of 250 micrograms/kg by bolus intravenous injection over 2 minutes has been suggested; a further dose of 350 micrograms/kg may be given after 15 minutes if the response is inadequate. Subsequent doses should be individualised for each patient. For those with atrial fibrillation or flutter, a continued reduction in heart rate may be achieved with an intravenous infusion of diltiazem hydrochloride after the bolus injection. An initial infusion rate of 5 to 10 mg/hour, may be increased as necessary in increments of 5 mg/hour up to a rate of 15 mg/hour. The infusion may be continued for up to 24 hours.

General reviews.

1. Buckley MM-T, *et al.* Diltiazem: a reappraisal of its pharmacological properties and therapeutic use. *Drugs* 1990; 39: 757–806.
2. Weir MR. Diltiazem: ten years of clinical experience in the treatment of hypertension. *J Clin Pharmacol* 1995; 35: 220–32.
3. Ezeugo U, Glasser SP. Clinical benefits versus shortcomings of diltiazem once-daily in the chronotherapy of cardiovascular diseases. *Expert Opin Pharmacother* 2009; 10: 485–91.

Action. The haemodynamic and electrophysiological effects of diltiazem appear to resemble those of verapamil more than those of nifedipine.[1] It inhibits sino-atrial and atrioventricular nodal function in doses used clinically. The effects on sino-atrial function are more pronounced than those seen after verapamil. Diltiazem causes a decrease in the rate-pressure product indicating that decreased oxygen demand is a likely mechanism of action in relieving angina pectoris. Like verapamil, but unlike nifedipine, diltiazem does not appear to cause significant increases in coronary blood flow. The negative inotropic effect of diltiazem is presumably counteracted by afterload reduction.

1. Soward AL, *et al.* The haemodynamic effects of nifedipine, verapamil and diltiazem in patients with coronary artery disease: a review. *Drugs* 1986; 32: 66–101.

Administration in hepatic or renal impairment. The dose of diltiazem hydrochloride may need to be reduced in patients with hepatic or renal impairment, and in the elderly. In the UK an initial oral dose of 120 mg daily is usually suggested, as a single dose or in 2 divided doses depending on the formulation. The dose may be increased cautiously, but only if the heart rate remains above 50 beats/minute.

Anorectal disorders. Topical nitrates have been commonly used in the management of chronic *anal fissure* (p. 2017.3) because of their ability to relax the anal sphincter. Calcium-channel blockers, including diltiazem, have also been used successfully. Oral diltiazem has been compared[1] with topical therapy; fewer adverse effects were reported in those given topical therapy, which also appeared to be more effective, although this did not reach statistical significance. A systematic review[2] that compared topical diltiazem 2% with topical glyceryl trinitrate found therapeutic effect and recurrence rate were similar with the two treatments, but those using diltiazem had fewer adverse effects; the use of diltiazem as a first-line drug was suggested. Diltiazem has also been tried[3] in patients with resistance to, or intolerance of, nitrates: about half of the patients were healed with diltiazem. A sustained benefit after a 6-week course of topical diltiazem 2% has been seen[4] in some (including a small number of nitrate-resistant cases) although many required further treatment during an average follow-up of 2 years.

Beneficial responses to diltiazem reported[5,6] in 2 patients with *proctalgia fugax* may have been due to smooth muscle relaxation. The resting pressure of the internal anal sphincter was decreased by a mean of 20.6% in all but 1 of 13 subjects given a single 60-mg oral dose of diltiazem.[6]

1. Jonas M, *et al.* A randomized trial of oral vs topical diltiazem for chronic anal fissures. *Dis Colon Rectum* 2001; 44: 1074–8.
2. Sajid MS, *et al.* The efficacy of diltiazem and glyceryltrinitrate for the medical management of chronic anal fissure: a meta-analysis. *Int J Colorectal Dis* 2008; 23: 1–6.
3. Jonas M, *et al.* Diltiazem heals glyceryl trinitrate-resistant chronic anal fissures: a prospective study. *Dis Colon Rectum* 2002; 45: 1091–5.
4. Nash GF, *et al.* The long-term results of diltiazem treatment for anal fissure. *Int J Clin Pract* 2006; 60: 1411–13.
5. Boquet J, *et al.* Diltiazem for proctalgia fugax. *Lancet* 1986; i: 1493.
6. Jonard P, Essamri B. Diltiazem and internal anal sphincter. *Lancet* 1987; i: 754.

Cardiomyopathies. Although calcium-channel blockers should be used with caution in patients with heart failure, symptomatic improvement has been reported in patients with dilated cardiomyopathy (p. 1261.3) given diltiazem.[1]

1. Figulla HR, *et al.* Diltiazem improves cardiac function and exercise capacity in patients with idiopathic dilated cardiomyopathy: results of the Diltiazem in Dilated Cardiomyopathy Trial. *Circulation* 1996; 94: 346–52.

Connective tissue and muscular disorders. Subcutaneous deposition of calcium (calcinosis) can occur in several inflammatory conditions, particularly in juvenile dermatomyositis (see Polymyositis and Dermatomyositis, p. 1611.1). Treatment of calcinosis is difficult, but there have been reports of the successful use of diltiazem in children[1-3] and adults[4,5] with dermatomyositis, as well as in adults with CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias) syndrome,[6] scleroderma,[7] Sjögren's syndrome,[8] and lupus panniculitis.[9] Another study,[10] however, found only a limited response in patients with systemic sclerosis.

1. Oliveri MB, *et al.* Regression of calcinosis during diltiazem treatment in juvenile dermatomyositis. *J Rheumatol* 1996; 23: 2152–5.
2. Ichiki Y, *et al.* An extremely severe case of cutaneous calcinosis with juvenile dermatomyositis, and successful treatment with diltiazem. *Br J Dermatol* 2001; 144: 894–7.
3. Jiang X, *et al.* A case of juvenile dermatomyositis with severe calcinosis and successful treatment with prednisone and diltiazem. *Int J Dermatol* 2011; 50: 74–7.
4. Vinen CS, *et al.* Regression of calcinosis associated with adult dermatomyositis following diltiazem therapy. *Rheumatology (Oxford)* 2000; 39: 333–4.
5. Abdallah-Lotf M, *et al.* Regression of cutis calcinosis with diltiazem in adult dermatomyositis. *Eur J Dermatol* 2005; 15: 102–4.
6. Palmieri GMA, *et al.* Treatment of calcinosis with diltiazem. *Arthritis Rheum* 1995; 38: 1646–54.

The symbol † denotes a preparation no longer actively marketed

7. Dolan AL, *et al.* Diltiazem induces remission of calcinosis in scleroderma. *Br J Rheumatol* 1995; 34: 576–8.
8. Llamas-Velasco M, *et al.* Calcinosis cutis and Sjögren's syndrome. *Lupus* 2010; 19: 762–4.
9. Morgan KW, *et al.* Calcifying lupus panniculitis in a patient with subacute cutaneous lupus erythematosus: response to diltiazem and chloroquine. *J Rheumatol* 2001; 28: 2129–32.
10. Vryssairat M, *et al.* Clinical significance of subcutaneous calcinosis in patients with systemic sclerosis: does diltiazem induce its regression? *Ann Rheum Dis* 1998; 57: 252–4.

Kidney disorders. Calcium-channel blockers may be of benefit in various forms of kidney disorder (see Nifedipine, p. 1449.1). Diltiazem has been reported to reduce urinary protein excretion without exacerbating pre-existing renal dysfunction in diabetic patients.[1,2] A small study[3] in 15 hypertensive patients with type 2 diabetes mellitus, albuminuria, and renal impairment found that diltiazem only reduced urinary albumin excretion when patients received a restricted dietary sodium intake of 50 mmol daily.

Diltiazem may also reduce the nephrotoxicity associated with certain drugs. Reduced nephrotoxicity has been reported when diltiazem is given to healthy subjects receiving netilmicin,[4] but diltiazem does not appear to modify the acute renal failure associated with tubular damage which may be caused by methotrexate.[5] Diltiazem may reduce ciclosporin-induced nephrotoxicity (see Transplantation, below).

1. Bakris GL. Effects of diltiazem or lisinopril on massive proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; 112: 707–8.
2. Demarie BK, Bakris GL. Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; 113: 987–8.
3. Bakris GL, Smith A. Effects of sodium intake on albumin excretion in patients with diabetic nephropathy treated with long-acting calcium antagonists. *Ann Intern Med* 1996; 125: 201–4.
4. Lortholary O, *et al.* Calcium antagonists and aminoglycoside nephrotoxicity. *Am J Med* 1990; 88: 445.
5. Deray G, *et al.* The effects of diltiazem on methotrexate-induced nephrotoxicity. *Eur J Clin Pharmacol* 1989; 37: 337–40.

Migraine. For reference to the use of calcium-channel blockers, including diltiazem, in the management of migraine, see under Nifedipine, p. 1449.1.

Myocardial infarction. For reference to the use of diltiazem in the acute and long-term management of myocardial infarction, see under Uses of Verapamil, p. 1523.2.

Peripheral vascular disease. Diltiazem has occasionally, like other calcium-channel blockers, been used in the treatment of Raynaud's syndrome, including in adolescents; the *BNFC* suggests that an oral dose of 30 to 60 mg two or three times daily may be appropriate from 12 years of age. For mention of the use of diltiazem in CREST syndrome, symptoms of which include secondary Raynaud's syndrome, see Connective Tissue and Muscular Disorders, p. 1359.3.

Pulmonary hypertension. For the use of calcium-channel blockers, including diltiazem, in pulmonary hypertension, see under Nifedipine, p. 1450.1.

Transplantation. Diltiazem increases blood-*ciclosporin* concentrations when given orally in doses of 60 to 180 mg daily to transplant patients receiving ciclosporin therapy.[1-3] In consequence, ciclosporin doses can be reduced by about one-third, at a considerable saving in cost.[2-4] However, the effect may not occur in all patients,[5] and may vary with differing formulations[6] (most studies have been with older formulations, although benefit has been reported with newer micro-emulsifying preparations of ciclosporin[4]), and it has been suggested that blood-ciclosporin concentrations should be closely monitored if diltiazem is used for this purpose. In addition to this effect, which is apparently due to non-competitive inhibition of ciclosporin metabolism by diltiazem,[7] there is evidence of improved renal graft-function in patients given the combined therapy, suggesting that diltiazem may reduce ciclosporin-induced nephrotoxicity.[1,2] However, a 4-year follow-up study in patients treated with ciclosporin and diltiazem found that diltiazem had no effect on the progression to chronic allograft nephropathy.[8] Improved survival has been reported[9,10] in retrospective studies of patients given diltiazem for its ciclosporin-sparing effect, perhaps because of a reduction in hepatotoxicity and ciclosporin-associated nephrotoxicity.[10]

A sparing effect has also been seen when diltiazem is used with *tacrolimus*.[11]

1. Wagner K, Neumayer H-H. Prevention of delayed graft function in cadaver kidney transplants by diltiazem. *Lancet* 1985; ii: 1355–6.
2. Neumayer H-H, Wagner K. Diltiazem and economic use of cyclosporin. *Lancet* 1986; ii: 523.
3. Bourge RC, *et al.* Diltiazem-cyclosporine interaction in cardiac transplant recipients: impact on cyclosporine dose and medication costs. *Am J Med* 1991; 90: 402–4.
4. Kumana CR, *et al.* Diltiazem co-treatment in renal transplant patients receiving microemulsion cyclosporin. *Br J Clin Pharmacol* 2003; 56: 670–8.
5. Jones TE, Morris RG. Diltiazem does not always increase blood cyclosporin concentration. *Br J Clin Pharmacol* 1996; 42: 642–4.
6. Jones TE, *et al.* Formulation of diltiazem affects cyclosporin-sparing activity. *Eur J Clin Pharmacol* 1997; 52: 55–8.
7. Brockmöller J, *et al.* Pharmacokinetic interaction between cyclosporin and diltiazem. *Eur J Clin Pharmacol* 1990; 38: 237–42.
8. Ingsathit A, *et al.* Co-administration of diltiazem and cyclosporine for kidney transplant recipients: a four year follow-up study. *J Med Assoc Thai* 2006; 89 (suppl 2): S235–S241.
9. McDonald SP, Russ GR. Associations between use of cyclosporine-sparing agents and outcome in kidney transplant recipients. *Kidney Int* 2002; 61: 2259–65.
10. Xue W, *et al.* Long-term follow-up of co-administration of diltiazem and cyclosporine in Chinese kidney transplant recipients. *Ren Fail* 2010; 32: 314–19.
11. Kothari J, *et al.* Diltiazem use in tacrolimus-treated renal transplant recipients. *J Clin Pharm Ther* 2004; 29: 425–30.

Adverse Effects

Treatment with diltiazem is generally well tolerated. Headache, ankle oedema, hypotension, dizziness, flushing, fatigue, mood disturbances, and nausea and other gastrointestinal disturbances (including anorexia, vomiting, constipation or diarrhoea, taste disturbances, and weight gain) may occur. Gingival hyperplasia has been reported. Rashes, possibly due to hypersensitivity, are normally mild and transient, but in a few cases erythema multiforme or exfoliative dermatitis has developed; photosensitivity reactions may also occur. Transient elevations in liver enzyme values, and occasionally hepatitis, have been reported.

Diltiazem may depress cardiac conduction and has led to AV block, bradycardia, and rarely asystole or sinus arrest.

Overdosage with diltiazem may be associated with bradycardia, with or without AV conduction defects, and hypotension.

Diltiazem has been shown to be teratogenic in *animal* studies.

Effects on mortality. For discussion of the possibility that calcium-channel blockers might be associated with increased cardiovascular mortality, see under Nifedipine, p. 1450.2.

Angioedema. Periorbital angioedema, accompanied by pruritus or burning and erythema developed in 2 patients given diltiazem.[1]

1. Sadick NS, *et al.* Angioedema from calcium channel blockers. *J Am Acad Dermatol* 1989; 21: 132–3.

Effects on the blood. Thrombocytopenia has been reported with diltiazem.[1,2]

1. Lahav M, Arav R. Diltiazem and thrombocytopenia. *Ann Intern Med* 1989; 110: 327.
2. Michalets EL, Jackson DV. Diltiazem-associated thrombocytopenia. *Pharmacotherapy* 1997; 17: 1345–8.

Effects on the bones and joints. For a report of arthralgia in a patient receiving diltiazem, see Effects on the Neuromuscular System under Nifedipine, p. 1451.3.

Effects on carbohydrate metabolism. Although raised blood-glucose concentrations and insulin requirements have been reported[1] in a patient with type 1 diabetes mellitus during diltiazem therapy, particularly at high doses, a study[2] in 11 obese black women, who were nondiabetic but had a family history of type 2 diabetes, failed to find any effect of diltiazem 240 mg daily on plasma-glucose and C-peptide concentrations, nor any clinical signs of glucose intolerance.

1. Pershadsingh HA, *et al.* Association of diltiazem therapy with increased insulin resistance in a patient with type I diabetes mellitus. *JAMA* 1987; 257: 930–1.
2. Jones RJ, *et al.* Effects of diltiazem hydrochloride on glucose tolerance in persons at risk for diabetes mellitus. *Clin Pharm* 1988; 7: 235–8.

Effects on the ears. There have been isolated reports[1] of tinnitus associated with several calcium-channel blockers including nifedipine, nicardipine, nitrendipine, diltiazem, verapamil, and cinnarizine.

1. Narváez M, *et al.* Tinnitus with calcium-channel blockers. *Lancet* 1994; 343: 1229–30.

Effects on the gastrointestinal tract. Gastrointestinal disturbances including nausea, vomiting, and constipation, may occur with calcium-channel blockers. A case[1] of intestinal pseudo-obstruction was reported in a 74-year-old neutropenic man receiving chemotherapy for leukaemia after diltiazem was added to treat new-onset atrial fibrillation. A diagnosis of neutropenic enterocolitis was ruled out and symptoms resolved when diltiazem was stopped; it was concluded that diltiazem was the probable cause.

A similar case attributed to verapamil[2] has been reported.

1. Young RP, Wu H. Intestinal pseudo-obstruction caused by diltiazem in a neutropenic patient. *Ann Pharmacother* 2005; 39: 1749–51.
2. Schultz HS, Vernon B. Intestinal pseudo-obstruction related to using verapamil. *West J Med* 1989; 151: 556–8.

Effects on the heart. *AV BLOCK.* AV block appears to be uncommon in patients taking diltiazem, but is potentially serious when it occurs. Prescription-event monitoring[1] of a cohort of 10 119 patients for 1 year found 22 reports of AV block during diltiazem use. At least 8 patients had third-degree heart block, and 12 required a pacemaker; 3 died within 72 hours of the onset of heart block. Many of these patients were also taking beta blockers, which is in line with other reports.[2,3] (See also Beta Blockers under Interactions, p. 1361.3.)

There is some evidence that the incidence of this effect may depend on the serum concentration of diltiazem. In a study[4] in patients taking diltiazem after myocardial infarction, patients with serum-diltiazem concentrations greater than 150 nanograms/mL were more likely to have AV block than patients with lower concentrations of diltiazem.

1. Waller PC, Inman WHW. Diltiazem and heart block. *Lancet* 1989; i: 617.
2. Hossack KF. Conduction abnormalities due to diltiazem. *N Engl J Med* 1982; 307: 953–4.
3. Ishikawa T, *et al.* Atrioventricular dissociation and sinus arrest induced by oral diltiazem. *N Engl J Med* 1983; 309: 1124–5.
4. Nattel S, *et al.* Determinants and significance of diltiazem plasma concentrations after acute myocardial infarction. *Am J Cardiol* 1990; 66: 1422–8.

MYOCARDIAL INFARCTION. Results from at least one large multicentre study (the Multicenter Diltiazem Postinfarction Trial) suggest that diltiazem, although apparently of benefit after myocardial infarction in patients with normal left ventricular function (as indicated by absence of pulmonary congestion), was associated with an increased risk of cardiac death or non-fatal re-infarction in patients with impaired left ventricular function.[1] Long-term follow-up[2] indicated that diltiazem also increased the risk of late-onset heart failure in postinfarction patients with left ventricular dysfunction.

1. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988; 319: 385–92.
2. Goldstein RE, *et al.* Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. *Circulation* 1991; 83: 52–60.

WITHDRAWAL. Life-threatening coronary vasospasm, which was fatal in one patient, occurred in 4 patients after coronary revascularisation for unstable angina.[1] Treatment with a calcium-channel blocker (diltiazem or nifedipine) had been stopped between 8 and 18 hours before the procedure and this abrupt withdrawal was thought to be responsible for the rebound vasospasm. The coronary vasospasm was managed with glyceryl trinitrate and nifedipine.

Withdrawal of diltiazem over a 4-day period from a patient with stable angina pectoris was followed by recurrence of anginal attacks.[2] Ambulatory ECG monitoring confirmed worsening myocardial ischaemia that responded to re-introduction of diltiazem. Two further patients had a similar withdrawal effect.

1. Engelman RM, *et al.* Rebound vasospasm after coronary revascularization in association with calcium antagonist withdrawal. *Ann Thorac Surg* 1984; 37: 469–72.
2. Subramanian VB, *et al.* Calcium antagonist withdrawal syndrome: objective demonstration with frequency-modulated ambulatory ST-segment monitoring. *BMJ* 1983; 286: 520–1.

Effects on the kidneys. Diltiazem may be of benefit in various kidney disorders (see under Uses, above). However, there are a few reports of acute renal failure associated with diltiazem use.[1,2] Acute interstitial nephritis has been proposed as a mechanism.[2,3]

1. ter Wee PM, *et al.* Acute renal failure due to diltiazem. *Lancet* 1984; ii: 1337–8.
2. Abadin JA, *et al.* Probable diltiazem-induced acute interstitial nephritis. *Ann Pharmacother* 1998; 32: 656–8.
3. Achenbach V, *et al.* Acute renal failure due to diltiazem. *Lancet* 1985; i: 176.

Effects on the lungs. Eosinophilic pleural effusion developed[1] in a 68-year-old woman given diltiazem for hypertension. Symptoms resolved on stopping the drug.

1. Raptis L, *et al.* Diltiazem-induced eosinophilic pleural effusion. *Pharmacotherapy* 2007; 27: 600–2.

Effects on mental function. By September 1989, the WHO collaborative programme for international drug monitoring had gathered 8 cases of mental depression (severe in 2) associated with diltiazem therapy.[1] Time of onset of symptoms varied from a few hours to a few months after starting treatment with diltiazem. There was some evidence that the problem might be dose-related as 5 of the 8 cases were receiving doses of 180 mg daily or more.

Psychoses have been reported rarely with diltiazem. A patient[2] who developed hallucinations (both auditory and visual) and paranoid delusions after 2 days of diltiazem therapy was subsequently treated with nifedipine without abnormal effects. For a report of a psychotic reaction attributed to an interaction between diltiazem and lithium, see p. 1361.3.

1. Biriell C, *et al.* Depression associated with diltiazem. *BMJ* 1989; 299: 796.
2. Bushe CJ. Organic psychosis caused by diltiazem. *J R Soc Med* 1988; 81: 296–7.

Effects on the mouth. A study involving 115 patients given nifedipine, diltiazem, or verapamil for at least 3 months indicated that gingival hyperplasia is an important adverse effect that may occur with calcium-channel blockers.[1]

1. Steele RM, *et al.* Calcium antagonist-induced gingival hyperplasia. *Ann Intern Med* 1994; 120: 663–4.

Effects on the skin. Contact dermatitis has been seen in patients using *topical* diltiazem for anal fissure.[1] Skin disorders have also been associated with oral therapy, including acute pustular dermatitis,[2–4] cutaneous vasculitis,[5,6] erythema multiforme,[7,8] pruritic macular rashes,[4,9] severe toxic erythema,[10] subacute lupus erythematosus-like eruptions,[11] and photosensitivity reactions.[12,13] Analysis of cutaneous adverse reactions to diltiazem indicated that acne, rash, and urticaria were among the commonest.[14] There have also been a few reports of exfoliative dermatitis, Stevens Johnson syndrome, and toxic epidermal necrolysis.[4,14]

For a report of periorbital skin rash associated with diltiazem, see Angioedema, p. 1360.2.

Cross-sensitivity, manifest as a pruritic maculopapular rash, has been reported between diltiazem and amlodipine.[15]

1. Rose RF, Wilkinson SM. Contact sensitization to topical diltiazem. *Contact Dermatitis* 2009; 60: 347–8.
2. Lambert DG, *et al.* Acute generalized exanthematous pustular dermatitis induced by diltiazem. *Br J Dermatol* 1988; 118: 308–9.
3. Vicente-Calleja JM, *et al.* Acute generalized exanthematous pustulosis due to diltiazem: confirmation by patch testing. *Br J Dermatol* 1997; 137: 837–9.
4. Knowles S, *et al.* The spectrum of cutaneous reactions associated with diltiazem: three cases and a review of the literature. *J Am Acad Dermatol* 1998; 38: 201–6.
5. Carmichael AJ, Paul CJ. Vasculitic leg ulcers associated with diltiazem. *BMJ* 1988; 297: 562.
6. Sheehan-Dare RA, Goodfield MJ. Severe cutaneous vasculitis induced by diltiazem. *Br J Dermatol* 1988; 119: 134.
7. Berbis P, *et al.* Diltiazem associated erythema multiforme. *Dermatologica* 1989; 179: 90.
8. Sanders CJG, Neumann HAM. Erythema multiforme, Stevens-Johnson syndrome, and diltiazem. *Lancet* 1993; 341: 967.
9. Wirebaugh SR, Geraets DR. Reports of erythematous macular skin eruptions associated with diltiazem therapy. *DICP Ann Pharmacother* 1990; 24: 1046–9.
10. Wakeel RA, *et al.* Severe toxic erythema caused by diltiazem. *BMJ* 1988; 296: 1071.
11. Crowson AN, Magro CM. Diltiazem and subacute cutaneous lupus erythematosus-like lesions. *N Engl J Med* 1995; 333: 1429.
12. Saladi RN, *et al.* Diltiazem induces severe photodistributed hyperpigmentation: case series, histoimmunopathology, management, and review of the literature. *Arch Dermatol* 2006; 142: 206–10.
13. Kubo Y, *et al.* Diltiazem-associated photodistributed hyperpigmentation: report of two Japanese cases and published work review. *J Dermatol* 2010; 37: 807–11.
14. Stern R, Khalsa JH. Cutaneous adverse reactions associated with calcium channel blockers. *Arch Intern Med* 1989; 149: 829–32.
15. Baker BA, Cacchione JG. Dermatologic cross-sensitivity between diltiazem and amlodipine. *Ann Pharmacother* 1994; 28: 118–19.

Extrapyramidal disorders. For reports of extrapyramidal disorders occurring with calcium-channel blockers including diltiazem, see under Nifedipine, p. 1452.2.

Overdosage. See under Treatment of Adverse Effects, below.

Treatment of Adverse Effects

As for Nifedipine, p. 1452.3, but see also below.

Diltiazem and its metabolites are poorly dialysable.

Overdosage. The consequences and treatment of diltiazem overdosage are similar to nifedipine (p. 1452.3), although death and life-threatening complications might be more common with diltiazem.[1] Up to 1994, 6 cases of fatal overdose with diltiazem had been reported in the literature.[2] Measurement of diltiazem concentrations to assist in diagnosis and management of overdosage has been suggested,[2] but others[3] have disputed its value.

The following are individual reports of overdosage with diltiazem:

- A patient who took about 10.8 g of diltiazem developed hypotension and complete heart block. Dopamine, isoprenaline, and calcium chloride were required to maintain the blood pressure. The ECG reverted to sinus rhythm after 31 hours. The plasma-diltiazem concentration was 1.67 micrograms/mL 43 hours after ingestion and fell to 12.1 nanograms/mL over a further 55.5 hours with an elimination half-life of 7.9 hours.[4]
- In a further case a patient took 5.88 g of diltiazem with alcohol, and developed severe junctional bradycardia, hypotension, and reduced cardiac function that did not respond to intravenous calcium gluconate. The peak plasma-diltiazem concentration of 6.09 micrograms/mL occurred 7 hours after presentation. About half of the dose was vomited after treatment with activated charcoal. The patient was treated with cardiac pacing and a dopamine infusion; he reverted to sinus rhythm within 24 hours, and a subsequent episode of atrial fibrillation was treated successfully with digoxin.[5]
- Charcoal haemoperfusion had a limited effect in improving the clearance of diltiazem in a patient who had taken 14.94 g of diltiazem.[6] The patient developed severe hypotension, complete heart block, and acute renal failure. Supportive care included cardiac pacing and several vasopressors including intravenous glucagon and infusions of dopamine, adrenaline, and noradrenaline.

As with other calcium-channel blockers the use of insulin in the management of overdose has been described.[7]

1. Buckley NA, *et al.* Overdose with calcium channel blockers. *BMJ* 1994; 308: 1639.
2. Roper TA. Overdose of diltiazem. *BMJ* 1994; 308: 1571.
3. Lip GYH, Ferner RE. Overdose of diltiazem. *BMJ* 1994; 309: 193.
4. Malcolm N, *et al.* Massive diltiazem overdosage: clinical and pharmacokinetic observations. *Drug Intell Clin Pharm* 1986; 20: 888.
5. Ferner RE, *et al.* Pharmacokinetics and toxic effects of diltiazem in massive overdose. *Hum Toxicol* 1989; 8: 497–9.
6. Williamson KM, Dunham GD. Plasma concentrations of diltiazem and desacetyldiltiazem in an overdose situation. *Ann Pharmacother* 1996; 30: 608–11.
7. Abeysinghe N, *et al.* Diltiazem overdose: a role for high-dose insulin. *Emerg Med J* 2010; 27: 802–3.

Precautions

Diltiazem is contra-indicated in patients with the sick sinus syndrome, pre-existing second- or third-degree AV block, or marked bradycardia, and should be used with care in patients with lesser degrees of AV block or bradycardia. Diltiazem has been associated with the development of heart failure and great care is required in patients with impaired left ventricular function. Sudden withdrawal of diltiazem might be associated with an exacerbation of angina.

Treatment with diltiazem should begin with reduced doses in elderly patients and in patients with hepatic or renal impairment.

Abuse. Abuse of diltiazem by body builders and rugby players has been alleged. Such abuse is possibly because of evidence that diltiazem increases maximum oxygen consumption after training. A body builder who admitted to taking diltiazem in high doses suffered severe abdominal cramps.[1]

1. Richards H, *et al.* Use of diltiazem in sport. *BMJ* 1993; 307: 940.

Breast feeding. Diltiazem is distributed into breast milk; in a woman taking oral diltiazem 60 mg four times daily, concentrations in breast milk were similar to those in serum.[1] Licensed product information therefore recommends that diltiazem should generally be avoided during breast feeding. However, in another report,[2] a mother breast fed twins for at least 6 months while taking diltiazem and no adverse effects were reported in the infants. Since there had been no reports of adverse effects, the last available guidance from the American Academy of Pediatrics considered[3] that diltiazem was usually compatible with breast feeding.

1. Okada M, *et al.* Excretion of diltiazem in human milk. *N Engl J Med* 1985; 312: 992–3.
2. Lubbe WF. Use of diltiazem during pregnancy. *N Z Med J* 1987; 100: 121.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies diltiazem as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Renal impairment. A patient with end-stage renal failure requiring haemodialysis developed hypotension, bradycardia, metabolic acidosis, hyperkalaemia, and acute congestive heart failure about 60 hours after his last haemodialysis.[1] The patient had been taking diltiazem 60 mg three times daily. The symptoms were attributed to diltiazem toxicity due to accumulation of diltiazem and its metabolites which are poorly dialysed and normally excreted partially in the urine.

1. Patel R, *et al.* Toxic effects of diltiazem in a patient with chronic renal failure. *J Clin Pharmacol* 1994; 34: 273–4.

Interactions

Increased depression of cardiac conduction with risk of bradycardia and AV block may occur when diltiazem is given with drugs such as amiodarone, beta blockers, digoxin, and mefloquine. Enhanced antihypertensive effect may occur if used with other antihypertensive drugs or drugs that cause hypotension such as aldesleukin and antipsychotics. Diltiazem is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 and may also inhibit the metabolism of drugs sharing the same pathway. Interactions may also be expected with enzyme inducers, such as carbamazepine, phenobarbital, phenytoin, and rifampicin, and with enzyme inhibitors, such as cimetidine and HIV-protease inhibitors.

Antidepressants. For a report of diltiazem increasing the bioavailability of *imipramine* and *nortriptyline*, see Calcium-channel Blockers under the Interactions of Amitriptyline, p. 407.1.

Antiepileptics. For reports of diltiazem use precipitating *carbamazepine* and *phenytoin* toxicity, see Calcium-channel Blockers, p. 517.2 and p. 544.2, respectively.

Benzodiazepines. For the effects of diltiazem on plasma concentrations of *midazolam* or *triazolam*, see Calcium-channel Blockers under Interactions of Diazepam, p. 1069.3.

Beta blockers. Profound bradycardia has been reported in several patients when diltiazem was used with a beta blocker.[1,2] Diltiazem decreases the clearance of a single dose of *propranolol* or *metoprolol*, though not *atenolol*, and elevated concentrations of beta blocker may be responsible for the bradycardic effects.[3] This is unlikely to be the full story, however, since atenolol, which was unaffected in this study, has been implicated in producing bradycardia when diltiazem was added in a patient with myocardial ischaemia.[2]

1. Hassell AB, Creamer JE. Profound bradycardia after the addition of diltiazem to a β blocker. *BMJ* 1989; 298: 675.
2. Nagle RE, *et al.* Diltiazem and heart block. *Lancet* 1989; i: 907.
3. Tateishi T, *et al.* Effect of diltiazem on the pharmacokinetics of propranolol, metoprolol and atenolol. *Eur J Clin Pharmacol* 1989; 36: 67–70.

Calcium-channel blockers. For the effect of diltiazem and *nifedipine* on each other's plasma concentrations, see p. 1454.1.

Ciclosporin. For reports of a potentially beneficial interaction between diltiazem and ciclosporin, see Transplantation under Uses and Administration, p. 1360.1.

Corticosteroids. Diltiazem has been reported to reduce the clearance of *methylprednisolone* (see Calcium-channel Blockers, p. 1620.2).

Digoxin. For a discussion of interactions between digoxin and calcium-channel blockers including diltiazem, see p. 1357.2.

General anaesthetics. Two patients on diltiazem therapy developed impaired myocardial conduction during anaesthesia with *enflurane*;[1] one of the patients had severe sinus bradycardia that progressed to asystole. Additive cardiodepressant effects of diltiazem and enflurane were considered responsible. The authors of a review[2] concluded that intravenous diltiazem or verapamil should not be used in patients anaesthetised with either halothane or enflurane, particularly in those with heart failure or conduction disturbances.

1. Handler CB, *et al.* Impaired myocardial conduction in patients receiving diltiazem therapy during enflurane anesthesia. *Anesthesiology* 1987; 67: 94–6.
2. Durand P-G, *et al.* Calcium-channel blockers and anaesthesia. *Can J Anaesth* 1991; 38: 75–89.

Histamine H_2-antagonists. *Cimetidine* caused increases in plasma-diltiazem concentrations and in plasma-deacetyldiltiazem concentrations in 6 subjects given a single oral dose of diltiazem 60 mg. *Ranitidine* produced a similar, though less marked effect.[1]

1. Winship LC, *et al.* The effect of ranitidine and cimetidine on single-dose diltiazem pharmacokinetics. *Pharmacotherapy* 1985; 5: 16–19.

Lithium. Extrapyramidal symptoms[1,2] including cogwheeling, rigidity, and ataxia, and in one case a psychotic reaction,[1] have been attributed to a synergistic interaction between diltiazem and lithium.

1. Binder EP, *et al.* Diltiazem-induced psychosis and a possible diltiazem-lithium interaction. *Arch Intern Med* 1991; 151: 373–4.
2. Valdiserri EV. A possible interaction between lithium and diltiazem: case report. *J Clin Psychiatry* 1985; 46: 540–1.

Muscle relaxants. For a report of hyperkalaemia occurring when *dantrolene* was given to a patient taking diltiazem, see Calcium-channel Blockers under Interactions of Dantrolene, p. 2024.3.

Theophylline. For the effect of diltiazem on plasma-theophylline concentrations, see Calcium-channel Blockers, p. 1235.3.

Tolvaptan. For the effect of diltiazem on tolvaptan concentrations, see p. 2633.1.

Pharmacokinetics

Diltiazem is almost completely absorbed from the gastrointestinal tract after oral doses, but undergoes extensive first-pass hepatic metabolism resulting in a bioavailability of about 40%. Peak plasma concentrations occur about 3 to 8 hours after an oral dose, depending on the dosage form. Diltiazem is about 80% bound to plasma proteins. It is distributed into breast milk. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4; one of the metabolites, desacetyldiltiazem, has been reported to have 25 to 50% of the activity of the parent compound. The half-life of diltiazem is reported to be about 3 to 8 hours, again depending on the dosage form. About 2 to 4% of a dose is excreted in urine as unchanged diltiazem with the remainder excreted as metabolites in bile and urine. Diltiazem and its metabolites are poorly dialysable.

General reviews.

1. Kelly JG, O'Malley K. Clinical pharmacokinetics of calcium antagonists: an update. *Clin Pharmacokinet* 1992; **22**: 416–33.

Bioavailability. Studies of the pharmacokinetics of diltiazem in healthy subjects after single and multiple doses,[1-3] indicated that bioavailability was increased after multiple doses, probably because of decreased presystemic elimination.[3]

1. Höglund P, Nilsson L-G. Pharmacokinetics of diltiazem and its metabolites after repeated multiple-dose treatments in healthy volunteers. *Ther Drug Monit* 1989; **11**: 543–50.
2. Höglund P, Nilsson L-G. Pharmacokinetics of diltiazem and its metabolites after repeated single dosing in healthy volunteers. *Ther Drug Monit* 1989; **11**: 551–7.
3. Höglund P, Nilsson L-G. Pharmacokinetics of diltiazem and its metabolites after single and multiple dosing in healthy volunteers. *Ther Drug Monit* 1989; **11**: 558–66.

Renal impairment. The pharmacokinetics of diltiazem and its major metabolite desacetyldiltiazem in patients with severe renal impairment were similar to those in patients with normal renal function.[1] Nevertheless, reduced doses may be necessary in patients with renal impairment (see under Uses and Administration p. 1359.3). See also under Precautions, p. 1361.2.

1. Pozet N, *et al.* Pharmacokinetics of diltiazem in severe renal failure. *Eur J Clin Pharmacol* 1983; **24**: 635–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acalix; Angular†; Corodrox; Dilahim†; Diltenk; Dilzen-G; Hart; Incoril; Kaltiazem; Tilazem; ***Austral.***: Cardizem; Coras; Diltahexal; Dilzem; Vasocardol; ***Austria***: Diltiastad; Dilzem†; ***Belg.***: Progor; Tildiem; ***Braz.***: Angiolong; Balcor; Calzem; Cardizem; Cordil; Dilcor; Diltiacor; Diltipress; Diltizem; Diltor†; Incoril; ***Canad.***: Apo-Diltiaz; Cardizem; Novo-Diltazem†; Nu-Diltiaz; Tiazac; ***Chile***: Acasmul; Grifodilzem; Incoril; Tilazem; Tildiem; ***China***: Ao De Zhen (奥的镇); Bei Luo Xin (贝洛信); Di Er Song (迪尔松); Ergolan (艾克朗); Herbesser (合贝爽); Hu Er Xing (平尔兴); Jian Er Xin (健尔信); Ling Shuang (灵爽); Mono-Tildiem (蒂尔丁); Qian Ke (芊克); Qin Er Kang (沁尔康); Tai Wei Te (太韦特); Tian Er Xin (恬尔新); Xintai (心泰); *Cz.*: Blocalcin†; Diacordin; ***Denm.***: Cardil; Cardizem; Dilcor†; Myonil; Tildiem; Tilker†; ***Fin.***: Cardizem; Dilmin; Dilpral†; Dilzem; ***Fr.***: Bi-Tildiem; Deltazen; Diacor†; Dilrene; Mono-Tildiem; Tildiem; ***Ger.***: Dil-Sanorania†; Dilsal†; Diltabeta†; Diltahexal†; Diltaretard†; Dilti†; Diltiagamma†; Dilzanton†; Dilzem; ***Gr.***: Alfener; Cardil; Corotrend; Corsenile; Diltelan; Diltem; Dilzanol; Dipen; Elvesil; Ergoclavin; Mavitalon; Mycarzem; Natasadol; Rubiten; Saubasin; Ternel; Tildiem; Usno; Zem; Zilden; ***Hong Kong***: Altiazem; Apo-Diltiaz; Coras†; Dazil†; Herbesser; Wontizem†; ***Hung.***: Blocalcin; Dilrene; Dilzem; ***India***: Angizem; Cardem; Cardisec; Channel; Corlem; Dicard; Dilam; Dilcal; Dilcardia; Dilcontin; Dilgard; Dilgina; Dilocor; Dilter CD; Diltiaz; Dilticard; Diltigesic; Diltime; Diltisyn; Diltp; Dilzem; Dilzor; DTM; DZ; Heartil; Herbesser; Icidil; Ionozem; Isdil; Iski; Kaizem; Masdil; Onzem; ***Indon.***: Cordizem; Dilmen; Dilso†; Farmabes; Herbesser; Lanodil; ***Irl.***: Adizem; Diacardyne; Diltam; Dilzem; DTZ†; Entrydil; Tildiem; ***Israel***: Adizem; Dilatam; ***Ital.***: Altiazem; Angizem; Diladel; Dilem; Dilter†; Dilzene; Etyzem; Longazem; Tildiem; ***Jpn***: Herbesser; ***Malaysia***: Cardil; Cascor; Herbesser; Mono-Tildiem; ***Mex.***: Angiotrofin; Anremed; Sertidel; Tilazem; ***Neth.***: Tildiem; ***Norw.***: Cardizem; ***NZ***: Cardizem; Diltahexal†; Dilzem; ***Philipp.***: Angiozem; Cordazem†; Corvizem; Dilatam; Dilcardia; Diltelan†; Diltime†; Dilzem; Dyalac; Filazem†; Mono-Tildiem†; Tildiem; Vasmulax; Zandil†; Zemtrial†; ***Pol.***: Blocalcin†; Diacordin†; Dilocard; Dilzem; Oxycardil; ***Port.***: Dilfar; Diltiangina; Diltiem; Etizem; Herbesser; Tilker†; ***Rus.***: Altiazem (Алтиазем); Blocalcin (Блокальцин)†; Cardil (Кардил); Diacordin (Диакордин); Diazem (Диазем); Dilcardia (Дилкардия)†; ***S.Afr.***: Adco-Zildem; Dilatam†; Tilazem; ***Singapore***: Beatizem; Cardil; Cardium; Herbesser; Mono-Tildiem; ***Spain***: Angiodrox; Cardiser; Carreldon; Clobendian†; Corolater†; Cronodine; Dilaclan; Diltiwas; Dinisor; Doclis; Lacerol; Masdil; Tilker; Trumsal; Uni Masdil; ***Swed.***: Cardizem; Coramil; ***Switz.***: Coridil; Dilzem; Tildiem†; ***Thai.***: Angizem; Cardil; Carzem†; Cascor; Denazox; Dilcardia; Dilem; Dilizem; Diltec; Dilzem; Ditizem; Herbesser; Herbie; Progor; ***Turk.***: Altizem; Dilticard; Diltizem; Kardil; Progor; Tildiem†; ***UK***: Adizem; Angitil; Calcicard; Dilcardia; Dilzem; Disogram; Optil; Slozem; Tildiem; Viazem; Zemtard; ***Ukr.***: Cardil (Кардил); ***USA***: Cardizem; Cartia; Dilacor; Dilt-CD; Dilt-XR; Diltia†; Diltzac; Matzim; Taztia; Tiazac; ***Venez.***: Acalix; Corazem; Cordisil; Daltazen; Presoquin; Tilazem.

Multi-ingredient Preparations. *USA*: Teczem.

Pharmacopoeial Preparations

BP 2014: Prolonged-release Diltiazem Tablets;
USP 36: Diltiazem Hydrochloride Extended-release Capsules; Diltiazem Hydrochloride Oral Solution; Diltiazem Hydrochloride Oral Suspension; Diltiazem Hydrochloride Tablets.

Dimetofrine Hydrochloride *(rINNM)* ⊗

Dimetofrina, hidrocloruro de; Dimétofrine, Chlorhydrate de; Dimetofrini Hydrochloridum; Dimetophrine Hydrochloride; Hidrocloruro de dimetofrina; Диметофрина Гидрохлорид.

4-Hydroxy-3,5-dimethoxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride.

$C_{11}H_{17}NO_4HCl$=263.7

CAS — 22950-29-4 (dimetofrine); 22775-12-8 (dimetofrine hydrochloride).

ATC — C01CA12.

ATC Vet — QC01CA12.

Profile

Dimetofrine hydrochloride is a sympathomimetic (p. 1507.3) that has been used for its vasopressor effects in the treatment of hypotensive states. It has also been used in preparations for cold and influenza symptoms.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Raffreddoremed.

Dipyridamole *(BAN, USAN, rINN)*

Dipiridamol; Dipiridamolis; Dipirydamol; Dipyridamol; Dipyridamoli; Dipyridamolum; NSC-515776; RA-8; Дипиридамол.

2,2′,2″,2‴-[(4,8-Dipiperidinopyrimido[5,4-*d*]pyrimidine-2,6-diyl)dinitrilo]tetraethanol.

$C_{24}H_{40}N_8O_4$=504.6

CAS — 58-32-2.

ATC — B01AC07.

ATC Vet — QB01AC07.

UNII — 64ALC7F90C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Dipyridamole). A bright yellow crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol; freely soluble in acetone. It dissolves in dilute solutions of mineral acids. Protect from light.

USP 36: (Dipyridamole). An intensely yellow, crystalline powder or needles. Slightly soluble in water; very soluble in chloroform, in alcohol, and in methyl alcohol; very slightly soluble in acetone and in ethyl acetate. Store in airtight containers. Protect from light.

Uses and Administration

Dipyridamole is an adenosine reuptake inhibitor and phosphodiesterase inhibitor with antiplatelet and vasodilating activity and is used in thromboembolic disorders (p. 1273.2). Oral dipyridamole is used for the prophylaxis of thromboembolism after cardiac valve replacement (p. 1264.3) and in the management of stroke (below); it has also been used in the management of myocardial infarction (p. 1257.1). Dipyridamole given intravenously results in marked coronary vasodilatation and is used in stress testing in patients with ischaemic heart disease (see Myocardial Imaging, below).

For the prophylaxis of **thromboembolism** after cardiac valve replacement, dipyridamole is given with an oral anticoagulant. The usual oral dose is 300 to 600 mg daily in divided doses before meals. For doses in children see below.

For the secondary prevention of **stroke** or transient ischaemic attack dipyridamole is given as a modified-release preparation, alone or with aspirin, in a dose of 200 mg twice daily.

General references.

1. FitzGerald GA. Dipyridamole. *N Engl J Med* 1987; 316: 1247–57.
2. Gibbs CR, Lip GYH. Do we still need dipyridamole? *Br J Clin Pharmacol* 1998; **45**: 323–8.
3. Kim H-H, Liao JK. Translational therapeutics of dipyridamole. *Arterioscler Thromb Vasc Biol* 2008; **28**: s39–s42.

Administration in children. Dipyridamole is not licensed in the UK for the prophylaxis of **thromboembolism** in children, but the *BNFC* suggests the following oral doses for prevention of thrombus formation after cardiac surgery:

- children 1 month to 12 years of age: 2.5 mg/kg twice daily
- 12 to 18 years: as for adults (above)

The *BNFC* also includes a suggested dose for dipyridamole in the management of childhood **Kawasaki disease** (p. 2405.2); children aged 1 month to 12 years may be given oral dipyridamole 1 mg/kg three times daily.

Intravenous dipyridamole may be used in stress testing in children similarly to in adults (see Myocardial Imaging, below).

Myocardial imaging. Perfusion abnormalities due to coronary artery disease are usually absent at rest but are present during stress, and stress imaging may therefore be used in the assessment of myocardial function. The stress is usually supplied by exercise, but when exercise is inappropriate pharmacological methods such as dipyridamole may be used.

Dipyridamole has been used with thallium-201 scintigraphy in adults and children and is usually given intravenously in a dose of 567 micrograms/kg over 4 minutes. Thallium-201 is given within 3 to 5 minutes after completion of the infusion of dipyridamole. Initial images are obtained after 5 minutes and delayed images are obtained 2.5 to 4 hours later. Dipyridamole (300 to 400 mg) has also been given as an oral suspension; thallium-201 is given about 45 minutes later to coincide with peak dipyridamole-serum concentrations.

Dipyridamole has also been used in echocardiography.[1,2] The intravenous dipyridamole dose used to obtain maximum sensitivity is often higher (750 to 840 micrograms/kg) than the dose used in scintigraphy.[1]

1. Beller GA. Pharmacologic stress imaging. *JAMA* 1991; **265**: 633–8.
2. Buchalter MB, *et al.* Dipyridamole echocardiography: the bedside stress test for coronary artery disease. *Postgrad Med J* 1990; **66**: 531–5.

Stroke. The value of long-term antiplatelet therapy with aspirin in patients who have suffered an ischaemic stroke (p. 1269.2) or transient ischaemic attack is well-established, with a reduction in the risk of both stroke and other vascular events.[1] The use of dipyridamole has been more controversial. Early studies with dipyridamole, used alone or with aspirin, failed to show any benefit over aspirin alone. The European Stroke Prevention Study-2 (ESPS-2),[2] which compared aspirin and dipyridamole, alone or together, with placebo, found that both drugs reduced the risk of stroke and that the effects appeared to be additive. The study used a low dose of aspirin and a modified-release formulation of dipyridamole, which may explain the discrepancy with earlier studies.[3] Subsequent meta-analyses[3-6] have confirmed that dipyridamole, alone or with aspirin, reduces the risk of recurrent stroke, but have been based mainly on the ESPS-2, which may be a limitation.[3] However, a further large study[7] comparing aspirin alone with aspirin and dipyridamole also found that the incidence of vascular events (including stroke) was lower in those receiving both drugs. Most guidelines[8,9] therefore now recommend aspirin with dipyridamole as one of the preferred options for long-term management of ischaemic stroke.

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308**: 81–106. Correction. *ibid.*; 1540.
2. Diener HC, *et al.* European Stroke Prevention Study 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996; **143**: 1–13.
3. Wilterdink JL, Easton JD. Dipyridamole plus aspirin in cerebrovascular disease. *Arch Neurol* 1999; **56**: 1087–92.
4. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324**: 71–86. Correction. *ibid.*; 141.
5. Leonardi-Bee J, *et al.* Dipyridamole for preventing recurrent ischemic stroke and other vascular events: a meta-analysis of individual patient data from randomized controlled trials. *Stroke* 2005; **36**: 162–8.
6. De Schryver ELLM, *et al.* Dipyridamole for preventing stroke and other vascular events in patients with vascular disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 19/03/08).
7. Halkes PH, *et al.* ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* 2006; **367**: 1665–73. Correction. *ibid.* 2007; **369**: 274.
8. European Stroke Organisation (ESO) Executive Committee. ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008; **25**: 457–507. Also available at: http://www.eso-stroke.org/pdf/ESO08_Guidelines_English.pdf (accessed 11/07/08)
9. Albers GW, *et al.* Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 630S–669S.

Adverse Effects, Treatment, and Precautions

Gastrointestinal disturbances, including nausea, vomiting, and diarrhoea, headache, dizziness, faintness, hypotension, facial flushing, and skin rash and other hypersensitivity reactions may occur after use of dipyridamole. Dipyridamole can also induce chest pain or lead to a worsening of the symptoms of angina. Cardiac arrhythmias have been reported in patients given dipyridamole during thallium-

201 imaging. Aminophylline may reverse some of the adverse effects.

Dipyridamole should be used with caution in patients with hypotension, unstable angina, aortic stenosis, recent myocardial infarction, heart failure, or coagulation disorders. Intravenous dipyridamole should not be given to patients with these conditions or to those with arrhythmias, conduction disorders, asthma, or a history of bronchospasm (but see Myocardial Imaging, below). Oral dipyridamole should be stopped 24 hours before intravenous use for stress testing.

Effects on the biliary tract. Gallstones containing unconjugated dipyridamole were removed from 2 patients who had been taking dipyridamole for 15 and 10 years, respectively.[1] A gallstone containing unconjugated dipyridamole recurred in a patient who continued to take the drug after endoscopic removal of a similar stone 18 months earlier.[2]

1. Moesch C, *et al.* Biliary drug lithiasis: dipyridamole gallstones. *Lancet* 1992; 340: 1352–3.
2. Sautereau D, *et al.* Recurrence of biliary drug lithiasis due to dipyridamole. *Endoscopy* 1997; 29: 421–3.

Effects on the heart. Transient myocardial ischaemia occurred in 4 patients with unstable angina and multivessel coronary artery disease during oral treatment with dipyridamole.[1] See Myocardial Imaging, below, for additional reports.

1. Keltz TN, *et al.* Dipyridamole-induced myocardial ischemia. *JAMA* 1987; 257: 1515–16.

Effects on the muscles. Symptoms resembling acute pseudopolymyalgia rheumatica developed in a patient taking dipyridamole.[1]

1. Chassagne P, *et al.* Pseudopolymyalgia rheumatica with dipyridamole. *BMJ* 1990; 301: 875.

Effects on taste. A disagreeable taste associated with other gastrointestinal symptoms occurred in a patient taking dipyridamole.[1] Two similar cases had been reported to the UK CSM.

1. Willoughby JMT. Drug-induced abnormalities of taste sensation. *Adverse Drug React Bull* 1983; 100: 368–71.

Myocardial imaging. Dipyridamole may be used in association with thallium-201 in myocardial stress imaging. Safety data from over 3900 patients has been summarised.[1] Adverse effects which occurred within 24 hours of dipyridamole intravenously (mean dose 560 micrograms/kg) were recorded. Ten patients had major adverse effects and 1820 patients experienced minor adverse effects. Myocardial infarction occurred in 4 patients, 3 of whom had unstable angina before scanning. Six patients developed acute bronchospasm, 4 of whom had a history of asthma or had wheezing before using dipyridamole. Adverse effects considered to be minor included chest pain in 19.7% of patients, ST-T-segment depression in 7.5%, ventricular extrasystoles in 5.2%, headache in 12.2%, dizziness in 11.8%, nausea in 4.6%, and hypotension in 4.6%. Aminophylline was effective in relieving symptoms of adverse effects in 97% of 454 patients.

Hypersensitivity reactions including anaphylaxis and angioedema have been reported.[2,3]

UK licensed product information contra-indicates intravenous dipyridamole in patients with hypotension, unstable angina, left ventricular outflow obstruction, recent myocardial infarction, decompensated heart failure, arrhythmias, conduction disorders, asthma, or a history of bronchospasm. However, a review[4] of pharmacological stress testing suggested that with appropriate patient selection and adequate monitoring, the incidence of life-threatening adverse reactions is negligible. It was also considered that dipyridamole-thallium-201 imaging could be safely performed in the early post-myocardial infarction period.

1. Ranhosky A, *et al.* The safety of intravenous dipyridamole thallium myocardial perfusion imaging. *Circulation* 1990; 81: 1205–9.
2. Weinmann P, *et al.* Anaphylaxis-like reaction induced by dipyridamole during myocardial scintigraphy. *Am J Med* 1994; 97: 488.
3. Angelides S, *et al.* Acute reaction to dipyridamole during myocardial scintigraphy. *N Engl J Med* 1999; 340: 394.
4. Beller GA. Pharmacologic stress imaging. *JAMA* 1991; 265: 633–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dipyridamole as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

Dipyridamole may enhance the actions of oral anticoagulants due to its antiplatelet effect and additive effects may also occur with other antiplatelet drugs. It inhibits the reuptake of adenosine and may enhance its effects; the dose of adenosine must be reduced if both drugs are given. Dipyridamole may also inhibit the uptake of fludarabine and may reduce its efficacy.

The absorption of dipyridamole may be reduced by drugs such as antacids that increase gastric pH.

Anticoagulants. Dipyridamole may induce bleeding in patients receiving oral anticoagulants without altering prothrombin times (see Antiplatelets, under Warfarin, Interactions, p. 1532.3).

Xanthines. Xanthines may antagonise some of the effects of dipyridamole due to their action as adenosine antagonists. *Aminophylline* may be used to reverse some of the adverse effects of dipyridamole. Intravenous *caffeine* has been reported[1] to attenuate the haemodynamic response to dipyridamole and it has been suggested that caffeine should be avoided for at least 24 hours before the test in patients receiving dipyridamole for myocardial imaging.

1. Smits P, *et al.* Dose-dependent inhibition of the hemodynamic response to dipyridamole by caffeine. *Clin Pharmacol Ther* 1991; 50: 529–37.

Pharmacokinetics

Dipyridamole is incompletely absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 75 minutes after an oral dose. Dipyridamole is more than 90% bound to plasma proteins. A terminal half-life of 10 to 12 hours has been reported. Dipyridamole is metabolised in the liver and is mainly excreted as glucuronides in the bile. Excretion may be delayed by enterohepatic recirculation. A small amount is excreted in the urine. Dipyridamole is distributed into breast milk.

References.

1. Mahony C, *et al.* Dipyridamole kinetics. *Clin Pharmacol Ther* 1982; 31: 330–8.
2. Mahony C, *et al.* Plasma dipyridamole concentrations after two different dosage regimens in patients. *J Clin Pharmacol* 1983; 23: 123–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Maxicardil; Persantin; Sedangor†; *Austral.*: Persantin; *Austria*: Persantin; *Belg.*: Coronair†; Docdipyri†; Persantine; *Braz.*: Persantin; *Canad.*: Persantine; *Chile*: Persantin; *China*: Ai Ke Xin (爱克辛); Kai Le Di (凯乐迪); Pu Qi Ao (普奇澳); Shengda (升达); *Denm.*: Persantin; Persantine; *Fin.*: Dipyrin†; Persantin; *Fr.*: Cleridium; Persantine; *Gr.*: Adezan; Ethrine; Persantin; *Hong Kong*: Persantin; Procardin†; *India*: Cardiwell; Deplatol; Dynacard; Persantin; *Indon.*: Cardial; Persantin; Vasokor; Vasotin; *Irl.*: Persantin; *Israel*: Cardoxin; *Ital.*: Corosan; Novodil†; Persantin; *Jpn*: Persantin; *Mex.*: Digal; Dipres; Dirinol; Lodimol; Persantin; Pracem; Trepol†; Vadinar; *Neth.*: Persantin; *Norw.*: Persantin; *NZ*: Persantin; Pytazen; *Philipp.*: Persantin; *Port.*: Persantin; *Rus.*: Curantyl (Курантил); Persantin (Персантин); *S.Afr.*: Persantin; Plato; *Singapore*: Perazodin; Persantin; Procardin; *Spain*: Persantin; *Swed.*: Persantin; *Thai.*: Agremol; Persantin; Posanin†; *Turk.*: Drisentin; Kardisentin; Tromboliz; Trombosentin; *UK*: Persantin; *Ukr.*: Curantil (Курантил); *USA*: Persantine; *Venez.*: Persantin.

Multi-ingredient Preparations. *Arg.*: Agrenox; Licuamon; *Austral.*: Asasantin; *Austria*: Asasantin; *Belg.*: Aggrenox; *Canad.*: Aggrenox; *China*: A Si Pan (阿司潘); De Li Shu (德力舒); Heng Yi (恒宜); SaiTong (赛同); SiNaGe (斯纳格); *Cz.*: Aggrenox; *Denm.*: Aggrenox; Asasantin; Asasantine; *Fin.*: Asasantin; Orisantin; *Fr.*: Asasantine; *Ger.*: Aggrenox; *Gr.*: Aggrenox; Fluxin; *Hong Kong*: Aggrenox; *Hung.*: Asasantin; *India*: Arreno; Cardiwell Plus; Dynasprin; *Indon.*: Aggrenox; *Irl.*: Asasantin; *Israel*: Aggrenox; *Ital.*: Aggrenox; *Neth.*: Asasantin; *Norw.*: Asasantin; *Philipp.*: Aggrenox; *Port.*: Aggrenox; *Rus.*: Aggrenox (Аренокс); *S.Afr.*: Asasantin; *Swed.*: Asasantin; *Switz.*: Asasantine; *Thai.*: Aggrenox; *UK*: Asasantin; *Ukr.*: Agrenox (Аренокс); *USA*: Aggrenox.

Pharmacopoeial Preparations

BP 2014: Dipyridamole Infusion; Dipyridamole Oral Suspension; Dipyridamole Tablets; Prolonged-release Dipyridamole Capsules; USP 36: Dipyridamole Injection; Dipyridamole Oral Suspension; Dipyridamole Tablets.

Disopyramide *(BAN, USAN, rINN)*

Disopiramida; Disopyramid; Disopyramidi; Disopyramidum; Dizopiramid; Dizopiramidas; SC-7031; Дизопирамид.

4-Diisopropylamino-2-phenyl-2-(2-pyridyl)butyramide.

$C_{21}H_{29}N_3O$=339.5.

CAS — 3737-09-5.

ATC — C01BA03.

ATC Vet — QC01BA03.

UNII — GFO926U8MQ.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Disopyramide). A white or almost white powder. Slightly soluble in water; soluble in alcohol; freely soluble in dichloromethane. Protect from light.

Disopyramide Phosphate *(BANM, USAN, rINNM)*

Disopiramida, fosfato de; Disopyramide, Phosphate de; Disopyramidfosfat; Disopyramid-fosfat; Disopyramidi Phosphas; Disopyramidifosfaatti; Disopyramidphosphat; Dizopiramid Fosfata; Dizopiramid-foszfát; Dizopiramido fosfatas; Dyzopiramidu fosforan; Fosfato de disopiramida; SC-13957; Дизопирамида Фосфат.

$C_{21}H_{29}N_3O.H_3PO_4$=437.5.

CAS — 22059-60-5.

UNII — N68OM1935W.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Disopyramide Phosphate). A white or almost white powder. Soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 36: (Disopyramide Phosphate). A white or practically white, odourless powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. pH of a 5% solution in water is between 4.0 and 5.0. Store in airtight containers. Protect from light.

Uses and Administration

Disopyramide is a class Ia antiarrhythmic (p. 1243.1) with an action on the heart similar to that of quinidine (p. 1481.3). It also has antimuscarinic and negative inotropic properties.

Disopyramide is used in the management of supraventricular and ventricular arrhythmias (p. 1266.1).

It may be given orally as either the base or the phosphate or intravenously as the phosphate; doses are expressed in terms of the base. Disopyramide phosphate 1.3 g is equivalent to about 1 g of disopyramide. The usual *oral* dose is 300 to 800 mg daily in divided doses adjusted according to response. A modified-release preparation can be used, enabling 12-hourly dosage intervals.

Disopyramide may be given by slow *intravenous* injection in a dose of 2 mg/kg to a maximum of 150 mg, at a rate not exceeding 30 mg/minute; this is followed by 200 mg orally immediately on completion of the injection and every 8 hours for 24 hours. If the arrhythmia recurs the intravenous injection may be repeated, but a total intravenous dose of 4 mg/kg (maximum 300 mg) should not be exceeded in the first hour, nor should the total by both intravenous and oral routes exceed 800 mg in 24 hours.

Alternatively, the initial intravenous injection may be followed by intravenous infusion of 400 micrograms/kg per hour (or 20 to 30 mg/hour) to a maximum of 800 mg daily. Patients receiving disopyramide intravenously or in high oral doses should be monitored by ECG.

Dosage reduction and/or increased dosage interval may be necessary in patients with hepatic or renal impairment (see below and p. 1364.1, respectively) and in some elderly patients (see, below). Doses should also be adjusted in patients with heart failure to compensate for the prolonged half-life.

For the dosage of disopyramide in children, see below.

Action. A study in 6 patients with atrial flutter suggested that the antiarrhythmic activity of racemic disopyramide resides in the S(+)-enantiomer.[1]

1. Lima JJ, *et al.* Antiarrhythmic activity and unbound concentrations of disopyramide enantiomers in patients. *Ther Drug Monit* 1990; 12: 23–8.

Administration in children. An optimum dosage regimen for children has not been fully established, but US product information suggests the following oral doses:

- under 1 year: 10 to 30 mg/kg daily
- age 1 to 4 years: 10 to 20 mg/kg daily
- age 4 to 12 years: 10 to 15 mg/kg daily
- age 12 to 18 years: 6 to 15 mg/kg daily

Administration in the elderly. The clearance of disopyramide was reduced in elderly non-smoking patients compared with young subjects, but the reduction was less marked in elderly patients who smoked more than 20 cigarettes daily.[1] It was recommended that the dose of disopyramide should be reduced by about 30% in elderly non-smokers.

1. Bonde J, *et al.* The influence of age and smoking on the elimination of disopyramide. *Br J Clin Pharmacol* 1985; 20: 453–8.

Administration in hepatic impairment. The plasma half-life of disopyramide may be increased in hepatic impairment and dosage reduction should be considered; US licensed product information recommends an oral dose of 400 mg daily in divided doses. In patients with liver cirrhosis there is also a significant reduction in the plasma concentration of α_1-acid glycoprotein;[1,2] in addition, its binding capacity for disopyramide is reduced.[1] This is associated with an increase in the free fraction of disopyramide such that measurement of total disopyramide in plasma may not be a safe indicator for dosing, and a thera-

peutic range 50% lower than in patients with normal hepatic function should be considered.[2]

1. Bonde J, *et al.* Kinetics of disopyramide in decreased hepatic function. *Eur J Clin Pharmacol* 1986; 31: 73–7.
2. Echizen H, *et al.* Protein binding of disopyramide in liver cirrhosis and in nephrotic syndrome. *Clin Pharmacol Ther* 1986; 40: 274–80.

Administration in renal impairment. Disopyramide is excreted mainly in the urine and a reduction in clearance with an increase in elimination half-life has been reported[1] in patients with renal impairment. Dosage reduction should therefore be considered. US licensed product information recommends the following oral doses based on creatinine clearance (CC):

- CC greater than 40 mL/minute: 400 mg daily in divided doses
- CC 30 to 40 mL/minute: 100 mg every 8 hours
- CC 15 to 30 mL/minute: 100 mg every 12 hours
- CC less than 15 mL/minute: 100 mg every 24 hours

Modified-release preparations should be avoided in patients with CC less than 40 mL/minute.

At therapeutic concentrations disopyramide is not significantly removed by haemodialysis;[2] the half-life is similar both on and off dialysis (16.8 versus 16.1 hours). An increased free fraction of disopyramide has been seen[3] during haemodialysis associated with an elevation in free fatty acids in plasma and in such cases free plasma-disopyramide concentrations should be monitored.

1. Francois B, *et al.* Pharmacokinetics of disopyramide in patients with chronic renal failure. *Eur J Drug Metab Pharmacokinet* 1983; 8: 85–92.
2. Sevka MJ, *et al.* Disopyramide hemodialysis and kinetics in patients requiring long-term hemodialysis. *Clin Pharmacol Ther* 1981; 29: 322–6.
3. Horiuchi T, *et al.* Inhibitory effect of free fatty acids on plasma protein binding of disopyramide in haemodialysis patients. *Eur J Clin Pharmacol* 1989; 36: 175–80.

Hypertrophic cardiomyopathy. Patients with hypertrophic cardiomyopathy (p. 1261.3) may have exercise intolerance due to left ventricular outflow obstruction. Beta blockers are usually used when symptoms are associated with exercise or emotional factors, but may not be effective in patients with symptoms at rest. Disopyramide has been used for its negative inotropic effect in such patients and a retrospective study[1] found that it improved symptoms without having a proarrhythmic effect. It has been reported to have a synergistic effect when combined with electrical pacing.[2]

For precautions in patients with cardiomyopathy see below.

1. Sherrid MV, *et al.* Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005; 45: 1251–8.
2. Haruki S, *et al.* Possible acute and chronic synergistic effect of dual chamber pacing and disopyramide in obstructive hypertrophic cardiomyopathy: a case report. *Eur J Heart Fail* 2010; 12: 94–7.

Hypotension. Disopyramide has been widely used in the management of neurally mediated hypotension (p. 1277.2) but there is limited evidence to support its use. Although some reports[1,2] have suggested benefit, a controlled study[3] found that it was no more effective than placebo in preventing tilt-induced syncope. Adverse effects also limit the use of disopyramide, and it is generally no longer considered first line.

1. Milstein S, *et al.* Usefulness of disopyramide for prevention of upright tilt-induced hypotension-bradycardia. *Am J Cardiol* 1990; 65: 1339–44.
2. Bhaumick SK, *et al.* Oral disopyramide in the treatment of recurrent neurocardiogenic syncope. *Int J Clin Pract* 1997; 51: 342.
3. Morillo CA, *et al.* A placebo-controlled trial of intravenous and oral disopyramide for prevention of neurally mediated syncope induced by head-up tilt. *J Am Coll Cardiol* 1993; 22: 1843–8.

Adverse Effects and Treatment

The adverse effects most commonly associated with disopyramide relate to its antimuscarinic properties and are dose-related. They include dry mouth, blurred vision, urinary hesitancy, impotence, and constipation; the most serious effect is urinary retention. Gastrointestinal effects, which are less common, include nausea, bloating, and abdominal pain. Other adverse effects reported include skin rashes, hypoglycaemia, dizziness, fatigue, muscle weakness, headache, and urinary frequency. Insomnia and depression have also been associated with disopyramide. There have been rare reports of psychosis, cholestatic jaundice, elevated liver enzymes, thrombocytopenia, and agranulocytosis. Disopyramide prolongs the QT interval and may induce or worsen arrhythmias, particularly ventricular tachycardia and fibrillation; heart block and conduction disturbances may occur. It is also a negative inotrope and may cause heart failure, and hypotension.

Over-rapid intravenous injection of disopyramide may cause profuse sweating and severe cardiovascular depression.

In overdose cardiovascular and antimuscarinic effects are pronounced, and there may be apnoea, loss of consciousness, loss of spontaneous respiration, and asystole. Treatment of overdosage is symptomatic and supportive. Activated charcoal may be considered if the patient presents within 1 hour of ingestion.

A review of the adverse effects associated with the class Ia antiarrhythmic drugs disopyramide, procainamide, and quinidine, and their clinical management.[1]

1. Kim SY, Benowitz NL. Poisoning due to class IA antiarrhythmic drugs quinidine, procainamide and disopyramide. *Drug Safety* 1990; 5: 393–420.

Incidence of adverse effects. During long-term therapy with disopyramide 400 to 1600 mg daily in 40 patients, 28 (70%) had one or more adverse effects.[1] Dry mouth occurred in 15 (38%), constipation in 12 (30%), blurred vision in 11 (28%), urinary hesitancy in 9 (23%), nausea in 9 (23%), impotence in 2 (5%), and dyspareunia in one patient (3%). In addition 3 of the 9 patients with pre-existing heart failure had worsening of their condition due to disopyramide. Adverse effects were sufficiently severe for disopyramide to be stopped in 7 patients, and for dosage reductions in another 7.

1. Bauman JL, *et al.* Long-term therapy with disopyramide phosphate: side effects and effectiveness. *Am Heart J* 1986; 111: 654–60.

Effects on the blood. Granulocytopenia was associated on 2 occasions with the use of disopyramide phosphate in a 61-year-old man.[1]

1. Conrad ME, *et al.* Agranulocytosis associated with disopyramide therapy. *JAMA* 1978; 240: 1857–8.

Effects on the eyes. The antimuscarinic activity of disopyramide may cause adverse effects such as dilated pupils,[1] severe blurring of vision,[1] and acute glaucoma.[2,3] Disopyramide should be avoided in patients with glaucoma and used with caution if there is a family history of glaucoma.

1. Frucht J, *et al.* Ocular side effects of disopyramide. *Br J Ophthalmol* 1984; 68: 890–1.
2. Trope GE, Hind VMD. Closed-angle glaucoma in patient on disopyramide. *Lancet* 1978; i: 329.
3. Ahmad S. Disopyramide: pulmonary complications and glaucoma. *Mayo Clin Proc* 1990; 65: 1030–1.

Effects on the heart. Disopyramide has a strong negative inotropic effect and reversible heart failure has been reported[1] after its use. As many as 50% of patients with a history of heart failure may have a recurrence of the disease with an incidence of less than 5% in other patients.

As disopyramide can prolong the QT interval it can induce ventricular tachyarrhythmias. A case of fatal torsade de pointes has been reported.[2]

1. Podrid PJ, *et al.* Congestive heart failure caused by oral disopyramide. *N Engl J Med* 1980; 302: 614–17.
2. Schattner A, *et al.* Fatal torsade de pointes following jaundice in a patient treated with disopyramide. *Postgrad Med J* 1989; 65: 333–4.

Effects on the liver. Cholestatic jaundice with raised liver enzyme values has been associated with disopyramide.[1-3] Laboratory and clinical abnormalities disappear on withdrawal although liver enzyme values may remain elevated for several months.

Severe hepatocellular damage with disseminated intravascular coagulation[4] has also been reported.

1. Cranz A, *et al.* Disopyramide and cholestasis. *Ann Intern Med* 1980; 93: 150–1.
2. Edmonds ME, Hayler AM. *Eur J Clin Pharmacol* 1980; 18: 285–6.
3. Bakris GL, *et al.* Disopyramide-associated liver dysfunction. *Mayo Clin Proc* 1983; 58: 265–7.
4. Doody FT. Disopyramide hepatotoxicity and disseminated intravascular coagulation. *South Med J* 1982; 75: 496–8.

Effects on mental state. Agitation and distress leading to paranoia and auditory and visual hallucinations have been reported[1,2] in patients shortly after starting disopyramide therapy. Complete recovery occurred on withdrawal.

1. Falk RH, *et al.* Mental distress in patient on disopyramide. *Lancet* 1977; i: 858–9.
2. Padfield PL, *et al.* Disopyramide and acute psychosis. *Lancet* 1977; i: 1152.

Effects on the nervous system. Peripheral neuropathy affecting the feet and severe enough to prevent walking was associated with disopyramide in a 72-year-old patient.[1] There was gradual improvement on withdrawal of disopyramide with the patient being symptom-free after 4 months. Another patient[2] developed a peripheral polyneuropathy 4 years after starting disopyramide; symptoms improved over several months after disopyramide was stopped.

A 75-year-old woman with atrial fibrillation suffered a tonic-clonic seizure followed by respiratory arrest after receiving disopyramide 150 mg intravenously over a period of 10 minutes.[3] On recovery she complained of a dry mouth and blurred vision and it was considered that the seizure was caused by the antimuscarinic action of disopyramide, although it may have been due to a direct stimulant action.

1. Dawkins KD, Gibson J. Peripheral neuropathy with disopyramide. *Lancet* 1978; i: 329.
2. Briani C, *et al.* Disopyramide-induced neuropathy. *Neurology* 2002; 58: 663.
3. Johnson NM, *et al.* Epileptiform convulsion with intravenous disopyramide. *Lancet* 1978; ii: 848.

Effects on sexual function. Impotence has been reported[1-3] in patients receiving disopyramide, and is usually attributed to its antimuscarinic effects, although other antimuscarinic symptoms may not be apparent. In one patient[1] full recovery of sexual function occurred when the dose was reduced (plasma concentration reduced from 14 to 3 micrograms/mL); another patient[3] developed impotence shortly after starting disopyramide, despite a low plasma concentration (1.5 micrograms/mL), but the condition resolved without changing therapy.

1. McHaffie DJ, *et al.* Impotence in patient on disopyramide. *Lancet* 1977; i: 859.
2. Ahmad S. Disopyramide and impotence. *South Med J* 1980; 73: 958.
3. Hasegawa J, Mashiba H. Transient sexual dysfunction observed during antiarrhythmic therapy by long-acting disopyramide in a male Wolff-Parkinson-White patient. *Cardiovasc Drugs Ther* 1994; 8: 277.

Effects on the urinary tract. In a report of 9 cases of urinary retention associated with disopyramide and a review of the literature,[1] it was noted that urinary retention secondary to disopyramide use was most likely to develop in male patients over the age of 65 in whom there was some pre-existing renal dysfunction; there was an increased risk in patients with evidence of prostatic hyperplasia.

1. Danziger LH, Horn JR. Disopyramide-induced urinary retention. *Arch Intern Med* 1983; 143: 1683–6.

Hypersensitivity. Worsening of ventricular arrhythmia and an anaphylactoid reaction occurred in a 58-year-old man after a single oral dose of disopyramide 300 mg.[1] Two hours later he complained of a swollen tongue and difficulty in breathing. He became cyanotic but his respiratory status improved when given diphenhydramine 25 mg intravenously.

1. Porterfield JG, *et al.* Respiratory difficulty after use of disopyramide. *N Engl J Med* 1980; 303: 584.

Hypoglycaemia. After the manufacturer received reports of hypoglycaemia associated with disopyramide, 2 controlled studies were conducted in healthy subjects.[1] Disopyramide produced a small decrease in blood-glucose concentration but there were no symptoms of hypoglycaemia although it was considered that the glucose-lowering effect might be clinically significant in patients with hepatic or renal impairment. A review[2] found that renal impairment, advanced age, and malnutrition were the main risk factors for hypoglycaemia, and hypoglycaemia with reduced insulin requirements has also been reported[3] in a patient with type 2 diabetes mellitus. An interaction with clarithromycin has also been reported as a possible cause (see Antibacterials under Interactions, p. 1365.2). However, the overall incidence appears to be low[2] and a case-control study[4] in 91 patients with hypoglycaemia failed to confirm an association with disopyramide.

For a report of severe hypoglycaemia associated with the use of disopyramide with glimepiride see Antidiabetics, under Interactions p. 1365.2.

1. Strathman L, *et al.* Hypoglycemia in patients receiving disopyramide phosphate. *Drug Intell Clin Pharm* 1983; 17: 635–8.
2. Cacoub P, *et al.* Disopyramide-induced hypoglycemia: case report and review of the literature. *Fundam Clin Pharmacol* 1989; 3: 527–35.
3. Reynolds RM, Walker JD. Hypoglycaemia induced by disopyramide in a patient with type 2 diabetes mellitus. *Diabet Med* 2001; 18: 1009–10.
4. Takada M, *et al.* The relationship between risk of hypoglycemia and use of cibenzoline and disopyramide. *Eur J Clin Pharmacol* 2000; 56: 335–42.

Overdosage. A 2-year-old boy suffered hypotension, cardiac arrhythmias, and convulsions and died 28 hours after ingestion of 600 mg of disopyramide.[1] In a report[2] of 5 cases of fatal overdosage with disopyramide the most common clinical finding appeared to be an early loss of consciousness after an episode of respiratory arrest. Four of the patients responded to resuscitation at first but then deteriorated rapidly, with cardiac arrhythmias and loss of spontaneous respiration; in 4 of the cases post-mortem examination found pulmonary congestion secondary to left ventricular failure.

1. Hutchison A, Kilham H. Fatal overdosage of disopyramide in a child. *Med J Aust* 1978; 2: 335–6.
2. Hayler AM, *et al.* Fatal overdosage with disopyramide. *Lancet* 1978; i: 968–9.

Precautions

Disopyramide is contra-indicated in complete heart block (unless the patient has a pacemaker) and in cardiogenic shock. It should be used with extreme caution in patients with other conduction disorders or uncompensated heart failure. As for quinidine (see Precautions for Quinidine, p. 1482.3), if disopyramide is used to treat atrial tachycardia it may be necessary to pre-treat with digoxin. Hypokalaemia should be corrected before disopyramide is started. Patients with cardiomyopathy should be given doses at the lower end of the range initially, and should be carefully monitored for the development of hypotension and heart failure.

Care should be taken in patients susceptible to hypoglycaemia, including those with heart failure, hepatic

or renal impairment, and patients taking drugs that affect glucose metabolism.

Intravenous injections of disopyramide should be given slowly to avoid hypotension and it is recommended that facilities for cardiac monitoring and defibrillation should be available when the injection is used.

Dosage reduction may be necessary in patients with hepatic or renal impairment and in patients with heart failure.

Owing to its antimuscarinic properties, disopyramide should be avoided in patients with glaucoma or a tendency to urinary retention, as in benign prostatic hyperplasia, and also in patients with myasthenia gravis because of the risk of precipitating a myasthenic crisis. It should be used with caution in patients with a family history of glaucoma.

For dosage adjustments in the elderly and in patients with hepatic or renal impairment, see under Uses and Administration, p. 1363.3 and p. 1364.1.

Breast feeding. Disopyramide is distributed into breast milk and milk to plasma ratios of 0.4, about 0.5, and 0.9 have been reported.[1-3] Disopyramide has been detected in the plasma of breast-fed infants, but was not associated with adverse effects. The American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding. However, the infant should be monitored for adverse effects, especially antimuscarinic effects.

1. MacKintosh D, Buchanan N. Excretion of disopyramide in human breast milk. *Br J Clin Pharmacol* 1985; 19: 856–7.
2. Hoppu K, *et al.* Disopyramide and breast feeding. *Br J Clin Pharmacol* 1986; 21: 353.
3. Barnett DB, *et al.* Disopyramide and its N-monodesalkyl metabolite in breast milk. *Br J Clin Pharmacol* 1982; 14: 310–12.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. (Retired May 2010) Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies disopyramide as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pregnancy. Disopyramide is not usually recommended in pregnancy since it may induce uterine contractions. Although no adverse effects were noted in a patient given disopyramide 200 mg every 8 hours from 26 weeks of gestation until delivery,[1] another patient who was given 4 oral doses of disopyramide 100 to 300 mg at six-hourly intervals in week 32 of pregnancy had uterine contractions 1 to 2 hours after each dose.[2] A further patient[3] given disopyramide at 36 weeks of gestation developed painful uterine contractions 40 minutes after a single 150-mg dose orally; active labour and haemorrhage developed after a second dose was given, and an emergency caesarean section was required. A double-blind, placebo-controlled study[4] involving 20 women hospitalised for induction of labour confirmed that disopyramide induces uterine contractions. All 10 women given disopyramide 150 mg every 6 hours for 48 hours began contractions and in 8 delivery was induced.

1. Shaxted EJ, Milton PJ. Disopyramide in pregnancy: a case report. *Curr Med Res Opin* 1979; 6: 70–2.
2. Leonard RF, *et al.* Initiation of uterine contractions by disopyramide during pregnancy. *N Engl J Med* 1978; 299: 84–5.
3. Abbi M, *et al.* Preterm labor and accidental hemorrhage after disopyramide therapy in pregnancy: a case report. *J Reprod Med* 1999; 44: 653–5.
4. Tadmor OP, *et al.* The effect of disopyramide on uterine contractions during pregnancy. *Am J Obstet Gynecol* 1990; 162: 482–6.

Interactions

Disopyramide should be used cautiously with drugs that have negative inotropic effects or that affect conduction, including beta blockers and other class I antiarrhythmics; it prolongs the QT interval and should not be given with other arrhythmogenic drugs. Disopyramide is metabolised by the cytochrome P450 isoenzyme CYP3A4 and interactions may occur with inhibitors or inducers of this enzyme and with other drugs metabolised by CYP3A4. Use of disopyramide with other antimuscarinic drugs produces enhanced antimuscarinic effects.

Anti-anginals. For reference to disopyramide reducing the efficacy of sublingual *isosorbide dinitrate*, see p. 1413.1.

Antiarrhythmics. The effects of disopyramide on cardiac conduction are additive to those of other class I antiarrhythmic drugs.[1] Disopyramide may prolong the QT interval, a factor associated with torsade de pointes, particularly when given with drugs that have a similar effect; this effect was noted in a few patients given *amiodarone* with disopyramide.[2] Also the serum concentration of disopyramide has been increased by *quinidine*;[3] there was a reciprocal decrease in the serum-quinidine concentration but this was less important clinically.

1. Ellrodt G, Singh BN. Adverse effects of disopyramide (Norpace): toxic interactions with other antiarrhythmic agents. *Heart Lung* 1980; 9: 469–74.
2. Tartini R, *et al.* Dangerous interaction between amiodarone and quinidine. *Lancet* 1982; i: 1327–9.
3. Baker BJ, *et al.* Concurrent use of quinidine and disopyramide: evaluation of serum concentrations and electrocardiographic effects. *Am Heart J* 1983; 105: 12–15.

Antibacterials. The metabolism of disopyramide may be increased by enzyme inducers such as *rifampicin*;[1,2] the increased clearance of disopyramide may lead to subtherapeutic plasma concentrations.

Conversely, enzyme inhibitors may increase serum-disopyramide concentrations[3] and ventricular arrhythmias have been noted in patients given azithromycin,[4] clarithromycin,[5-7] and erythromycin.[3] Hypoglycaemia attributed to increased disopyramide concentrations has also been reported[8,9] with clarithromycin.

1. Aitio M-L, *et al.* The effect of enzyme induction on the metabolism of disopyramide in man. *Br J Clin Pharmacol* 1981; 11: 279–85.
2. Staum JM. Enzyme induction: rifampin-disopyramide interaction. *DICP Ann Pharmacother* 1990; 24: 701–3.
3. Ragosta M, *et al.* Potentially fatal interaction between erythromycin and disopyramide. *Am J Med* 1989; 86: 465–6.
4. Granowitz EV, *et al.* Potentially fatal interaction between azithromycin and disopyramide. *Pacing Clin Electrophysiol* 2000; 23: 1433–5.
5. Paar D, *et al.* Life-threatening interaction between clarithromycin and disopyramide. *Lancet* 1997; 349: 326–7.
6. Hayashi Y, *et al.* Torsades de pointes ventricular tachycardia induced by clarithromycin and disopyramide in the presence of hypokalemia. *Pacing Clin Electrophysiol* 1999; 22: 672–4.
7. Choudhury L, *et al.* Torsades de pointes due to drug interaction between disopyramide and clarithromycin. *Heart Dis* 1999; 1: 206–7.
8. Iida H, *et al.* Hypoglycemia induced by interaction between clarithromycin and disopyramide. *Jpn Heart J* 1999; 40: 91–96.
9. Morlet-Barla N, *et al.* Hypoglycémie grave et récidivante secondaire à l'interaction disopyramide-clarithromicine. *Presse Med* 2000; 29: 1351.

Antidiabetics. Disopyramide can induce hypoglycaemia and care is needed if it is used with drugs that can lower blood glucose. Severe hypoglycaemia developed in a woman with type 2 diabetes when disopyramide was added to existing therapy with low-dose *glimepiride*; she had no previous history of such episodes and hypoglycaemia resolved once disopyramide was stopped.[1] Subsequent study *in vitro* suggested that each drug blocked K_{ATP} potassium channels by about 50 to 60% but when given together they produced almost total inhibition, which would result in membrane depolarisation of islet cells and stimulate release of insulin.

1. Negishi M, *et al.* Mechanism of disopyramide-induced hypoglycaemia in a patient with type 2 diabetes. *Diabet Med* 2009; 26: 76–8.

Antiepileptics. The clearance of disopyramide may be increased by enzyme inducers such as *phenytoin* and *phenobarbital*, and a small study[1] found that phenytoin reduced serum-disopyramide concentrations.

1. Aitio M-L, *et al.* The effect of enzyme induction on the metabolism of disopyramide in man. *Br J Clin Pharmacol* 1981; 11: 279–85.

Beta blockers. Beta blockers have negative inotropic effects that may be potentiated if they are given with disopyramide. A pharmacokinetic interaction may also occur with beta blockers since the clearance of disopyramide has been reported[1] to be reduced by about 16% during *atenolol* therapy.

1. Bonde J, *et al.* Atenolol inhibits the elimination of disopyramide. *Eur J Clin Pharmacol* 1985; 28: 41–3.

Pharmacokinetics

Disopyramide is readily and almost completely absorbed from the gastrointestinal tract; peak plasma concentrations occur about 0.5 to 3 hours after oral doses.

Disopyramide is partially metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4. The major metabolite is mono-*N*-dealkylated disopyramide which retains some antiarrhythmic and antimuscarinic activity. The major route of excretion is through the kidney, about 50% as the unchanged drug, 20% as the *N*-dealkylated metabolite, and 10% as other metabolites. About 10% is excreted in the faeces. The clearance of disopyramide does not appear to be influenced by urinary pH.

Disopyramide protein binding varies with the plasma concentration, limiting the usefulness of plasma concentration monitoring as a guide to therapy; protein binding is reported to be 50 to 65% at therapeutic plasma concentrations (about 2 to 4 micrograms/mL). Estimations of the plasma half-life of disopyramide range from about 4 to 10 hours. The half-life is increased in hepatic and renal impairment, and in heart failure.

Disopyramide crosses the placental barrier and is distributed into breast milk.

Reviews.

1. Siddoway LA, Woosley RL. Clinical pharmacokinetics of disopyramide. *Clin Pharmacokinet* 1986; 11: 214–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Rythmodan; *Belg.*: Rythmodan; *Braz.*: Dicorantil; *Canad.*: Rythmodan; *Fin.*: Dismet†; *Fr.*: Rythmodan; *Gr.*: Dicorynan; Ritmodan; Rythmodan; *Hung.*: Palpitin-PP; *India*: Norpace; *Irl.*: Rythmodan; *Israel*: Rythmical; *Ital.*: Ritmodan; *Jpn*: Rythmodan; *Mex.*: Biolytan; Dimodan; *Mon.*: Isorythm; *Neth.*: Ritmoforine; *Norw.*: Durbis; *NZ*: Rythmodan; *S.Afr.*: Norpace; Rythmodan; *Spain*: Dicorynan; *Swed.*: Durbis; *Turk.*: Norpace; *UK*: Rythmodan; *USA*: Norpace.

Pharmacopoeial Preparations

BP 2014: Disopyramide Capsules; Disopyramide Phosphate Capsules;

USP 36: Disopyramide Phosphate Capsules; Disopyramide Phosphate Extended-release Capsules.

Ditazole *(rINN)*

Diethamphenazole; Ditazol; Ditazolum; S-222; Дитазол.

2,2'-[(4,5-Diphenyloxazol-2-yl)imino]diethanol.

$C_{19}H_{20}N_2O_3$=324.4

CAS — 18471-20-0.

ATC — B01AC01.

ATC Vet — QB01AC01.

UNII — H28QI5Z8FT.

Profile

Ditazole is an inhibitor of platelet aggregation used in the management of thromboembolic disorders (p. 1273.2) in oral doses of 400 mg two or three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Spain*: Ageroplast†.

Dobutamine Hydrochloride

(BANM, USAN, rINNM)

46236; Compound 81929 (dobutamine); Dobutamiinihydroklorid; Dobutamina, hidrocloruro de; Dobutamine, chlorhydrate de; Dobutamin-hidroklorid; Dobutaminhydrochlorid; Dobutamin-hydrochlorid; Dobutaminhydroklorid; Dobutamini Hydrochloridum; Dobutamino hidrochloridas; Hidrocloruro de dobutamina; LY-174008 (dobutamine tartrate); Добутамина гидрохлорид.

(±)-4-(2-[[3-(*p*-Hydroxyphenyl)-1-methylpropyl]amino]ethyl) pyrocatechol hydrochloride.

$C_{18}H_{23}NO_3$,HCl=337.8

CAS — 34368-04-2 (dobutamine); 49745-95-1 (dobutamine hydrochloride); 101626-66-8 (dobutamine tartrate).

ATC — C01CA07.

ATC Vet — QC01CA07.

UNII — 0WR771DJXV.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Dobutamine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water and in alcohol; soluble in methyl alcohol. Protect from light.

USP 36: (Dobutamine Hydrochloride). A white to practically white crystalline powder. Sparingly soluble in water and in methyl alcohol; soluble in alcohol and in pyridine. Store in airtight containers at a temperature of 15 degrees to 30 degrees.

Incompatibility. Dobutamine is incompatible with alkaline solutions such as sodium bicarbonate 5% and alkaline drugs such as aminophylline, furosemide,[1] and thiopental sodium;[1] physical incompatibility with bumetanide, calcium gluconate, insulin, diazepam, and phenytoin has also been suggested. There have also been reports of incompatibility with alteplase,[2] heparin,[3] and warfarin sodium.[4]

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; 54: 64–5.
2. Lee CY, *et al.* Visual and spectrophotometric determination of compatibility of alteplase and streptokinase with other injectable drugs. *Am J Hosp Pharm* 1990; 47: 606–8.
3. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; 53: 1048–51.
4. Babal SM, *et al.* Visual compatibility of warfarin sodium injection with selected medications and solutions. *Am J Health-Syst Pharm* 1997; 54: 2599–2600.

Uses and Administration

Dobutamine is a sympathomimetic (p. 1507.3) with direct effects on $beta_1$-adrenergic receptors, giving it a prominent inotropic action on the heart. It also has some alpha- and $beta_2$-agonist properties. Although it is structurally related to dopamine (p. 1367.2), it has no specific dopaminergic properties; however, like dopamine, the inotropic action of

dobutamine on the heart is associated with less cardiac-accelerating effect than that of isoprenaline.

Dobutamine is used to increase the contractility of the heart in acute heart failure, as occurs in cardiogenic shock (p. 1279.3) and myocardial infarction (p. 1257.1); it is also used in septic shock. Other circumstances in which its inotropic activity may be useful are during cardiac surgery and positive end-expiratory pressure ventilation.

Dobutamine is used as the hydrochloride but doses are expressed in terms of the base: 1.12 micrograms of the hydrochloride is equivalent to about 1 microgram of base. It is given by intravenous infusion as a dilute solution (0.25 to 5 mg/mL), in glucose 5% or sodium chloride 0.9%; other fluids may also be suitable and the manufacturers' guidelines should be consulted.

In the management of **acute heart failure**, dobutamine is given at a usual rate of 2.5 to 10 micrograms/kg per minute, according to the patient's heart rate, blood pressure, cardiac output, and urine output. A range of 0.5 up to 40 micrograms/kg per minute has occasionally been required. It has been recommended that treatment with dobutamine should be stopped gradually.

Dobutamine is also used as an alternative to exercise in **cardiac stress testing**. A solution containing 1 mg/mL is given via an infusion pump in a dose of 5 micrograms/kg per minute for 8 minutes. The dose is then increased by increments of 5 micrograms/kg per minute up to a usual maximum of 20 micrograms/kg per minute, with each dose being infused for 8 minutes before the next increase; doses of up to 40 micrograms/kg per minute have sometimes been used. The ECG should be monitored continuously and the infusion stopped if arrhythmias, marked ST segment depression, or other adverse effects occur.

For doses in children, see below.

Action. Although dobutamine is usually considered to be a $beta_1$ agonist, *animal* studies suggest that its ability to stimulate $alpha_1$- and $beta_2$-adrenergic receptors may be as great as its $beta_1$-stimulant properties. It has been proposed that the inotropic action results from a combination of alpha-stimulant activity on myocardial $alpha_1$ receptors, a property residing mainly in the (-)-enantiomer, with $beta_1$ stimulation by the (+)-enantiomer; peripherally, alpha-mediated vasoconstriction would be opposed by the $beta_2$-agonist properties of the (+)-enantiomer, resulting in the net inotropic action with relatively little effect on blood pressure seen with the racemic mixture used clinically.[1]

Dobutamine has a thermogenic effect,[2] increasing oxygen delivery and utilisation in healthy individuals. However, using it for this purpose in critically ill patients did not improve patient outcome and in some cases might have been harmful.[3]

1. Ruffolo RR. The mechanism of action of dobutamine. *Ann Intern Med* 1984; 100: 313–14.
2. Bhatt SB, *et al.* Effect of dobutamine on oxygen supply and uptake in healthy volunteers. *Br J Anaesth* 1992; 69: 298–303.
3. Hayes MA, *et al.* Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994; 330: 1717–22.

Administration in children. Dobutamine and dopamine are both used for inotropic support in children. A study[1] in children undergoing cardiac surgery suggested that dobutamine may be preferred to dopamine since the latter could cause pulmonary vasoconstriction (see under Precautions for Dopamine, p. 1368.2). In preterm infants, low systemic blood flow is associated with cerebral haemorrhage and neurodevelopmental disability, and both dobutamine and dopamine have been studied for their effects on outcomes. Of the two drugs, dopamine produces the greater reduction in hypotension,[2,3] but dobutamine increases superior vena cava flow to a greater extent.[3] Although it has been argued[3] that superior vena cava flow, rather than blood pressure, provides a more meaningful indication of systemic blood flow in neonates, in reality the difference may not be clinically important: while low superior vena cava flow was associated with neurodevelopmental delays at 3 years of age, there was no significant difference in combined death and disability rates between infants given dobutamine or dopamine to correct it.[4]

Neonates, infants, and children may be given dobutamine by continuous intravenous infusion for inotropic support in an initial dose of 5 micrograms/kg per minute, adjusted according to response to between 2 and 20 micrograms/kg per minute.

1. Booker PD, *et al.* Comparison of the haemodynamic effects of dopamine and dobutamine in young children undergoing cardiac surgery. *Br J Anaesth* 1995; 74: 419–23.
2. Osborn D, *et al.* Randomized trial of dobutamine versus dopamine in preterm infants with low systemic blood flow. *J Pediatr* 2002; 140: 183–91.
3. Subhedar NV, Shaw NJ. Dopamine versus dobutamine for hypotensive preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 07/10/05).
4. Osborn DA, *et al.* Low superior vena cava flow and effect of inotropes on neurodevelopment to 3 years in preterm infants. *Pediatrics* 2007; 120: 372–80.

Diagnosis and testing. Dynamic exercise is the established mode of stress for the assessment of cardiac function. In patients who are unable to exercise, a dobutamine infusion is one of the best alternative ways of producing a pharmacological stress.[1,2] It is widely used as an adjunct in echocardiography, often combined with atropine, and may give better sensitivity than adenosine or dipyridamole;[1,3] it may also have a role with other imaging techniques such as magnetic resonance imaging.[4] However there have been instances of severe cardiovascular complications attributable to dobutamine,[5] a topic which has been reviewed.[6,7]

1. Cheitlin MD, *et al.* ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). Summary article: *Circulation* 2003; 108: 1146–62. Full text: http://www.americanheart.org/downloadable/heart/1060182581039Echocleanfulltext.pdf (accessed 07/10/05)
2. Marwick TH. Stress echocardiography. *Heart* 2003; 89: 113–18.
3. Martin TW, *et al.* Comparison of adenosine, dipyridamole, and dobutamine in stress echocardiography. *Ann Intern Med* 1992; 116: 190–6.
4. Paetsch I, *et al.* Comparison of dobutamine stress magnetic resonance, adenosine stress magnetic resonance, and adenosine stress magnetic resonance perfusion. *Circulation* 2004; 110: 835–42.
5. Lattanzi F, *et al.* Dobutamine stress echocardiography: safety in diagnosing coronary artery disease. *Drug Safety* 2000; 22: 251–62.
6. Karabinos I, *et al.* Prevalence and potential mechanisms of sustained ventricular arrhythmias during dobutamine stress echocardiography: a literature review. *J Am Soc Echocardiogr* 2008; 21: 1376–81.
7. Geleijnse ML, *et al.* Incidence, pathophysiology, and treatment of complications during dobutamine-atropine stress echocardiography. *Circulation* 2010; 121: 1756–67.

Heart failure. Dobutamine may be used in the management of acute heart failure, including decompensated chronic heart failure (see Cardiogenic Shock, under Shock, p. 1279.3). It may also have a role in patients with severe chronic heart failure (p. 1262.3), either as a bridge to transplantation or for palliative therapy. In less severe cases, intermittent infusions of dobutamine have been tried. A study[1] using pulsed therapy with dobutamine (30 minutes daily for 4 days each week for 3 weeks) reported symptomatic improvements similar to those achieved with exercise, but another study[2] using intermittent therapy (24 hours every 2 to 3 weeks for 6 months) failed to show any benefit. There have also been reports of sudden death in patients receiving dobutamine as infusions for 48 hours per week, and another study[3] was halted for this reason. Long-term use of intermittent dobutamine is therefore not generally recommended.[4]

1. Adamopoulos S, *et al.* Effects of pulsed β-stimulant therapy on β-adrenoceptors and chronotropic responsiveness in chronic heart failure. *Lancet* 1995; 345: 344–9.
2. Elis A, *et al.* Intermittent dobutamine treatment in patients with chronic refractory congestive heart failure: a randomized, double-blind, placebo-controlled study. *Clin Pharmacol Ther* 1998; 63: 682–5.
3. Dies F, *et al.* Intermittent dobutamine in ambulatory outpatients with chronic cardiac failure. *Circulation* 1986; 74: (suppl II): 38.
4. Hunt SA, *et al.* ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Summary article: *J Am Coll Cardiol* 2005; 46: 1116–43. Full version: http://content.onlinejacc.org/cgi/reprint/46/6/e1.pdf (accessed 19/08/08)

Adverse Effects and Treatment

As for Sympathomimetics, p. 1508.2 and p. 1508.3. Dobutamine has mainly $beta_1$-agonist properties and its principal adverse effects include dose-related increases in heart rate and blood pressure, ectopic beats, angina or chest pain, and palpitations; dosage should be reduced or temporarily stopped if they occur. Ventricular tachycardia may occur rarely; cardiac rupture has been reported rarely during dobutamine stress testing.

Effects on body temperature. A 71-year-old woman with heart failure developed a fever on 2 separate occasions 8 to 12 hours after starting an infusion of dobutamine.[1]

1. Robison-Strane SR, Bubik JS. Dobutamine-induced fever. *Ann Pharmacother* 1992; 26: 1523–4.

Effects on the cardiovascular system. For reference to severe cardiovascular complications of dobutamine stress echocardiography, see Diagnosis and Testing under Uses and Administration, above.

For reference to fatalities occurring in patients given dobutamine, see Heart Failure under Uses and Administration, above.

Effects on the neuromuscular system. Myoclonus has been reported[1,2] in patients with renal impairment given dobutamine infusion for heart failure.

1. Wierre L, *et al.* Dobutamine-induced myoclonia in severe renal failure. *Nephrol Dial Transplant* 2004; 19: 1336–7.
2. Boord A, Benson B. Myoclonus associated with continuous dobutamine infusion in a patient with end-stage renal disease. *Am J Health-Syst Pharm* 2007; 64: 2241–3.

Effects on the skin. Troublesome pruritus of the scalp has been reported[1] in a patient receiving dobutamine infusions. It was suggested that this might be a direct effect of dobutamine since the reaction was so localised.

1. McCauley CS, Blumenthal MS. Dobutamine and pruritus of the scalp. *Ann Intern Med* 1986; 109: 966.

Hypersensitivity. Hypersensitivity reactions have been reported in patients receiving dobutamine infusions, possibly due to sodium sulfite in the formulation. Redness, swelling, itching, and a sensation of warmth developed around the infusion site in a patient receiving dobutamine; the reaction recurred when the infusion was repeated a week later. Eosinophilic reactions have also been reported, including hypersensitivity myocarditis[2-4] and asthma.[5]

1. Cernek PK. Dermal cellulitis—a hypersensitivity reaction from dobutamine hydrochloride. *Ann Pharmacother* 1994; 28: 964.
2. Spear GS. Eosinophilic explant carditis with eosinophilia: ?hypersensitivity to dobutamine infusion. *J Heart Lung Transplant* 1995; 14: 755–62.
3. Takkenberg JJM, *et al.* Eosinophilic myocarditis in patients awaiting heart transplantation. *Crit Care Med* 2004; 32: 714–21.
4. Butany J, *et al.* Hypersensitivity myocarditis complicating hypertrophic cardiomyopathy heart. *Can J Cardiol* 2004; 20: 911–14.
5. Aranda JM, *et al.* Dobutamine-related asthma in a patient awaiting cardiac transplantation: the eosinophilic dilemma. *J Heart Lung Transplant* 2004; 23: 260–1.

Overdosage. A patient received an accidental overdose of dobutamine when given an intravenous infusion at a rate of more than 130 micrograms/kg per minute for 30 minutes, this being three times the recommended maximum. Characteristic adverse effects such as emesis, palpitations, chest pain, dyspnoea, and paraesthesia developed, together with urinary incontinence, an effect not previously associated with dobutamine.

1. Paulman PM, *et al.* Dobutamine overdose. *JAMA* 1990; 264: 2386–7.

Precautions

As for Sympathomimetics, p. 1508.3. Dobutamine has inotropic effects and should be avoided or used only with great caution in patients with marked obstruction of cardiac ejection, such as idiopathic hypertrophic subaortic stenosis. It should also be used with caution in patients with acute myocardial infarction, and in cardiogenic shock complicated by severe hypotension. Hypovolaemia should be corrected before treatment.

Interference with diagnostic tests. Contamination of blood samples with dobutamine has been reported to produce falsely decreased creatinine values in an enzymatic test.[1] Colorimetric measurements of creatinine were not affected.

1. Daly TM, *et al.* "Bouncing" creatinine levels. *N Engl J Med* 1996; 334: 1749–50.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dobutamine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Sympathomimetics, p. 1508.3. Most interactions with dobutamine are due to its direct $beta_1$ agonist effects on the heart, but use with beta blockers may allow its alpha- and $beta_2$-agonist effects to become apparent.

Pharmacokinetics

Like adrenaline (p. 1295.1), dobutamine is inactive when given orally, and it is rapidly inactivated in the body by similar processes. It has a half-life of about 2 minutes. Conjugates of dobutamine and its major metabolite 3-*O*-methyldobutamine are excreted mainly in urine, with small amounts eliminated in the faeces.

The main mechanism of clearance of dobutamine appears to be distribution to other tissues, and not metabolism or elimination. It has a half-life of about 2 minutes and plasma concentrations of dobutamine reach steady state about 10 to 12 minutes after the start of an infusion. Dobutamine is used mainly for the short-term treatment of heart failure and any pharmacokinetic changes in this condition have no clinical implications in dosage titration.[1]

The pharmacokinetics of dobutamine and other cardiovascular drugs in children have been reviewed.[2]

1. Shammas FV, Dickstein K. Clinical pharmacokinetics in heart failure: an updated review. *Clin Pharmacokinet* 1988; 15: 94–113.
2. Steinberg C, Notterman DA. Pharmacokinetics of cardiovascular drugs in children: inotropes and vasopressors. *Clin Pharmacokinet* 1994; 27: 345–67.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dobucard; Duvig; *Austral.*: Dobutrex; *Austria*: Inotop; *Belg.*: Dobutrexmylan; *Braz.*: Dobtan; Dobutabbott; Dobuton; Neobutamina; *China*: Anchang (安畅); Ao Wan Yuan (奥万源); Bin Fen (疾纷); Chen Sheng Fen (辰生芬); Dobutrex (独步催); Feng Hai Fen (丰海芬); Kang Li Tuo (康利托); *Cz.*: Dobuject; Dobutrex†; *Denm.*: Dobutrex; *Fin.*: Dobuject; *Gr.*: Dobutan; Inotrex; *India*: Cardiforce; Cardiject; Dobicard; Dobier; Dobion; Dobonis; Dobucard; Dobucef; Dobucin; Dobugen; Dobunex; Doburan; Dobusol; Dobustat; Dobutam; Dobutasys; Dobutrex; Dobutrop; Dotamin; Icidob; Inoject; Kardia; *Indon.*: Cardiject; Dobucef; Dobuject; Doburan; Dobutel; Dominic; Inotrop; *Irl.*: Posiject; *Israel*: Butamine; Dobuject; *Ital.*: Miozac; *Jpn*: Dobupum; *Mex.*: Cryobutol; Dobuject; Dobutrex; Oxiken†; *Philipp.*: Cardomin; Dobuject; Dobulex; Dobunex; Dobutrex; Dobutrim; Inocard†; *Pol.*: Dobuject; *Port.*: Dasomin; Dobucor; Dobutina; Inotrex; *S.Afr.*: Cardiject; Dobutrex; *Singapore*: Dobuject; *Spain*: Dobucor†; *Swed.*: Dobutrex†; *Switz.*: Dobutrex; *Thai.*: Cardiject; Dobuject; *Turk.*: Dobuject; Dobutabag; Dobutrex; *Venez.*: Doburan; Dobuxin.

Pharmacopoeial Preparations

BP 2014: Dobutamine Infusion;

USP 36: Dobutamine for Injection; Dobutamine in Dextrose Injection; Dobutamine Injection.

Docarpamine *(rINN)*

Docarpamina; Docarpaminum; TA-870; TA-8704; Докарпамин.

(-)-(*S*)-2-Acetamido-*N*-(3,4-dihydroxyphenethyl)-4-(methylthio)butyramide bis(ethyl carbonate) ester.

$C_{21}H_{30}N_2O_8S$=470.5

CAS — 74639-40-0.

UNII — RPQ57D8S72.

Profile

Docarpamine is an orally active prodrug of dopamine (below) that has been used in the treatment of acute heart failure in a usual oral dose of 750 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Tanadopa.

Dofetilide *(BAN, USAN, rINN)*

Dofetilid; Dofetilida; Dofétilide; Dofetilidi; Dofetilidum; UK-68798; Дофетилид.

β-[(*p*-Methanesulfonamidophenethyl)methylamino]methanesulfono-*p*-phenetidide.

$C_{19}H_{27}N_3O_5S_2$=441.6

CAS — 115256-11-6.

ATC — C01BD04.

ATC Vet — QC01BD04.

UNII — R4Z9X1N2ND.

Pharmacopoeias. In *US*.

USP 36: (Dofetilide). A white to off-white powder. Very slightly soluble in water and in isopropyl alcohol; soluble in acetone, in 0.1N hydrochloric acid, and in 0.1N sodium hydroxide. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Dofetilide is a class III antiarrhythmic (p. 1243.1); it selectively blocks one of the potassium channels involved in repolarisation and therefore prolongs the action potential. It is used in the treatment of atrial fibrillation and flutter (p. 1266.1) in patients who are highly symptomatic. The initial oral dose in patients with a corrected QT interval of 440 milliseconds or less is 500 micrograms twice daily; the maintenance dose must be reduced if the QT interval becomes prolonged after the first dose, and treatment should be stopped if the QT interval exceeds 500 milliseconds. Doses should be reduced in renal impairment (see below).

References.

1. McClellan KJ, Markham A. Dofetilide: a review of its use in atrial fibrillation and atrial flutter. *Drugs* 1999; 58: 1043–59.
2. Kalus JS, Mauro VF. Dofetilide: a class III-specific antiarrhythmic agent. *Ann Pharmacother* 2000; 34: 44–56.
3. Mounsey JP, DiMarco JP. Dofetilide. *Circulation* 2000; 102: 2665–70.
4. Roukoz H, Saliba W. Dofetilide: a new class III antiarrhythmic agent. *Expert Rev Cardiovasc Ther* 2007; 5: 9–19.

Administration in renal impairment. Doses of dofetilide should be reduced in patients with renal impairment based on creatinine clearance (CC). Initial doses are:

- CC 40 to 60 mL/minute: 250 micrograms twice daily
- CC 20 to 39 mL/minute: 125 micrograms twice daily
- CC below 20 mL/minute: contra-indicated

Adverse Effects and Precautions

The most frequent adverse effects with dofetilide are headache, chest pain, and dizziness. Dofetilide prolongs the QT interval and may cause severe ventricular arrhythmias, including torsade de pointes; it should not be given to patients with congenital or acquired long QT syndromes. Hypokalaemia increases the risk of arrhythmias and potassium concentrations should be corrected before starting dofetilide. The dosage of dofetilide must be individualised according to QT interval and creatinine clearance, which must be measured before starting therapy; dofetilide is contra-indicated if the corrected QT interval is above 440 milliseconds (or above 500 milliseconds in patients with ventricular conduction abnormalities) or if the creatinine clearance is less than 20 mL/minute. Treatment should begin under ECG monitoring, which must be continued for at least 3 days, and both ECG and renal function should be monitored at least every 3 months during treatment.

Interactions

Dofetilide should not be given with other drugs that prolong the QT interval. Class I or class III antiarrhythmics should be stopped at least 3 half-lives before dofetilide is given. Potassium-depleting diuretics may cause hypokalaemia or hypomagnesaemia, increasing the potential for torsade de pointes; US licensed product information for dofetilide states that hydrochlorothiazide is contra-indicated since it also causes significant increases in plasma-dofetilide concentrations. Dofetilide is metabolised to a small extent by the cytochrome P450 isoenzyme CYP3A4, and drugs or foods that inhibit this isoenzyme, such as macrolide antibacterials, HIV-protease inhibitors, diltiazem, and grapefruit juice, should be used with caution. Cimetidine, dolutegravir, trimethoprim, ketoconazole, prochlorperazine, and megestrol, should not be given as they inhibit the renal excretion of dofetilide; verapamil is also contra-indicated as it too may substantially increase dofetilide concentrations.

References.

1. Yamreudeewong W, *et al.* Potentially significant drug interactions of class III antiarrhythmic drugs. *Drug Safety* 2003; 26: 421–38.

Pharmacokinetics

The oral bioavailability of dofetilide is more than 90%. Peak plasma concentrations occur after 2 to 3 hours and steady state concentrations after 2 to 3 days. The terminal half-life is about 10 hours. Protein binding is 60 to 70%. Dofetilide undergoes limited metabolism. About 80% of a dose is excreted in the urine, with about 80% of this as unchanged drug and 20% as 5 minimally active or inactive metabolites; metabolism may be mediated to some extent by the cytochrome P450 isoenzyme CYP3A4. Renal elimination involves both glomerular filtration and active tubular secretion via the cation transport system. The clearance of dofetilide decreases with decreasing creatinine clearance.

References.

1. Allen MJ, *et al.* The pharmacokinetics and pharmacodynamics of oral dofetilide after twice daily and three times daily dosing. *Br J Clin Pharmacol* 2000; 50: 247–53.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Tikosyn.

Dopamine Hydrochloride

(BANM, USAN, pINNM)

ASL-279; Dopamiinihydrokloridi; Dopamin Hidroklorür; Dopamina, hidrocloruro de; Dopamine, chlorhydrate de; Dopamin-hidroklorid; Dopaminhydrochlorid; Dopamin-hydrochlorid; Dopaminhydroklorid; Dopamini Hydrochloridum; Dopamino hidrochloridas; Dopaminy chlorowodorek; Hidrocloruro de dopamina; 3-Hydroxytyramine Hydrochloride; Допамина Гидрохлорид.

4-(2-Aminoethyl)pyrocatechol hydrochloride.

$C_8H_{11}NO_2$,HCl=189.6

CAS — 51-61-6 (dopamine); 62-31-7 (dopamine hydrochloride).

ATC — C01CA04.

ATC Vet — QC01CA04.

UNII — 7L3E38N0L.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Dopamine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; soluble in alcohol; sparingly soluble in acetone and in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Dopamine Hydrochloride). A white to off-white crystalline powder that may have a slight odour of hydrochloric acid. Freely soluble in water and in aqueous solutions of alkali hydroxides; insoluble in chloroform and in ether; soluble in methyl alcohol. pH of a 4% solution in water is between 3.0 and 5.5. Store in airtight containers.

Incompatibility. Dopamine is inactivated in alkaline solutions such as sodium bicarbonate 5% and is incompatible with alkaline drugs such as furosemide[1] and thiopental sodium;[1] incompatibility with insulin[2] and with alteplase[3] has also been reported, and licensed product information states that it is incompatible with ampicillin and with amphotericin B, and that mixtures with gentamicin sulfate, cefalotin sodium, or oxacillin sodium should be avoided.

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; 54: 64–5.
2. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; 53: 1048–51.
3. Lee CY, *et al.* Visual and spectrophotometric determination of compatibility of alteplase and streptokinase with other injectable drugs. *Am J Hosp Pharm* 1990; 47: 606–8.

Uses and Administration

Dopamine is a catecholamine sympathomimetic (p. 1507.3) with both direct and indirect effects. It is formed in the body by the decarboxylation of levodopa, and is both a neurotransmitter in its own right (notably in the brain) and a precursor of noradrenaline. Dopamine differs from adrenaline and noradrenaline in dilating renal and mesenteric blood vessels and increasing urine output, apparently by a specific dopaminergic mechanism. This effect is predominant at low infusion rates (about 2 micrograms/kg per minute); at slightly higher infusion rates (around 2 to 10 micrograms/kg per minute) it also stimulates $beta_1$-adrenergic receptors in the myocardium, and at 10 to 20 micrograms/kg per minute the effects of alpha-adrenergic stimulation, such as vasoconstriction, predominate. The inotropic action of dopamine on the heart is associated with less cardiac-accelerating effect, and a lower incidence of arrhythmias, than that of isoprenaline.

Dopamine also inhibits release of prolactin from the anterior pituitary.

Dopamine is used in acute heart failure, as occurs in cardiogenic shock (p. 1279.3) and myocardial infarction (p. 1257.1); it is also used in renal failure (but see below, under Surgery and Intensive Care), in cardiac surgery, and in septic shock.

Dopamine is given as the hydrochloride by intravenous infusion as a dilute solution (usually 1.6 or 3.2 mg/mL, although more dilute solutions may be used where fluid expansion is not a problem), in glucose 5%, sodium chloride 0.9%, or other suitable diluents; many fluids are suitable and licensed product information should be consulted. The initial rate is 2 to 5 micrograms/kg per minute, gradually increased by up to 5 to 10 micrograms/kg per minute according to the patient's blood pressure, cardiac output, and urine output. Up to 20 to 50 micrograms/kg per minute may be required in seriously ill patients; higher doses have been given. A reduction in urine flow, without hypotension, may indicate a need to reduce the dose. To avoid tissue necrosis dopamine is best given via a large vein. When gradually stopping dopamine it is advised that care be taken to avoid undue hypotension associated with very low dosage levels, where vasodilatation could predominate.

For doses in children, see below.

Administration in children. The *BNFC* suggests that dopamine hydrochloride may be given for inotropic support by intravenous infusion to neonates in an initial dose of 3 micrograms/kg per minute, and to those aged over 1 month up to 18 years in an initial dose of 5 micrograms/kg per minute. Doses may be adjusted according to response to a maximum dose of 20 micrograms/kg per minute.

For a discussion of the use of dopamine in the treatment of low systemic blood flow in preterm infants, see under Dobutamine, p. 1366.1.

Surgery and intensive care. Dopamine has an established role as an inotrope in cardiogenic shock and in cardiac surgery; it has also been used as a **renal protectant**, due to the apparently beneficial effects of lower doses on renal function. Studies in healthy *animals* and human subjects have shown that low-dose dopamine increases renal blood flow, natriuresis, diuresis, and possibly glomerular filtration rate. Low doses of dopamine (sometimes termed 'renal-dose' dopamine) have therefore been widely used in patients at risk of renal failure, such as those undergoing major surgery or in intensive care, as well as for the treatment of acute renal failure. However, clinical studies have failed to convincingly show that low-dose dopamine is effective in either preventing acute renal failure in patients at high risk, or in improving renal function or outcome in patients with established acute renal failure. A

placebo-controlled, randomised study[1] in critically-ill patients with early renal dysfunction and meta-analyses[2,3] including studies of varying design, failed to show any clinical benefit in those receiving dopamine. It is now generally considered[2,4,5] that low-dose dopamine has no place as a renal protectant in the routine management of critically ill patients.

Dopexamine, which like dopamine acts as a peripheral dopamine agonist, has been used similarly but evidence of benefit is limited and it is generally not recommended (see Critical Care under Dopexamine, below).

1. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. *Lancet* 2000; 356: 2139–43.
2. Kellum JA, Decker JM. Use of dopamine in acute renal failure: a meta-analysis. *Crit Care Med* 2001; 29: 1526–31.
3. Friedrich JO, *et al.* Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med* 2005; 142: 510–24.
4. Galley HF. Renal-dose dopamine: will the message now get through? *Lancet* 2000; 356: 2112–13. Correction. *ibid.* 2001; 357: 890.
5. Holmes CL, Walley KR. Bad medicine: low-dose dopamine in the ICU. *Chest* 2003; 123: 1266–75.

Adverse Effects and Treatment

As for Sympathomimetics, p. 1508.2 and p. 1508.3; dopamine may have adverse effects relating to both its alpha- and beta-agonist properties.

Dopamine has a short duration of action and most adverse effects respond to stopping the infusion or reducing its rate; infiltration with phentolamine may relieve pain and prevent necrosis following extravasation.

Effects on the CNS. Movement disorders are well known adverse effects of the dopamine precursor, levodopa (p. 902.2) but do not usually occur with dopamine since it does not enter the CNS. However, there has been a report[1] of choreoathetosis in a patient receiving dopamine infusion; it was suggested that there must have been disruption to her blood-brain barrier to allow this to occur.

1. Walker VA, Massoumi M. Choreoathetosis with dopamine. *Ann Intern Med* 2005; 142: 478–9.

Effects on the endocrine system. Dopamine has complex actions on the anterior pituitary[1] and dopamine infusion is associated with endocrine effects including suppression of prolactin, growth hormone, and thyroid hormone release. In postoperative or critically ill patients, dopamine infusion may affect the endocrine response to stress, even when given in low doses. Depression of serum-prolactin concentrations has been reported[2] in critically ill patients given dopamine in a dose of 2.5 micrograms/kg per minute to maintain renal blood flow, while a study[3] in postoperative patients given dopamine 5 micrograms/kg per minute to maintain splanchnic blood flow found that serum concentrations of both prolactin and thyroid stimulating hormone were decreased. It was suggested that these changes could adversely affect immunological function and add to morbidity in such patients.

1. Van den Berghe G, de Zegher F. Anterior pituitary function during critical illness and dopamine treatment. *Crit Care Med* 1996; 24: 1580–90.
2. Bailey AR, Burchett KR. Effect of low-dose dopamine on serum concentrations of prolactin in critically ill patients. *Br J Anaesth* 1997; 78: 97–9.
3. Schilling T, *et al.* Endocrine effects of dopexamine vs. dopamine in high-risk surgical patients. *Intensive Care Med* 2001; 27: 1908–15.

Effects on the heart. For mention of the arrhythmogenic effects of dopamine on the heart, see p. 1508.2.

Ischaemia and gangrene. Dopamine is converted to noradrenaline, a powerful vasoconstrictor, and there have been reports[1-3] of ischaemia and gangrene of the extremities in patients receiving dopamine infusion, as well as local necrosis after extravasation.[4] Extravasation of catecholamines is usually treated with an alpha blocker such as phentolamine, but there have also been reports of the use of topical glyceryl trinitrate ointment to improve capillary blood flow in patients with dopamine-induced ischaemia of the digits. The ointment was applied either to the affected area,[5] or to the warmest area of skin,[6] such as the chest or abdominal wall.

1. Alexander CS, *et al.* Pedal gangrene associated with the use of dopamine. *N Engl J Med* 1975; 293: 591.
2. Julka NK, Nora JR. Gangrene aggravation after use of dopamine. *JAMA* 1976; 235: 2812–13.
3. Maggi JC, *et al.* Gangrene in a neonate following dopamine therapy. *J Pediatr* 1982; 100: 323–5.
4. Boltax RS, *et al.* Gangrene resulting from infiltrated dopamine solution. *N Engl J Med* 1977; 296: 823.
5. Gibbs NM, Oh TE. Nitroglycerine ointment for dopamine induced peripheral digital ischaemia. *Lancet* 1983; ii: 290.
6. Coakley J. Nitroglycerin ointment for dopamine-induced peripheral ischaemia. *Lancet* 1983; ii: 633.

Precautions

As for Sympathomimetics, p. 1508.3.

Children. There have been reports of increased pulmonary artery pressure with the use of dopamine in children after cardiac surgery,[1] and in premature infants with hypotension.[2] It has therefore been suggested that dopamine should be used with caution in children at risk of developing pulmonary hypertension.

1. Booker PD, *et al.* Comparison of the haemodynamic effects of dopamine and dobutamine in young children undergoing cardiac surgery. *Br J Anaesth* 1995; 74: 419–23.
2. Liet J-M, *et al.* Dopamine effects on pulmonary artery pressure in hypotensive preterm infants with patent ductus arteriosus. *J Pediatr* 2002; 140: 373–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dopamine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Sympathomimetics, p. 1508.3. Dopamine has both direct and indirect actions and may therefore interact with MAOIs; the dose of dopamine should be substantially reduced in patients taking MAOIs, and an initial dose of one-tenth the usual dose has been suggested.

Antiepileptics. Following a report in 1976 to the FDA of hypotension in patients given *phenytoin* in addition to dopamine infusion, a study[1] of this potential interaction found that dopamine given by intravenous infusion with phenytoin infusion to *dogs*, did not alter the CNS effects of phenytoin nor result in hypotension and cardiovascular collapse. Large doses of phenytoin alone had a reproducible hypotensive effect that was reduced by dopamine, suggesting a possible supportive role in phenytoin-induced hypotension.

1. Smith RD, Lomas TE. Modification of cardiovascular responses to intravenous phenytoin by dopamine in dogs: evidence against an adverse interaction. *Toxicol Appl Pharmacol* 1978; 45: 665–73.

Dopaminergics. Severe hypertension occurred[1] in a patient who had been receiving *selegiline* for Parkinson's disease when a dopamine infusion was started. Although selegiline is considered to be a selective monoamine oxidase type B inhibitor, at higher doses it also affects monoamine oxidase type A and could have reduced the metabolism of dopamine in this patient. Caution may be necessary if dopamine is given to patients who have been receiving selegiline within the previous 2 weeks.

1. Rose LM, *et al.* A hypertensive reaction induced by concurrent use of selegiline and dopamine. *Ann Pharmacother* 2000; 34: 1020–4.

Histamine. For the effect of dopamine on histamine given exogenously, see p. 2525.3.

Pharmacokinetics

The vasoconstrictor properties of dopamine preclude its use by the subcutaneous or intramuscular route. Like adrenaline (p. 1295.1) it is inactive when given orally, and it is rapidly inactivated in the body by similar processes, with a half-life of about 2 minutes. Dopamine is a metabolic precursor of noradrenaline and a proportion is excreted as the metabolites of noradrenaline. Nevertheless, the majority appears to be directly metabolised into dopamine-related metabolites.

References.

1. Steinberg C, Notterman DA. Pharmacokinetics of cardiovascular drugs in children: inotropes and vasopressors. *Clin Pharmacokinet* 1994; 27: 345–67.
2. Juste RN, *et al.* Dopamine clearance in critically ill patients. *Intensive Care Med* 1998; 24: 1217–20.
3. MacGregor DA, *et al.* Pharmacokinetics of dopamine in healthy male subjects. *Anesthesiology* 2000; 92: 338–46.
4. Johnston AJ, *et al.* Pharmacokinetics and pharmacodynamics of dopamine and norepinephrine in critically ill head-injured patients. *Intensive Care Med* 2004; 30: 45–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dopatropin; Inotropin; Megadose; *Austria*: Giludop; *Belg.*: Dynatra; *Braz.*: Constriction; Dopabane; Dopacris; Dopaflex†; Reviminet†; Revivan†; *China*: A Si Ke Ding (阿斯克丁); *Cz.*: Tensamin; *Denm.*: Abbodop†; Dopmin; *Fin.*: Abbodop†; Dopmin; *Gr.*: Giludop; *India*: Domin; Dopacard; Dopacef; Dopanis; Dopaplus; Dopar; Dopasol; Dopinga; Dopress; *Indon.*: Cetadop; Dopac; Indop; Proinfark; Udopa; *Israel*: Docard†; *Ital.*: Revivan; *Jpn*: Catabon; Inovan; PReDopa; *Malaysia*: Dopmin; *Mex.*: Drinalken; Inotropisa†; Miocina; Zetarina; *Neth.*: Dynatra; *Norw.*: Abbodop†; *Philipp.*: Cardiolast; Docard†; Dokard; Dopamax; Dopnax; Myocard; *Port.*: Cordodopa; Medopa; *Rus.*: Dopmin (Допмин); *S.Afr.*: Dynos†; Intropin†; *Swed.*: Abbodop†; Giludop; *Thai.*: Dopamex; Dopaminex†; Dopin; Dopmin†; Inopin; *Turk.*: Dopmin; Giludop; Predopam; *Venez.*: Dopina.

Pharmacopoeial Preparations
BP 2014: Dopamine Infusion;
USP 36: Dopamine Hydrochloride and Dextrose Injection; Dopamine Hydrochloride Injection.

Dopexamine Hydrochloride

(BANM, USAN, rINNM) ⊗

Dopeksamiinihydrokloridi; Dopeksamin Hidroklorür; Dopexamina, hidrocloruro de; Dopexamindihydrochlorid; Dopexamine, Chlorhydrate de; Dopexamine, dichlorhydrate de; Dopexamine dihydrochloride; Dopeksaminhydroklorid; Dopexamini dihydrochloridum; Dopexamini Hydrochloridum; FPL-60278 (dopexamine); FPL-60278AR; Hidrocloruro de dopexamina; Допексамина гидрохлорид.

4-[2-[6-(Phenethylamino)hexylamino]ethyl]pyrocatechol dihydrochloride.

$C_{22}H_{32}N_2O_2.2HCl$=429.4

CAS — 86197-47-9 (dopexamine); 86484-91-5 (dopexamine dihydrochloride).

ATC — C01CA14.

ATC Vet — QC01CA14.

UNII — 0VN909S60Y.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dopexamine Dihydrochloride). A white or almost white, crystalline powder. Soluble in water; sparingly soluble in alcohol and in methyl alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 3.7 to 5.7. Protect from light.

Incompatibility. Dopexamine is inactivated in alkaline solutions such as sodium bicarbonate 5%.

Uses and Administration

Dopexamine is a sympathomimetic (p. 1507.3) with direct and indirect effects. It stimulates $beta_2$ adrenoceptors and peripheral dopamine receptors and also inhibits the neuronal reuptake of noradrenaline. These actions result in an increased cardiac output, peripheral vasodilatation, and an increase in renal and mesenteric blood flow.

Dopexamine hydrochloride is used to provide short-term haemodynamic support, for example after cardiac surgery or in exacerbations of chronic heart failure. It is given as an intravenous infusion of either 400 or 800 micrograms/mL in glucose 5%, sodium chloride 0.9%, or other suitable diluents, through a central or large peripheral vein; more concentrated solutions may be given via a central vein but concentrations should not exceed 4 mg/mL. The initial dose is generally 500 nanograms/kg per minute and is then increased to 1 microgram/kg per minute; further increases, in increments of 0.5 to 1 microgram/kg per minute at intervals of not less than 15 minutes, may be made up to a total of 6 micrograms/kg per minute if necessary. Heart rate, blood pressure, urine output, and cardiac output should be monitored. On withdrawal, the dose should be reduced gradually.

References.

1. Fitton A, Benfield P. Dopexamine hydrochloride. *Drugs* 1990; 39: 308–30.
2. Anonymous. Dopexamine after cardiac surgery. *Drug Ther Bull* 1995; 33: 30–2.

Critical care. Dopexamine has been reported to increase splanchnic blood flow and it has been used with the aim of preventing renal and gastrointestinal dysfunction in critically-ill patients.[1] Although there may be a reduction in ischaemic damage to the gut,[2] a study[3] in critically-ill patients failed to show any improvement in outcome with the use of dopexamine. Studies[4,5] using dopexamine to increase oxygen delivery in high-risk surgical patients have also failed to show any benefit in terms of postoperative mortality or organ function, and a systematic review[6] found insufficient evidence to recommend the use of dopexamine in either patient group. A later meta-analysis[7] found that overall, perioperative dopexamine infusion reduced the length of hospital stay in patients having major surgery, but showed no survival benefit; however, at low doses (up to 1 microgram/kg per minute) dopexamine infusion seemed also to be associated with improved survival.

Use of low-dose dopamine for renal protection is not recommended (see Surgery and Intensive Care, p. 1367.3).

1. Lisbon A. Dopexamine, dobutamine, and dopamine increase splanchnic blood flow: what is the evidence? *Chest* 2003; 123 (suppl): 460S–463S.
2. Baguneid MS, *et al.* A randomized study to evaluate the effect of a perioperative infusion of dopexamine on colonic mucosal ischemia after aortic surgery. *J Vasc Surg* 2001; 33: 758–63.
3. Ralph CJ, *et al.* A randomised controlled trial investigating the effects of dopexamine on gastrointestinal function and organ dysfunction in the critically ill. *Intensive Care Med* 2002; 28: 884–90. Correction. *ibid*; 1001. [dose]
4. Takala J, *et al.* Effect of dopexamine on outcome after major abdominal surgery: a prospective, randomized, controlled multicenter study. *Crit Care Med* 2000; 28: 3417–23.

5. Stone MD, *et al.* Effect of adding dopexamine to intraoperative volume expansion in patients undergoing major elective abdominal surgery. *Br J Anaesth* 2003; 91: 619–24.
6. Renton MC, Snowden CP. Dopexamine and its role in the protection of hepatosplanchnic and renal perfusion in high-risk surgical and critically ill patients. *Br J Anaesth* 2005; 94: 459–67.
7. Pearse RM, *et al.* Effect of dopexamine infusion on mortality following major surgery: individual patient data meta-regression analysis of published clinical trials. *Crit Care Med* 2008; 36: 1323–9.

Adverse Effects and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3. Dopexamine has mainly beta-agonist and dopaminergic actions; its most common adverse effect is tachycardia, and transient hypotension may also occur. Dopexamine may cause a small reduction in platelet counts and should not be given to thrombocytopenic patients.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dopexamine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Sympathomimetics, p. 1508.3. The interactions of dopexamine are mainly due to its beta-agonist and dopaminergic actions; it may also potentiate the effects of noradrenaline and some other sympathomimetics by inhibiting neuronal uptake of noradrenaline.

Pharmacokinetics

Dopexamine has a short half-life in blood of about 6 to 7 minutes. It is excreted as metabolites in bile and in urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Dopacard†; *Ger.*: Dopacard†; *Irl.*: Dopacard†; *UK*: Dopacard.

Doxazosin Mesilate *(BANM, rINNM)*

Doksazosyny mezylan; Doxazosin Mesylate (USAN); Doxazosin Methanesulphonate; Doxazosina, mesilato de; Doxazosine, Mésilate de; Doxazosini Mesilas; Doxazosinmesilat; Doxazosin-mesylát; Mesilato de doxazosina; UK-33274-27; Доксазозина Мезилат.

1-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-4-(1,4-benzodioxan-2-ylcarbonyl)piperazine methanesulphonate.

$C_{23}H_{25}N_5O_5.CH_3SO_3H$=547.6

CAS — 74191-85-8 (doxazosin); 77883-43-3 (doxazosin mesilate).

ATC — C02CA04.

ATC Vet — QC02CA04.

UNII — 86P6PQK0MU.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Doxazosin Mesilate). A white or almost white crystalline powder. It exhibits polymorphism and some forms may be hygroscopic. Slightly soluble in water and in methyl alcohol; soluble in a mixture of 15 volumes of water and 35 volumes of tetrahydrofuran; practically insoluble in acetone. Store in airtight containers.

USP 36: (Doxazosin Mesylate). A white to tan-coloured powder. Very slightly soluble in water and in methyl alcohol; freely soluble in formic acid. Store at a temperature below 30 degrees.

Uses and Administration

Doxazosin is an alpha$_1$-adrenoceptor blocker (p. 1243.1) with actions and uses similar to those of prazosin (p. 1474.1), but a longer duration of action. It is used in the management of hypertension and in benign prostatic hyperplasia to relieve symptoms of urinary obstruction (below).

Doxazosin is given orally as the mesilate, but doses are usually expressed in terms of the base. Doxazosin mesilate 1.2 mg is equivalent to about 1 mg of doxazosin. After an oral dose maximum reduction in blood pressure is reported to occur in 2 to 6 hours and the effects are maintained for 24 hours, permitting once daily dosage.

To avoid the risk of collapse which may occur in some patients after the first dose, the initial dose is 1 mg, preferably at bedtime. The dose may be doubled at 1 to 2 week intervals according to response. Usual maintenance doses for **hypertension** are up to 4 mg once daily; doses of 16 mg daily should not be exceeded. For **benign prostatic hyperplasia** the usual maintenance dose is 2 to 4 mg daily; doses of 8 mg daily should not be exceeded.

Doxazosin may also be given as a modified-release preparation.

Reviews.

1. Fulton B, *et al.* Doxazosin: an update of its clinical pharmacology and therapeutic applications in hypertension and benign prostatic hyperplasia. *Drugs* 1995; 49: 295–320.

Benign prostatic hyperplasia. References to the use of doxazosin in patients with benign prostatic hyperplasia (p. 2347.1).

1. Doggrell SA. After ALLHAT: doxazosin for the treatment of benign prostatic hyperplasia. *Expert Opin Pharmacother* 2004; 5: 1957–64.
2. MacDonald R, *et al.* Doxazosin for treating lower urinary tract symptoms compatible with benign prostatic obstruction: a systematic review of efficacy and adverse effects. *BJU Int* 2004; 94: 1263–70.
3. Goldsmith DR, Plosker GL. Doxazosin gastrointestinal therapeutic system: a review of its use in benign prostatic hyperplasia. *Drugs* 2005; 65: 2037–47.
4. Wilt TJ, MacDonald R. Doxazosin in the treatment of benign prostatic hypertrophy: an update. *Clin Interv Aging* 2006; 1: 389–401.
5. Bhardwa J, *et al.* Finasteride and doxazosin alone or in combination for the treatment of benign prostatic hyperplasia. *Expert Opin Pharmacother* 2007; 8: 1337–44.

Hypertension. Alpha blockers are among the drug groups that have been used as first-line therapy for hypertension (p. 1251.1). However, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[1] the doxazosin arm of the study was terminated early due to an increased incidence of heart failure in patients receiving doxazosin compared with those receiving chlortalidone, and alpha blockers are now only recommended for third-line therapy unless indicated for another reason. The role of doxazosin in hypertension has subsequently been reviewed.[2,3] It has been reported to have additional beneficial effects on blood lipoproteins and atherosclerotic plaque formation, perhaps related to a drug-specific effect on HDL-cholesterol biosynthesis,[4] and it has been suggested that it might be of value in hypertensive patients with the metabolic syndrome.[2,4] However, evidence to support the latter is currently lacking.

1. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2000; 283: 1967–75. Correction. *ibid.* 2002; 288: 2976.
2. Dell'Omo G, *et al.* Doxazosin in metabolically complicated hypertension. *Expert Rev Cardiovasc Ther* 2007; 5: 1027–35.
3. Wykretowicz A, *et al.* Doxazosin in the current treatment of hypertension. *Expert Opin Pharmacother* 2008; 9: 625–33.
4. Remaley AT. Old drug, new tricks: the unexpected effect of doxazosin on high-density lipoprotein. *Circ Res* 2007; 101: 116–18.

Pain. For reference to the use of doxazosin in pain, see under Uses of Phentolamine Mesilate, p. 1469.2.

Renal calculi. References[1-3] to the use of doxazosin to assist expulsion of stones from the distal ureter. For further reference to the potential use of alpha blockers to aid the passage of renal calculi see under Uses of Tamsulosin Hydrochloride, p. 2369.2.

1. Liatsikos EN, *et al.* Doxazosin for the management of distal-ureteral stones. *J Endourol* 2007; 21: 538–41.
2. Aydogdu O, *et al.* Effectiveness of doxazosin in treatment of distal ureteral stones in children. *J Urol (Baltimore)* 2009; 182: 2880–4.
3. Zehri AA, *et al.* Preliminary study of efficacy of doxazosin as a medical expulsive therapy of distal ureteric stones in a randomized clinical trial. *Urology* 2010; 75: 1285–8.

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p. 1474.3.

Effects on mental function. For a report of acute psychosis associated with doxazosin use, see under Adverse Effects of Prazosin Hydrochloride, p. 1474.3.

Hypotension. Six of 18 hypertensive patients had first-dose orthostatic hypotension after receiving doxazosin 1 mg; three others had substantial but asymptomatic reductions in supine systolic blood pressure after the first dose.[1] The effect might have been exacerbated since all these patients were also receiving beta blockers or diuretics, or both. A further patient, who was also taking methyldopa, withdrew from the study with persistent orthostatic hypotension.

1. Oliver RM, *et al.* The pharmacokinetics of doxazosin in patients with hypertension and renal impairment. *Br J Clin Pharmacol* 1990; 29: 417–22.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies doxazosin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Urinary incontinence. For reference to urinary incontinence associated with doxazosin, see under Adverse Effects of Prazosin Hydrochloride, p. 1475.1.

Interactions

As for Prazosin Hydrochloride, p. 1475.1.

Pharmacokinetics

Doxazosin is well absorbed after oral doses, peak plasma concentrations occurring 2 to 3 hours after a dose. Oral bioavailability is about 65%. It is extensively metabolised in the liver, and excreted in faeces as metabolites and a small amount of unchanged drug. Elimination from plasma is biphasic, with a mean terminal half-life of about 22 hours. The pharmacokinetics are not altered in patients with renal impairment. Doxazosin is about 98% bound to plasma proteins and is not removed by dialysis. Studies in *animals* indicate that doxazosin accumulates in breast milk.

Reviews.

1. Elliott HL, *et al.* Pharmacokinetic overview of doxazosin. *Am J Cardiol* 1987; 59: 78G–81G.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cardura; Doxasin; Doxolbran; Lafedoxin; Prostazosina; Vazosin; ***Austria***: Ascalan; Doxapress; Hibadren; Prostadilat; Supressin; ***Braz.***: Carduran; Doxaprost; Doxsol; Doxuran; *Euprostatin; Mesidox; Prostaflux;* Unoprost; Zoflux; ***Canad.***: Cardura; ***Chile***: Alfadoxin; Angicon; Cardura; Dorbantil; ***China***: Beyacin (必亚欣); Cardura (可多华); Dong Gang Tian Le (东港天乐); Duo Xi Lin (多喜林); Jin Chang (今偿); Luo Xin Ping (络欣平); Shuang Jiang Ping (双将平); Yi Li Ping (伊粒平); Yi Shu Tong (伊舒通); Zhong Wei (仲维); ***Cz.***: Cardura; Dosano†; Dozonet†; Kamiren; Windoxa; Zoxon; ***Denm.***: Cardoreg; Cardosin; Cardotard; Carduran; Hypereze; Myocard; ***Fr.***: Zoxan; ***Ger.***: Alfamedin†; Cardular; Diblocin†; Doxa-Puren†; Doxacor†; Doxagamma; Doxanar†; Doxazoflo†; Jutalar†; Uriduct†; ***Gr.***: Cardura; Maguran; Protectura; ***Hong Kong***: Cardura; Doxasyn†; Pencor; Prostazocin†; ***Hung.***: Cardura; Doxagal; Doxicard; Dozone; ***India***: Alfazosin; Doxacard; Doxapress; Duracard; Duraten; ***Indon.***: Cardura; ***Irl.***: Cardura; Carsem; Doxacar; Doxane; Doxatan; Doxel; Farmadura; Kamiren; Raporsin; ***Israel***: Cadex; Cardoral; Doxaloc†; ***Ital.***: Atensil; Benur; Cardura; Dedralen; Noradox; Normothen; Quorum; ***Jpn***: Cardenalin; ***Malaysia***: Cardura; Dophilin; Magurol; Pencor; ***Mex.***: Cardura; ***Neth.***: Cardura; Doxacharvi; ***Norw.***: Carduran; ***NZ***: Cardoxan; Dosan†; ***Philipp.***: Alfadil; ***Pol.***: Apo-Doxan; Cardura; Doxagen; Doxanorm; Doxar; Doxaratio†; Doxonex; Kamiren; Prostatic; Vaxosin†; Zoxon; ***Port.***: Cardura; ***Rus.***: Artezine (Артезин); Cardura (Кардура); Doxaprostan (Доксапростан); Kamiren (Камирен); Magurol (Магурол); Tonocardin (Тонокардин); Zoxon (Зоксон); ***S.Afr.***: Cardugen; Cardura; Carzin; ***Singapore***: Cardura; Pencor; ***Spain***: Carduran; Doxatensa; Doximax Neo†; Progandol; ***Swed.***: Alfadil; ***Switz.***: Cardura; ***Thai.***: Cardoxa; Cardura; Carxasin; Cazosin; Dezcard; Dovizin; Dozozin; Duracard; Genzosin; Pencor; Xadosin; ***Turk.***: Cardura; Doksura; Dostineva; Doxacor; Doxamerck; Kardozin; Tendura; ***UK***: Cardozin; Cardura; Doxadura; Raporsin; Slocinx; ***Ukr.***: Cardura (Кардура); Doxonex (Доксонекс)†; Kamiren (Камирен); Zoxon (Зоксон); ***USA***: Cardura; ***Venez.***: Cardura.

Multi-ingredient Preparations. ***Arg.***: Prosdox Duo.

Pharmacopoeial Preparations

USP 36: Doxazosin Tablets.

Dronedarone *(BAN, rINN)*

Dronedarona; Dronédarone; Dronedaronum; SR-33589; Дронедарон.

N-(2-Butyl-3-{*p*-[3-(dibutylamino)propoxy]benzoyl}-5-benzofuranyl)methanesulfonamide.

$C_{31}H_{44}N_2O_5S$=556.8

CAS — 141626-36-0.

ATC — C01BD07.

ATC Vet — QC01BD07.

UNII — JQZ1L091Y2.

Dronedarone Hydrochloride

(BANM, USAN, rINNM)

Dronédarone, Chlorhydrate de; Dronedaroni Hydrochloridum; Hidrocloruro de dronedarona; SR-33598B; Дронедарона Гидрохлорид.

$C_{31}H_{44}N_2O_5.HCl$=593.2

CAS — 141625-93-6.

ATC — C01BD07.

ATC Vet — QC01BD07.

UNII — FA36DV299Q.

Uses and Administration

Dronedarone is an antiarrhythmic drug that is structurally related to amiodarone, but has a shorter half-life since it is less lipophilic; it also lacks the iodine moiety. It is reported to have properties of all four Vaughn Williams classes,

although it is unclear which of these contribute to its clinical effects.

Dronedarone is used to reduce the risk of hospitalisation due to atrial fibrillation in clinically stable patients with paroxysmal or persistent atrial fibrillation. It is used in such patients who are in sinus rhythm or who currently have atrial fibrillation and will undergo cardioversion. It should only be used after alternative treatment options have been considered. Dronedarone is given as the hydrochloride, but doses are expressed in terms of the base; dronedarone hydrochloride 426.2 mg is equivalent to about 400 mg of dronedarone. It is given with food in an oral dose equivalent to 400 mg twice daily.

References.

1. Dale KM, White CM. Dronedarone: an amiodarone analog for the treatment of atrial fibrillation and atrial flutter. *Ann Pharmacother* 2007; 41: 599–605.
2. Singh BN, *et al.* EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007; 357: 987–99.
3. Davy J-M, *et al.* ERATO Study Investigators. Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation (ERATO) study. *Am Heart J* 2008; 156: 527.e1–527.e9. Available at: http://download.journals.elsevierhealth.com/pdfs/journals/0002-8703/PIIS0002870308004778.pdf (accessed 19/08/09)
4. Hohnloser SH, *et al.* ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009; 360: 668–78. Corrections. *ibid.*: 2487, *ibid.* 2011; 364: 1481.
5. Patel C, *et al.* Dronedarone. *Circulation* 2009; 120: 636–44.
6. Hoy SM, Keam SJ. Dronedarone. *Drugs* 2009; 69: 1647–63.
7. Schafer JA, *et al.* Dronedarone: current evidence and future questions. *Cardiovasc Ther* 2010; 28: 38–47.
8. Christiansen CB, *et al.* Efficacy and safety of dronedarone: a review of randomized trials. *Expert Opin Drug Safety* 2010; 9: 189–99.

Adverse Effects

The most common adverse effects of dronedarone are gastrointestinal, and include diarrhoea, nausea, vomiting, abdominal pain, and dyspepsia. Rashes and asthenia are also common. Bradycardia has also occurred and prolongation of the QT interval has been noted. An increase in plasma creatinine has been seen after starting treatment with dronedarone; usually, it reaches a plateau after 7 days and is reversible after stopping treatment. Interstitial lung disease including pneumonitis and pulmonary fibrosis has also been reported. Rare but severe cases of hepatocellular liver injury and hepatic failure may occur.

Effects on the liver. The FDA was aware of several reports of liver injury in patients treated with dronedarone,[1] including two cases of acute liver failure necessitating liver transplants in elderly females.

1. FDA. FDA Drug Safety Communication: severe liver injury associated with the use of dronedarone (marketed as Multaq) (issued 14th January, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm240011.htm (accessed 20/01/11)

Precautions

Dronedarone is contra-indicated in patients with permanent atrial fibrillation in whom normal sinus rhythm cannot be restored and in those with symptomatic heart failure with recent decompensation requiring hospitalisation or with NYHA class IV heart failure. For more information, see Cardiovascular Disorders, below. ECGs should be performed at least every 6 months and treatment stopped in patients who develop symptoms of heart failure or permanent atrial fibrillation while taking the drug. It is also contra-indicated in those with bradycardia (heart rate less than 50 beats/minute), second- or third-degree AV block or sick sinus syndrome (unless a pacemaker is present), or prolonged QT or PR interval. Hypokalaemia and hypomagnesaemia may increase the risk of arrhythmias; electrolyte imbalances should be corrected before starting treatment. Use with drugs that prolong the QT interval or can induce torsade de pointes, or with inhibitors of the cytochrome P450 isoenzyme CYP3A4, should be avoided. For more information on these precautions, see Interactions, below.

Dronedarone is contra-indicated in patients with severe hepatic or renal impairment (creatinine clearance below 30 mL/min). It should also not be given to those with liver or lung toxicity related to the previous use of amiodarone. Due to reports of severe liver injury, regulatory authorities have suggested that liver function is tested before starting treatment, and closely monitored during it; dronedarone should be stopped if there are signs of potential liver damage.

Dronedarone is contra-indicated in **pregnancy**, since teratogenicity has been seen in *animals*.

Cardiovascular disorders. A randomised, placebo-controlled study (referred to as the ANDROMEDA study),[1] in which hospitalised patients with symptomatic heart failure and severe left ventricular dysfunction were given dronedarone, was terminated early when excess mortality (due to worsening heart failure) and hospitalisation (for cardiovascular reasons) were seen in the dronedarone group. Most patients enrolled in this study had NYHA class II (42.3%) or III (55.8%) heart failure, and only 23.2% had atrial fibrillation at randomisation.

Similarly, a later randomised, placebo-controlled study (referred to as the PALLAS study),[2] in patients with permanent atrial fibrillation and additional cardiovascular risk factors was also terminated early because of significant increase in mortality, stroke (within the first 2 weeks of treatment), and hospitalisations for heart failure in the dronedarone group. Most deaths in the dronedarone group were from cardiovascular causes, including those associated with arrhythmia.

1. Køber L, *et al.* Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008; 358: 2678–87.
2. Connolly SJ, *et al.* PALLAS Investigators. Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med* 2011; 365: 2268–76.

Interactions

Dronedarone should be used with caution with other drugs liable to induce bradycardia, such as beta blockers or calcium-channel blockers, and with other antiarrhythmic drugs. Use with arrhythmogenic drugs, particularly those that prolong the QT interval or can induce torsade de pointes, such as phenothiazine antipsychotics, tricyclic antidepressants, bepridil, some macrolides, class I and III antiarrhythmics, and terfenadine, should be avoided. Drugs that cause hypokalaemia or hypomagnesaemia may also increase the risk of arrhythmias with dronedarone.

Dronedarone is metabolised by the cytochrome P450 isoenzyme CYP3A4; inhibitors (such as ketoconazole, ciclosporin, HIV-protease inhibitors, cimetidine, clarithromycin, erythromycin, nefazodone, and grapefruit juice) or inducers (such as rifampicin, phenobarbital, carbamazepine, phenytoin, and St John's wort) of this enzyme may affect its plasma concentrations, and concomitant use should be avoided. In addition, dronedarone is a moderate inhibitor of CYP3A4 and CYP2D6, and can increase plasma concentrations of other drugs metabolised by these enzymes, including statins, sirolimus and tacrolimus, beta blockers, and calcium-channel blockers. Dronedarone is also a potent inhibitor of P-glycoprotein and raises plasma concentrations of P-glycoprotein substrates, such as warfarin and other vitamin K antagonists, and digoxin (see also p. 1356.2 for advice on dose reductions for digoxin).

Pharmacokinetics

After an oral dose, dronedarone undergoes extensive first-pass metabolism and has an absolute bioavailability of 4%, which increases to 15% when taken with food. Peak plasma concentrations occur within 3 to 6 hours, and steady state occurs within 4 to 8 days of regular use. Dronedarone is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4 to a less active *N*-debutyl metabolite, and several inactive metabolites. Both dronedarone and its active metabolite are extensively bound (more than 98%) to plasma proteins, mainly albumin. The elimination half-life of dronedarone is about 25 to 30 hours, and that of its *N*-debutyl metabolite around 20 to 25 hours. About 6% of an oral dose is excreted in the urine (entirely metabolites) and 84% in the faeces (metabolites and unchanged drug).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Multaq; ***Canad.***: Multaq; ***Cz.***: Multaq; ***Denm.***: Multaq; ***Fr.***: Multaq; ***Ger.***: Multaq; ***Gr.***: Multaq; ***Hong Kong***: Multaq; ***Hung.***: Multaq; ***Irl.***: Multaq; ***Israel***: Multaq; ***Malaysia***: Multaq; ***Neth.***: Multaq; ***Norw.***: Multaq; ***Philipp.***: Multaq; ***Pol.***: Multaq; ***Port.***: Multaq; ***Singapore***: Multaq; ***Spain***: Multaq; ***Swed.***: Multaq; ***Switz.***: Multaq; ***Thai.***: Multaq; ***UK***: Multaq; ***Ukr.***: Multaq (Мультак); ***USA***: Multaq.

Edaravone *(rINN)*

Edaravona; Édaravone; Edaravonum; MCI-186; Norphenazone; Эдаравон.

3-Methyl-1-phenyl-2-pyrazolin-5-one.

$C_{10}H_{10}N_2O$=174.2

CAS — 89-25-8.

UNII — 5798V6YJRP.

Profile

Edaravone is a free-radical scavenger used in the management of acute ischaemic stroke (p. 1269.2). It is given by intravenous infusion in a dose of 30 mg twice daily, infused over 30 minutes, beginning within 24 hours of stroke onset and continued for up to 14 days.

Edaravone is also under investigation in other pathologies thought to involve oxidative insult, including cerebral haemorrhage and amyotrophic lateral sclerosis.

References.

1. Edaravone Acute Infarction Study Group. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction: randomized, placebo-controlled, double-blind study at multicenters. *Cerebrovasc Dis* 2003; 15: 222–9.
2. Tsujita K, *et al.* Effects of edaravone on reperfusion injury in patients with acute myocardial infarction. *Am J Cardiol* 2004; 94: 481–4.
3. Tsujita K, *et al.* Long-term efficacy of edaravone in patients with acute myocardial infarction. *Circ J* 2006; 70: 832–7.
4. Hishida A. Clinical analysis of 207 patients who developed renal disorders during or after treatment with edaravone reported during post-marketing surveillance. *Clin Exp Nephrol* 2007; 11: 292–6.
5. Watanabe T, *et al.* The novel antioxidant edaravone: from bench to bedside. *Cardiovasc Ther* 2008; 26: 101–14.
6. Shinohara Y, *et al.* Edaravone (radical scavenger) versus sodium ozagrel (antiplatelet agent) in acute noncardioembolic ischemic stroke (EDO trial). *Cerebrovasc Dis* 2009; 27: 485–92.
7. Unno Y, *et al.* Does functional outcome in acute ischaemic stroke patients correlate with the amount of free-radical scavenger treatment? A retrospective study of edaravone therapy. *Clin Drug Investig* 2010; 30: 143–55.

Adverse effects and precautions. Edaravone has been associated with acute deterioration of renal and liver function, and fatal cases of disseminated intravascular coagulation. Renal and liver function should be monitored, and blood counts taken before, during, and after administration, and the infusion stopped immediately if abnormal values are seen.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bi Cun (必存); Yi Da Sheng (易达生); Youmin (积华尤敏); ***India***: Edvo; Nuravon; ***Jpn***: Radicut.

Edoxaban *(USAN, rINN)*

DU-176; Édoxaban; Edoxabán; Edoxabanum; Эдоксабан.

N-(5-Chloropyridin-2-yl)-*N*′-[(1*S*,2*R*,4*S*)-4-(*N*,*N*-dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydro[1,3]pyridine-2-carboxamido)cyclohexyl]oxamide.

$C_{24}H_{30}ClN_7O_4S$=548.1

CAS — 480449-70-5.

UNII — NDU3J18APO.

Edoxaban Tosilate

DU-176b; Edoxaban Tosylate (USAN).

$C_{24}H_{30}ClN_7O_4S,C_7H_8O_3S$=720.3

CAS — 480449-71-6.

Profile

Edoxaban is an oral direct inhibitor of factor Xa (activated factor X). It is used for the prevention of venous thromboembolism.

References.

1. Ogata K, *et al.* Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. *J Clin Pharmacol* 2010; 50: 743–53.
2. Chung N, *et al.* Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. *Thromb Haemost* 2011; 105: 535–44.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Lixiana.

Efonidipine Hydrochloride *(rINNM)*

Efonidipine; Chlorhydrate d'Efonidipinhydrochlorid; Efonidipini Hydrochloridum; Efonidipino hidrocloruro de; Hidrocloruro de efonidipino; NZ-105; Serefodipine Hydrochloride; Эфонидипина Гидрохлорид.

Cyclic 2,2-dimethyltrimethylene ester of 2-(*N*-benzylanilino) ethyl (±)-1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-5-phosphononicontinate hydrochloride.

$C_{34}H_{38}N_3O_7P.HCl$=668.1

CAS — 111011-63-3 (efonidipine); 111011-53-1 (efonidipine hydrochloride); 111011-76-8 (efonidipine hydrochloride ethanolate).

UNII — 3BR983K69O.

Profile

Efonidipine hydrochloride is a dihydropyridine calcium-channel blocker with general properties similar to those of nifedipine (p. 1447.2). It is used as the ethanolate in the treatment of hypertension in usual oral doses equivalent to efonidipine hydrochloride 10 to 20 mg twice daily; in angina pectoris, a dose of 40 mg once daily has typically been given.

References.

1. Tanaka H, Shigenobu K. Efonidipine hydrochloride: a dual blocker of L- and T-type Ca^{2+} channels. *Cardiovasc Drug Rev* 2002; 20: 81–92.

2. JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Hypertens Res* 2008; 31: 2115–27.
3. Sasaki H, *et al.* Protective effects of efonidipine, a T- and L-type calcium channel blocker, on renal function and arterial stiffness in type 2 diabetic patients with hypertension and nephropathy. *J Atheroscler Thromb* 2009; 16: 568–75.
4. Rakugi H, *et al.* JATOS Study Group. Comparison of strict- and mild-blood pressure control in elderly hypertensive patients: a per-protocol analysis of JATOS. *Hypertens Res* 2010; 33: 1124–8.
5. Nakano N, *et al.* Effects of efonidipine, an L- and T-type calcium channel blocker, on the renin-angiotensin-aldosterone system in chronic hemodialysis patients. *Int Heart J* 2010; 51: 188–92.
6. Oh IY, *et al.* Beneficial effect of efonidipine, an L- and T-type dual calcium channel blocker, on heart rate and blood pressure in patients with mild-to-moderate essential hypertension. *Korean Circ J* 2010; 40: 514–19.

Emoxypine Succinate

Emoxipin Succinate; Emoxipine Succinate.
3-Oxy-6-methyl-2-ethylpyridine succinate; 2-Ethyl-6-methyl-3-hydroxypyridine succinate.
$C_8H_{11}NO.C_4H_6O_4$=255.3
CAS — 2364-75-2 (emoxypine); 127464-43-1 (emoxypine succinate).

Profile

Emoxypine has antioxidant properties and has been used as the succinate in cardiovascular disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Cerecard (Церекард); Medomexi (Медомекси); Mexicor (Мексикор); Mexidant (Мексидант); Mexidol (Мексидол); Mexiftn (Мексифин); Mexiprim (Мексиприм); Neurox (Нейрокс); *Ukr.*: Armadin (Армадин); Mexicor (Мексикор); Mexidol (Мексидол); Mexiprim (Мексиприм).

Enalapril (BAN, rINN)

Enalaprilli; Enalapril; Enalaprilum; Эналаприл.
N-[*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-L-proline.
$C_{20}H_{28}N_2O_5$=376.5
CAS — 75847-73-3.
ATC — C09AA02.
ATC Vet — QC09AA02.
UNII — 69PN84IO1A.

Enalapril Maleate (BANM, USAN, rINNM)

Enalaprilimaleaatti; Enalapril Maleat; Enalapril, Maléate d'; Enalapril, maleato de; Enalapril maleinat; Enalapril Maleas; Enalaprilio maleatas; Enalaprilmaleat; Enalapril-maleát; Maleato de enalapril; MK-421; Эналаприла малеат.
N-[*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-L-proline hydrogen maleate.
$C_{20}H_{28}N_2O_5.C_4H_4O_4$=492.5
CAS — 76095-16-4.
ATC — C09AA02.
ATC Vet — QC09AA02.
UNII — 9O25354EPJ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Enalapril Maleate). A white or almost white crystalline powder. Sparingly soluble in water; practically insoluble in dichloromethane; freely soluble in methyl alcohol. It dissolves in dilute solutions of alkali hydroxides. A 1% solution in water has a pH of 2.4 to 2.9. Protect from light.

USP 36: (Enalapril Maleate). An off-white crystalline powder. Sparingly soluble in water; soluble in alcohol; freely soluble in dimethylformamide and in methyl alcohol; slightly soluble in semipolar organic solvents; practically insoluble in nonpolar organic solvents.

Stability. Enalapril has been reported[1,2] to be stable for at least 56 days in extemporaneously compounded oral liquids containing enalapril maleate 1 mg/mL in several vehicles.

1. Nahata MC, *et al.* Stability of enalapril maleate in three extemporaneously prepared oral liquids. *Am J Health-Syst Pharm* 1998; 55: 1155–7.
2. Allen LV, Erickson MA. Stability of alprazolam, chloroquine phosphate, cisapride, enalapril maleate, and hydralazine hydrochloride in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1998; 55: 1915–20.

Enalaprilat (BAN, USAN, rINN)

Enalaprilate; Enalaprilate dihydrate; Enalaprilatum; Enalaprilatum dihydricum; Enalaprilic acid; MK-422; Эналаприлат.
N-[*N*-[(*S*)-1-Carboxy-3-phenylpropyl]-L-alanyl]-L-proline dihydrate.
$C_{18}H_{24}N_2O_5.2H_2O$=384.4
CAS — 76420-72-9 (anhydrous enalaprilat); 84680-54-6 (enalaprilat dihydrate).
UNII — GV0O7ES0R3 (enalaprilat dihydrate); Q508Q118JM (anhydrous enalaprilat).

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Enalaprilat Dihydrate). A white or almost white, hygroscopic, crystalline powder. It exhibits pseudo-polymorphism. Very slightly soluble or slightly soluble in water; sparingly soluble in methyl alcohol; practically insoluble in acetonitrile. Store in airtight containers.

USP 36: (Enalaprilat). A white to nearly white, hygroscopic, crystalline powder. Soluble 1 in 200 of water, 1 in 40 of dimethylformamide, and 1 in 68 of methyl alcohol; very slightly soluble in alcohol, in acetone, and in hexane; practically insoluble in acetonitrile and in chloroform; slightly soluble in isopropyl alcohol.

Incompatibility. Enalaprilat was visually incompatible[1] with phenytoin sodium in sodium chloride 0.9%, producing a crystalline precipitate; there was also some visual evidence of incompatibility when mixed with amphotericin B in glucose 5%.

1. Thompson DF, *et al.* Visual compatibility of enalaprilat with selected intravenous medications during simulated Y-site injection. *Am J Hosp Pharm* 1990; 47: 2530–1.

Uses and Administration

Enalapril is an ACE inhibitor (p. 1282.2) used in the treatment of hypertension (p. 1251.1) and heart failure (p. 1262.3). It may also be given prophylactically to patients with asymptomatic left ventricular dysfunction to delay the onset of symptomatic heart failure, and has been used in patients with left ventricular dysfunction to reduce the incidence of coronary ischaemic events, including myocardial infarction (p. 1257.1).

Enalapril owes its activity to enalaprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after about 4 to 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic action lasts for about 24 hours, allowing once-daily dosing. Enalapril is given orally as the maleate.

Enalaprilat is not absorbed orally but is given by intravenous injection; its haemodynamic effects develop within 15 minutes of injection and reach a peak in 1 to 4 hours. The action lasts for about 6 hours at recommended doses. Enalaprilat is given as the dihydrate, but doses are expressed in terms of the anhydrous substance. Enalaprilat 1.38 mg as the dihydrate is equivalent to about 1.25 mg of anhydrous enalaprilat.

In the treatment of **hypertension**, an initial oral dose of 5 mg of enalapril maleate daily may be given. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. An initial dose of 2.5 mg daily should be given to patients who are receiving a *diuretic*; if possible, the diuretic should be withdrawn 2 or 3 days before enalapril is started and resumed later if necessary. The usual maintenance dose is 10 to 20 mg given once daily, although doses of up to 40 mg daily may be required in severe hypertension. It may be given in 2 divided doses if control is inadequate with a single dose.

When oral therapy of hypertension is impractical enalaprilat may be given in a dose of 1.25 mg by slow intravenous injection or infusion over at least 5 minutes, repeated every 6 hours if necessary; the initial dose should be halved in patients who are receiving a diuretic.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision. In patients with heart failure or asymptomatic left ventricular dysfunction enalapril maleate is given orally in an initial dose of 2.5 mg daily. The usual maintenance dose is 20 mg daily as a single dose or in 2 divided doses although up to 40 mg daily in 2 divided doses has been given.

For dosage reduction in renal impairment, see below.

For doses in children, see below.

Administration in children. Enalapril has been subject to both dose-finding and efficacy studies in children with hypertension or heart failure[1-4] and is licensed for use in hypertension in both the UK and the US.

In the UK, recommended oral doses of enalapril maleate for **hypertension** are given according to weight as follows:

- 20 kg to < 50 kg: initial dose of 2.5 mg once daily, increased if necessary to a maximum of 20 mg once daily
- ⩾ 50 kg: initial dose of 5 mg once daily, increased if necessary to a maximum of 40 mg once daily

In the USA, an initial dose of 80 micrograms/kg (maximum of 5 mg) once daily is recommended.

The *BNFC* suggests the following doses, which may be given to neonates and children in the treatment of **hypertension**, **heart failure**, or **proteinuria** in nephritis:

- neonate: initial dose of 10 micrograms/kg once daily with careful monitoring of blood pressure for 1 to 2 hours after the first dose, increased if necessary to a maximum of 500 micrograms/kg daily in 1 to 3 divided doses
- 1 month to 12 years: initial dose of 100 micrograms/kg once daily with careful monitoring of blood pressure for 1 to 2 hours after the first dose, increased if necessary to a maximum of 1 mg/kg daily in 1 or 2 divided doses
- 12 to 18 years: initial dose of 2.5 mg once daily with careful monitoring of blood pressure for 1 to 2 hours after the first dose, increased to a usual maintenance dose of 10 to 20 mg daily in 1 or 2 divided doses. Those weighing over 50 kg may be given up to 40 mg daily in 1 or 2 divided doses.

The *BNFC* also suggests the same dose in children aged 12 years and over with **diabetic neuropathy**.

1. Wells T, *et al.* A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of enalapril for children with hypertension. *J Clin Pharmacol* 2002; 42: 870–80.
2. Prenneaux M, *et al.* Enalapril for severe heart failure in infancy. *Arch Dis Child* 1989; 64: 219–23.
3. Lloyd TR, *et al.* Orally administered enalapril for infants with congestive heart failure: a dose-finding study. *J Pediatr* 1989; 114: 650–4.
4. Leversha AM, *et al.* Efficacy and dosage of enalapril in congenital and acquired heart disease. *Arch Dis Child* 1994; 70: 35–9.

Administration in renal impairment. An initial oral daily dose of enalapril maleate 2.5 mg, adjusted subsequently according to response, has been recommended for those with a creatinine clearance of 30 mL/min or less; this dose may also be considered in elderly patients. Enalapril is dialysable and an oral dose of 2.5 mg should be given on dialysis days. Where oral therapy is impractical, the initial intravenous dose of enalaprilat for those with a creatinine clearance of less than 30 mL/min and those on haemodialysis is 625 micrograms, given over at least 5 minutes (but preferably longer; up to 1 hour is suggested). This dose may be repeated after 1 hour if there is an inadequate response; additional doses of 1.25 mg may be given at 6-hour intervals if needed and tolerated.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Incidence of adverse effects. Postmarketing surveillance for enalapril was carried out by prescription-event monitoring of 12 543 patients.[1] There were 374 skin events including facial oedema or angioedema in 29 (leading to withdrawal of treatment in 10), 15 cases of photosensitivity, and urticaria in 32 (leading to withdrawal in 5). Syncope and dizziness occurred in 155 and 483 patients respectively, sometimes in association with hypotension. Hypotension occurred in 218 patients, 71 in the first month. Treatment was stopped in 121 patients with hypotension, and dosage reduced in 36. Other adverse effects reported included headache in 310 patients, paraesthesias in 126, taste disturbances in 25, conjunctivitis in 67, tachycardia in 194, cough in 360, renal failure in 82, muscle cramp in 96, diarrhoea in 236, and nausea and vomiting in 326. Of 1098 deaths only 10, due to renal failure, were thought possibly related to enalapril therapy. Dysgeusia and skin reactions appeared to be less common than has been reported for captopril, but precise comparisons were difficult; the range of adverse effects was similar.[2]

Deafness was a possible adverse effect of enalapril noted earlier;[2] it was reported in 19 of the 12 543 patients monitored, but only while they were taking enalapril, there being no record of deafness after treatment stopped.

For further reference to some of these adverse effects, see under ACE Inhibitors, p. 1285.2.

1. Inman WHW, *et al.* Postmarketing surveillance of enalapril I: results of prescription-event monitoring. *BMJ* 1988; 297: 826–9.
2. Inman WHW, Rawson NSB. Deafness with enalapril and prescription event monitoring. *Lancet* 1987; i: 872.

Breast feeding. After a single dose of enalapril 20 mg in 5 women enalaprilat was detected[1] in breast milk in concentrations of 1 to 2.3 nanograms/mL (mean peak 1.72 nanograms/mL); enalapril was also present (mean peak 1.74 nanograms/mL). This compared with peak serum values of 39 to 112 nanograms/mL for enalaprilat and 92 to 151 nanograms/mL for enalapril. Another study[2] found no detectable enalaprilat in the milk of 3 women, while in a further woman[3] both enalapril and enalaprilat were detected, but the concentrations were low. Although enalapril and its metabolite are thus present in small amounts in breast milk it was calculated that the average total daily dose to the neonate would only be about 2 micrograms of enalaprilat.[1] The American Academy of Pediatrics[4] lists no reports of any clinical effect on the

infant associated with the use of enalapril by breast-feeding mothers, and states that therefore it may be considered to be usually compatible with breast feeding.

For advice from UK regulatory authorities against the use of any ACE inhibitor during at least the early weeks of breast feeding see under Precautions of ACE Inhibitors, p. 1287.3.

1. Redman CWG, *et al.* The excretion of enalapril and enalaprilat in human breast milk. *Eur J Clin Pharmacol* 1990; 38: 99.
2. Huttunen K, *et al.* Enalapril treatment of a nursing mother with slightly impaired renal function. *Clin Nephrol* 1989; 31: 278.
3. Rush JE, *et al.* Comment. *Clin Nephrol* 1991; 35: 234.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 05/07/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies enalapril as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Enalapril acts as a prodrug of the diacid enalaprilat, its active form, which is poorly absorbed orally. About 60% of an oral dose of enalapril is absorbed from the gastrointestinal tract and peak plasma concentrations occur within about 1 hour. Enalapril is extensively hydrolysed in the liver to enalaprilat; peak plasma concentrations of enalaprilat occur 3 to 4 hours after an oral dose of enalapril. Enalaprilat is 50 to 60% bound to plasma proteins. After an oral dose, enalapril is excreted in the urine and in faeces, as enalaprilat and unchanged drug, with the urinary route predominating; more than 90% of an intravenous dose of enalaprilat is excreted in the urine. The elimination of enalaprilat is multiphasic but the effective half-life for accumulation after multiple doses of enalapril is reported to be about 11 hours in patients with normal renal function. Enalaprilat is removed by haemodialysis and by peritoneal dialysis.

References.

1. MacFadyen RJ, *et al.* Enalapril clinical pharmacokinetics and pharmacokinetic-pharmacodynamic relationships: an overview. *Clin Pharmacokinet* 1993; 25: 274–82.
2. Wells T, *et al.* The pharmacokinetics of enalapril in children and infants with hypertension. *J Clin Pharmacol* 2001; 41: 1064–74.
3. Rouini M, *et al.* Relationship of serum ACE inhibition to oral dose of enalapril in normotensive volunteers. *J Clin Pharm Ther* 2002; 27: 121–6.
4. Zapater P, *et al.* Gender differences in angiotensin-converting enzyme (ACE) activity and inhibition by enalaprilat in healthy volunteers. *J Cardiovasc Pharmacol* 2004; 43: 737–44.
5. Arafat T, *et al.* Pharmacokinetics and pharmacodynamics profiles of enalapril maleate in healthy volunteers following determination of enalapril and enalaprilat by two specific enzyme immunoassays. *J Clin Pharm Ther* 2005; 30: 319–28.

Renal impairment. Comparison of the pharmacokinetics of enalapril in 6 diabetics with persistent proteinuria and glomerular filtration rates (GFR) of 44.1 to 58.4 mL/minute with those in 8 age-matched controls showed that in the diabetic group the peak serum concentration of enalaprilat was higher, the time to peak concentration longer, renal clearance lower, and the areas under the concentration/time curve greater than in controls.[1] Renal clearance of enalaprilat in the diabetics ranged from 56 to 66 mL/minute compared with 105 to 133 mL/minute in controls; clearance correlated with GFR. In another study[2] involving 59 patients with chronic renal failure the pharmacokinetics of enalapril and enalaprilat were investigated in 9, who were given a once-daily oral dose of enalapril between 2.5 and 20 mg. In these patients GFR was between 6 and 60 mL/minute/1.73 m^2, and the clearance of enalaprilat was between 16 and 68 mL/minute. Markedly raised 24-hour trough values of serum enalaprilat were seen in all patients.

1. Baba T, *et al.* Enalapril pharmacokinetics in diabetic patients. *Lancet* 1989; i: 226–7.
2. Elung-Jensen T, *et al.* High serum enalaprilat in chronic renal failure. *J Renin Angiotensin Aldosterone Syst* 2001; 2: 240–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Baypril; Defluin; Dentromin; Drepatil; Ecaprilat; Eitan†; Enalafel; Enalapoten; Enaldun; Enatral; Enatrial†; Enitril; Fabotensil; Gadopril; Glioten; Hipertan; Kinfil; Lotrial; Maxen; Nalapril; Presi Regul; Priltenk; Renitec; Sulocten; Tencas; Vapresan; Vasopril; *Austral.*: Acetec; Alphapril; Amprace; Auspril; Enahexal†; Enalabell†; Renitec; *Austria*: Alapril; Enac; Enapril; Mepril; Renistad; Renitec; *Belg.*: Renitec; *Braz.*: Atens; Enalabal; Enalamed; Enalatec; Enalil†; Enalprin; Enaprotec; Enatil†; Eupressin; Glioten; Malena; Multipressim; Pressel; Pressotec; Prodopressin†; Pryltec; Renalapril; Renipress; Renitec; Renopril; Sanvapress†; Vasopril; *Canad.*: Vasotec; *Chile*: Bajaten; Enalten; Enatrial; Esalfon; Glioten†; Grifopril; Hiperson; Hipoartel; Lotrial†; *China*: Ai Li Ya (埃利雅); Benalapril (柏纳力); Pu Tan Le (福天乐); Invoril (因弗尔); Qin Ke Xi (勤可息); Renitec (悦宁定); Yi Na Lin (怡那林); Yi Su (依苏); *Cz.*: Berlipril; Ednyt; Enalatin; Enap; Enapril; Invoril†; Renitec; *Denm.*: Corodil; Enacodan; Enamaxin; *Fin.*: Enalatin†; Linatil; Renitec; *Fr.*: Renitec; *Ger.*: Benalapril; Corvo†; Ena-Puren†; Ena; Enabeta; Enadigal†; Enahexal†; Enalagamma; EnaLich†; Jutaxan†; Xanef; *Gr.*: Agioten; Analept; Antiprex; Arnaril; Erxetilan; Gnostocardin; Kaparion-S; Kontic; Leovinezal; Megapress; Octorax; Ofnifenil; Protal; Rablas; Renitec; Stadelant; Supotron; Ulticadex; Virfen; Vitobel; *Hong Kong*: CP-Enala†; Danssan†; Enaldun†; Enap; Lapril; Renitec; *Hung.*: Acepril; Berlipril; Ednyt; Enalatidin; Enap; Enapril; Renapril†; Renitec; *India*: Anze; BQL; Canvas; Converten; Dilpril; Dilvas; E-Pril; El; Ena; EnAce; Enal; Enalap; Enam; Enamate; Enapil; Enapril; Encardil; Enlacard; Enlow; Enpril; ENTP; Envas; EPM; Hytrol; Invoril; Lupinace; Minipril; Myoace; Newace; Normace; Nuril; Oren; *Indon.*: Meipril; Renacardon; Tenace; Tenaten; *Irl.*: Enap; Enapril; Innovace; *Israel*: Convertin; Enaladex; Enalapri; *Ital.*: Converten; Enapren; Lanex; Naprilene; Prilenor; Silverit; *Malaysia*: Acetec; Danssan; Enapril; Invoril; Renitec; *Mex.*: Adytenn; Albec†; Apo-Pyl; Bimetdad; Bionafil; Blocatril; EK-3; Enaladil; Enoval; Euronal; Feliberal; Glioten; Imotoran; Lipraken; Nalabest; Norpril; Olavac; Palane; Pulsol; Ralser; Renitec; Vexotil; *Neth.*: Renitec; *Norw.*: Renitec; *NZ*: Enahexal†; Renitec; *Philipp.*: Acebitor; Enace; Hipertal; Hypace; Hypril; Naprilate; Renitec; Stadenace; Vasopress; *Pol.*: Benalapril; Ednyt; Enap†; Enarenal; Enazil†; Epril†; Mapryl; *Port.*: Balpril; Cetampril; Chipil†; Denapril; Diasistol; Enapress; Hipobar†; Prilan; Renitec; Tensazol; *Rus.*: Bagopril (Багоприл); Berlipril (Берлиприл); Ednyt (Эднит); Enafarm (Энафарм); Enam (Энам); Enan (Энан); Enap (Энап); Enarenal (Энаренал); Envas (Энвас); Invoril (Инворил); Kalpiren (Кальпирен)†; Myopril (Миоприл)†; Renipril (Рениприл); Renitec (Ренитек); Vasopren (Вазопрен)†; *S.Afr.*: Alapren; Ciplatec; Enap; Envas; Pharmapress; Renitec; *Singapore*: Anapril; Corprilor; Enap; Enaril; Glioten; Invoril; Korandil; Renitec; *Spain*: Acetensil; Baripril; Bitensil; Clipto; Controlvas†; Crinoren; Dabonal; Ditensor†; Herten; Hipoartel; Iecatec; Insup; Naprilene; Neotensin†; Pressitan†; Reca†; Renitec; *Swed.*: Linatil†; Renitec; *Switz.*: Acepril†; Elpradil; Enapril; Enatec; Epril; Reniten; *Thai.*: Anapril; Enace; Enam; Enapril†; Enaril; Envas; Iecatec; Invoril; Istopril†; Korandil; Lapril; Myopril; Nalopril; Naritec†; Renitec; Unaril†; *Turk.*: Enalap; Enapril; Konveril; Renitec; Vasolapril; *UAE*: Naprapril; *UK*: Innovace; *Ukr.*: Berlipril (Берлиприл); Enahexal (Энагексал)†; Enalozid Mono (Эналозид Моно); Enam (Энам); Enap (Энап); *USA*: Epaned; Vasotec; *Venez.*: Cosil; Dinid; Enecal; Fibrosan; Hiperpril; Prilace; Redopril; Reminal; Renitec.

Multi-ingredient Preparations. *Arg.*: Co-Renitec; Defluin Plus; Eritril Plus; Fabotensil D; Gadopril D; Gliocarvedil; Glioten zide; Kinfil D; Lotrial D; Maxen D; Presi Regul D; Sulocten D; Tencas D; Vapresan Diur; *Austral.*: Renitec Plus; Zan-Extra; *Austria*: Cenipres; Co-Enac; Co-Enalapril; Co-Mepril; Co-Renistad; Co-Renitec; Enac Plus; Enalacomp; Enalapril Comp; Enalapril-HCT; Lercaprel; Renitec Plus; Zanipril; *Belg.*: Co-Enalapril; Co-Renitec; Zanicombo; *Braz.*: Atens H†; Atmos; Co-Enalil†; Co-Pressoless; Co-Pressotec; Co-Renitec; Coenaplex; Duopril; Eupressin-H; Gliotenzide; Malena HCT; Pryltec-H; Sinergen; Vasopril Plus; *Canad.*: Vaseretic; *Chile*: Bajaten D; Enalten D; Enalten DN; Esalfon-D; Grifopril-D; Hiperson-D; Lotrial D†; Normaten Plus; Normaten; *China*: Jiu Bao Ke (久保克); Yi Shuang (依双); *Cz.*: Enap-H; Enap-HL; Lercaprel; Zanicombo; *Denm.*: Corodil Comp; Enabeta comp; Enacecor; Enahexal comp; Enahyton; Enarese comp; Synerpril†; Zanipress; *Fin.*: Enalapril Comp; Linatil Comp; Renitec Comp; Renitec Plus; Zanipress; *Fr.*: Co-Renitec; Lercapress; Zanextra; *Ger.*: Benalapril Plus; Carmen ACE; Corvo HCT†; Enabeta comp; Enadigal HCT†; Enahexal comp†; Enala-Q comp†; Enalagamma HCT; Enalapril Comp; Enalapril HCT†; Enalapril plus†; Enalapril-saar Plus†; EnaLich comp†; Enaplus†; Eneas; Renacor; Zaneril; Zanipress; *Gr.*: Bumetryl; Co-Renitec; Coredopril; Eneas; Enit; Hemodilax; Iperton; Lercaprel; Modinexil; Nolarmin; Penopril; Protal complex; Savosan; Siberian; Zaneril; *Hong Kong*: Co-Renitec; CP-Enala Co†; *Hung.*: Acepril PlusZ; Co-Enalapril; Co-Renitec; Ednyt HCT; Ednyt Plus†; Enalapril Hexal Plus; Enalapril-HCT†; Enap-HL; Renapril Plus†; Renitec Plus; *India*: Amace; Amlogen-HL; Amtas-E; Amzel-HL; Dilvas AM; EnAce-D; Enam-D; Enapril-HT; Enapril-LD; Enaretic; ENTP-A; Envas-E; Envas-RB; Enzide; Hytrol-AM; Invozide; Klodip Ace; Lo-E; Normace-D; *Indon.*: Tenazide; *Irl.*: Innozide; Lercaril; *Israel*: Naprizide†; Vasodip Combo; *Ital.*: Acesistem; Condiuren; Elektra; Gentipress; Keprilan; Lanetik; Neoprex; Sinertec; Vasoretic; *Mex.*: Co-Feliberal; Co-Renitec; Gliotenzide; *Neth.*: Co-Renitec; Lercaprel†; Lertec; Renitec Plus; *Norw.*: Enalapril Comp; Renitec Comp; Zanipress; *NZ*: Co-Renitec; *Philipp.*: Co-Renitec; *Pol.*: Enap H; Enap HL; *Port.*: Diasistol Plus; Enatia; Eneas; Enit; Laprilen†; Lesten; Neodur†; Norpramin; Renidur; Renipril Plus; Zanipress; Zanitek; *Rus.*: Co-Renitec (Ко-Ренитек); Enam-H (Энам-Н); Enap-H (Энап Н); Enap-HL (Энап-НЛ); Enzix (Энзикс); Prilenap (Прилепап); Renipril HT (Ренприл ГТ); *S. Afr.*: Co-Renitec; Enap-Co; Pharmapress Co; Zaneril; *Singapore*: Co-Renitec; Enap-HL; Gliotenzide; *Spain*: Acediur; Acetensil Plus; Baripril Diu; Bitensil Diu; Co-Renitec; Coripren; Crinoretic; Dabonal Plus; Ditenside†; Eneas; Enit; Herten Plus; Hipoartel Plus; Lercapress; Neotensin Diu†; Pressitan Plus†; Renitecmax; Vipres; Zanipress; *Swed.*: Enalapril Comp; Linatil Comp; Renitec Comp; Synerpril; *Switz.*: Co-Acepril; Co-Enalapril; Co-Enatec; Co-Epril; Co-Reniten; Elpradil HCT; Epril Plus; Reniten Plus; Zanipress; *Turk.*: Eneas; Enit; Konveril Plus; *UK*: Innozide; *Ukr.*: Berlipril Plus (Берлиприл Плюс); Coripren (Коприпен); Enafril (Энафрил); Enahexal Compositum (Энагексал Композитум)†; Enalapril-H (Эналаприл-Н); Enalozid (Эналозид); Enap H (Энап Н); Enap HL (Энап HL); Eneas (Энеас); Enzix (Энзикс); *USA*: Teczem; Vaseretic; *Venez.*: Corprilor; Renitec; Duopres; Reminalet.

Pharmacopoeial Preparations

BP 2014: Enalapril Maleate Tablets;

USP 36: Enalapril Maleate and Hydrochlorothiazide Tablets; Enalapril Maleate Oral Suspension; Enalapril Maleate Tablets; Enalaprilat Injection.

Enoxaparin Sodium *(BAN, USAN, rINN)*

Enoksapariininatrium; Enoksaparin Sodyum; Enoksaparin natrio druska; Enoksaparyna sodowa; Enoxaparin-Natrium; Enoxaparin sodná sůl; Enoxaparina sódica; Enoxaparine sodique; Enoxaparinnatrium; Enoxaparin-nátrium; Enoxaparinum Natricum; PK-10169; RP-54563; Эноксапарин Натрий.

CAS — 9041-08-1; 679809-58-6.

ATC — B01AB05.

ATC Vet — QB01AB05.

UNII — 8NZ41MIK1O.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Enoxaparin Sodium). The sodium salt of a low-molecular-mass heparin that is obtained by alkaline depolymerisation of the benzyl ester derivative of heparin from porcine intestinal mucosa. The majority of the components have a 4-enopyranose uronate structure at the non-reducing end of their chain; 15 to 25% of the components have a 1,6-anhydro structure at the reducing end of their chain. The mass-average molecular mass ranges between 3800 and 5000 with a characteristic value of about 4500. The degree of sulfation is about 2 per disaccharide unit.

The potency is not less than 90 units and not more than 125 units of anti-factor Xa activity per mg, calculated with reference to the dried substance. The anti-factor IIa activity is not less than 20 units and not more than 35 units per mg calculated with reference to the dried substance. The ratio of anti-factor Xa activity to anti-factor IIa activity is between 3.3 and 5.3.

A 10% solution in water has a pH of 6.2 to 7.7.

USP 36: (Enoxaparin Sodium). The sodium salt of a depolymerised heparin obtained by alkaline depolymerisation of the benzyl ester derivative of heparin from porcine intestinal mucosa. Enoxaparin sodium consists of a complex set of oligosaccharides that have not yet been completely characterised. The majority of the components have a 4-enopyranose uronate structure at the non-reducing end of their chain. About 20% of the components contain a 1,6-anhydro derivative on the reducing end of the chain. The mass-average molecular weight of enoxaparin sodium is 4,500, the range being between 3,800 and 5,000.

It has a potency of not less than 90 units and not more than 125 units of anti-factor Xa per mg, and not less than 20 units and not more than 35 units of anti-factor IIa per mg, calculated with reference to the dried substance. The ratio of anti-factor Xa activity to anti-factor IIa activity is between 3.3 and 5.3.

A 10% solution in water has a pH of 6.2 to 7.7. Store in airtight containers at a temperature below 40 degrees.

Units

As for Low-molecular-weight Heparins, p. 1426.2.

Uses and Administration

Enoxaparin sodium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant properties. It is used in the treatment and prophylaxis of venous thromboembolism (p. 1274.1) and to prevent clotting during extracorporeal circulation. It is also used in the management of unstable angina (p. 1254.3) and in myocardial infarction (p. 1257.1).

In the *prophylaxis* of **venous thromboembolism** during surgical procedures, enoxaparin sodium is given by subcutaneous injection; treatment is usually continued for 7 to 10 days or until the patient is ambulant.

- Patients at low to moderate risk are given 20 mg (2000 units) once daily with the first dose about 2 hours pre-operatively.
- In patients at high risk, such as those undergoing orthopaedic surgery, the dose should be increased to 40 mg (4000 units) once daily with the initial dose given about 12 hours before the procedure. Alternatively, a dose of 30 mg (3000 units) may be given subcutaneously twice daily, starting within 12 to 24 hours after the operation. After hip replacement surgery, enoxaparin sodium may be continued in a dose of 40 mg (4000 units) once daily for a further 3 weeks.
- For the prophylaxis of thromboembolism in immobilised medical patients, the dose is 40 mg (4000 units) once

daily for at least 6 days; treatment should be continued until the patient is fully ambulant, up to a maximum of 14 days.

For the *treatment* of deep-vein thrombosis enoxaparin sodium is given subcutaneously in a dose of 1 mg/kg (100 units/kg) every 12 hours, or 1.5 mg/kg (150 units/kg) once daily, for at least 5 days and until oral anticoagulation is established. (In pregnant patients, early-pregnancy bodyweight should be used to calculate the dose.)

For prevention of clotting in the extracorporeal circulation during **haemodialysis**, enoxaparin sodium 1 mg/kg (100 units/kg) is introduced into the arterial line of the circuit at the beginning of the dialysis session. A further dose of 0.5 to 1 mg/kg (50 to 100 units/kg) may be given if required. The dose should be reduced in patients at high risk of haemorrhage.

In the management of **unstable angina** or **non ST-elevation myocardial infarction**, enoxaparin sodium is given subcutaneously in a dose of 1 mg/kg (100 units/kg) every 12 hours. Treatment is usually continued for 2 to 8 days.

In **acute ST-elevation myocardial infarction** the initial dose of enoxaparin is 30 mg (3000 units) intravenously, with a subcutaneous dose of 1 mg/kg (100 units/kg) given at the same time. Further doses of 1 mg/kg (100 units/kg) should be given subcutaneously every 12 hours for 8 days or until hospital discharge. The first 2 subcutaneous doses should not exceed 100 mg (10 000 units) each. For patients who undergo a percutaneous coronary intervention, an additional intravenous dose of 300 micrograms/kg (30 units/kg) should be given at the time of the procedure if the last subcutaneous dose was given more than 8 hours previously. Patients aged 75 years and older should be given subcutaneous doses only; the recommended dose is 750 micrograms/kg (75 units/kg) every 12 hours, with a maximum of 75 mg (7500 units) for each of the first 2 doses.

The dose of enoxaparin sodium should be reduced in patients with severe renal impairment (see below).

References.
1. Noble S, *et al.* Enoxaparin: a reappraisal of its pharmacology and clinical applications in the prevention and treatment of thromboembolic disease. *Drugs* 1995; 49: 388–410.
2. Noble S, Spencer CM. Enoxaparin: a review of its clinical potential in the management of coronary artery disease. *Drugs* 1998; 56: 259–72.
3. Harvey DM, Offord RH. Management of venous and cardiovascular thrombosis: enoxaparin. *Hosp Med* 2000; 61: 628–36.
4. Ibbotson T, Goa KL. Enoxaparin: an update of its clinical use in the management of acute coronary syndromes. *Drugs* 2002; 62: 1407–31.
5. Fareed J, *et al.* Pharmacodynamic and pharmacokinetic properties of enoxaparin: implications for clinical practice. *Clin Pharmacokinet* 2003; 42: 1043–57.
6. Siddiqui MAA, Wagstaff AJ. Enoxaparin: a review of its use as thromboprophylaxis in acutely ill, nonsurgical patients. *Drugs* 2005; 65: 1025–36.
7. Carter NJ, *et al.* Enoxaparin: a review of its use in ST-segment elevation myocardial infarction. *Drugs* 2008; 68: 691–710.
8. Schwarz AK, Zeymer U. Enoxaparin in patients with primary percutaneous coronary intervention for acute ST segment elevation myocardial infarction. *Future Cardiol* 2009; 5: 43–9.

Administration in children. Increasing numbers of infants and children are given anticoagulants for the management of thromboembolism. Few controlled studies have been carried out in this age group and recommendations for therapy have generally been adapted from adult guidelines. Low-molecular-weight heparins may have several advantages in children. Enoxaparin has been used for the prophylaxis[1] of thromboembolism in children including neonates, and for treatment in children including neonates[1-3] and preterm infants.[1,3-5] Younger children (and in particular neonates[6]) may require a higher dose than older children. US guidelines recommend the following doses for *treatment*[7] of thromboembolism:

- under 2 months of age: 1.5 mg/kg (150 units/kg) every 12 hours
- over 2 months of age: 1 mg/kg (100 units/kg) every 12 hours

Doses for *prophylaxis*[7] are:

- under 2 months of age: 750 micrograms/kg (75 units/kg) every 12 hours
- over 2 months of age: 500 micrograms/kg (50 units/kg) every 12 hours

Similar doses are recommended in the UK by the *BNFC*, although it specifies slightly modified *treatment* doses for neonates, in whom it recommends enoxaparin sodium 1.5 to 2 mg/kg (150 to 200 units/kg) twice daily. A maximum daily dose of 40 mg (4000 units) for *prophylaxis* in children over 2 months of age is also suggested.

1. Dix D, *et al.* The use of low molecular weight heparin in pediatric patients: a prospective cohort study. *J Pediatr* 2000; 136: 439–45.
2. Massicotte P, *et al.* Low-molecular-weight heparin in pediatric patients with thrombotic disease: a dose finding study. *J Pediatr* 1996; 128: 313–18.
3. Streif W, *et al.* Use of low molecular mass heparin (enoxaparin) in newborn infants: a prospective cohort study of 62 patients. *Arch Dis Child Fetal Neonatal Ed* 2003; 88: F365–F370.
4. Dunaway KK, *et al.* Use of enoxaparin in a preterm infant. *Ann Pharmacother* 2000; 34: 1410–13.
5. Michaels LA, *et al.* Low molecular weight heparin in the treatment of venous and arterial thromboses in the premature infant. *Pediatrics* 2004; 114: 703–7.
6. Malowany JI, *et al.* Enoxaparin for neonatal thrombosis: a call for a higher dose for neonates. *Thromb Res* 2008; 122: 826–30.
7. Monagle P, *et al.* Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133 (suppl): 887S–968S.

Administration in renal impairment. Careful monitoring is required when enoxaparin sodium is given to patients with mild to moderate renal impairment.[1] In severe renal impairment (creatinine clearance less than 30 mL/minute) the dose should be reduced. For *prophylaxis* of venous thromboembolism, UK licensed product information recommends a dose of 20 mg (2000 units) subcutaneously once daily whereas US licensed product information recommends a subcutaneous dose of 30 mg (3000 units) once daily. For *treatment* of venous thromboembolism, unstable angina, or non ST-elevation myocardial infarction, a dose of 1 mg/kg (100 units/kg) is given subcutaneously once daily. This dose may also be used to treat patients with acute ST-elevation myocardial infarction, in which case those aged under 75 years are given an additional single intravenous injection of 30 mg (3000 units) with the first subcutaneous dose. However, the adequacy of a once-daily dose in patients with acute coronary syndromes has been questioned and alternative dosage regimens have been suggested.[2,3]

1. Brophy DF, Sica DA. Use of enoxaparin in patients with chronic kidney disease: safety considerations. *Drug Safety* 2007; 30: 991–4.
2. Hulot J-S, *et al.* Dosing strategy in patients with renal failure receiving enoxaparin for the treatment of non-ST-segment elevation acute coronary syndrome. *Clin Pharmacol Ther* 2005; 77: 342–52.
3. Green B, *et al.* Dosing strategy for enoxaparin in patients with renal impairment presenting with acute coronary syndromes. *Br J Clin Pharmacol* 2005; 59: 281–90.

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p. 1426.3. Patients with low body-weight (women below 45 kg, men below 57 kg) may be at higher risk of bleeding with prophylactic doses of enoxaparin and require careful monitoring.

Caution is required in renal impairment, and doses may need to be reduced.

Severe bleeding with enoxaparin may be reduced by the slow intravenous injection of protamine sulfate; 1 mg of protamine sulfate is stated to inhibit the effects of about 1 mg (100 units) of enoxaparin sodium.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies enoxaparin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/10/11)

Interactions

As for Heparin, p. 1400.2.

Pharmacokinetics

Enoxaparin is rapidly and almost completely absorbed after subcutaneous injection with a bioavailability of about 100%. Peak plasma activity occurs within 1 to 5 hours. The elimination half-life is about 4 to 5 hours but anti-factor Xa activity may persist for up to 24 hours after a 40-mg dose. Elimination is prolonged in patients with renal impairment. Enoxaparin is metabolised in the liver and excreted in the urine, as unchanged drug and metabolites.

References.
1. Hulot JS, *et al.* Effect of renal function on the pharmacokinetics of enoxaparin and consequences on dose adjustment. *Ther Drug Monit* 2004; 26: 305–10.
2. Kruse MW, Lee JJ. Retrospective evaluation of a pharmacokinetic program for adjusting enoxaparin in renal impairment. *Am Heart J* 2004; 148: 582–9.
3. Lebaudy C, *et al.* Changes in enoxaparin pharmacokinetics during pregnancy and implications for antithrombotic therapeutic strategy. *Clin Pharmacol Ther* 2008; 84: 370–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Clexane; Dilutol; Enoxdown; Fibrinox†; Loparine; Omatex; *Austral.*: Clexane; *Austria*: Lovenox; *Belg.*: Clexane; *Braz.*: Clexane; Dripanina†; Endocris; Enoxalow; *Canad.*: Lovenox; *Chile*: Clexane; Henoxil; Nu-Rox; *China*: Clexane (克赛); *Cz.*: Clexane; *Denm.*: Klexane; *Fin.*: Klexane; *Fr.*: Lovenox; *Ger.*: Clexane; *Gr.*: Clexane; *Hong Kong*: Clexane; *Hung.*: Clexane; *India*: Clexane; Cutenox; Dynalix; Enoxarin; Exowin; Flothin; Grefac; Hepanox; LMWX; Lomonox; Lomorin-NX; Loparin; Lupenox; Macparin; Maxiparine; Megaparin; *Indon.*: Lovenox; *Irl.*: Clexane; *Israel*: Clexane; *Ital.*: Clexane; *Malaysia*: Clexane; *Mex.*: Clexane; *Neth.*: Clexane; *Norw.*: Klexane; *NZ*: Clexane; *Philipp.*: Clexa†; Clexane; Hepaclex; Lomoh; *Pol.*: Clexane; *Port.*: Klexane†; Lovenox; *Rus.*: Clexane (Клексан); Hemapaxan (Гемапаксан); *S. Afr.*: Clexane; *Singapore*: Clexane; *Spain*: Clexane; *Swed.*: Klexane; *Switz.*: Clexane; *Thai.*: Clexane; *Turk.*: Clexane; *UK*: Clexane; *Ukr.*: Clexane (Клексан); Flenox (Фленокс); *USA*: Lovenox; *Venez.*: Clexane; Enoparin.

Multi-ingredient Preparations. *Cz.*: Clexane anti Xa-IU†.

Pharmacopoeial Preparations
BP 2014: Enoxaparin Sodium Injection;
USP 36: Enoxaparin Sodium Injection.

Enoximone *(BAN, USAN, rINN)*

Enoksimoni; Enoximon; Enoximona; Enoximone; Enoximonum; Fenoximone; MDL-17043; MDL-19438; RMI-17043; YMDL-17043; Эноксимон.

4-Methyl-5-[4-(methylthio)benzoyl]-4-imidazolin-2-one.

$C_{12}H_{12}N_2O_2S$=248.3

CAS — 77671-31-9.

ATC — C01CE03.

ATC Vet — QC01CE03.

UNII — C7Z4M7L7.

Incompatibility. Crystal formation has occurred when enoximone injection was mixed in glass containers or syringes; licensed product information recommends that only plastic containers or syringes are used for dilutions. It also recommends that only sodium chloride 0.9% or water be used as diluents. Glucose solutions should not be used for dilution as crystal formation may occur.

Uses and Administration

Enoximone is a phosphodiesterase type 3 inhibitor similar to amrinone (p. 1305.1) with positive inotropic and vasodilator activity. It is given intravenously in the short-term management of heart failure. In some long-term studies it was given orally, but an increased mortality rate was reported.

The usual initial dose of enoximone by intravenous injection is 0.5 to 1.0 mg/kg given at a rate not greater than 12.5 mg/minute. This may be followed by doses of 500 micrograms/kg every 30 minutes until a satisfactory response is obtained or a total dose of 3 mg/kg has been given. Alternatively, the initial dose may be given as a continuous intravenous infusion in a dose of 90 micrograms/kg per minute over 10 to 30 minutes until the desired response is achieved.

For maintenance therapy the initial dose (up to a total of 3 mg/kg) may be repeated as required every 3 to 6 hours or a continuous or intermittent infusion may be given in a dose of 5 to 20 micrograms/kg per minute.

The total dose over 24 hours should not exceed 24 mg/kg.

Dosage may need to be reduced in patients with hepatic or renal impairment (see below).

General references.
1. Vernon MW, *et al.* Enoximone: a review of its pharmacological properties and therapeutic potential. *Drugs* 1991; 42: 997–1017.

Administration in hepatic and renal impairment. The elimination half-life of enoximone after intravenous administration was 2.16 hours in a patient with hepatic impairment and 1.33 hours in a patient with renal impairment. The mean elimination half-life in patients with normal hepatic and renal function was 1.26 hours. It was suggested that patients with renal impairment should be monitored and have plasma concentrations measured during continuous infusions and that in hepatic disease the dosage may need to be modified.[1] Similarly, in a study[2] in paediatric patients receiving intravenous enoximone clearance was reduced in those with renal or hepatic impairment and it was suggested that the infusion rate should be decreased in such patients.

1. Desager JP, *et al.* Plasma enoximone concentrations in cardiac patients. *Curr Ther Res* 1990; 47: 743–52.
2. Booker PD, *et al.* Enoximone pharmacokinetics in infants. *Br J Anaesth* 2000; 85: 205–10.

Beta blocker overdosage. Enoximone, given intravenously as a bolus dose of 500 micrograms/kg followed by an infusion of 15 micrograms/kg per minute, successfully increased the cardiac output and stroke volume in a woman who had ingested 10 g of metoprolol.[1] It was suggested that enoximone may be useful in such patients since its action does not involve the beta-adrenergic system. Use to treat propranolol overdose has also been described.[2]

1. Hoeper MM, Boeker KHW. Overdose of metoprolol treated with enoximone. *N Engl J Med* 1996; 335: 1538.
2. Sandroni C, *et al.* Enoximone in cardiac arrest caused by propranolol: two case reports. *Acta Anaesthesiol Scand* 2006; 50: 759–61.

Heart failure. Enoximone is one of several drugs that may be used in heart failure (p. 1262.3), but because of an increased mortality rate reported following long-term oral use of phosphodiesterase type 3 inhibitors[1] it is only given intravenously for short-term management of heart failure

unresponsive to other treatments. In a comparison of oral enoximone and placebo in patients with moderate to moderately severe heart failure,[2] enoximone was no better than placebo in improving exercise duration over the 16-week study period. Although the overall incidence of adverse effects was similar in the two groups, 5 patients receiving enoximone died compared with none in the placebo group. In a later study,[3] low doses of oral enoximone (generally 25 or 50 mg three times daily) appeared to be safe when given to patients with advanced heart failure also taking beta blockers, but again outcomes were not improved. Similar oral doses have also been tried in an attempt to wean patients with severe (NYHA class IV) heart failure from intravenous inotropic support, but with little or only limited success.[4]

1. Amsallem E, *et al.* Phosphodiesterase III inhibitors for heart failure. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 29/04/10).
2. Uretsky BF, *et al.* Multicenter trial of oral enoximone in patients with moderate to moderately severe congestive heart failure: lack of benefit compared with placebo. *Circulation* 1990; 82: 774–80.
3. Metra M, *et al.* ESSENTIAL Investigators. Effects of low-dose oral enoximone administration on mortality, morbidity, and exercise capacity in patients with advanced heart failure: the randomized, double-blind, placebo-controlled, parallel group ESSENTIAL trials. *Eur Heart J* 2009; 30: 3015–26.
4. Feldman AM, *et al.* EMOTE Study Group. Low-dose oral enoximone enhances the ability to wean patients with ultra-advanced heart failure from intravenous inotropic support: results of the oral enoximone in intravenous inotrope-dependent subjects trial. *Am Heart J* 2007; 154: 861–9.

Adverse Effects

Long-term oral treatment with enoximone has been reported to increase the mortality rate and enoximone is now only given intravenously for short-term use.

Enoximone may cause ventricular and supraventricular tachyarrhythmias, ectopic beats, and hypotension.

Adverse effects of enoximone affecting the gastrointestinal tract include diarrhoea, nausea, and vomiting. Other adverse effects include headache, insomnia, chills, oliguria, fever, urinary retention, and limb pain. There have been reports of thrombocytopenia and abnormal liver enzyme values.

Effects on the nervous system. Tonic-clonic convulsions have been reported[1] in a patient given enoximone 6 micrograms/kg per minute by intravenous infusion. The convulsions subsided when enoximone was stopped.

1. Appadurai I, *et al.* Convulsions induced by enoximone administered as a continuous intravenous infusion. *BMJ* 1990; 300: 613–14.

Hyperosmolality. Hyperosmolality occurred in an infant during intravenous infusion of enoximone 20 micrograms/kg per minute. The probable cause was propylene glycol in the enoximone injection providing a dose of 2.4 mg/kg per minute.[1]

1. Huggon I, *et al.* Hyperosmolality related to propylene glycol in an infant treated with enoximone infusion. *BMJ* 1990; 301: 19–20.

Precautions

Enoximone should be used with caution in patients with hypertrophic cardiomyopathy or severe obstructive aortic or pulmonary valvular disease.

Blood pressure, heart rate, ECG, fluid and electrolyte status, and renal function should be monitored during therapy. Platelet count and liver enzyme values should also be monitored.

The injection has a high pH (about 12) and must be diluted before use (but see Incompatibility, p. 1373.3). Extravasation should be avoided.

Doses may need to be reduced in hepatic or renal impairment (see under Uses and Administration, p. 1373.3).

Pharmacokinetics

Although enoximone is absorbed from the gastrointestinal tract it is no longer given orally. The plasma elimination half-life varies widely; it may be about 1 to 4 hours in healthy subjects and about 3 to 8 hours in patients with heart failure, but longer times have been reported. Enoximone is about 85% bound to plasma proteins. It is metabolised in the liver and is excreted in the urine, mainly as metabolites. After intravenous doses about 70% of a dose is excreted in the urine as metabolites and less than 1% as unchanged drug.

General references.

1. Rocci ML, Wilson H. The pharmacokinetics and pharmacodynamics of newer inotropic agents. *Clin Pharmacokinet* 1987; 13: 91–109. Correction. *ibid.* 1988; 14:(contents page).
2. Booker PD, *et al.* Enoximone pharmacokinetics in infants. *Br J Anaesth* 2000; 85: 205–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Perfan†; *Fr.*: Perfane; *Ger.*: Perfan; *Irl.*: Perfan; *Ital.*: Perfan; *Neth.*: Perfan; *UK*: Perfan.

Epitizide *(BAN, rINN)* ⊗

Epithiazide (USAN); Epitizida; Epitizide; Epitizidum; Eptizida; NSC-108164; P-2105; Эпитизид.

6-Chloro-3,4-dihydro-3-(2,2,2-trifluoroethylthiomethyl)-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_{10}H_{11}ClF_3N_3O_4S_3$=425.8

CAS — 1764-85-8.

UNII — 5B266B85J1.

Profile

Epitizide is a thiazide diuretic (see Hydrochlorothiazide, p. 1403.2) used in the treatment of hypertension and oedema, often with triamterene.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Belg.*: Dyta-Urese; *Neth.*: Dyta-Urese.

Eplerenone *(BAN, USAN, rINN)* ⊗

CGP-30083; Eplerenona; Éplérénone; Eplerenonum; Epoxymexrenone; SC-66110; Эплеренон.

9,11α-Epoxy-17-hydroxy-3-oxo-17α-pregn-4-ene-7α,21-dicarboxylic acid γ-lactone methyl ester.

$C_{24}H_{30}O_6$=414.5

CAS — 107724-20-9.

ATC — C03DA04.

ATC Vet — QC03DA04.

UNII — 6995V82D0B.

Uses and Administration

Eplerenone is an aldosterone antagonist with properties similar to those of spironolactone (p. 1500.1) but with a higher selectivity for the aldosterone receptor. It is given orally in the management of hypertension (p. 1251.1) and heart failure (p. 1262.3).

In the management of **hypertension**, eplerenone may be given alone or with other antihypertensives. It is given in an initial dose of 50 mg daily, increasing if necessary to a maximum of 50 mg twice daily. While eplerenone should not be given with potent CYP3A4 inhibitors (see Interactions, below), patients taking mild to moderate inhibitors may be given eplerenone; the initial dose should be reduced to 25 mg daily.

Eplerenone is given as an adjunct to standard therapy for the management of **heart failure** in patients with NYHA class II symptoms and left ventricular ejection fraction (LVEF) ≤ 30%, or in those with clinical evidence of heart failure and LVEF ≤ 40% after a recent myocardial infarction. It is given in an initial dose of 25 mg daily, increasing to 50 mg daily within 4 weeks if tolerated. Eplerenone should be withdrawn or the dose should be reduced to 25 mg daily, or on alternate days, if hyperkalaemia develops. Eplerenone may be used in patients given mild to moderate CYP3A4 inhibitors, at a dose not exceeding 25 mg daily.

Doses of eplerenone may need to be adjusted in patients with renal impairment. For details, see Administration in Renal Impairment, below.

References and reviews.

1. Zillich AJ, Carter BL. Eplerenone—a novel selective aldosterone blocker. *Ann Pharmacother* 2002; 36: 1567–76.
2. Pitt B, *et al.*, for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; 348: 1309–21. Correction. *ibid.*: 2271.
3. Keating GM, Plosker GL. Eplerenone: a review of its use in left ventricular systolic dysfunction and heart failure after acute myocardial infarction. *Drugs* 2004; 64: 2689–707.
4. Pitt B, *et al.* Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol* 2005; 46: 425–31.
5. Anonymous. Eplerenone after myocardial infarction? *Drug Ther Bull* 2008; 46: 1–3.
6. McManus P, *et al.* Eplerenone, a mineralocorticoid-receptor antagonist. *Nat Clin Pract Endocrinol Metab* 2008; 4: 44–52.
7. Muldowney JA, *et al.* The clinical pharmacology of eplerenone. *Expert Opin Drug Metab Toxicol* 2009; 5: 425–32.
8. Zannad F, *et al.* EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; 364: 11–21.
9. Swedberg K, *et al.* Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure) study. *J Am Coll Cardiol* 2012; 59: 1598–603.

Administration in renal impairment. There is an increased risk of hyperkalaemia with eplerenone in patients with renal impairment and, as such, its use in all patients with a creatinine clearance (CC) of 30 mL/minute or less should be avoided. In addition, patients with a CC of 50 mL/minute or less should not receive eplerenone for the treatment of hypertension.

In those with less severe impairment, the judicious use of eplerenone is permitted. Serum-potassium levels should be monitored and dosages adjusted accordingly. UK licensed product information suggests that, for heart failure patients, no initial dose adjustment is needed in those with mild impairment (CC above 60 mL/minute); a starting dose of 25 mg orally on alternate days may be considered in those with moderate impairment (CC 30 to 60 mL/minute).

Adverse Effects

As for Spironolactone, p. 1501.2. Hypercholesterolaemia, hypertriglyceridaemia, and increases in liver enzymes have also occurred.

Precautions

As for Spironolactone, p. 1502.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies eplerenone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Spironolactone, p. 1502.2.

Eplerenone is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4, and significantly increased plasma concentrations of eplerenone have occurred when potent inhibitors of this enzyme have been given. These include clarithromycin, telithromycin, itraconazole, ketoconazole, nefazodone, nelfinavir, and ritonavir, and use with eplerenone is contra-indicated. Mild to moderate inhibitors of this enzyme, such as erythromycin, fluconazole, saquinavir, and verapamil, have a less marked effect, although a reduced dose of eplerenone may be necessary (see under Uses, above). Grapefruit juice causes only a small increase in exposure to eplerenone. Conversely, inducers of this enzyme system, such as carbamazepine, St John's wort, phenobarbital, phenytoin, and rifampicin, may reduce plasma concentrations of eplerenone.

Pharmacokinetics

Peak plasma concentrations of eplerenone occur about 1.5 hours after an oral dose; they are dose proportional for doses of 25 to 100 mg, and less than proportional above 100 mg. Protein binding, primarily to α_1-acid glycoprotein, is about 50%. Eplerenone metabolism is mainly mediated by the cytochrome P450 isoenzyme CYP3A4; less than 5% of a dose is excreted unchanged. About 32% of a dose is excreted in the faeces, and the remainder in the urine. The elimination half-life is about 4 to 6 hours. Eplerenone is not removed by dialysis.

References.

1. Ravis WR, *et al.* Pharmacokinetics of eplerenone after single and multiple dosing in subjects with and without renal impairment. *J Clin Pharmacol* 2005; 45: 810–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aldactone EP; Oldren; Sufficard; *Austral.*: Inspra; *Austria*: Inspra; *Belg.*: Inspra; *Canad.*: Inspra; *Chile*: Inspra†; *Cz.*: Inspra; *Denm.*: Inspra; *Fin.*: Inspra; *Fr.*: Inspra; *Ger.*: Inspra; *Gr.*: Inspra; *Hong Kong*: Inspra; *Hung.*: Inspra; *India*: Epleran; Eptus; *Irl.*: Eplefa; Inspra; *Israel*: Inspra; *Mex.*: Inspra; *Neth.*: Inspra; *Norw.*: Inspra; *Pol.*: Inspra; *Port.*: Inovic; Inspra; *S.Afr.*: Inspra; *Singapore*: Inspra; *Spain*: Elecor; Inspra; *Swed.*: Inspra; *Switz.*: Inspra; *UK*: Inspra; *Ukr.*: Inspra (Инспра); *USA*: Inspra.

Epoprostenol *(USAN, rINN)*

Epoprosténol; Epoprostenoli; Epoprostenolum; PGI$_2$; PGX; Prostacyclin; Prostacyclinum; Prostacyklin; Prostaglandin I$_2$; Prostaglandin X; Prostasykliini; U-53217; Эпопростенол.

(5*Z*,13*E*)-(8*R*,9*S*,11*R*,12*R*,15*S*)-6,9-Epoxy-11,15-dihydroxyprosta-5,13-dienoic acid; (*Z*)-5-[(3a*R*,4*R*,5*R*,6a*S*)-5-Hydroxy-4-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]perhydrocyclopenta[*b*]furan-2-ylidene]valeric acid.

$C_{20}H_{32}O_5$=352.5

CAS — 35121-78-9.

ATC — B01AC09.

ATC Vet — QB01AC09.
UNII — DCR9Z582X0.

NOTE. In *Martindale* the term epoprostenol is used for the exogenous substance and prostacyclin for the endogenous substance.

Epoprostenol Sodium *(BAN, USAN, rINNM)*

Epoprostenol sódico; Époprosténol Sodique; Natrii Epoprostenolum; U-53217A; Натрий Эпопростенол.

$C_{20}H_{31}NaO_5$=374.5

CAS — 61849-14-7.
ATC — B01AC09.
ATC Vet — QB01AC09.
UNII — 4K04IQ1OF4.

Stability in solution. Epoprostenol is unstable at physiological pH and solutions for infusion are prepared in an alkaline glycine buffer at pH 10.5. The half-life in aqueous solution of pH 7.4 has been reported[1] to be less than 3 minutes at 37 degrees, but increased stability has been reported in plasma, albumin, or whole blood.[1,2]

1. El Tahir KEH, *et al.* Stability of prostacyclin in human plasma. *Clin Sci* 1980; **59**: 28P–29P.
2. Mikhailidis DP, *et al.* Infusion of prostacyclin (epoprostenol). *Lancet* 1982; **ii**: 767.

Uses and Administration

Epoprostenol is a prostaglandin (p. 2598.1) that causes vasodilatation and prevents platelet aggregation. The endogenous substance is termed prostacyclin. Epoprostenol is used mainly in extracorporeal procedures and in pulmonary hypertension.

Epoprostenol is given as the sodium salt and doses are expressed in terms of the base: 1.06 nanograms of epoprostenol sodium is equivalent to about 1 nanogram of epoprostenol. The drug is unstable in solution at physiological pH and also has a very short duration of action because of its rapid hydrolysis *in vivo*. It must therefore be given by continuous infusion. Great care must be taken in preparing a suitably diluted solution for infusion and only diluent as supplied by the manufacturer should be used to reconstitute epoprostenol.

Epoprostenol is used to **prevent platelet aggregation** when blood is brought into contact with nonbiological surfaces in procedures such as extracorporeal circulation, especially in renal dialysis patients. It is indicated for use when heparin carries a high risk of causing or exacerbating bleeding, or is otherwise contra-indicated. Epoprostenol is given by continuous intravenous infusion or into the blood supplying the extracorporeal circulation. The usual dose for renal dialysis is 4 nanograms/kg per minute intravenously before dialysis, then 4 nanograms/kg per minute into the arterial inlet of the dialyser during dialysis.

In the long-term treatment of **pulmonary hypertension**, including that associated with scleroderma, epoprostenol is given by continuous intravenous infusion through a central catheter, although a peripheral intravenous catheter may be used until central access is established. A dose-ranging procedure is performed first. Epoprostenol infusion is started at a rate of 2 nanograms/kg per minute, then increased by increments of 2 nanograms/kg per minute at intervals of at least 15 minutes until the maximum haemodynamic benefit or dose-limiting effects occur. Epoprostenol is then given at a rate 4 nanograms/kg per minute *less than* the maximum-tolerated infusion rate; if the maximum-tolerated infusion rate is less than 5 nanograms/kg per minute, then the initial rate should be one-half of this maximum rate. The maintenance dose is subsequently adjusted according to the patient's response. If symptoms recur or if adverse effects occur the dosage may be increased or decreased by steps of 1 to 2 nanograms/kg per minute at intervals of at least 15 minutes until a new maintenance dose is established.

For the use of epoprostenol in neonates and children, see below.

Action. The discovery, properties, and clinical applications of prostacyclin have been reviewed.[1] Prostacyclin is the main product of arachidonic acid in vascular tissues, endothelial cells from vessel walls being the most active producers. It is a strong hypotensive agent through vasodilatation of vascular beds, including the pulmonary and cerebral circulations, and is also a potent endogenous inhibitor of platelet aggregation. Inhibition of aggregation is achieved by stimulation of adenylate cyclase, leading to an increase in cyclic adenosine monophosphate (cAMP) levels in the platelets. By inhibiting several steps in the activation of the arachidonic acid metabolic cascade, prostacyclin exerts an overall control of platelet aggregability.

Endogenous prostacyclin and thromboxane A_2 may be of more physiological and pathological importance[2] than the more classical prostanoids prostaglandin E_2 and prostaglandin $F_{2\alpha}$. They have directly opposing pharmacological actions in many systems, such as on platelet function, vascular smooth muscle, bronchopulmonary function, and gastrointestinal integrity. Thus prostanoid-mediated control of cellular and tissue function may reflect an interactive modulation between prostacyclin and thromboxane A_2 with imbalance resulting in dysfunction, for example in platelet and vascular disorders. Thromboxane A_2 has both bronchoconstrictor and pulmonary irritant actions and has brought about marked changes in respiratory function in experimental models; prostacyclin may oppose these effects on both the pulmonary vasculature and bronchial smooth muscle. Thromboxane A_2 has induced marked renal vasoconstriction *in vitro* whereas renal vasodilatation and stimulation of the release of renin has followed the administration of epoprostenol [exogenous prostacyclin] in *animals*. In contrast to the pro-ulcerogenic actions of thromboxane A_2, epoprostenol and its analogues, like other prostaglandins, have potent gastrointestinal anti-ulcer properties which can be disassociated from their gastric antisecretory properties. The term 'cytoprotection' has been used to describe this ability of exogenous prostaglandins to prevent gastrointestinal damage; endogenous prostaglandins might have a similar protective role. Epoprostenol also has a cytoprotective effect against experimental damage in the gastric mucosa, myocardium, and liver whereas thromboxane A_2 has a cytolytic effect.

1. Vane JR, Botting RM. Pharmacodynamic profile of prostacyclin. *Am J Cardiol* 1995; **75**: 3A–10A.
2. Whittle BJR, Moncada S. Pharmacological interactions between prostacyclin and thromboxanes. *Br Med Bull* 1983; **39**: 232–8.

Acute respiratory distress syndrome. Encouraging results[1-3] have been seen with inhaled epoprostenol in the treatment of acute respiratory distress syndrome (p. 1599.3).

1. Walmrath D, *et al.* Aerosolised prostacyclin in adult respiratory distress syndrome. *Lancet* 1993; **342**: 961–2.
2. Walmrath D, *et al.* Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1996; **153**: 991–6.
3. van Heerden PV, *et al.* Dose-response to inhaled aerosolized prostacyclin for hypoxemia due to ARDS. *Chest* 2000; **117**: 819–27.

Administration in children. Although epoprostenol is not licensed for the treatment of children, it has been used successfully in children with pulmonary hypertension[1,2] and in neonates with persistent pulmonary hypertension of the newborn.[3] It is usually given by continuous intravenous infusion, but in neonates the inhaled[4] and endotracheal[5] routes have also been used.

For children aged 1 month to 18 years with *idiopathic pulmonary arterial hypertension*, the *BNFC* suggests that epoprostenol may be given by continuous intravenous infusion in an initial dose of 2 nanograms/kg per minute, increasing as necessary to 40 nanograms/kg per minute. Children on prolonged treatment can become tolerant to epoprostenol and higher doses have been used.[1,2]

For neonates with *persistent pulmonary hypertension of the newborn*, the *BNFC* suggests that epoprostenol may be given by continuous intravenous infusion in an initial dose of 2 nanograms/kg per minute, adjusted according to response up to a usual maximum of 20 nanograms/kg per minute (rarely up to 40 nanograms/kg per minute).

1. Barst RJ, *et al.* Vasodilator therapy for primary pulmonary hypertension in children. *Circulation* 1999; **99**: 1197–1208.
2. Lammers AE, *et al.* Epoprostenol treatment in children with severe pulmonary hypertension. *Heart* 2007; **93**: 739–43.
3. Ersonen M, *et al.* Prostacyclin treatment for persistent pulmonary hypertension of the newborn. *Pediatr Cardiol* 1997; **18**: 3–7.
4. Kelly LK, *et al.* Inhaled prostacyclin for term infants with persistent pulmonary hypertension refractory to inhaled nitric oxide. *J Pediatr* 2002; **141**: 830–2.
5. De Jaegere APMC, van den Anker JN. Endotracheal instillation of prostacyclin in preterm infants with persistent pulmonary hypertension. *Eur Respir J* 1998; **12**: 932–4.

Heart failure. Epoprostenol has been investigated for the treatment of heart failure but development was abandoned due to an increase in mortality associated with long-term use.[1,2]

1. Phillips BB, Gandhi AJ. Epoprostenol in the treatment of congestive heart failure. *Am J Health-Syst Pharm* 1997; **54**: 2613–15.
2. Califf RM, *et al.* A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). *Am Heart J* 1997; **134**: 44–54.

Peripheral vascular disease. Various prostaglandins including epoprostenol have been used for their vasodilating effect in the treatment of peripheral vascular disorders (p. 1272.3), although their role remains unclear. They may be of benefit in severe Raynaud's syndrome (see Vasospastic Arterial Disorders, p. 1275.3) that is complicated by ulceration and gangrene.

References.

1. Szczeklik A, *et al.* Successful therapy of advanced arteriosclerosis obliterans with prostacyclin. *Lancet* 1979; **i**: 1111–14.
2. Belch JJF, *et al.* Intermittent epoprostenol (prostacyclin) infusion in patients with Raynaud's syndrome: a double-blind controlled trial. *Lancet* 1983; **i**: 313–15.
3. Belch JJF, *et al.* Epoprostenol (prostacyclin) and severe arterial disease: a double-blind trial. *Lancet* 1983; **i**: 315–17.
4. De San Lazaro C, *et al.* Prostacyclin in severe peripheral vascular disease. *Arch Dis Child* 1985; **60**: 370–84.
5. Leaker B, *et al.* Treatment of acute renal failure, symmetrical peripheral gangrene, and septicaemia with plasma exchange and epoprostenol. *Lancet* 1987; **i**: 156.
6. Negus D, *et al.* Intra-arterial prostacyclin compared to Praxilene in the management of severe lower limb ischaemia: a double-blind trial. *J Cardiovasc Surg* 1987; **28**: 196–9.
7. Kingma K, *et al.* Double-blind, placebo-controlled study of intravenous prostacyclin on hemodynamics in severe Raynaud's phenomenon: the acute vasodilatory effect is not sustained. *J Cardiovasc Pharmacol* 1995; **26**: 388–93.
8. Denton CP. Black CM. Raynaud's phenomenon and scleroderma. In: Snaith ML, ed. *ABC of rheumatology*. 3rd ed. London: BMJ Publishing Group, 2004: 87–91.

Pulmonary hypertension. Epoprostenol was originally introduced into the management of end-stage pulmonary hypertension (p. 1278.2) to sustain patients long enough for them to have heart-lung transplantation. There is good evidence of short-term benefit from intravenous use.[1] However, long-term therapy may also have a role as an alternative to transplantation; sustained clinical improvement and improved survival have been reported[2-5] in some patients with idiopathic pulmonary arterial hypertension given long-term intravenous therapy using portable infusion pumps, as well as in patients with pulmonary arterial hypertension associated with other diseases.[5-8] It has been combined with sildenafil.[9]

Inhaled epoprostenol, a route that may overcome some of the adverse effects associated with parenteral use, has had some success in adults[1,10-12] with pulmonary hypertension and in neonates[13,14] with persistent pulmonary hypertension.

1. Paramothayan NS, *et al.* Prostacyclin for pulmonary hypertension in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 08/03/10).
2. Higenbottam T, *et al.* Long term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension. *Heart* 1998; **80**: 151–5.
3. Herner SJ, Mauro LS. Epoprostenol in primary pulmonary hypertension. *Ann Pharmacother* 1999; **33**: 340–7.
4. McLaughlin VV, *et al.* Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002; **106**: 1477–82.
5. Kuhn KP, *et al.* Outcome in 91 consecutive patients with pulmonary arterial hypertension receiving epoprostenol. *Am J Respir Crit Care Med* 2003; **167**: 580–6.
6. McLaughlin VV, *et al.* Compassionate use of continuous prostacyclin in the management of secondary pulmonary hypertension: a case series. *Ann Intern Med* 1999; **130**: 740–3.
7. Badesch DB, *et al.* Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease: a randomized, controlled trial. *Ann Intern Med* 2000; **132**: 425–34.
8. Fisher KA, *et al.* Sarcoidosis-associated pulmonary hypertension: outcome with long-term epoprostenol treatment. *Chest* 2006; **130**: 1481–8.
9. Simonneau G, *et al.* PACES Study Group. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008; **149**: 521–30. Corrections. *ibid.* 2009; **150**: 63 and151: 435.
10. Olschewski H, *et al.* Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. *Ann Intern Med* 1996; **124**: 820–4.
11. Mikhail G, *et al.* An evaluation of nebulized prostacyclin in patients with primary and secondary pulmonary hypertension. *Eur Heart J* 1997; **18**: 1499–1504.
12. Buckley MS, Feldman JP. Inhaled epoprostenol for the treatment of pulmonary arterial hypertension in critically ill adults. *Pharmacotherapy* 2010; **30**: 728–40.
13. Bindl L, *et al.* Aerosolised prostacyclin for pulmonary hypertension in neonates. *Arch Dis Child Fetal Neonatal Ed* 1994; **71**: F214–F216.
14. Kelly LK, *et al.* Inhaled prostacyclin for term infants with persistent pulmonary hypertension refractory to inhaled nitric oxide. *J Pediatr* 2002; **141**: 830–2.

Stroke. Results with epoprostenol in patients with acute stroke have been inconclusive and a systematic review of randomised studies concluded that too few patients had been studied for the effect of epoprostenol on survival to be determined.[1]

1. Bath PMW. Prostacyclin and analogues for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 04/07/05).

Thrombotic microangiopathies. Platelet aggregation has a major role in the pathogenesis of thrombotic thrombocytopenic purpura and the related disorder, haemolytic-uraemic syndrome (p. 1159.1). Prostacyclin deficiency has been found in both conditions, but case reports of epoprostenol[1,2] or iloprost[3,4] treatment have indicated variable results.

1. Bobbio-Pallavicini E, *et al.* Intravenous prostacyclin (as epoprostenol) infusion in thrombotic thrombocytopenic purpura: four case reports and review of the literature. *Haematologica* 1994; **79**: 429–37.
2. Series C, *et al.* Interet de la prostacycline dans le traitement du syndrome hémolytique et urémique: à propos d'un cas. *Rev Med Interne* 1996; **17**: 76–8.
3. Sagripanti A, *et al.* Iloprost in the treatment of thrombotic microangiopathy: report of thirteen cases. *Biomed Pharmacother* 1996; **50**: 350–6.
4. Salvi F, *et al.* Unsuccessful treatment of resistant thrombotic thrombocytopenic purpura with prostacyclin. *Haematologica* 2000; **85**: 1329–30.

Adverse Effects and Precautions

The incidence of adverse reactions to epoprostenol is dose-related. Adverse effects during intravenous infusion

commonly include hypotension, increased heart rate, flushing, and headache. Dosage should be reduced or the epoprostenol infusion stopped if excessive hypotension occurs. Bradycardia with pallor, sweating, nausea, and abdominal discomfort may occur. Erythema over the intravenous infusion site has been noted. Other adverse effects reported have included nausea and vomiting, diarrhoea, jaw pain or non-specific musculoskeletal pain, anxiety, nervousness, tremor, flu-like symptoms, hyperglycaemia, drowsiness, and chest pain.

Epoprostenol is a potent inhibitor of platelet aggregation and should be used with caution in patients at risk of bleeding. Coagulation of blood in the dialysis circuit has been reported rarely in patients given epoprostenol but no conventional anticoagulant. The use of epoprostenol for pulmonary hypertension is contra-indicated in patients with congestive heart failure due to severe left ventricular systolic dysfunction, and in patients who develop pulmonary oedema during dose-ranging. Sudden withdrawal of epoprostenol should be avoided because of the risk of rebound pulmonary hypertension. Haematological and cardiovascular monitoring is required in patients receiving epoprostenol infusions. Care should be taken to avoid extravasation.

Incidence of adverse effects. A study in 24 healthy subjects investigated the incidence of adverse effects with intravenous infusions of epoprostenol of up to 10 nanograms/kg per minute for up to 100 minutes.[1] Subjects varied in their susceptibility to epoprostenol but the same sequence of events was usually present. A change in pre-ejection period and facial flushing was often apparent at an infusion rate of 2 to 2.5 nanograms/kg per minute. A rise in heart rate and change in other cardiovascular variables was present when the infusion rate had increased to 4 to 5 nanograms/kg per minute; headache, generally the dose-limiting factor, was usually present at this dose and increased as the dose was raised, as did the other effects. Erythema over the vein and 'vagal reflex' only appeared after at least 1 hour of infusion; 'vagal reflex' took only a few seconds to develop.

Early studies showing that high doses were well tolerated had been conducted using a form of epoprostenol probably only half as potent as the commercially available product. It was proposed that 4 nanograms/kg per minute should in general be the maximum infusion rate for prolonged infusions, although higher rates could be tolerated in anaesthetised patients. Careful attention to infusion technique is necessary and monitoring of the heart rate is advisable in view of the suddenness with which the 'vagal reflex' can occur. Most of the adverse effects reported here have responded to a reduction in dosage.

1. Pickles H, O'Grady J. Side effects occurring during administration of epoprostenol (prostacyclin, PGI_2), in man. *Br J Clin Pharmacol* 1982; 14: 177–85.

Effects on the blood. Reports of rebound platelet activation during continuous epoprostenol infusion.[1,2]

1. Yardumian DA, Machin SJ. Altered platelet function in patients on continuous infusion of epoprostenol. *Lancet* 1984; i: 1357.
2. Sinzinger H, *et al.* Rebound platelet activation during continuous epoprostenol infusion. *Lancet* 1984; ii: 759.

Effects on the cardiovascular system. Evidence that epoprostenol and its analogue iloprost can induce myocardial ischaemia in patients with coronary artery disease.[1]

1. Bugiardini R, *et al.* Myocardial ischemia induced by prostacyclin and Iloprost. *Clin Pharmacol Ther* 1985; 38: 101–8.

Effects on mental state. Symptoms of depression were associated with intravenous epoprostenol therapy in 4 patients.[1]

1. Ansell D, *et al.* Depression and prostacyclin infusion. *Lancet* 1986; ii: 509.

Hypersensitivity. Severe erythroderma occurred in a woman with undifferentiated connective tissue disease who was treated with epoprostenol for pulmonary hypertension.[1] Diffuse erythema, pruritus, and scaling, with chills, nausea, vomiting, and diarrhoea, developed about 2 months after starting therapy, and resolved with epoprostenol withdrawal and corticosteroid treatment.

1. Ahearn GS, *et al.* Severe erythroderma as a complication of continuous epoprostenol therapy. *Chest* 2002; 122: 378–80.

Interactions

Since epoprostenol is a potent vasodilator and inhibitor of platelet aggregation, care should be taken in patients receiving other vasodilators or anticoagulants. Epoprostenol may slightly increase serum concentrations of digoxin, and may reduce the thrombolytic effect of alteplase by increasing its hepatic clearance. The hypotensive effects of epoprostenol may be exacerbated by using acetate in dialysis fluids.

Anticoagulants. The incidence of bleeding complications was examined in a retrospective review[1] of 31 patients with pulmonary arterial hypertension who had been treated with continuous intravenous epoprostenol and oral *warfarin*. Nine patients developed 11 bleeding episodes, including 9 episodes of alveolar haemorrhage. The international normalised ratio (INR) was maintained in the therapeutic range for 8 of these patients, suggesting that the effect was not caused by overdose of warfarin. The risk of bleeding appeared to be increased in patients who received high-dose epoprostenol (mean dose 89 nanograms/kg per minute).

1. Ogawa A, *et al.* Risk of alveolar hemorrhage in patients with primary pulmonary hypertension—anticoagulation and epoprostenol therapy. *Circ J* 2005; 69: 216–20.

Pharmacokinetics

Endogenous prostacyclin is a product of arachidonic acid metabolism with a very short half-life. On intravenous infusion epoprostenol is hydrolysed rapidly to the more stable but much less active 6-keto-prostaglandin $F_{1\alpha}$ (6-oxo-prostaglandin $F_{1\alpha}$). A second metabolite, 6,15-diketo-13,14-dihydro-prostaglandin $F_{1\alpha}$, is formed by enzymatic degradation. Unlike many other prostaglandins, epoprostenol is not inactivated in the pulmonary circulation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Flolan; ***Belg.***: Flolan; ***Canad.***: Flolan; ***Cz.***: Flolan; ***Denm.***: Flolan; ***Fr.***: Flolan; ***Gr.***: Flolan; ***Irl.***: Flolan; ***Israel***: Flolan; ***Ital.***: Flolan; ***Neth.***: Flolan; ***Norw.***: Flolan; ***Singapore***: Flolan; ***Spain***: Dynovase; Flolan; ***Switz.***: Flolan; Veletri; ***UK***: Flolan; Veletri; ***USA***: Flolan; Veletri.

Eprosartan Mesilate *(BANM, rINNM)*

Eprosartan, Mésilate d'; Eprosartán, mesilato de; Eprosartan Mesylate (USAN); Eprosartani Mesilas; Mesilato de eprosartán; SKF-108566-J; Эпросартана Мезилат.

(*E*)-2-Butyl-1-(*p*-carboxybenzyl)-α-2-thenylimidazole-5-acrylic acid methanesulfonate.

$C_{23}H_{24}N_2O_4S,CH_4O_3S$=520.6

CAS — 133040-01-4 (eprosartan); 144143-96-4 (eprosartan mesilate).

ATC — C09CA02.

ATC Vet — QC09CA02.

UNII — 8N2L1NX8S3.

Uses and Administration

Eprosartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p. 1422.2). It is used in the management of hypertension (p. 1251.1).

Eprosartan is given orally as the mesilate but doses are expressed in terms of the base; eprosartan mesilate 1.2 mg is equivalent to about 1 mg of eprosartan. The onset of antihypertensive effect occurs about 1 to 2 hours after a dose and the maximum effect is achieved within 2 to 3 weeks of starting therapy.

In the management of hypertension, eprosartan is given in an initial dose of 600 mg once daily. The dose should be adjusted according to response; the usual maintenance dose is 400 to 800 mg daily in a single dose or in two divided doses. For advice on dose adjustments in patients with renal impairment, see below.

Reviews.

1. McClellan KJ, Balfour JA. Eprosartan. *Drugs* 1998; 55: 713–18.
2. Robins GW, Scott LJ. Eprosartan: a review of its use in the management of hypertension. *Drugs* 2005; 65: 2355–77.
3. Ram CV, Rudmann MA. Unique dual mechanism of action of eprosartan: effects on systolic blood pressure, pulse pressure, risk of stroke and cognitive decline. *Expert Rev Cardiovasc Ther* 2007; 5: 1003–11.
4. Blankestijn PJ, Rupp H. Clinical profile of eprosartan: a different angiotensin II receptor blocker. *Cardiovasc Hematol Agents Med Chem* 2008; 6: 253–7.
5. Plosker GL. Eprosartan: a review of its use in hypertension. *Drugs* 2009; 69: 2477–99.
6. Xu FY, *et al.* Antihypertensive effects and safety of eprosartan: a meta-analysis of randomized controlled trials. *Eur J Clin Pharmacol* 2012; 68: 195–205.

Administration in renal impairment. In patients with moderate or severe renal impairment (creatinine clearance < 60 mL/minute), the maximum daily oral dose of eprosartan should not exceed 600 mg.

Adverse Effects and Precautions

As for Losartan Potassium, p. 1424.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies eprosartan as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

As for Losartan Potassium, p. 1424.3.

Pharmacokinetics

Eprosartan is absorbed from the gastrointestinal tract with an absolute oral bioavailability of about 13%. Peak plasma concentrations occur about 1 to 2 hours after an oral dose in the fasted state; giving doses with food delays absorption but this is not clinically significant. Eprosartan is about 98% bound to plasma proteins. It is excreted in the bile and in the urine, mainly as the unchanged drug; after oral doses about 7% of the drug is excreted in the urine, with about 2% as the acyl glucuronide. The terminal elimination half-life is about 5 to 9 hours.

References.

1. Martin DE, *et al.* Pharmacokinetics and protein binding of eprosartan in healthy volunteers and in patients with varying degrees of renal impairment. *J Clin Pharmacol* 1998; 38: 129–37.
2. Tenero DM, *et al.* Effect of age and gender on the pharmacokinetics of eprosartan. *Br J Clin Pharmacol* 1998; 46: 267–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Teveten; ***Austria***: Teveten; ***Belg.***: Teveten; ***Canad.***: Teveten; ***China***: Teveten (泰格欣); ***Cz.***: Teveten; ***Denm.***: Teveten†; Tevetenz†; ***Fin.***: Teveten; ***Fr.***: Teveten; ***Ger.***: Emestar Mono†; Teveten; ***Gr.***: Epratenz; Teveten; ***Hong Kong***: Teveten; ***Hung.***: Teveten; ***Indon.***: Teveten; ***Irl.***: Teveten; ***Ital.***: Teveten; ***Mex.***: Teveten; ***Neth.***: Teveten; ***Norw.***: Teveten; ***NZ***: Teveten; ***Philipp.***: Teveten; ***Pol.***: Teveten; ***Port.***: Larutan†; Teveten; ***Rus.***: Naviten (Навитен); Teveten (Теветен); ***S.Afr.***: Teveten; ***Spain***: Futuran; Navixen; Regulaten; Tevetens; ***Swed.***: Teveten; ***Switz.***: Eprotan; Teveten; ***Thai.***: Teveten†; ***Turk.***: Teveten; ***UK***: Teveten; ***Ukr.***: Teveten (Теветен); ***USA***: Teveten.

Multi-ingredient Preparations. ***Austral.***: Teveten Plus; ***Austria***: Coepratenz Plus; Teveten Plus; ***Belg.***: Teveten Plus; ***Canad.***: Teveten Plus; ***Cz.***: Teveten Plus H; ***Denm.***: Teveten Comp; ***Fin.***: Coepratenz Comp†; Teveten Comp; ***Fr.***: Coteveten†; ***Ger.***: Emestar plus; Eprosartan comp; Teveten Plus; ***Gr.***: Epratenz Plus; Teveten Plus; ***Hong Kong***: Teveten Plus; ***Irl.***: Coepratenz Plus; Teveten Plus; ***Ital.***: Tartan; ***Mex.***: Tevetenz Dox; ***Neth.***: Teveten Plus; ***Norw.***: Teveten Comp; ***Philipp.***: Teveten Plus; ***Port.***: Medinor†; Tensival†; Teveten Plus; ***Rus.***: Teveten Plus (Тевентен Плюс); ***S.Afr.***: Teveten Plus; ***Spain***: Futuran Plus; Navixen Plus; Regulaten Plus; Tevetens Plus; ***Swed.***: Teveten Comp; ***Switz.***: Eprotan Plus; Teveten Plus; ***Turk.***: Teveten Plus; ***USA***: Teveten HCT.

Eptifibatide *(BAN, rINN)*

C68-22; Eptifibatid; Eptifibatida; Eptifibatidi; Eptifibatidum; Integrelin; Intrifiban; SB-1; Sch-60936; Эптифибатид.

N^6-Amidino-N^2-(3-mercaptopropionyl)-L-lysylglycyl-L-α-aspartyl-L-tryptophyl-L-prolyl-L-cysteinamide, cyclic (1→6)-disulfide; $3^1,5^6$-Cyclo[N^6-carbamimidoyl-N^2-(3-sulfanylpropanoyl)-L-lysylglycyl-L-α-aspartyl-L-tryptophyl-L-prolyl-L-cysteinamide].

$C_{35}H_{49}N_{11}O_9S_2$=832.0

CAS — 148031-34-9; 157630-07-4.

ATC — B01AC16.

ATC Vet — QB01AC16.

UNII — NA8320J834.

Uses and Administration

Eptifibatide is an antiplatelet drug that reversibly inhibits binding of fibrinogen, von Willebrand factor, and other adhesive molecules to the glycoprotein IIb/IIIa receptor of platelets. It is used, usually with aspirin and heparin, in the management of unstable angina and in patients undergoing coronary angioplasty and stenting procedures.

In the management of **unstable angina**, eptifibatide is given in an initial dose of 180 micrograms/kg by intravenous injection, followed by 2 micrograms/kg per minute by intravenous infusion, for up to 72 hours. If percutaneous coronary intervention is performed during eptifibatide therapy, the infusion should be continued for 18 to 24 hours after the procedure, to a maximum total duration of 96 hours of therapy.

In patients undergoing **angioplasty**, though not presenting with unstable angina, eptifibatide is given in an initial dose of 180 micrograms/kg by intravenous injection immediately before the procedure, followed by 2 micrograms/kg per minute by intravenous infusion, with a second 180 micrograms/kg intravenous injection given 10 minutes after the first. The infusion should be continued until hospital discharge or for up to 18 to 24 hours; a minimum of 12 hours is recommended.

The dose of eptifibatide may need to be reduced in patients with renal impairment (see p. 1377.1).

General references.
1. Gilchrist IC. Platelet glycoprotein IIb/IIIa inhibitors in percutaneous coronary intervention: focus on the pharmacokinetic-pharmacodynamic relationships of eptifibatide. *Clin Pharmacokinet* 2003; 42: 703–20.
2. Curran MP, Keating GM. Eptifibatide: a review of its use in patients with acute coronary syndromes and/or undergoing percutaneous coronary intervention. *Drugs* 2005; 65: 2009–35.
3. Tricoci P, *et al.* Present and evolving role of eptifibatide in the treatment of acute coronary syndromes. *Expert Rev Cardiovasc Ther* 2007; 5: 401–12.
4. Zeymer U. The role of eptifibatide in patients undergoing percutaneous coronary intervention. *Expert Opin Pharmacother* 2007; 8: 1147–54.
5. Zeymer U, Wienbergen H. A review of clinical trials with eptifibatide in cardiology. *Cardiovasc Drug Rev* 2007; 25: 301–15.

Administration in renal impairment. The clearance of eptifibatide is reduced in renal impairment and plasma-eptifibatide concentrations are about doubled in patients with a creatinine clearance (CC) below 50 mL/minute.[1] Eptifibatide should not be used in severe renal impairment; it is contra-indicated in patients with CC below 30 mL/minute in the UK, and in dialysis-dependent patients in the USA. In patients with moderate renal impairment (CC below 50 mL/minute), the same bolus doses may be given as in those with normal renal function but the infusion dose should be reduced to 1 microgram/kg per minute.

1. Gretler DD, *et al.* Pharmacokinetic and pharmacodynamic properties of eptifibatide in subjects with normal or impaired renal function. *Clin Ther* 2004; 26: 390–398.

Ischaemic heart disease. Patients with acute coronary syndromes may be treated either medically or with percutaneous coronary interventions such as angioplasty or stenting. In patients with *unstable angina* (p. 1254.3), eptifibatide has been used as an adjunct to both medical and interventional therapy. In the PURSUIT study,[1] which compared eptifibatide with placebo in over 10 000 patients with ischaemic chest pain, the incidence of death and non-fatal myocardial infarction up to 30 days after treatment was reduced in those receiving eptifibatide; most patients also received aspirin and heparin and the number of percutaneous interventions was similar in each group. The optimal timing of such use has, however, yet to be determined. The EARLY ACS study[2] found no advantage from early use of eptifibatide before angiography in patients with acute coronary syndromes without ST-segment elevation, compared with provisional use after angiography.

Eptifibatide has also been of benefit as an adjunct to standard therapy in patients undergoing *elective percutaneous interventions* (see Reperfusion and Revascularisation Procedures, p. 1259.2). In the IMPACT-II study[3] of over 4000 patients undergoing elective or emergency percutaneous coronary revascularisation, the incidence of death, myocardial infarction, and further unplanned coronary intervention was reduced in those receiving eptifibatide compared with placebo. Similar results were also obtained in a further study (ESPRIT)[4] in patients who were undergoing percutaneous coronary revascularisation with stent implantation, and benefit was maintained at 6-month follow-up.[5] Although most studies have given eptifibatide with unfractionated heparin, use with low-molecular-weight heparin also appears to be safe.[6]

In patients with *acute myocardial infarction* (p. 1257.1), eptifibatide has been tried as an adjunct to thrombolysis or percutaneous intervention. In a study (INTRO AMI)[7] comparing eptifibatide and thrombolysis with thrombolysis alone, early patency rates were improved in those receiving eptifibatide but there was no significant difference in outcomes at 30 days. In patients undergoing interventional therapy, an observational study[8] found that eptifibatide was less effective than abciximab, but other studies[9,10] have reported similar outcomes in patients treated with abciximab or eptifibatide. Positive results have also been seen[11] with eptifibatide given in addition to thrombolytics before percutaneous intervention.

There have been reports of successful intracoronary use[12,13] of eptifibatide, and also prolonged intravenous use[14] in a patient unable to take oral antiplatelet drugs. It has also been used as bridging therapy to prevent stent thrombosis in patients with coronary stents who subsequently require coronary artery bypass grafts (in whom clopidogrel must therefore be stopped several days before surgery to prevent excess bleeding).[15]

1. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998; 339: 436–43.
2. Giugliano RP, *et al.* Early versus delayed, provisional eptifibatide in acute coronary syndromes. *N Engl J Med* 2009; 360: 2176–90.
3. The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. *Lancet* 1997; 349: 1422–8.
4. The ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet* 2000; 356: 2037–44. Correction. *ibid.* 2001; 357: 1370.
5. O'Shea JC, *et al.* Platelet glycoprotein IIb/IIIa integrin blockade with eptifibatide in coronary stent intervention: the ESPRIT Trial: a randomized controlled trial. *JAMA* 2001; 285: 2468–73.
6. Bhatt DL, *et al.* Safety of concomitant therapy with eptifibatide and enoxaparin in patients undergoing percutaneous coronary intervention: results of the Coronary Revascularization Using Integrilin and Single bolus Enoxaparin Study. *J Am Coll Cardiol* 2003; 41: 20–5.
7. Brener SJ, *et al.* Eptifibatide and low-dose tissue plasminogen activator in acute myocardial infarction: the integrilin and low-dose thrombolysis in acute myocardial infarction (INTRO AMI) trial. *J Am Coll Cardiol* 2002; 39: 377–86.
8. Deliargyris EN, *et al.* Superior in-hospital and 30-day outcomes with abciximab versus eptifibatide: a contemporary analysis of 495 consecutive percutaneous coronary interventions. *J Invasive Cardiol* 2004; 16: 611–16.
9. Suleiman M, *et al.* Comparison of two platelet glycoprotein IIb/IIIa inhibitors, eptifibatide and abciximab: outcomes, complications and thrombocytopenia during percutaneous coronary intervention. *J Invasive Cardiol* 2003; 15: 319–23.
10. Raveendran G, *et al.* Eptifibatide vs abciximab as adjunctive therapy during primary percutaneous coronary intervention for acute myocardial infarction. *Mayo Clin Proc* 2007; 82: 196–202.
11. ADVANCE MI Investigators. Facilitated percutaneous coronary intervention for acute ST-segment elevation myocardial infarction: results from the prematurely terminated ADdressing the Value of facilitated ANgioplasty after Combination therapy or Eptifibatide monotherapy in acute Myocardial Infarction (ADVANCE MI) trial. *Am Heart J* 2005; 150: 116–22. Correction. *ibid.*: 391.
12. Deibele AJ, *et al.* Intracoronary bolus administration of eptifibatide during percutaneous coronary stenting for non ST elevation myocardial infarction and unstable angina. *J Thromb Thrombolysis* 2006; 22: 47–50.
13. Deibele AJ, *et al.* Intracoronary eptifibatide bolus administration during percutaneous coronary revascularization for acute coronary syndromes with evaluation of platelet glycoprotein IIb/IIIa receptor occupancy and platelet function: the Intracoronary Eptifibatide (ICE) Trial. *Circulation* 2010; 121: 784–91.
14. Jaffe R, *et al.* Prolonged intravenous eptifibatide infusion for prevention of coronary stent thrombosis. *Int J Cardiol* 2007; 114: 409–11.
15. Pickett AM, *et al.* Prolonged infusion of eptifibatide as bridge therapy between bare-metal stent insertion and cardiovascular surgery: case report and review of the literature. *Pharmacotherapy* 2010; 30: 127e–133e.

Adverse Effects

Bleeding is the most common adverse effect of eptifibatide. Hypotension has been reported. Antibodies to eptifibatide have not been detected.

Effects on the blood. Thrombocytopenia is an established adverse effect of the glycoprotein IIb/IIIa-receptor antagonist abciximab (see p. 1281.3) but appears to be less common with eptifibatide. However, there have been several reports[1–6] of severe thrombocytopenia associated with eptifibatide.

1. Paradiso-Hardy FL, *et al.* Severe thrombocytopenia possibly related to readministration of eptifibatide. *Catheter Cardiovasc Interv* 2001; 54: 63–7.
2. Hongo RH, Brent BN. Association of eptifibatide and acute profound thrombocytopenia. *Am J Cardiol* 2001; 88: 428–31.
3. Yoder M, Edwards RF. Reversible thrombocytopenia associated with eptifibatide. *Ann Pharmacother* 2002; 36: 628–30.
4. Coons JC, *et al.* Eptifibatide-associated acute, profound thrombocytopenia. *Ann Pharmacother* 2005; 39: 368–72.
5. Refaat M, *et al.* Eptifibatide-induced thrombocytopenia. *J Thromb Thrombolysis* 2008; 25: 204–6.
6. Russell KN, *et al.* Acute profound thrombocytopenia associated with readministration of eptifibatide: case report and review of the literature. *Pharmacotherapy* 2009; 29: 867–74.

Precautions

As for Abciximab, p. 1282.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies eptifibatide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Pharmacokinetics

Antiplatelet effects of eptifibatide persist for about 4 hours after stopping a continuous infusion. Plasma elimination half-life is about 2.5 hours. Eptifibatide is about 25% bound to plasma proteins. Renal clearance, as eptifibatide and metabolites excreted in the urine, accounts for about 50% of total body clearance.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Integrilin; *Austria*: Integrilin; *Belg.*: Integrilin; *Canad.*: Integrilin; *Cz.*: Integrilin; *Denm.*: Integrilin; *Fin.*: Integrilin; *Fr.*: Integrilin; *Ger.*: Integrilin; *Gr.*: Integrilin; *Hong Kong*: Integrilin; *Hung.*: Integrilin; *India*: Antigrilin; Clotide; Coromax; Eptifab; Fleta Bolus; *Indon.*: Integrilin; *Irl.*: Integrilin; *Israel*: Integrilin; *Ital.*: Integrilin; *Malaysia*: Integrilin; *Neth.*: Integrilin; *Norw.*: Integrilin; *NZ*: Integrilin; *Philipp.*: Integrilin†; *Pol.*: Integrilin; *Port.*: Integrilin; *Rus.*: Integrilin (Интегрилин); *S.Afr.*: Integrilin; *Singapore*: Integrilin; *Spain*: Integrilin; *Swed.*: Integrilin; *Switz.*: Integrilin; *Thai.*: Integrilin; *UK*: Integrilin; *Ukr.*: Integrilin (Интегрилин); *USA*: Integrilin.

Esatenolol (*rINN*) ⊗

(-)-Atenolol; S-Atenolol; Esatenololum; Эзатенолол.

2-{*p*-[(2*S*)-2-Hydroxy-3-(isopropylamino)propoxy]phenyl} acetamide.

$C_{14}H_{22}N_2O_3$=266.3

CAS — 93379-54-5.

ATC — C07AB11.

ATC Vet — QC07AB11.

UNII — DPF7578QSR.

Profile

Esatenolol, the *S* (-)-isomer of atenolol, has been used similarly to atenolol (p. 1308.2) in the treatment of cardiovascular disorders in usual oral doses of 25 to 100 mg daily.

References.
1. McCoy RA, *et al.* Pharmacodynamics of racemic and S(-)-atenolol in humans. *J Clin Pharmacol* 1994; 34: 816–22.
2. Clementi WA, *et al.* Single dose pharmacokinetics of (S)-atenolol administered orally as a single enantiomer formulation and as a racemic mixture (Tenormin). *Chirality* 1994; 6: 169–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Adbeta; Atpure; *Thai.*: Esmolol; *Ukr.*: Asoten (Азотен)†.

Multi-ingredient Preparations. *India*: Adbeta-H.

Esmolol Hydrochloride

(*BANM, USAN, rINNM*) ⊗

ASL-8052; Esmolol, Chlorhydrate d'; Esmolol, hidrocloruro de; Esmolol Hidroklorür; Esmololi Hydrochloridum; Hidrocloruro de esmolol; Эсмолола Гидрохлорид.

Methyl 3-[4-(2-hydroxy-3-isopropylaminopropoxy)phenyl] propionate hydrochloride.

$C_{16}H_{25}NO_4$,HCl=331.8

CAS — 81147-92-4 (esmolol); 84057-94-3 (esmolol); 103598-03-4 (esmolol); 81161-17-3 (esmolol hydrochloride).

ATC — C07AB09.

ATC Vet — QC07AB09.

UNII — V05260LC8D.

Pharmacopoeias. In *US.*

USP 36: (Esmolol Hydrochloride). A white to off-white crystalline powder. Very soluble in water; freely soluble in alcohol. pH 3.0 to 5.0. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Do not allow to freeze.

Incompatibility. Licensed product information advises against mixing esmolol hydrochloride with sodium bicarbonate because of incompatibility. There has also been a report[1] of immediate haze formation after admixture of esmolol hydrochloride with warfarin sodium.

1. Bahal SM, *et al.* Visual compatibility of warfarin sodium injection with selected medications and solutions. *Am J Health-Syst Pharm* 1997; 54: 2599–2600.

Uses and Administration

Esmolol is a cardioselective short-acting beta blocker (p. 1316.3). It is reported to be lacking in intrinsic sympathomimetic and membrane-stabilising properties.

Esmolol is used as the hydrochloride in the management of supraventricular arrhythmias (p. 1266.1). It is also used for the control of hypertension (p. 1251.1) and tachycardia during the perioperative period.

Esmolol hydrochloride is given intravenously at a concentration usually not exceeding 10 mg/mL.

For the rapid temporary control of ventricular rate in patients with **supraventricular arrhythmias**, a loading dose of 500 micrograms/kg given over 1 minute is followed by an initial maintenance infusion of 50 micrograms/kg per minute for 4 minutes. If the response is satisfactory this maintenance infusion should be continued at 50 micrograms/kg per minute. If a suitable response is not obtained within the first 5 minutes a further loading dose of 500 micrograms/kg over 1 minute may be given and the maintenance infusion may be increased to 100 micrograms/kg per minute for 4 minutes. If necessary, this procedure may be repeated once or twice more, until a satisfactory response is obtained, increasing the maintenance infusion each time by 50 micrograms/kg per minute to a maximum of 200 micrograms/kg per minute. Little additional benefit is obtained from further increases in maintenance dosage. Once a satisfactory response is obtained infusion may be continued, if necessary, for up to 48 hours.

When transferring a patient to another antiarrhythmic drug, the infusion rate of esmolol hydrochloride is reduced by 50% thirty minutes after starting the alternative drug, and may be stopped one hour after the second dose of that drug.

In the control of perioperative **hypertension** and/or **tachycardia**, esmolol hydrochloride may be given intravenously as follows:

- *during* anaesthesia, a loading dose of 80 mg over 15 to 30 seconds followed by an infusion of 150 micrograms/kg per minute, increased as necessary up to 300 micrograms/kg per minute
- on *waking* from anaesthesia, an infusion of 500 micrograms/kg per minute for 4 minutes, followed by an infusion of 300 micrograms/kg per minute as required
- *postoperatively*, a stepped dosage schedule, as described under control of supraventricular arrhythmias above, although maintenance infusions may be increased up to 300 micrograms/kg per minute as necessary.

For the use of esmolol in children, see below.

References.

1. Wiest D. Esmolol: a review of its therapeutic efficacy and pharmacokinetic characteristics. *Clin Pharmacokinet* 1995; 28: 190–202.

Administration in children. Although esmolol is unlicensed for use in children, the *BNFC* suggests that it may be given for the treatment of **cardiac arrhythmias** or **hypertensive emergencies** in those aged 1 month and over. An intravenous loading dose of 500 micrograms/kg given over 1 minute may be followed by an intravenous infusion of 50 micrograms/kg per minute for 4 minutes. (The dose may be given at a slower rate if the blood pressure or heart rate is too low.) If the response is inadequate, the loading dose may be repeated, and the maintenance infusion increased by 50 microgram/kg per minute increments, until a satisfactory response is obtained or a maximum infusion rate of 200 micrograms/kg per minute is reached.

For doses given in the treatment of **tetralogy of Fallot**, see below.

References.

1. Trippel DL, *et al.* Cardiovascular and antiarrhythmic effects of esmolol in children. *J Pediatr* 1991; 119: 142–7.
2. Wiest DB, *et al.* Esmolol for the management of pediatric hypertension after cardiac operations. *J Thorac Cardiovasc Surg* 1998; 115: 890–7.
3. Tabbutt S, *et al.* The safety, efficacy, and pharmacokinetics of esmolol for blood pressure control immediately after repair of coarctation of the aorta in infants and children: a multicenter, double-blind, randomized trial. *J Thorac Cardiovasc Surg* 2008; 136: 321–8.

Tetralogy of Fallot. Beta blockers have been used in the management of tetralogy of Fallot (see under Uses of Propranolol, p. 1479.3). The *BNFC* recommends that neonates may be given esmolol hydrochloride in an initial dose of 600 micrograms/kg by intravenous injection over 1 to 2 minutes; if necessary, this may be followed by an intravenous infusion at a dose of 300 to 900 micrograms/kg per minute.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Hypotension is the most frequently reported adverse effect associated with the infusion of esmolol hydrochloride; it generally resolves within 30 minutes once the dosage is reduced or the infusion is stopped. Local irritation at the site of infusion, inflammation, induration, and thrombophlebitis have occurred and necrosis is a hazard of extravasation. These local effects have occurred with concentrations of 20 mg/mL and it is recommended that concentrations of standard formulations should not normally exceed 10 mg/mL, particularly if given peripherally, and that the infusion should not be made into a small vein.

Effects on the CNS. Generalised tonic-clonic seizures occurred in an elderly patient given esmolol hydrochloride.[1]

1. Das G, Ferris JC. Generalized convulsions in a patient receiving ultra short-acting beta-blocker infusion. *Drug Intell Clin Pharm* 1988; 22: 484–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies esmolol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

After intravenous doses esmolol is rapidly hydrolysed by esterases in the red blood cells. Steady-state blood concentrations occur within 30 minutes with doses of 50 to 300 micrograms/kg per minute. The time to steady state may be reduced to 5 minutes by giving an appropriate loading dose. Blood concentrations decline in a biphasic manner with a distribution half-life of about 2 minutes and an elimination half-life of about 9 minutes. Esmolol has low lipid solubility and is about 55% bound to plasma proteins. It is excreted in urine, mainly as the de-esterified metabolite.

References.

1. Adamson PC, *et al.* The pharmacokinetics of esmolol in pediatric subjects with supraventricular arrhythmias. *Pediatr Cardiol* 2006; 27: 420–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dublon; *Austral.*: Brevibloc; *Austria*: Brevibloc; *Belg.*: Brevibloc; *Braz.*: Brevibloc; Esmolan; *Canad.*: Brevibloc; *China*: Ai Luo (爱络); Ao Yi Xin (奥一心); Xin Luo Ping (欣洛平); *Cz.*: Brevibloc; Esmocard; *Denm.*: Brevibloc; *Fin.*: Brevibloc; Esmocard; *Fr.*: Brevibloc; *Ger.*: Brevibloc; Esmocard; *Gr.*: Brevibloc; Esmocard; *Hong Kong*: Brevibloc; *Hung.*: Brevibloc; *India*: Cardesmo; Esmocard; Esocard; Miniblock; Neotach; *Irl.*: Brevibloc; Esmocard; *Ital.*: Brevibloc; *Neth.*: Brevibloc; *Norw.*: Brevibloc; *NZ*: Brevibloc; *Port.*: Brevibloc; Esmocard; *Rus.*: Brevibiok (Бревиблок); *S.Afr.*: Brevibloc†; *Singapore*: Brevibloc; *Spain*: Brevibloc; *Swed.*: Brevibloc; *Switz.*: Brevibloc; *Thai.*: Brevibloc; *Turk.*: Brevibloc; *UK*: Brevibloc; *USA*: Brevibloc.

Etacrynic Acid *(BAN, rINN)* ⊗

Acide étacrynique; Acide Étacrynique; Ácido etacrínico; Acidum Etacrynicum; Etacrínico, ácido; Etacrynsäure; Etakrino rūgštis; Etakrinsav; Etakrynsyra; Etakryynihappo; Ethacrynic Acid (USAN); Kwas etakrynowy; Kyselina etakrynová; MK-595; NSC-85791; Этакриновая Кислота.

[2,3-Dichloro-4-(2-ethylacryloyl)phenoxy]acetic acid; [2,3-Dichloro-4-(2-methylene-1-oxobutyl)phenoxy]acetic acid.

$C_{13}H_{12}Cl_2O_4$=303.1

CAS — 58-54-8.

ATC — C03CC01.

ATC Vet — QC03CC01.

UNII — M5DP350VZV.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Etacrynic Acid). A white or almost white, crystalline powder. Very slightly soluble in water; freely soluble in alcohol. It dissolves in ammonia and in dilute solutions of alkali hydroxides and carbonates.

USP 36: (Ethacrynic Acid). A white or practically white, odourless or practically odourless, crystalline powder. Very slightly soluble in water; soluble 1 in 1.6 of alcohol, 1 in 6 of chloroform, and 1 in 3.5 of ether. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Sodium Etacrynate *(BANM, rINNM)* ⊗

Etacrinato sódico; Étacrynate de Sodium; Etacrynate Sodium; Ethacrynate Sodium (USAN); Natril Etacrynas; Sodium Ethacrynate; Натрий Этакринат.

$C_{13}H_{11}Cl_2NaO_4$=325.1

CAS — 6500-81-8.

ATC — C03CC01.

ATC Vet — QC03CC01.

UNII — K41MYV7MPM.

Pharmacopoeias. In *Chin.*

Pol. and *US* include sodium etacrynate for injection.

Stability. Solutions in water of sodium etacrynate containing the equivalent of etacrynic acid 0.1% have a pH of 6.3 to 7.7. Solutions are relatively stable at about pH 7 at room temperatures for short periods and less stable at higher pH values and temperatures. They are incompatible with solutions with a pH below 5. The injection should be protected from light.

Uses and Administration

Although chemically unrelated, etacrynic acid is a loop diuretic with actions and uses similar to those of furosemide (p. 1387.1). Etacrynic acid is used in the treatment of oedema associated with heart failure (p. 1262.3) and with renal and hepatic disorders.

Diuresis begins within about 30 minutes after an oral dose, peaks after 2 hours, and lasts for about 6 to 8 hours; after intravenous injection of its sodium salt, the effects are evident within a few minutes.

In the treatment of **oedema**, the usual initial oral dose is 50 mg in the morning. The dose may be increased, if necessary, by 25- to 50-mg increments daily to the minimum effective dose. Severe cases have required gradual titration of the dose up to a maximum of 400 mg daily, but the effective range is usually between 50 and 200 mg daily. Dosage of more than 50 mg daily should be given in divided doses. All doses should be taken with food. Maintenance doses may be taken daily or intermittently.

In emergencies, such as acute pulmonary oedema, or when oral therapy cannot be given, etacrynic acid may be given intravenously. It is given as its salt, sodium etacrynate, but doses are expressed in terms of the acid. 10.7 mg of sodium etacrynate is equivalent to about 10 mg of etacrynic acid. The usual dose is 50 mg, or 0.5 to 1 mg/kg, as a 1 mg/mL solution in glucose 5% (provided the pH is above 5) or sodium chloride 0.9%, given by slow intravenous injection either directly or into the tubing of a running infusion. Should a subsequent injection be required the site should be changed to avoid thrombophlebitis. Single doses of 100 mg have been given intravenously in critical situations. It is not suitable for subcutaneous or intramuscular injection.

For doses in children, see below.

If very high doses of etacrynic acid are used careful laboratory control is essential as described for furosemide (p. 1387.1; high-dose therapy).

Administration in children. Etacrynic acid may be given to children aged over 2 years in the treatment of oedema at an initial oral dose of 25 mg daily, increased cautiously as necessary by 25 mg daily.

Adverse Effects

As for Furosemide, p. 1388.3. Gastrointestinal disturbances may be more common and severe with etacrynic acid; profuse watery diarrhoea is an indication for stopping therapy. Gastrointestinal bleeding has been associated with etacrynic acid. Tinnitus and deafness, particularly after high parenteral doses, may also be more common. Other adverse effects include confusion, fatigue, nervousness, and apprehension. Haematuria has been reported rarely.

Local irritation and pain may follow intravenous injection.

Effects on carbohydrate metabolism. Although etacrynic acid is generally considered to have less pronounced effects on carbohydrate metabolism than furosemide or the thiazide diuretics, adverse effects have been reported. Reductions in glucose tolerance[1] after etacrynic acid 200 mg daily for 6 weeks were similar to those produced by hydrochlorothiazide 200 mg daily. The effect was most pronounced in diabetic patients. Hyperosmolar hyperglycaemic coma[2] and symptomatic hypoglycaemia with convulsions[3] have been reported in patients receiving high doses of etacrynic acid.

1. Russell RP, *et al.* Metabolic and hypotensive effects of ethacrynic acid: comparative study with hydrochlorothiazide. *JAMA* 1968; 205: 11–16.
2. Cowley AJ, Elkeles RS. Diabetes and therapy with potent diuretics. *Lancet* 1978; i: 154.
3. Maher JF, Schreiner GE. Studies on ethacrynic acid in patients with refractory edema. *Ann Intern Med* 1965; 62: 15–29.

Effects on the ears. Drug-induced deafness occurred in 2 of 184 patients given etacrynic acid intravenously.[1,2] Deafness accompanied by nystagmus was reported in a patient[3] after an intravenous infusion of etacrynic acid. Symptoms resolved within 1 hour. He had previously been taking furosemide and etacrynic acid orally.

1. Boston Collaborative Drug Surveillance Program. Drug-induced deafness: a cooperative study. *JAMA* 1973; 224: 515–16.
2. Porter J, Jick H. Drug-induced anaphylaxis, convulsions, deafness, and extrapyramidal symptoms. *Lancet* 1977; i: 587–8.
3. Gomolin IH, Garshick E. Ethacrynic acid-induced deafness accompanied by nystagmus. *N Engl J Med* 1980; 303: 702.

Precautions

Etacrynic acid's precautions and contra-indications are generally dependent on its effects on fluid and electrolyte balance and are similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1406.1). Etacrynic acid, especially in the form of dust, is irritating to the skin, eyes, and mucous membranes.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies etacrynic acid as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Furosemide, p. 1389.3. The risks of gastrointestinal bleeding may be enhanced by use of etacrynic acid with other gastric irritants or with anticoagulants.

Anticoagulants. For reference to the interaction between *warfarin* and etacrynic acid, see p. 1533.3.

Pharmacokinetics

Etacrynic acid is fairly rapidly absorbed from the gastrointestinal tract. The plasma half-life is 30 to 60 minutes. It is excreted both in the bile and the urine, partly

unchanged and partly in the form of metabolites. It is extensively bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Edecrin; *Canad.*: Edecrin; *Hung.*: Uregyt; *Ital.*: Reomax; *Rus.*: Uregyt (Уреигт); *Ukr.*: Uregyt (Уреигт); *USA*: Edecrin.

Pharmacopoeial Preparations
BP 2014: Sodium Etacrynate Injection;
USP 36: Ethacrynate Sodium for Injection; Ethacrynic Acid Tablets.

Ethacizine

Aethacizin; Etacizin; Ethacizin; Ethacyzin; EZ-55; NIK-244; Этацизин.

Ethyl 10-[3-(diethylamino)propionyl]phenothiazine-2-carbamate.

$C_{22}H_{27}N_3O_3S$=413.5

CAS — 33414-33-4 (ethacizine); 57530-40-2 (ethacizine hydrochloride).

Profile

Ethacizine, an analogue of moracizine (p. 1441.2), is reported to be a class Ic antiarrhythmic. It is used in the treatment of ventricular and supraventricular arrhythmias and has been given orally in doses starting at 50 mg three times daily, increased if necessary to a maximum of 100 mg three times daily. It has also been given intravenously.

Etilefrine Hydrochloride *(BANM, rINNM)* ⊗

Ethyladrianol Hydrochloride; Ethylnorphenylephrine Hydrochloride; Etilefrinihydrokloridi; Etilefrina, hidrocloruro de; Étiléfrine, chlorhydrate d'; Etilefrin-hidroklorid; Etilefrinhydrochlorid; Etilefrin-hydrochlorid; Etilefrinhydroklorid; Etilefrini Hydrochloridum; Etilefrino hidrochloridas; Hidrocloruro de etilefrina; M+36; Этилэфрина Гидрохлорид.

2-Ethylamino-1-(3-hydroxyphenyl)ethanol hydrochloride.

$C_{10}H_{15}NO_2$,HCl=217.7

CAS — 709-55-7 (etilefrine); 943-17-9 (etilefrine hydrochloride).

ATC — C01CA01.

ATC Vet — QC01CA01.

UNII — ZBI6QSFH3S.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Etilefrine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

Profile

Etilefrine is a direct-acting sympathomimetic (p. 1507.3) with $beta_1$-agonist properties, and some alpha- and $beta_2$-agonist actions. It is used for the treatment of hypotensive states (p. 1277.2). It is given orally as the hydrochloride in usual doses of 5 or 10 mg three times daily; modified-release dosage forms may be given in doses of 25 mg once or twice daily. Etilefrine hydrochloride can also be given parenterally.

Etilefrine polistirex has been used in the management of rhinitis.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies etilefrine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Priapism. Priapism is a common complication of sickle-cell disease (p. 1123.2) and is often treated with intracavernosal alpha agonists (see under Uses of Metaraminol, p. 1430.2). There have also been reports of the successful use of etilefrine, both by intracavernosal injection for acute treatment,[1,2] and orally for prophylaxis.[1-3]

1. Virag R, *et al.* Preventive treatment of priapism in sickle cell disease with oral and self-administered intracavernous injection of etilefrine. *Urology* 1996; 47: 777–81.
2. Gbadoé AD, *et al.* Management of sickle cell priapism with etilefrine. *Arch Dis Child* 2001; 85: 52–3.
3. Okpala I, *et al.* Etilefrine for the prevention of priapism in adult sickle cell disease. *Br J Haematol* 2002; 118: 918–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Corcanfol; Effortil; Etil Adrianol; Menegradil; *Austria*: Effortil; *Belg.*: Effortil; *Braz.*: Effortil; Etilefril; *Chile*: Effortil†; *Fin.*: Effortil; *Fr.*: Effortil; *Ger.*: Bioflutin; Effortil; Etil; Pholdyston; Thomasin; *Gr.*: Effortil; Effortil; *Ital.*: Effortil; *Jpn*: Effortil; *Mex.*: Effortil; Quimtatil; *Pol.*: Effortil; *Port.*: Effortil; *S.Afr.*: Effortil†; *Spain*: Efortil; *Swed.*: Effortil; *Switz.*: Effortil; *Thai.*: Buracard; Circula; Circuman; Effortil†; Effrine; Efrine; Hyposla; Hyprosla†; *Venez.*: Effontil.

Multi-ingredient Preparations. *Austria*: Agilan; Amphodyn†; Effortil comp; Hypodyn†; Influbene†; *Ger.*: Dihydergot plus; Effortil plus†; *Switz.*: Dihydergot plus†; Effortil plus†.

Etofibrate *(rINN)*

Etofibrate; Etofibrato; Etofibratum; Этофибрат.

2-Nicotinoyloxyethyl 2-(4-chlorophenoxy)-2-methylpropionate.

$C_{18}H_{18}ClNO_5$=363.8

CAS — 31637-97-5.

ATC — C10AB09.

ATC Vet — QC10AB09.

UNII — 23TF67G79M.

Profile

Etofibrate, a derivative of clofibrate (p. 1338.3) and nicotinic acid (p. 2083.1), is a lipid regulating drug used in the treatment of hyperlipidaemias (p. 1248.1). The usual oral dose is 500 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Tricerol; *Ger.*: Lipo-Merz†; *Hong Kong*: Lipo-Merz; *Port.*: Lipo-Merz.

Etofylline Clofibrate *(rINN)*

Clofibrato de etofilina; Etofillina, clofibrato de; Étofylline, Clofibrate d'; Etofyllini Clofibras; ML-1024; Theofibrate (USAN); Theofibrate; Этофиллина Клофибрат.

2-(Theophyllin-7-yl)ethyl 2-(4-chlorophenoxy)-2-methylpropionate.

$C_{19}H_{21}ClN_4O_5$=420.8

CAS — 54504-70-0.

UNII — 14UH1JQP6L.

Profile

Etofylline clofibrate, a fibric acid derivative (see Bezafibrate, p. 1323.2), is a lipid regulating drug that has been used in the treatment of hyperlipidaemias (p. 1248.1). An oral dose of 250 mg two or three times daily has been given.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Duolip†; *Ger.*: Duolip†; *Hong Kong*: Duolip†.

Ezetimibe *(BAN, USAN, rINN)*

Ezetimiba; Ézétimibe; Ezetimibum; Sch-58235; Эзетимиб.

(3*R*,4*S*)-1-(*p*-Fluorophenyl)-3-[(3*S*)-3-(*p*-fluorophenyl)-3-hydroxypropyl]-4-(*p*-hydroxyphenyl)-2-azetidinone.

$C_{24}H_{21}F_2NO_3$=409.4

CAS — 163222-33-1.

ATC — C10AX09.

ATC Vet — QC10AX09.

UNII — EOR26LQQ24.

Uses and Administration

Ezetimibe is an inhibitor of intestinal sterol absorption and inhibits the absorption of cholesterol and plant sterols. It is used to reduce total cholesterol, low-density lipoprotein (LDL)-cholesterol, and apolipoprotein B in the management of hyperlipidaemias (below), and to reduce sitosterol and campesterol in patients with homozygous familial sitosterolaemia. It is given orally in a usual dose of 10 mg once daily.

For use in children, see below.

Reviews.
1. Sudhop T, von Bergmann K. Cholesterol absorption inhibitors for the treatment of hypercholesterolaemia. *Drugs* 2002; 62: 2333–47.
2. Mauro VF, Tuckerman CB. Ezetimibe for management of hypercholesterolemia. *Ann Pharmacother* 2003; 37: 839–48.
3. Bays HE, *et al.* Ezetimibe: cholesterol lowering and beyond. *Expert Rev Cardiovasc Ther* 2008; 6: 447–70.
4. Anonymouse. Ezetimibe—an update. *Drug Ther Bull* 2009; 47: 91–5.

Administration in children. Experience with ezetimibe in children is limited, but UK licensed product information states that adolescent boys of Tanner stage II and above, and girls at least 1 year post-menarche, and who are aged over 10 years, may be given ezetimibe for the same indications and at the same doses as in adults (see above).

Hyperlipidaemias. Ezetimibe inhibits the absorption of dietary cholesterol[1] and, although there is a compensatory increase in cholesterol synthesis in the liver,[1] overall plasma LDL-cholesterol concentrations are reduced.[2] Ezetimibe may be used alone[3] in the management of hyperlipidaemias (p. 1248.1) but use with lipid regulating drugs that act by reducing cholesterol synthesis may produce additive effects. In patients already taking statins, addition of ezetimibe results in a further reduction in LDL-cholesterol,[4] which may increase the number of patients achieving lipid targets, or allow lower doses of statins to be used. However, the clinical relevance of this is unclear; a study[5] in patients with familial hypercholesterolaemia found no difference in the progression of carotid atherosclerosis (measured by intima-media thickness) in those given ezetimibe with simvastatin compared with those given simvastatin alone, despite a larger reduction in LDL-cholesterol. Similar effects on LDL-cholesterol have been reported[6] for ezetimibe with fibrates.

As well as inhibiting cholesterol absorption, ezetimibe also blocks the absorption of plant sterols such as campesterol and sitosterol, and may be effective in patients with sitosterolaemia,[7] an inherited disorder in which increased absorption of plant sterols leads to premature atherosclerosis.

1. Sudhop T, *et al.* Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation* 2002; 106: 1943–8.
2. Knopp RH, *et al.* Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. *Eur Heart J* 2003; 24: 729–41.
3. Pandor A, *et al.* Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. *J Intern Med* 2009; 265: 568–80.
4. Pearson TA, *et al.* A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. *Mayo Clin Proc* 2005; 80: 587–95.
5. Kastelein JJP, *et al.* The ENHANCE Investigators. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008; 358: 1431–43.
6. McKenney JM, *et al.* Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. *J Am Coll Cardiol* 2006; 47: 1584–7.
7. Salen G, *et al.* Ezetimibe effectively reduces plasma plant sterols in patients with sitosterolemia. *Circulation* 2004; 109: 966–71.

Adverse Effects and Precautions

Ezetimibe is generally well tolerated. The most common adverse effects include headache, abdominal pain, and diarrhoea; other gastrointestinal disorders, hypersensitivity reactions including rash and angioedema, fatigue, chest pain, and arthralgia have also been reported. Rare adverse effects include raised liver enzymes or hepatitis, pancreatitis, thrombocytopenia, cholelithiasis, and cholecystitis. Myalgia has occurred in patients taking ezetimibe either alone or when added to a statin (see Effects on Skeletal Muscle, p. 1380.1). Ezetimibe should be stopped if myopathy is suspected or creatine phosphokinase increases significantly.

Ezetimibe should be avoided in patients with moderate or severe hepatic impairment.

Reviews.
1. Jacobson TA, *et al.* Safety considerations with gastrointestinally active lipid-lowering drugs. *Am J Cardiol* 2007; 99 (Issue 6 suppl 1): 47C–55C.
2. Kashani A, *et al.* Review of side-effect profile of combination ezetimibe and statin therapy in randomized clinical trials. *Am J Cardiol* 2008; 101: 1606–13.

Carcinogenicity. *Statins* are not thought to cause cancer (for a discussion, see Malignant Neoplasms under Uses and Administration of Simvastatin, p. 1491.3). However, an excess of incident cancer and fatal cancer was seen[1] in patients given combination therapy with simvastatin and ezetimibe when compared with placebo. To better examine the association, the data were pooled with those of two large, uncompleted studies;[2] the authors concluded that there was no evidence that the combination caused cancer, a conclusion that has been criticised.[3-5] Neither the FDA[6] nor MHRA[7] considered that a conclusion could be drawn as to the effect of ezetimibe on cancer.

1. Rossebø AB, *et al.* SEAS Investigators. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008; 359: 1343–56.
2. Peto R, *et al.* Analyses of cancer data from three ezetimibe trials. *N Engl J Med* 2008; 359: 1357–66.
3. Drazen JM, *et al.* Ezetimibe and cancer—an uncertain association. *N Engl J Med* 2008; 359: 1398–9.
4. Nissen SE. Analyses of cancer data from three ezetimibe trials. *N Engl J Med* 2009; 360: 86–7.
5. Fleming TR. Identifying and addressing safety signals in clinical trials. *N Engl J Med* 2008; 359: 1400–2.
6. FDA. Early communication about an ongoing safety review of ezetimibe/simvastatin (marketed as Vytorin), simvastatin (marketed as Zocor) and ezetimibe (marketed as Zetia) (issued 21st August 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm162899.htm (accessed 12/06/09)
7. MHRA/CHM. Ezetimibe and results of SEAS study: possible increased risk of cancer. *Drug Safety Update* 2008; 2 (4): 7. Available at: http://

www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0309245&RevisionSelectionMethod=LatestReleased (accessed 12/06/09)

Effects on the liver. Ezetimibe may cause an increase in liver enzymes and there have also been reports of acute hepatitis,[1,2] sometimes developing after addition of ezetimibe to long-term statin therapy.[3,4] Both auto-immune[3,4] and cholestatic hepatitis[4] have been described. In some patients,[1-3] symptoms resolved and liver enzymes normalised when ezetimibe was stopped, and in 1 patient a statin was successfully restarted.[3] However, of 2 patients who had been receiving ezetimibe and atorvastatin, 1 required treatment with corticosteroids,[4] while the other[4] had persistent liver changes 4 months later, despite both drugs being stopped in each case.

1. Liu Q, *et al.* Drug-induced liver injury associated with ezetimibe therapy. *Dig Dis Sci* 2007; **52**: 602–5.
2. Casteilote J, *et al.* Serious drug-induced liver disease secondary to ezetimibe. *World J Gastroenterol* 2008; **14**: 5098–9.
3. van Heyningen C. Drug-induced acute autoimmune hepatitis during combination therapy with atorvastatin and ezetimibe. *Ann Clin Biochem* 2005; **42**: 402–4.
4. Stolk MF, *et al.* Severe hepatic side effects of ezetimibe. *Clin Gastroenterol Hepatol* 2006; **4**: 908–11.

Effects on the pancreas. Pancreatitis has been reported[1] in patients taking ezetimibe. In one case,[2] acute pancreatitis developed 2 weeks after starting ezetimibe and resolved when the drug was stopped, suggesting an immunological cause.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Drug induced pancreatitis. *Aust Adverse Drug React Bull* 2006; **25**: 22. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0612.pdf (accessed 30/05/08)
2. Ahmad I, *et al.* Ezetimibe-induced acute pancreatitis. *South Med J* 2007; **100**: 409–10.

Effects on skeletal muscle. Muscle disorders such as myalgia and myopathy are well known to occur with lipid regulating drugs such as statins and fibrates and have also been reported with ezetimibe, both alone,[1,2] and when added to treatment with statins;[1,3] rhabdomyolysis has also occurred, but is rare in patients taking ezetimibe alone. Up to August 2005, the Australian Adverse Drug Reactions Advisory Committee[4] had received 44 reports of muscle disorders with ezetimibe, including myalgia, muscle cramp, weakness and pain; in 5 of these cases a statin was also being taken.

1. Simard C, Poirier P. Ezetimibe-associated myopathy in monotherapy and in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. *Can J Cardiol* 2006; **22**: 141–4.
2. Havranek JM, *et al.* Monotherapy with ezetimibe causing myopathy. *Am J Med* 2006; **119**: 285–6.
3. Pux R, *et al.* Ezetimibe and statin-associated myopathy. *Ann Intern Med* 2004; **140**: 671–2.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Ezetimibe and muscle disorders. *Aust Adverse Drug React Bull* 2005; **24**: 15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0508.pdf (accessed 30/05/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ezetimibe as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

Colestyramine reduces the absorption of ezetimibe and should not be given at the same time of day. Ciclosporin has been reported to increase the plasma concentration of ezetimibe (see below) and patients receiving both drugs should be carefully monitored; the effect may be greater in patients with severe renal impairment. An increased INR has been reported in patients given ezetimibe and oral anticoagulants.

Ciclosporin. Pharmacokinetic studies[1] have shown that plasma-ezetimibe concentrations are higher in renal transplant patients taking ciclosporin than in historical controls, and there has been a report[2] of a supratherapeutic response to ezetimibe in a heart transplant patient taking ciclosporin. Ezetimibe causes a small increase in plasma-ciclosporin concentrations,[3] but the clinical relevance of this is not clear.

1. Bergman AJ, *et al.* Interaction of single-dose ezetimibe and steady-state cyclosporine in renal transplant patients. *J Clin Pharmacol* 2006; **46**: 328–36.
2. Koshman SL, *et al.* Supratherapeutic response to ezetimibe administered with cyclosporine. *Ann Pharmacother* 2005; **39**: 1561–5.
3. Bergman AJ, *et al.* Effects of ezetimibe on cyclosporine pharmacokinetics in healthy subjects. *J Clin Pharmacol* 2006; **46**: 321–7.

Pharmacokinetics

Ezetimibe is rapidly absorbed when given orally and undergoes extensive conjugation in the small intestine and liver to an active glucuronide metabolite, which is the main circulating form. Both ezetimibe and the glucuronide are more than 90% bound to plasma proteins. Ezetimibe is excreted primarily in the faeces via bile and undergoes enterohepatic recycling; after an oral dose, about 78% is excreted in the faeces, mainly as ezetimibe, and about 11% is excreted in the urine, mainly as the glucuronide. The elimination half-life for both ezetimibe and the glucuronide is about 22 hours. Ezetimibe is distributed into breast milk in *rats*.

Reviews

1. Kosoglou T, *et al.* Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2005; **44**: 467–94.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acotral; Alin; Alipas; Cercleral; Cetrakam†; Coracil; Enedilex; Ezetrol; Ixacor; Lipimibe†; Nalecol; Sinterol; Trilip; Vadel; Zetia; *Austral.*: Ezetrol; *Austria*: Ezetrol; *Belg.*: Ezetrol; *Braz.*: Ezetrol; Zetia; *Canad.*: Ezetrol; *Chile*: Ezetrol; Zient; *China*: Ezetrol (益适纯); *Cz.*: Ezetrol; Zient†; *Denm.*: Ezetrol; *Fin.*: Ezetrol; *Fr.*: Ezetrol; *Ger.*: Ezetrol; *Gr.*: Ezetrol; *Hong Kong*: Ezetrol; *Hung.*: Ezetrol; *India*: Esia; Ezedoc; Ezentia; Ezerem; Ezetib†; Ezibloc; Ezta; Ezzicad; Imbibe†; Lipezet; Mibe; *Indon.*: Ezetrol; *Irl.*: Ezetrol; *Israel*: Ezetrol; *Ital.*: Ezetrol; Zetia; *Malaysia*: Ezetrol; *Mex.*: Ezetrol; Zient; *Neth.*: Ezetrol; *Norw.*: Ezetrol; *NZ*: Ezetrol; *Philipp.*: Ezetrol; *Pol.*: Ezetrol; *Port.*: Adacai; Ezetrol; *Rus.*: Ezetrol (Эзетрол); *S.Afr.*: Ezetrol; *Singapore*: Ezetrol; *Spain*: Absorcol; Ezetrol; *Swed.*: Ezetrol; *Switz.*: Ezetrol; *Thai.*: Ezetrol; *Turk.*: Colebyn; Ezetrol; Kolez; *UK*: Ezetrol; *USA*: Zetia; *Venez.*: Ezetrol; Zetia; Zient.

Multi-ingredient Preparations. *Arg.*: Alipas Duo; Ampliar Duo; Ampliar Plus; Ateroclar Combi; Ateroclar Duo; Coleflux Duo; Colmibe; Craveril Duo; Labistatin Duo; Liparex Duo; Liparex Plus; Lipibec Duo; Lipibec Plus; Lipocambi Plus; Liponorm Duo; Minuslip Duo; Plan Duo; Redusterol Duo; Salvaxil Plus; Sinterol Compuesto; Torimibe; Vasotenal EZ; Vytorin; Zimetek; *Austral.*: Vytorin; *Austria*: Inegy; *Belg.*: Inegy; *Braz.*: Vytorin; Zetsim; *Chile*: Adacai; Vytorin; Zintrepid; *China*: Vytorin (葆至能); *Cz.*: Inegy; *Denm.*: Inegy; *Fin.*: Inegy; *Fr.*: Inegy; Vytorin; *Ger.*: Inegy; *Gr.*: Inegy; Vytorin; *Hong Kong*: Vytorin; *Hung.*: Inegy; *India*: Alnavas-BZ; Altovas-EZ; Aova-EZ; Atheart-EZ; Atherotwo; Atix-EZ; Atofast-EZ; Atorin-EZ; Atorlip-EZ; Atoroll-EZ; Atortus-EZ; Atorvik-EZ; Avas EZ; Avascare-EZ; Aztor EZ; Bitorva; Cardisoz-AT; Dilutex Plus; Dyslip-EZ; Dysliptin-EZ; Ecostat; Etovas-EZ; Ezemax-A; Ezevas; Fibator EZ; Genlip-EZ; Jvastor-EZ; LDTor-Z; Lesstrol-EZ; Lipi-EZ; Lipikind-EZ; Lipivas EZ; Lipofix-EX; Liponorm-EZ; Lorlip-EZ; Modlip-EZ; Noclog-EZ; Omnitor-EZ; Orvaz-EZ; Zetitor; *Indon.*: Vytorin; *Irl.*: Inegy; *Israel*: Inegy; *Ital.*: Goltor; Inegy; Vytorin; Zeklen; *Malaysia*: Vytorin; *Mex.*: Vytorin; Zintrepid; *Neth.*: Inegy; *Norw.*: Inegy; *NZ*: Vytorin; *Philipp.*: Vytorin; *Port.*: Inegy; Vytorin; *Rus.*: Inegy (Инегжи); *Singapore*: Vytorin; *Spain*: Inegy; Vytorin; *Swed.*: Inegy; *Switz.*: Inegy; *Thai.*: Vytorin; *Turk.*: Inegy; *UK*: Inegy; *Ukr.*: Azi-Ator (Азы-Атор); *USA*: Liptruzet; Vytorin; *Venez.*: Adacai; Vytorin; Zintrepid.

Fasudil Hydrochloride *(rINNM)*

AT-877; Fasudil, Chlorhydrate de; Fasudil, hidrocloruro de; Fasudilli Hydrochloridum; HA-1077; Hidrocloruro de fasudil; Фазудила Гидрохлорид.

Hexahydro-1-(5-isoquinolylsulfonyl)-1*H*-1,4-diazepine hydrochloride.

$C_{14}H_{17}N_3O_2S,HCl$=327.8

CAS — 103745-39-7 (fasudil); 105628-07-7 (fasudil hydrochloride).

ATC — C04AX32.

ATC Vet — QC04AX32.

UNII — SCQ4N8S7BR.

Profile

Fasudil is a selective inhibitor of Rho-kinase, a protein kinase involved in contraction of vascular smooth muscle. Fasudil is used as the hydrochloride hemihydrate for its vasodilating properties in the management of cerebrovascular disorders including vasospasm after surgery for subarachnoid haemorrhage. It is under investigation for the treatment of angina pectoris, acute cerebral thrombosis, and pulmonary hypertension.

References.

1. Shibuya M, *et al.* Effect of AT877 on cerebral vasospasm after aneurysmal subarachnoid hemorrhage: results of a prospective placebo-controlled double-blind trial. *J Neurosurg* 1992; **76**: 571–7.
2. Masumoto A, *et al.* Suppression of coronary artery spasm by the Rho-kinase inhibitor fasudil in patients with vasospastic angina. *Circulation* 2002; **105**: 1545–7.
3. Shimokawa H, *et al.* Anti-anginal effect of fasudil, a Rho-kinase inhibitor, in patients with stable effort angina: a multicenter study. *J Cardiovasc Pharmacol* 2002; **40**: 751–61.
4. Vicari RM, *et al.* Efficacy and safety of fasudil in patients with stable angina: a double-blind, placebo-controlled, phase 2 trial. *J Am Coll Cardiol* 2005; **46**: 1803–11.
5. Suzuki Y, *et al.* A postmarketing surveillance study of fasudil treatment after aneurysmal subarachnoid hemorrhage. *Surg Neurol* 2007; **68**: 126–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Chuanwei (川威); Eril (依立尔); *Jpn*: Eril.

Felodipine *(BAN, USAN, rINN)*

Felodipini; Felodipin; Felodipina; Felodipinas; Felodipine; Felodipino; Felodipinum; H-154/82; Феноципин.

Ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate.

$C_{18}H_{19}Cl_2NO_4$=384.3

CAS — 72509-76-3; 86189-69-7.

ATC — C08CA02.

ATC Vet — QC08CA02.

UNII — OL96TR6O2C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Felodipine). A white or light yellow, crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, in dichloromethane, and in methyl alcohol. Protect from light.

USP 36: (Felodipine). A light yellow to yellow, crystalline powder. Insoluble in water; freely soluble in acetone and in methyl alcohol; very slightly soluble in heptane. Store in airtight containers. Protect from light.

Uses and Administration

Felodipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p. 1447.2). It is used in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3).

Felodipine is given orally, generally in a modified-release formulation for use once daily in the morning. In **hypertension** the usual initial dose is 5 mg daily, adjusted as required; the usual maintenance dose is 2.5 to 10 mg daily and doses above 20 mg daily are not usually needed. In **angina** the usual initial dose is 5 mg daily increased if necessary to 10 mg daily.

Lower doses may be required in patients with hepatic impairment (see below) and in the elderly.

Reviews.

1. Todd PA, Faulds D. Felodipine: a review of the pharmacology and therapeutic use of the extended release formulation in cardiovascular disorders. *Drugs* 1992; **44**: 251–77.
2. Walton T, Symes LR. Felodipine and isradipine: new calcium-channel-blocking agents for the treatment of hypertension. *Clin Pharm* 1993; **12**: 261–75.

Administration in hepatic impairment. In 9 patients with liver cirrhosis given felodipine 750 micrograms by intravenous infusion over 20 minutes and 10 mg orally as single doses on separate occasions the mean oral bioavailability was 17.1% which was not significantly different from published values in healthy subjects, but the peak plasma concentrations were almost twice as high as normal, apparently due to reduced systemic clearance and volume of distribution.[1] The fact that bioavailability was not increased suggests that much pre-systemic metabolism takes place in the gut rather than the liver. Although increased adverse effects were not associated with the raised felodipine concentrations in this study it is recommended that therapy in cirrhotic patients begin at lower doses than in patients with normal liver function. US licensed product information recommends that an initial dose of 2.5 mg once daily should be used in patients with hepatic impairment.

1. Regårdh CG, *et al.* Pharmacokinetics of felodipine in patients with liver disease. *Eur J Clin Pharmacol* 1989; **36**: 473–9.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies felodipine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Pharmacokinetics

Felodipine is almost completely absorbed from the gastrointestinal tract after oral doses but undergoes extensive first-pass metabolism, with a bioavailability of about 15% (range 10 to 25%). It is extensively metabolised

in the gut and the liver and is excreted almost entirely as metabolites, about 70% of a dose being excreted in urine and the remainder in faeces. The terminal elimination half-life is reported to be about 11 to 16 hours after oral dosage with an immediate-release preparation, but longer with a modified-release formulation. Felodipine is about 99% bound to plasma proteins (mainly albumin).

Reviews.
1. Dunselman PHJM, Edgar B. Felodipine clinical pharmacokinetics. *Clin Pharmacokinet* 1991; 21: 418–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Munobal; Plendil; ***Austral.***: Felodil; Felodur; Plendil; ***Austria***: Felodistad; Munobal; Plendil; ***Belg.***: Plendil; Renedil; ***Braz.***: Splendil; ***Canad.***: Plendil; Renedil; ***Chile***: Splendil; ***China***: DeWei (得维); Keliping (可立平); Lianhuan-Erding (联环尔定); Plendil (波依定); XiaoDing (笑定); ***Cz.***: Auronal; Felocor; Plendil; Presid; ***Denm.***: Felodin; Plendil; Plendur†; ***Fin.***: Hydac; Plendil; ***Fr.***: Flodil; ***Ger.***: Felo-Puren†; Felobeta; Felocor†; Felogamma; Modip; Munobal; ***Gr.***: Plendil; ***Hong Kong***: Felogard; Plendil; ***Hung.***: Plendil; Presid; ***India***: Felogard; ***Indon.***: Nirmadil; Plendil; ***Irl.***: Plendil; ***Israel***: Penedil; ***Ital.***: Feloday; Plendil; Prevex; ***Jpn***: Splendil; ***Malaysia***: Plendil; ***Mex.***: Dylofen; Eutens; Fedin; Hofodilan; Munobal; Nafapin; Nafpin; Plendil; Xysvol; ***Neth.***: Plendil; ***Norw.***: Plendil; ***NZ***: Felo; Plendil; ***Philipp.***: Dilatiex; Dilofen; Felim†; Felop; Pelpin; Lodistad; Plendil; Versant; ***Pol.***: Felohexal†; Plendil; ***Port.***: Mencor†; Plendil; Preslow; ***Rus.***: Felodip (Фелодип); Plendil (Плендил); ***S.Afr.***: Plendil; ***Singapore***: Plendil; ***Spain***: Perfudal†; Plendil; ***Swed.***: Plendil; ***Switz.***: Felodil†; Plendil; ***Thai.***: Fedil; Felim; Felohexal†; Pelopine; Peloten; Plendil; Topidil; ***Turk.***: Plendil; ***UK***: Cardioplen; Felotens; Keloc; Neofel; Parmid; Plendil; Vascalpha; ***Ukr.***: Felodip (Фелодип); Felohexal (Фелогексал)†; ***Venez.***: Plendil.

Multi-ingredient Preparations. ***Arg.***: Atacand Duo; Triacor; ***Austral.***: Triasyn; ***Belg.***: Logimat; Tazko; ***Braz.***: Atacand Comb; ***Canad.***: Altace Plus Felodipine; ***Cz.***: Triasyn; ***Denm.***: Logimax; ***Fin.***: Logimax; Unimax; ***Fr.***: Logimax; ***Ger.***: Delmuno; Mobloc Unimax; ***Gr.***: Logimax; Triacor; Unitens; ***Hong Kong***: Logimax; ***Hung.***: Logimax; Triasyn; ***Irl.***: Triapin; ***Israel***: Logimax†; ***Ital.***: Triapin; ***Mex.***: Logimax; Triacor; ***Neth.***: Triapin; ***Philipp.***: Logimax; Triapin; ***Pol.***: Delmuno; ***Port.***: Triapin; Unimax†; ***Rus.***: Logimax (Логимакс); ***S.Afr.***: Tri-Plen; ***Spain***: Logimax; Triapin; ***Swed.***: Logimax; ***Switz.***: Logimax; Unimax†; ***UK***: Triapin.

Pharmacopoeial Preparations
BP 2014: Prolonged-release Felodipine Tablets;
USP 36: Felodipine Extended-Release Tablets.

Fendiline Hydrochloride *(pINNM)*

Fendilina, hidrocloruro de; Fendiline, Chlorhydrate de; Fendilini Hydrochloridum; Hidrocloruro de fendilina; Фендилина Гидрохлорид.

N-(2-Benzhydrylethyl)-α-methylbenzylamine hydrochloride.

$C_{23}H_{25}N,HCl$=351.9.

CAS — 13042-18-7 (fendiline); 13636-18-5 (fendiline hydrochloride).

ATC — C08EA01.

ATC Vet — QC08EA01.

UNII — HEM3Z10IIK.

Profile

Fendiline hydrochloride is a calcium-channel blocker used as a vasodilator in ischaemic heart disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Sensit.

Fenofibrate *(BAN, rINN)*

Fenofibraatti; Fenofibrat; Fenofibrát; Fenofibratas; Fénofibrate; Fenofibrato; Fenofibratum; LF-178; Procetofen; Procetofene; Фенофибрат.

Isopropyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionate.

$C_{20}H_{21}ClO_4$=360.8

CAS — 49562-28-9 (fenofibrate); 42017-89-0 (fenofibric acid).

ATC — C10AB05.

ATC Vet — QC10AB05.

UNII — U202363UOS.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Fenofibrate). A white or almost white, crystalline powder. M.p. 79 degrees to 82 degrees. Practically insoluble in water; slightly soluble in alcohol; very soluble in dichloromethane. Protect from light.

USP 36: (Fenofibrate). A white or almost white, crystalline powder. M.p. 79 degrees to 82 degrees. Practically insoluble in water; slightly soluble in alcohol; very soluble in dichloromethane. Protect from light.

Choline Fenofibrate *(USAN, rINN)*

ABT-335; Cholini Fenofibratum; Fénofibrate de Choline; Fenofibrato de colina; Холин Фенофибрат.

2-Hydroxy-*N*,*N*,*N*-trimethylethanaminium 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate.

$C_5H_{14}NO,C_{17}H_{14}ClO_4$=421.9

CAS — 856676-23-8.

ATC — C10AB05.

ATC Vet — QC10AB11.

UNII — 4BMH7IZT98.

Uses and Administration

Fenofibrate, a fibric acid derivative, is a lipid regulating drug with actions on plasma lipids similar to those of bezafibrate (p. 1323.2).

It is used to reduce low-density lipoprotein (LDL)-cholesterol, total cholesterol, triglycerides, and apolipoprotein B, and to increase high-density lipoprotein (HDL)-cholesterol, in the management of hyperlipidaemias (p. 1248.1), including type IIa, type IIb, type III, type IV, and type V hyperlipoproteinaemias.

Fenofibrate is given orally as the base or choline salt. It is usually given with food to improve bioavailability although this may not be necessary with all preparations (see Bioavailability, below). It is available in a range of formulations with differing bioavailabilities and the dose is therefore specific to the preparation.

Standard micronised formulations of fenofibrate are available as 67-mg capsules to be taken several times daily, or as 200- or 267-mg capsules for once daily dosage. The usual initial dose is 67 mg three times daily or 200 mg once daily; the dose may be reduced to 67 mg twice daily or increased to 67 mg four times daily or 267 mg once daily according to response.

Preparations with improved bioavailability may be given in doses of around 40 to 160 mg once daily.

Non-micronised formulations may also be available and are given in an initial dose of 200 to 300 mg daily in divided doses, adjusted according to response to between 200 and 400 mg daily; 100 mg of non-micronised fenofibrate is therapeutically equivalent to 67 mg of the standard micronised form.

Choline fenofibrate is also given orally; doses are expressed in terms of fenofibric acid. It is given in a dose of 45 to 135 mg once daily.

Doses of fenofibrate and choline fenofibrate should be reduced in renal impairment (see below). For the dose of fenofibrate in children, see also below.

Fenofibric acid is also used similarly to fenofibrate.

Reviews.
1. Keating GM, Croom KF. Fenofibrate: a review of its use in primary dyslipidaemia, the metabolic syndrome and type 2 diabetes mellitus. *Drugs* 2007; 67: 121–53.

Administration in children. Experience with fenofibrate in children is limited and it should only be given under specialist advice. The *BNFC* considers that, given the limited evidence supporting its use in children, fenofibrate should be used only when a statin or bile-acid binding drug is unsuitable. The dose depends on the formulation:

- For *standard micronised* fenofibrate the *BNFC* recommends that children are given the 67-mg capsule formulation. The oral dose is one 67-mg capsule per 20 kg bodyweight daily for children aged 4 to 15 years; those aged 15 to 18 years may be given the adult dose (see above).
- *Non-micronised* fenofibrate is licensed for use in some countries in children from the age of 10 years, in a maximum oral dose of 5 mg/kg daily.

Administration in renal impairment. A single-dose study[1] in patients with mild (creatinine clearance (CC) 30 to 50 mL/minute) or severe renal impairment (CC below 10 mL/minute or undergoing haemodialysis) found that the plasma elimination half-life of fenofibric acid was prolonged, with a range of 54 to 362 hours; no correlation was found between half-life and serum creatinine or CC. Fenofibrate metabolites were not removed by haemodialysis, and repeated dosing in patients undergoing regular haemodialysis led to significant accumulation of fenofibric acid.[1]

Fenofibrate is therefore not generally recommended in patients with severe renal impairment although UK licensed product information allows a dose of 134 mg of *standard micronised* fenofibrate daily for patients with CC between 20 and 60 mL/minute and 67 mg daily for patients with CC below 20 mL/minute.

US licensed product information for *improved bioavailability formulations* suggests initial daily doses of about 40 to 50 mg (equivalent to about 67 mg of standard micronised fenofibrate) in patients with renal impairment, but contra-indicates use in those with severe impairment. *Choline fenofibrate* may be given to those with mild to moderate renal impairment in an initial dose of 45 mg once daily; the dose may be increased if necessary after evaluation of the effect on renal function. It should be avoided in severe renal impairment.

1. Desager JP, *et al.* Effect of hemodialysis on plasma kinetics of fenofibrate in chronic renal failure. *Nephron* 1982; 31: 51–4.

Biliary disorders. For mention of the use of fenofibrate with ursodeoxycholic acid in the treatment of primary biliary cirrhosis see under Bezafibrate, p. 1323.3.

Adverse Effects and Precautions

As for Bezafibrate, p. 1324.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fenofibrate as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Bezafibrate, p. 1325.2.

UK licensed product information for fenofibrate suggests that in patients taking oral anticoagulants, the dose of anticoagulant should be reduced by about one-third when treatment with fenofibrate is started, and then adjusted gradually if necessary.

Pharmacokinetics

Fenofibrate is readily absorbed from the gastrointestinal tract when taken with food; absorption may be reduced if fenofibrate is given on an empty stomach, although this depends on the formulation (see Bioavailability, below). When given as the choline salt, which is also readily absorbed from the gastrointestinal tract, its bioavailability is not affected by food.

Fenofibrate is rapidly hydrolysed to its active metabolite fenofibric acid which is about 99% bound to plasma albumin. The plasma elimination half-life is about 20 hours. Fenofibric acid is excreted mainly in the urine, mainly as the glucuronide conjugate, but also as a reduced form of fenofibric acid and its glucuronide. It is not removed by haemodialysis.

References.
1. Chapman MJ. Pharmacology of fenofibrate. *Am J Med* 1987; 83 (suppl 5B): 21–5.

Bioavailability. Fenofibrate is poorly soluble in water and has a low bioavailability when given orally.[1] Bioavailability is increased by food, particularly if there is a high fat content, and fenofibrate is therefore usually given with meals. Changes to the formulation, particularly with regard to the particle size, have been made to improve solubility,[1] with the aim of increasing bioavailability and reducing the influence of food. Micronisation improves bioavailability to a certain extent, and allows a lower dose to be given; 300 mg of non-micronised fenofibrate is usually considered equivalent to about 200 mg of the standard micronised form. Microcoating may further improve bioavailability,[2] but absorption is still affected by the presence of food.[3] Nanoparticle,[4] stabilised microparticle,[3] or semi-solid formulations,[5] however, appear to have a more consistent bioavailability and may be given with or without food, as may choline fenofibrate.

1. Vogt M, *et al.* Dissolution enhancement of fenofibrate by micronization, cogrinding and spray-drying: comparison with commercial preparations. *Eur J Pharm Biopharm* 2008; 68: 283–8.
2. Guichard JP, *et al.* A new formulation of fenofibrate: suprabioavailable tablets. *Curr Med Res Opin* 2000; 16: 134–8.
3. Guivarc'h PH, *et al.* A new fenofibrate formulation: results of six single-dose, clinical studies of bioavailability under fed and fasting conditions. *Clin Ther* 2004; 26: 1456–69.
4. Sauron R, *et al.* Absence of a food effect with a 145 mg nanoparticle fenofibrate tablet formulation. *Int J Clin Pharmacol Ther* 2006; 44: 64–70.
5. Sonet B, *et al.* Randomised crossover studies of the bioequivalence of two fenofibrate formulations after administration of a single oral dose in healthy volunteers. *Arzneimittelforschung* 2002; 52: 200–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Controlip; Craveril; Daunlip; Fenobrate; Minuslip; Procetoken; Sclerofin; ***Austral.***: Lipidil; ***Austria***: Apteor; Penolip; Lipanthyl; Lipcor; Lipsin; ***Belg.***: Docfenofi†; Fenofitop†; Fenogal; Fenosup; Lipanthyl; Lipanthylnano; ***Braz.***: Lipanon; Lipidil; Reducofen; ***Canad.***: Apo-Feno; Feno-Micro; Fenomax; Lipidil; Pro-Feno; ***Chile***: Fibronil; Lipidil†; ***China***: Eticer (爱得生)†; Guan Zhi Ning (冠之柠); Ke Li Qing (可立清); Lipanthyl (力平之); Lipilfen (利必非); Lipilo (非诺贝特); Qi Shu (祺抒); Tai Wei Luo (太韦络); ***Cz.***: Apo-Feno; Febira; Fenofix; Lipanthyl; Lipirex; Lipohexal; Suprelip; ***Fin.***: CIL; Fenosup; Lipanthyl; ***Fr.***: Fegenor; Lipanthyl; Secalip; ***Ger.***: CIL†; Fenobeta; Fenofanton†; Lipidil;

The symbol † denotes a preparation no longer actively marketed

Normalip pro†; *Gr.*: Chlorosteran; Climage; Fagratyl; Fenobrat; Gestefol; Letomode; Lichol; Lipanthyl; Liperial; Lipidil; Lisomyex; Neo-Disterin; Planitrix; Sitronella; Xafenor; Zerlubron; ***Hong Kong***: Apo-Feno; Fegenor†; Lexemin; Lipanthyl; Qualipantyl; ***Hung.***: Feno-Micro†; Fenobrat; Fenoswiss; Lipanthyl; Lipidil; ***India***: Fenacor; Fenobate; Fenocor; Fenolip; Fibral; Fibrate; Finate; Lipicard; Lotgl; ***Indon.***: Evothyl; Felosma; Fibramed; Hyperchol; Lifen; Lipanthyl; Profibrat; Trichol; Trolip; Yosenob; Zumafib; ***Irl.***: Lipantil; ***Ital.***: Fulcro; Fulcrosupra; Liperial; Lipofene; Lipsin; Nolipax†; Tilene; ***Jpn***: Tricor; ***Malaysia***: Apo-Feno-Micro; Fenosup; Lexemin; Lipanthyl; ***Mex.***: Controlip; Lipidil; ***Philipp.***: Fenof; Fenoflex; Fenogal; Fibrafen; Fibril; Lipanthyl; Lipiduce; Lipilfen; Lipway; Lofibra; Lofibra; Nubrex; Trichek; Trolip; ***Pol.***: Apo-Feno; Fenardin; Fenoratio; Grofibrat; Lipanthyl; ***Port.***: Apteor†; Catalip; Lipanthyl†; Lipofen; Supralip; ***Rus.***: Lipanthyl (Липантил); Tricor (Трайкор); ***S. Afr.***: Lipanthyl; ***Singapore***: Apo-Feno-Micro; Fenogal Lidose; Fenosup; Lexemin; Lipanthyl; Trolip; ***Spain***: Liparison†; Secalip; ***Swed.***: Lipanthyl; ***Switz.***: Lipanthyl; ***Thai.***: Adfen; Colestrim; Febrate; Fenomed; Fenosup†; Fenox; Fibril; Fibrolan; Lexemin; Lipanthyl; Lipothin; Stanlip; Supralip; ***Turk.***: Fenogal; Lipanthyl; Lipofen; Secalip; ***UK***: Fenogal; Lipantil; Supralip; ***Ukr.***: Lipanthyl (Липантил)†; Lipicard (Ліпікард); Lipofen (Ліпофен); Tricor (Трайкор)†; ***USA***: Antara; Fenoglide; Fibricor; Lipofen; Lofibra; Tricor; Triglide; Trilipix.

Multi-ingredient Preparations. *Arg.*: Craveril Duo; Minuslip Duo; Cz.: Pravafenix; ***India***: AFF; Aova-F; Atchol-F; Atofast-F; Atorem-F; Atorfen; Atorin-F; Atorlip-F; Atormac-TG; Atornet-F; Atorva-TG; Atozide-F; Diplitor; Dyslip-TG; Dysliptin-TG; Fenostat; Fibator EZ; Fibator; Fibmet; Fibrovas; Genxvast-F; Inovas-F; Lipicard AV; Liplofin; Lorisk; Lorlip-EZ; Lorlip; Orvaz-FT; *Irl.*: Pravafenix; ***Mex.***: Felocor.

Pharmacopoeial Preparations
USP 36: Fenofibrate Capsules; Fenofibrate Tablets.

Fenoldopam Mesilate *(BANM, rINNM)*

Fénoldopam, Mésilate de; Fenoldopam, mesilato de; Fenoldopam Mesylate (USAN); Fenoldopami Mesilas; Mesilato de fenoldopam; SKF-82526-J; Фенолдопама Мезилат.

6-Chloro-2,3,4,5-tetrahydro-1-(*p*-hydroxyphenyl)-1*H*-3-benzazepine-7,8-diol methanesulfonate.

$C_{16}H_{16}ClNO_3.CH_4O_3S$=401.9

CAS — 67227-56-9 (fenoldopam); 67227-57-0 (fenoldopam mesilate).

ATC — C01CA19.

ATC Vet — QC01CA19.

UNII — HA3R0MY016.

Pharmacopoeias. In *US*.

USP 36: (Fenoldopam Mesylate). A white to off-white powder. Soluble in water. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from moisture.

Incompatibility. Physical incompatibility has been reported[1] with fenoldopam 80 micrograms/mL (as the mesilate) in 0.9% sodium chloride injection and the following drugs during simulated Y-site administration: aminophylline; ampicillin sodium; amphotericin B; bumetanide; cefoxitin sodium; dexamethasone sodium phosphate; diazepam; fosphenytoin sodium; furosemide; ketorolac tromethamine; methohexital sodium; methylprednisolone sodium succinate; pentobarbital sodium; phenytoin sodium; prochlorperazine edisilate; sodium bicarbonate; and thiopental sodium.

1. Trissel LA, *et al.* Compatibility of fenoldopam mesylate with other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 2003; 60: 80–5.

Stability. Fenoldopam mesilate, at concentrations ranging from 4 to 300 micrograms/mL in glucose 5% or sodium chloride 0.9%, has been reported[1] to be stable for 72 hours when stored at temperatures of 4 degrees or 23 degrees.

1. Trissel LA, *et al.* Stability of fenoldopam mesylate in two infusion solutions. *Am J Health-Syst Pharm* 2002; 59: 846–8.

Uses and Administration

Fenoldopam is a dopamine agonist that is reported to have a selective action at dopamine D_1-receptors, leading to vasodilatation. It is used in the short-term management of severe hypertension (below) and has also been tried in heart failure.

Fenoldopam is given intravenously as the mesilate, although doses are expressed in terms of the base; 1.31 micrograms of fenoldopam mesilate is equivalent to about 1 microgram of fenoldopam.

In the management of hypertensive crises, fenoldopam mesilate is given by continuous intravenous infusion for up to 48 hours, as a solution containing 40 micrograms/mL of fenoldopam. The dose should be adjusted according to response, in usual increments of 50 to 100 nanograms/kg per minute at not less than 15-minute intervals. The usual dose range is from 100 to 1600 nanograms/kg per minute.

For the use of fenoldopam in children, see below.

Administration in children. Fenoldopam has been used to induce hypotension in children undergoing surgery. A placebo-controlled study[1] in 76 children aged between 3 weeks and 12 years found that infusion at rates below 200 nanograms/kg per minute was ineffective, and that a dose of 800 nanograms/kg per minute was the most effective and well tolerated. Dose increases beyond this were associated with tachycardia but no further blood pressure reduction.

Fenoldopam has also been investigated to protect renal function and improve urine output in neonates undergoing cardiopulmonary bypass[2,3] (for example by infusion of 100 nanograms/kg per minute over 72 hours[3]) and in critically ill children,[4] but as in adults (see Nephrotoxicity, below) the extent of any benefit is unclear.

1. Hammer GB, *et al.* Pharmacokinetics and pharmacodynamics of fenoldopam mesylate for blood pressure control in pediatric patients. *BMC Anesthesiol* 2008; 8: 6.
2. Costello JM, *et al.* Initial experience with fenoldopam after cardiac surgery in neonates with an insufficient response to conventional diuretics. *Pediatr Crit Care Med* 2006; 7: 28–33.
3. Ricci Z, *et al.* Fenoldopam in newborn patients undergoing cardiopulmonary bypass: controlled clinical trial. *Interact Cardiovasc Thorac Surg* 2008; 7: 1049–53.
4. Moffett BS, *et al.* Renal effects of fenoldopam in critically ill pediatric patients: a retrospective review. *Pediatr Crit Care Med* 2008; 9: 403–6.

Hypertension. Fenoldopam has a rapid onset of action and short elimination half-life and may be used as an alternative to sodium nitroprusside in the management of hypertensive crises (see under Hypertension, p. 1251.1). Its use has been reviewed.[1-3] Comparative studies with sodium nitroprusside in patients with acute severe hypertension have shown fenoldopam to be equally effective in rapidly lowering blood pressure. Additionally, in contrast to nitroprusside, urine output, creatinine clearance, and sodium excretion may be increased by fenoldopam. Fenoldopam may therefore be particularly useful in patients with renal impairment, although this remains to be established.

1. Brogden RN, Markham A. Fenoldopam: a review of its pharmacodynamic and pharmacokinetic properties and intravenous clinical potential in the management of hypertensive urgencies and emergencies. *Drugs* 1997; 54: 634–50.
2. Post JB, Prishman WH. Fenoldopam: a new dopamine agonist for the treatment of hypertensive urgencies and emergencies. *J Clin Pharmacol* 1998; 38: 2–13.
3. Murphy MB, *et al.* Fenoldopam: a selective peripheral dopamine-receptor agonist for the treatment of severe hypertension. *N Engl J Med* 2001; 345: 1548–57.

Nephrotoxicity. Fenoldopam increases renal blood flow and has been tried to reduce the renal toxicity that may be associated with use of contrast media (see Effects on the Kidneys under Adverse Effects of Amidotrizoic Acid, p. 1582.2). Small studies in patients at risk of renal toxicity have shown benefit with fenoldopam,[1,2] but larger randomised studies[3,4] have found no advantage with fenoldopam plus hydration compared with hydration using sodium chloride 0.45% alone. However, a later meta-analysis[5] in patients undergoing cardiovascular surgery, who are at risk of acute renal failure, found that fenoldopam consistently reduced the need for renal replacement therapy, and reduced mortality. For mention of use in children and neonates see above.

A study[6] in patients undergoing liver transplantation (p. 1940.3) suggested that fenoldopam may have a role in preserving renal function, possibly by counteracting the renal toxicity associated with ciclosporin.

1. Chu VL, Cheng JWM. Fenoldopam in the prevention of contrast media-induced acute renal failure. *Ann Pharmacother* 2001; 35: 1278–82. Correction. *ibid.*: 1677.
2. Lepor NE. A review of contemporary prevention strategies for radiocontrast nephropathy: a focus on fenoldopam and N-acetylcysteine. *Rev Cardiovasc Med* 2003; 4 (suppl 1): S15–S20.
3. Allaqaband S, *et al.* Prospective randomized study of N-acetylcysteine, fenoldopam, and saline for prevention of radiocontrast-induced nephropathy. *Catheter Cardiovasc Interv* 2002; 57: 279–83.
4. Stone GW, *et al.* Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. *JAMA* 2003; 290: 2284–91.
5. Landoni G, *et al.* Fenoldopam reduces the need for renal replacement therapy and in-hospital death in cardiovascular surgery: a meta-analysis. *J Cardiothorac Vasc Anesth* 2008; 22: 27–33.
6. Biancofiore G, *et al.* Use of fenoldopam to control renal dysfunction early after liver transplantation. *Liver Transpl* 2004; 10: 986–92.

Adverse Effects and Precautions

The adverse effects of fenoldopam are mainly due to vasodilatation and include hypotension, flushing, dizziness, headache, and reflex tachycardia. Nausea and vomiting, and ECG abnormalities have also been reported. Hypokalaemia has occurred and serum-electrolyte concentrations should be monitored during therapy; blood pressure and heart rate should also be monitored. Fenoldopam may increase intra-ocular pressure and it should be used with caution in patients with glaucoma. Caution is also required in patients in whom hypotension could be deleterious, such as those with acute cerebral infarction or haemorrhage.

Effects on the heart. Although fenoldopam is usually associated with reflex tachycardia, precipitous bradycardia in 2 patients given fenoldopam infusion in a clinical study[1] forced the drug to be stopped.

1. Taylor AA, *et al.* Sustained hemodynamic effects of the selective dopamine-1 agonist, fenoldopam, during 48-hour infusions in hypertensive patients: a dose-tolerability study. *J Clin Pharmacol* 1999; 39: 471–9.

Interactions

The hypotensive effects of fenoldopam may be enhanced by other drugs with hypotensive actions. Beta blockers may block fenoldopam-induced reflex tachycardia and use of the drugs together is not recommended.

Pharmacokinetics

Steady-state plasma concentrations of fenoldopam occur about 20 minutes after starting continuous intravenous infusion. Fenoldopam is extensively metabolised with only about 4% of a dose being excreted unchanged. It is metabolised by conjugation (mainly glucuronidation, methylation, and sulfation). Fenoldopam and its metabolites are excreted mainly in the urine, and the remainder in the faeces. The elimination half-life of fenoldopam is about 5 minutes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Corlopam; *USA*: Corlopam.

Pharmacopoeial Preparations
USP 36: Fenoldopam Mesylate Injection.

Fibrinolysin ⊗

Fibrinase; Fibrinolisina (humana); Fibrinolysin (Human) (BAN); Fibrinolysin (Human) (rINN); Fibrinolysine (humaine); Fibrinolysinum (humanum); Plasmiini; Plasmin; Plasminum; Фибринолизин (Человека).

CAS — 9001-90-5 (fibrinolysin); 9004-09-5 (human fibrinolysin).

ATC — B01AD05.

ATC Vet — QB01AD05.

UNII — A4028U842W.

NOTE. In *Martindale* the term fibrinolysin is used for the exogenous substance and plasmin for the endogenous substance.

Profile

Fibrinolysin is a proteolytic enzyme derived from the activation of human plasminogen. Fibrinolysin derived from cattle (bovine fibrinolysin) and other animals is also available. Fibrinolysin converts fibrin into soluble products and also hydrolyses some other proteins. The role of plasmin (endogenous fibrinolysin) in the control of haemostasis is described further on p. 1124.3.

Fibrinolysin is used (generally as bovine fibrinolysin) with deoxyribonuclease for the debridement of wounds. It was formerly given parenterally for the treatment of thrombotic disorders. Ocriplasmin (p. 2574.1), a truncated form of fibrinolysin, is used in the treatment of vitreomacular adhesion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Saibai (赛百).

Multi-ingredient Preparations. *Arg.*: Clorfibrase; ***Austria***: Fibrolan; ***Braz.***: Cauterex; Fibrabene; Fibrase; Fibrinase c/Cloranfenicol; Gino Cauterex; Gino Fibrase; ***Chile***: Elase; *Cz.*: Fibrolan†; *Fr.*: Elase; ***Hung.***: Fibrolan; ***Indon.***: Plasmin; ***Malaysia***: Elase; ***Mex.***: Fibrase SA; Fibrase; ***Philipp.***: Plasmin; ***Pol.***: Fibrolan; ***Switz.***: Fibrolan.

Flecainide Acetate *(BANM, USAN, rINNM)*

Acetato de flecainida; Flecainida, acetato de; Flecainidacetat; Flécaïnide, acétate de; Flecainidi Acetas; Flekainidacetat; Flekainid-acetát; Flekainidlasetaatti; Flekainido acetatas; R-818; Флекаинида Ацетат.

N-(2-Piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide acetate.

$C_{17}H_{20}F_6N_2O_3.C_2H_4O_2$=474.4

CAS — 54143-55-4 (flecainide); 54143-56-5 (flecainide acetate).

ATC — C01BC04.

ATC Vet — QC01BC04.

UNII — M8U465Q1WQ.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Flecainide Acetate). A white or almost white, very hygroscopic crystalline powder. Soluble in water and in dehydrated alcohol; freely soluble in dilute acetic acid; practically insoluble in dilute hydrochloric acid. A 2.5% solution in water has a pH of 6.7 to 7.1. Store in airtight containers. Protect from light.

USP 36: (Flecainide Acetate). A white to slightly off-white crystalline powder; pK_a is 9.3. Soluble in water; freely soluble in alcohol.

Stability. Storage of an extemporaneously prepared flecainide syrup in a refrigerator led to crystallisation of the drug and a toxic dose being given.[1] It was suggested that oral liquid formulations of flecainide should be freshly reconstituted from a powder before each dose. However, other extemporaneous formulations have been reported[2,3] to be stable at room temperature and under refrigeration.

1. Stuart AG, *et al.* Is there a genetic factor in flecainide toxicity? *BMJ* 1989; 298: 117–18.
2. Wiest DB, *et al.* Stability of flecainide acetate in an extemporaneously compounded oral suspension. *Am J Hosp Pharm* 1992; 49: 1467–70.
3. Allen LV, Erickson MA. Stability of baclofen, captopril, diltiazem hydrochloride, dipyridamole, and flecainide acetate in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1996; 53: 2179–84.

Uses and Administration

Flecainide is a class Ic antiarrhythmic (p. 1243.1) used for the treatment of severe symptomatic ventricular arrhythmias such as sustained ventricular tachycardia; for premature ventricular contractions or non-sustained ventricular tachycardia resistant to other therapy; and for severe symptomatic supraventricular arrhythmias (AV nodal reciprocating tachycardia, arrhythmias associated with the Wolff-Parkinson-White syndrome, and paroxysmal atrial fibrillation in the absence of left ventricular dysfunction).

Flecainide is given orally or intravenously as the acetate. Treatment should be started in hospital. Doses should be adjusted after 3 to 5 days and reduced once control has been achieved. A suggested therapeutic plasma concentration range is 0.2 to 1 micrograms/mL.

In ventricular arrhythmias the usual initial oral dose of flecainide acetate is 100 mg twice daily; the maximum total dose is 400 mg daily although most patients will not need more than 300 mg daily. In supraventricular arrhythmias the usual initial oral dose is 50 mg twice daily and the maximum total dose is 300 mg daily.

For rapid control of arrhythmias flecainide acetate 2 mg/kg may be given intravenously over 10 to 30 minutes, to a maximum dose of 150 mg; the ECG should be monitored. If longer term parenteral therapy is necessary it is started with intravenous injection of 2 mg/kg over 30 minutes, as above, then continued by intravenous infusion of 1.5 mg/kg over the first hour, and 100 to 250 micrograms/kg per hour thereafter. The maximum cumulative dose in the first 24 hours should not exceed 600 mg. Infusion should not generally continue for more than 24 hours and oral therapy should be substituted as soon as possible.

The dose of flecainide should be reduced in renal impairment (see below).

For the use of flecainide in children, see below.

Flecainide has also been tried in the treatment of refractory neuropathic pain.

Administration. Flecainide is usually given orally or intravenously, but rapid and reliable absorption has been reported from a rectal solution in healthy subjects.[1] The mean time to achieve peak serum concentration was 0.67 hours and the mean bioavailability was 98%, compared with 1 hour and 78% for an oral solution and 4 hours and 81% for a tablet. The absorption of flecainide given rectally to 2 critically ill patients was good in one but poor in the other[2] and it was recommended that rectal dosage be reserved for patients unresponsive to maximal parenteral therapy and in whom the oral or nasogastric routes cannot be used.

1. Lie-A-Huen L, *et al.* Absorption kinetics of oral and rectal flecainide in healthy subjects. *Eur J Clin Pharmacol* 1990; 38: 595–8.
2. Quattrocchi FP, Karim A. Flecainide acetate administration by enema. *DICP Ann Pharmacother* 1990; 24: 1233–4.

Administration in children. Flecainide has been used successfully to treat arrhythmias in children,[1,2] including neonates,[2,3] and beneficial results have also been reported[4] with flecainide and sotalol together. US licensed product information recommends an initial oral dose of flecainide acetate 50 mg/m² daily in divided doses for those aged under 6 months and 100 mg/m² daily for those aged over 6 months; a dose of 200 mg/m² daily should not be exceeded.

The *BNFC* recommends the following doses of flecainide acetate:

- neonates: an **oral** dose of 2 mg/kg 2 or 3 times daily, adjusted according to response, or 1 to 2 mg/kg **intravenously** over 10 to 30 minutes, followed if necessary by continuous infusion at a rate of 100 to 250 micrograms/kg per hour until arrhythmia is controlled
- children aged 1 month to 12 years: an **oral** dose of 2 mg/kg 2 or 3 times daily, adjusted according to response to a maximum of 8 mg/kg or 300 mg daily, or 2 mg/kg **intravenously** over 10 to 30 minutes, followed if necessary by continuous infusion at a rate of 100 to 250 micrograms/kg per hour until arrhythmia is controlled (maximum cumulative dose 600 mg in 24 hours)
- children aged 12 to 18 years: as for adults (see Uses and Administration, above); the maximum oral dose should not exceed 300 mg daily in most children

1. Perry JC, Garson A. Flecainide acetate for treatment of tachyarrhythmias in children: review of world literature on efficacy, safety, and dosing. *Am Heart J* 1992; 124: 1614–21.
2. O'Sullivan JJ, *et al.* Digoxin or flecainide for prophylaxis of supraventricular tachycardia in infants? *J Am Coll Cardiol* 1995; 26: 991–4.
3. Ferlini M, *et al.* Flecainide as first-line treatment for supraventricular tachycardia in newborns. *J Cardiovasc Med (Hagerstown)* 2009; 10: 372–5.
4. Price JF, *et al.* Flecainide and sotalol: a new combination therapy for refractory supraventricular tachycardia in children <1 year of age. *J Am Coll Cardiol* 2002; 39: 517–20.

Administration in renal impairment. The plasma elimination half-life for flecainide may be prolonged in patients with renal impairment[1-3] and doses should be reduced. For patients with a creatinine clearance equal to or less than 35 mL/minute per 1.73 m² licensed product information states that the initial oral dose of flecainide acetate should not exceed 100 mg daily and plasma concentrations should be monitored; intravenous doses should be halved.

Special care with dosage adjustments should be taken in patients with renal impairment who are also poor metabolisers (see Metabolism, p. 1384.3).

1. Braun J, *et al.* Pharmacokinetics of flecainide in patients with mild and moderate renal failure compared with patients with normal renal function. *Eur J Clin Pharmacol* 1987; 31: 711–14.
2. Forland SC, *et al.* Oral flecainide pharmacokinetics in patients with impaired renal function. *J Clin Pharmacol* 1988; 28: 259–67.
3. Williams AJ, *et al.* Pharmacokinetics of flecainide acetate in patients with severe renal impairment. *Clin Pharmacol Ther* 1988; 43: 449–55.

Cardiac arrhythmias. Flecainide has an established role in the management of ventricular and supraventricular arrhythmias (p. 1266.1). It has been used in children (see above) and has also been successfully given to pregnant women (transplacental therapy) to treat fetal arrhythmias,[1,2] although there have been reports[3,4] of neonatal toxicity.

Use in patients with asymptomatic arrhythmias after myocardial infarction is not recommended since an increase in mortality was found in the Cardiac Arrhythmia Suppression Trial (CAST), in which flecainide[5-7] and the related class Ic antiarrhythmics encainide[5-7] and moracizine[8] were used in an attempt to reduce the risk of sudden death in post-infarction patients with premature ventricular contractions.

Flecainide has also been used in the diagnosis of Brugada syndrome.[9] This syndrome is characterised by syncope or aborted cardiac arrest due to ventricular tachycardia in the absence of organic heart disease, and is thought to be due to a deficiency in the inward sodium current in cardiac cells. Flecainide, because of its sodium-channel blocking action, exaggerates this deficiency and the resulting ST-segment elevation, and aids in diagnosis; however, it may precipitate serious ventricular arrhythmias[10] and must not be used for treatment.

1. Simpson JM, Sharland GK. Fetal tachycardias: management and outcome of 127 consecutive cases. *Heart* 1998; 79: 576–81.
2. Krapp M, *et al.* Flecainide in the intrauterine treatment of fetal supraventricular tachycardia. *Ultrasound Obstet Gynecol* 2002; 19: 158–64.
3. Rasheed A, *et al.* Neonatal ECG changes caused by supratherapeutic flecainide following treatment for fetal supraventricular tachycardia. *Heart* 2003; 89: 470.
4. Hall CM, Ward Platt MP. Neonatal flecainide toxicity following supraventricular tachycardia treatment. *Ann Pharmacother* 2003; 37: 1343–4.
5. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. CAST and beyond: implications of the cardiac arrhythmias suppression trial. *Circulation* 1990; 81: 1123–7.[Simultaneous publication occurred in *Eur Heart J* 1990; 11: 194–9].
6. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989; 321: 406–12.
7. Echt DS, *et al.* Mortality and morbidity in patients receiving encainide, flecainide, or placebo: The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991; 324: 781–8.
8. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992; 327: 227–33.
9. Singleton CB, McGuire MA. The Brugada syndrome: a recently recognised genetic disease causing sudden cardiac death. *Med J Aust* 2000; 173: 415–8.
10. Gasparini M, *et al.* Flecainide test in Brugada syndrome: a reproducible but risky tool. *Pacing Clin Electrophysiol* 2003; 26: 338–41.

Pain. Class Ic antiarrhythmics such as flecainide are among the drugs that have been used as analgesic adjuvants in neuropathic pain (p. 10.1), although the evidence for benefit with flecainide is limited. A positive response has been reported[1,2] in patients with severe pain due to nerve infiltration, but a controlled study had to be stopped[3] when supplies of the drug were withdrawn after the finding of increased mortality in a study in post-infarction patients (CAST; see Cardiac Arrhythmias, above), and later studies[4,5] found that flecainide was effective in only a minority of patients with cancer pain, although its effects could be substantial in responders.[5] A small study[4] has suggested that flecainide may be effective in postherpetic neuralgia.

1. Dunlop R, *et al.* Analgesic effects of oral flecainide. *Lancet* 1988; i: 420–1.
2. Sinnott C, *et al.* Flecainide in cancer nerve pain. *Lancet* 1991; 337: 1347.
3. Dunlop RJ, *et al.* Flecainide in cancer nerve pain. *Lancet* 1991; 337: 1347.
4. Chong SP, *et al.* Pilot study evaluating local anesthetics administered systemically for treatment of pain in patients with advanced cancer. *J Pain Symptom Manage* 1997; 13: 112–17.
5. von Gunten CF, *et al.* Flecainide for the treatment of chronic neuropathic pain: a Phase II trial. *Palliat Med* 2007; 21: 667–72.
6. Ichimata M, *et al.* Analgesic effects of flecainide on postherpetic neuralgia. *Int J Clin Pharmacol Res* 2001; 21: 15–19.

Adverse Effects

The most common adverse effects caused by flecainide affect the CNS and include dizziness, visual disturbances, and lightheadedness. Nausea, vomiting, headache, tremor, peripheral neuropathy, ataxia, and paraesthesia may also occur. These effects are generally transient and respond to dosage reduction. Other adverse CNS effects that have been reported rarely include hallucinations, amnesia, confusion, depression, dyskinesias, and convulsions. Skin reactions, including rare cases of urticaria, have also occurred and there have been isolated cases of photosensitivity. Disturbances of liver function have been reported rarely. Corneal deposits, pulmonary fibrosis, and pneumonitis have occurred during long-term therapy. Cardiovascular effects are less common than those on the CNS, but can be serious and sometimes fatal. Ventricular tachyarrhythmias have been reported, particularly in patients with a history of ventricular tachyarrhythmias and taking high doses of flecainide. Chest pain and myocardial infarction have also occurred. Flecainide produced an increased mortality rate when it was assessed for the control of asymptomatic ventricular arrhythmias in patients who had previously suffered a myocardial infarction (see Cardiac Arrhythmias under Uses and Administration, above).

Incidence of adverse effects. In a report of the non-cardiac adverse effects of flecainide from 1 short-term and 3 longer-term studies,[1] the most common adverse effects during both short- and long-term studies were dizziness and visual disturbances, which occurred in about 30% of patients. Headache and nausea both occurred in about 10% of patients. Other adverse effects reported include dyspnoea, chest pain, asthenia, fatigue, and tremor. Therapy was stopped because of non-cardiac adverse effects in 10% of patients in the short-term study, and in 6% of those in the chronic studies. A review of 60 studies using flecainide[2] reported that non-cardiac adverse effects (mainly gastrointestinal and CNS adverse effects) occurred in 12% of patients. The UK CSM stated in June 1991 that it had received reports of neurological (4 patients with sensory neuropathy, 2 with ataxia), corneal (2 with corneal deposits), and pulmonary (3 with pulmonary fibrosis and pneumonitis) reactions associated with the long-term use of flecainide.[3]

1. Gentzkow GD, Sullivan JY. Extracardiac adverse effects of flecainide. *Am J Cardiol* 1984; 53: 101B–105B.
2. Hohnloser SH, Zabel M. Short- and long-term efficacy and safety of flecainide acetate for supraventricular arrhythmias. *Am J Cardiol* 1992; 70: 3A–10A.
3. CSM. Multi-system adverse reactions following long-term flecainide therapy. *Current Problems* 31 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024449&RevisionSelectionMethod=LatestReleased (accessed 08/05/07)

Effects on the blood. Severe granulocytopenia believed to be related to flecainide occurred in a 66-year-old man 3 months after starting therapy.[1] Haematological findings suggested an immune-mediated reaction in which flecainide binds to normal neutrophils with subsequent recognition by specific antibodies resulting in enhanced destruction of mature granulocytes in peripheral blood and bone marrow.

1. Samlowski WE, *et al.* Flecainide-induced immune neutropenia: documentation of a hapten-mediated mechanism of cell destruction. *Arch Intern Med* 1987; 147: 383–4.

Effects on the eyes. In addition to visual disturbance, symptomatic corneal deposits have been reported[1] in patients taking flecainide. A study[2] in 38 patients found small corneal deposits in 14.5%, but visual function tests were normal.

1. Ulrik H, *et al.* Corneal deposits associated with flecainide. *BMJ* 1991; 302: 506–7.
2. Ikäheimo K, *et al.* Adverse ocular effects of flecainide. *Acta Ophthalmol Scand* 2001; 79: 175–6.

Effects on the heart. Like most antiarrhythmics, flecainide can have proarrhythmic effects,[1] and severe ventricular arrhythmias have been reported,[2] including fatal ventricular fibrillation[3] in a neonate given flecainide for supraventricular tachycardia. There has also been a report[4] of torsade de pointes, although this is generally less common with class Ic than with class Ia antiarrhythmics. For reports of increased cardiac mortality in patients given flecainide for asymptomatic arrhythmias, see Cardiac Arrhythmias under Uses and Administration, p. 1383.2.

1. Herre JM, *et al.* Inefficacy and proarrhythmic effects of flecainide and encainide for sustained ventricular tachycardia and ventricular fibrillation. *Ann Intern Med* 1990; 113: 671–6.
2. Falk RH. Flecainide-induced ventricular tachycardia and fibrillation in patients treated for atrial fibrillation. *Ann Intern Med* 1989; 111: 107–11.
3. Ackland F, *et al.* Flecainide induced ventricular fibrillation in a neonate. *Heart* 2003; 89: 1261.
4. Nogales Asensio JM, *et al.* Torsade-de-pointes in a patient under flecainide treatment: an unusual case of proarrhythmicity. *Int J Cardiol* 2007; 114: e65–e67.

Effects on the liver. Elevated liver enzymes and jaundice, reversible on stopping treatment, have been reported rarely with flecainide.

Conjugated hyperbilirubinaemia with jaundice developed in a newborn infant after maternal treatment with flecainide for fetal supraventricular tachycardia.[1]

1. Vanderhal AL, *et al.* Conjugated hyperbilirubinemia in a newborn infant after maternal (transplacental) treatment with flecainide acetate for fetal tachycardia and fetal hydrops. *J Pediatr* 1995; 126: 988–90.

Effects on the lungs. There have been reports[1-4] of interstitial pneumonitis associated with flecainide. See also under Incidence of Adverse Effects, p. 1383.3.

1. Akoun GM, *et al.* Flecainide-associated pneumonitis. *Lancet* 1991; 337: 49.
2. Hanston P, *et al.* Flecainide-associated interstitial pneumonitis. *Lancet* 1991; 337: 371–2.
3. Robain A, *et al.* Flecainide-associated pneumonitis with acute respiratory failure in a patient with the LEOPARD syndrome. *Acta Cardiol* 2000; 55: 45–7.
4. Pesenti S, *et al.* Diffuse infiltrative lung disease associated with flecainide: report of two cases. *Respiration* 2002; 69: 182–5.

Effects on mental state. Dysarthria and visual hallucinations were associated with elevated plasma concentration of flecainide (2500 nanograms/mL) in a patient.[1] A serial rise and fall in plasma-bilirubin concentration during flecainide therapy also suggested possible direct hepatotoxicity. There has also been a report[2] of paranoid psychosis in a patient receiving flecainide for neuropathic pain.

1. Ramhamadany E, *et al.* Dysarthria and visual hallucinations due to flecainide toxicity. *Postgrad Med J* 1986; 62: 61–2.
2. Bennett MI. Paranoid psychosis due to flecainide toxicity in malignant neuropathic pain. *Pain* 1997; 70: 93–4.

Effects on the nervous system. Peripheral neuropathy, reversible on stopping treatment, has been reported[1,2] in patients receiving flecainide long-term. The authors of one report[1] stated that, at the time (1992), the UK CSM had received 4 other reports possibly associated with flecainide and 3 reports of aggravation of pre-existing neuropathy;[1] not all cases were reversible.

1. Palace J, *et al.* Flecainide induced peripheral neuropathy. *BMJ* 1992; 305: 810.
2. Malesker MA, *et al.* Flecainide-induced neuropathy. *Ann Pharmacother* 2005; 39: 1580.

Lupus erythematosus. There has been a report[1] of a patient who developed painful eye movement during flecainide therapy. The pain resolved on withdrawal but recurred when flecainide was restarted, and was accompanied by lateral rectus spasm, a facial rash, and positive antinuclear factor, suggestive of lupus erythematosus.

1. Skander M, Isaacs PET. Flecainide, ocular myopathy, and antinuclear factor. *BMJ* 1985; 291: 450.

Treatment of Adverse Effects

In oral overdosage with flecainide activated charcoal may be considered if the patient presents within 1 hour of ingestion. Treatment is largely symptomatic and supportive and may need to be continued for extended periods of time because of the long half-life and the possibility of non-linear elimination at very high doses. Haemodialysis or haemoperfusion are unlikely to enhance elimination.

Overdosage. Severe cardiovascular toxicity in flecainide overdosage may be resistant to pacing and inotropes, and hypoperfusion of the kidneys and liver may reduce the elimination of flecainide, prolonging the toxic effects. Gastric decontamination is of uncertain benefit; forced diuresis has been used,[1] but probably had a negligible effect, and haemodialysis and haemoperfusion are not effective.[2] Patients may therefore require intensive and prolonged supportive treatment,[1,3] and there have been reports of the use of extracorporeal membrane oxygenation,[4] cardiopulmonary bypass,[5,6] or intra-aortic balloon pumping,[7] to maintain organ perfusion and allow flecainide elimination to occur, with complete recovery in some cases.[3,4,6,7] There have been reports[8-10] of the successful use of intravenous hypertonic sodium bicarbonate, including in children,[10] and it has been suggested that it may antagonise the sodium channel blockade produced by flecainide, as well as reversing the metabolic acidosis that commonly occurs. Magnesium sulfate has also been used in the management of electrocardiographic abnormalities secondary to overdosage.[11]

1. Winkelmann BR, Leinberger H. Life-threatening flecainide toxicity: a pharmacodynamic approach. *Ann Intern Med* 1987; 106: 807–14.
2. Braun J, *et al.* Failure of haemoperfusion to reduce flecainide intoxication: a case study. *Med Toxicol* 1987; 2: 463–7.
3. Hanley NA, *et al.* Survival in a case of life-threatening flecainide overdose. *Intensive Care Med* 1998; 24: 740–2.
4. Auzinger GM, Scheinkestel CD. Successful extracorporeal life support in a case of severe flecainide intoxication. *Crit Care Med* 2001; 29: 887–90.
5. Yasui RK, *et al.* Flecainide overdose: is cardiopulmonary support the treatment? *Ann Emerg Med* 1997; 29: 680–2.
6. Corkeron MA, *et al.* Extracorporeal circulatory support in near-fatal flecainide overdose. *Anaesth Intensive Care* 1999; 27: 405–8.
7. Timperley J, *et al.* Flecainide overdose—support using an intra-aortic balloon pump. *BMC Emerg Med* 2005; 5: 10.
8. Goldman MJ, *et al.* Sodium bicarbonate to correct widened QRS in a case of flecainide overdose. *J Emerg Med* 1997; 15: 183–6.
9. Lovecchio F, *et al.* Hypertonic sodium bicarbonate in an acute flecainide overdose. *Am J Emerg Med* 1998; 16: 534–7.
10. D'Alessandro LC, *et al.* Life-threatening flecainide intoxication in a young child secondary to medication error. *Ann Pharmacother* 2009; 43: 1522–7.
11. Williamson DG, *et al.* Management of persistent wide QRS in flecainide overdose with magnesium sulphate. *Emerg Med J* 2010; 27: 487–8.

Precautions

Flecainide treatment should be started in hospital or under specialist supervision and pacing rescue should be available when it is used in patients with conduction defects. Its use is limited to serious or life-threatening arrhythmias and it should not be given to control asymptomatic arrhythmias especially in patients with a history of myocardial infarction (see Cardiac Arrhythmias under Uses and Administration, p. 1383.2). Flecainide has some negative inotropic activity and may precipitate or aggravate heart failure in patients with compromised left ventricular function; it should therefore be used with extreme caution, if at all, in patients with heart failure. Flecainide has been shown to increase the endocardial pacing threshold and should be used with caution in patients with pacemakers. Electrolyte imbalances should be corrected before starting flecainide therapy. Reduction of dosage may be necessary in patients with renal impairment; extreme caution is needed in patients with pronounced hepatic impairment.

Breast feeding. Flecainide is distributed into breast milk but there have been no reports of infant exposure. Flecainide 100 mg was given orally every 12 hours to 11 healthy women, beginning 1 day after delivery and continuing for 5½ days.[1] The mean elimination half-life of flecainide from milk was 14.7 hours, very similar to the plasma elimination half-life. The mean milk to plasma ratios on study days 2 to 5 were 3.7, 3.2, 3.5, and 2.6 respectively but it was considered that the risk to breast-fed infants of ingesting toxic amounts of flecainide in breast milk would be very low. In another woman[2] who had been taking flecainide 100 mg twice daily since before pregnancy for ventricular arrhythmias, the ratio was 1.57 on day 5 postpartum and 2.18 on day 7. The American Academy of Pediatrics considers[3] flecainide to be usually compatible with breast feeding.

1. McQuinn RL, *et al.* Flecainide excretion in human breast milk. *Clin Pharmacol Ther* 1990; 48: 262–7.
2. Wagner X, *et al.* Coadministration of flecainide acetate and sotalol during pregnancy: lack of teratogenic effects, passage across the placenta, and excretion in human breast milk. *Am Heart J* 1990; 119: 700–2.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies flecainide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pregnancy. Flecainide crosses the placenta (see under Pharmacokinetics, p. 1385.1) and has been used for transplacental therapy of fetal cardiac arrhythmias (see under Uses and Administration, p. 1383.2). However, hyperbilirubinaemia was reported in an infant after maternal treatment with flecainide for fetal supraventricular tachycardia (see Effects on the Liver, above).

Interactions

Use of flecainide with other antiarrhythmics or arrhythmogenic drugs may increase the incidence of cardiac arrhythmias. Use with a beta blocker produces additive negative inotropic effects. Flecainide undergoes hepatic metabolism and its activity may be influenced by drugs that affect the enzymes responsible for its metabolism, including the cytochrome P450 isoenzyme CYP2D6.

Antiarrhythmics. *Amiodarone* increases the plasma-flecainide concentration when the two drugs are given together.[1] It has been recommended that the dose of flecainide should be reduced by about one-half, but because the effect of amiodarone differs widely between patients, plasma-flecainide concentrations should be monitored. The clearance of flecainide may be decreased by *quinidine* in patients who are extensive metabolisers, since quinidine inhibits the enzyme responsible for the metabolism of flecainide.[2] Cardiogenic shock and asystole occurred in 2 patients receiving flecainide when *verapamil* was added to their therapy.[3]

1. Shea P, *et al.* Flecainide and amiodarone interaction. *J Am Coll Cardiol* 1986; 7: 1127–30.
2. Birgersdotter UM, *et al.* Stereoselective genetically-determined interaction between chronic flecainide and quinidine in patients with arrhythmias. *Br J Clin Pharmacol* 1992; 33: 275–80.
3. Buss J, *et al.* Asystole and cardiogenic shock due to combined treatment with verapamil and flecainide. *Lancet* 1992; 340: 546.

Antimalarials. *Quinine* has been reported[1] to inhibit metabolism of flecainide in healthy subjects without altering its renal elimination, resulting in a reduction of total clearance and prolongation of the elimination half-life.

1. Munafo A, *et al.* Altered flecainide disposition in healthy volunteers taking quinine. *Eur J Clin Pharmacol* 1990; 38: 269–73.

Beta blockers. Use of flecainide and *propranolol* in healthy subjects increases the plasma concentration of both drugs. The negative inotropic effects of the two drugs on cardiac function are at most only additive, but combined treatment should be started with caution in patients with impaired left ventricular function.[1] Addition of *sotalol* to flecainide has produced profound bradycardia and AV block followed by cardiac arrest and death in a man with ventricular tachycardia.[2]

1. Holtzman JL, *et al.* The pharmacodynamic and pharmacokinetic interaction of flecainide acetate with propranolol: effects on cardiac function and drug clearance. *Eur J Clin Pharmacol* 1987; 33: 97–9.
2. Warren R, *et al.* Serious interactions of sotalol with amiodarone and flecainide. *Med J Aust* 1990; 152: 277.

Digoxin. For reference to an interaction between flecainide and digoxin leading to increased concentrations of digoxin, see Antiarrhythmics, under Interactions of Digoxin, p. 1356.2.

Food. *Milk* feeds reduced the absorption of flecainide in an infant who required a dose of 40 mg/kg daily to control supraventricular tachycardias. When milk feeds were replaced by glucose, the serum-flecainide concentration increased from 990 to 1824 nanograms/mL. Milk-fed infants on high doses of flecainide should have the dose reduced if milk is stopped or reduced.[1]

1. Russell GAB, Martin RP. Flecainide toxicity. *Arch Dis Child* 1989; 64: 860–2.

Histamine H_2-antagonists. *Cimetidine* has been reported to increase the bioavailability of flecainide in healthy subjects, probably due to a decrease in the metabolism of flecainide. Elimination half-life and renal clearance were unchanged.[1]

1. Tjandra-Maga TB, *et al.* Altered pharmacokinetics of oral flecainide by cimetidine. *Br J Clin Pharmacol* 1986; 22: 108–10.

Pharmacokinetics

Flecainide is almost completely absorbed after oral doses and does not undergo extensive first-pass hepatic metabolism. Although absorption is not affected by food or antacids, milk may inhibit absorption in infants (see above). Flecainide is metabolised to 2 major metabolites, *m-O*-dealkylated flecainide and *m-O*-dealkylated lactam of flecainide; both may have some activity, but this is unlikely to be clinically significant. Metabolism of flecainide appears to involve the cytochrome P450 isoenzyme CYP2D6 and is subject to genetic polymorphism (see Metabolism, below). It is excreted mainly in the urine, about 30% as unchanged drug and the remainder as metabolites. About 5% is excreted in the faeces. Excretion of flecainide is decreased in renal impairment, heart failure, and in alkaline urine. Haemodialysis removes only about 1% of an oral dose as unchanged flecainide.

The therapeutic plasma concentration range is generally accepted as 0.2 to 1 micrograms/mL. The elimination half-life of flecainide is about 20 hours and it is about 40% bound to plasma proteins.

Flecainide crosses the placenta and is distributed into breast milk.

Metabolism. Oxidative metabolism is an important route of flecainide elimination.[1] It is mediated by the cytochrome P450 isoenzyme CYP2D6, which shows genetic polymorphism. The mean elimination half-life of flecainide in poor metabolisers (5 to 10% of the population) was

found to be 11.8 hours compared with 6.8 hours in extensive metabolisers and the amounts of a dose excreted as unchanged drug in the urine were 51% and 31% respectively. These differences in pharmacokinetics will not usually be of clinical importance. However, in patients with renal impairment who are poor metabolisers, special care should be taken with dosage adjustments.

1. Mikus G, *et al.* The influence of the sparteine-debrisoquin phenotype on the disposition of flecainide. *Clin Pharmacol Ther* 1989; 45: 562–7.

Pregnancy. A study of the pharmacokinetics of flecainide, given to a mother during the third trimester of pregnancy for the treatment of fetal supraventricular tachycardia,[1] indicated that close to term flecainide crosses the placenta easily without accumulating in fetal blood, but with a high concentration in the amniotic fluid.

See also Effects on the Liver, p. 1384.1.

1. Bourget P, *et al.* Flecainide distribution, transplacental passage and accumulation in the amniotic fluid during the third trimester of pregnancy. *Ann Pharmacother* 1994; 28: 1031–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Diondel; *Austral.*: Flecatab; Tambocor; *Austria*: Aristocor; *Belg.*: Apocard; Docflecai†; Tambocor; *Canad.*: Tambocor; *Chile*: Tambocor†; *Cz.*: Tambocor; *Denm.*: Flecin; Tambocor; *Fin.*: Tambocor; *Fr.*: Flecaine; *Ger.*: Flecagamma; Tambocor; *Gr.*: Tambocor; *Hong Kong*: Tambocor; *Irl.*: Tambocor; *Israel*: Tambocor; *Ital.*: Almarytm; *Malaysia*: Tambocor; *Mex.*: Tambocor; *Neth.*: Flecajuna; Tambocor; *Norw.*: Tambocor; *NZ*: Tambocor; *Philipp.*: Tambocor; *Port.*: Apocard; *S.Afr.*: Tambocor; *Singapore*: Tambocor; *Spain*: Apocard; *Swed.*: Tambocor; *Switz.*: Tambocor; *Thai.*: Tambocor; *UK*: Tambocor; *USA*: Tambocor.

Pharmacopoeial Preparations
BP 2014: Flecainide Injection; Flecainide Tablets;
USP 36: Flecainide Acetate Oral Suspension; Flecainide Acetate Tablets.

Fluindione *(rINN)*

Fluindiona; Fluindionum; Fluorindione; LM-123; Флуиндион.
2-(4-Fluorophenyl)indan-1,3-dione.
$C_{15}H_9FO_2$=240.2
CAS — 957-56-2.
UNII — EQ35YMS20Q.

Profile

Fluindione is an oral indanedione anticoagulant with actions similar to those of warfarin (p. 1526.3). It is used in the management of thromboembolic disorders (p. 1273.2) but, as the indanediones are generally more toxic than warfarin (see Phenindione, p. 1467.3), its use is limited.

The usual initial dose is 20 mg daily; the dose is then adjusted according to coagulation tests.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Previscan.

Fluvastatin Sodium *(BANM, USAN, rINNM)*

Fluvastatin-Natrium; Fluvastatina sódica; Fluvastatine Sodique; Fluvastatinum natricum; Natrii Fluvastatinum; XU-62-320; Натрий Флувастатин.
Sodium (±)-(3*R**,5*S**,6*E*)-7-[3-(*p*-Fluorophenyl)-1-isopropylindol-2-yl]-3,5-dihydroxy-6-heptenoate.
$C_{24}H_{25}FNNaO_4$=433.5
CAS — 93957-54-1 (fluvastatin); 93957-55-2 (fluvastatin sodium).
ATC — C10AA04.
ATC Vet — QC10AA04.
UNII — PYF7O1FV7F.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Fluvastatin Sodium). A white or almost white, or pale yellow to pale reddish-yellow, very hygroscopic, amorphous or crystalline powder. It exhibits polymorphism. It may be anhydrous or contain a variable quantity of water. Soluble in water; freely soluble in methyl alcohol; practically insoluble in acetonitrile. A 5% solution in water has a pH of 8 to 10. Store in airtight containers. Protect from light.

USP 36: (Fluvastatin Sodium). A white to pale yellow, brownish-pale yellow, or reddish-pale yellow, hygroscopic powder. Soluble in water, in alcohol, and in methyl alcohol. A 1% solution in water has a pH of 8.0 to 10.0. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light and moisture.

Uses and Administration

Fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p. 1489.3). It is used to reduce total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol, in the treatment of hyperlipidaemias (p. 1248.1), including hypercholesterolaemias and combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias). It is also given as secondary prophylaxis for cardiovascular risk reduction (p. 1246.1) in patients with ischaemic heart disease, including patients who have had a percutaneous coronary intervention.

Fluvastatin is given orally as the sodium salt, but doses are expressed in terms of the base; 21.06 mg of fluvastatin sodium is equivalent to about 20 mg of base. The usual initial dose is 20 to 40 mg of fluvastatin once daily in the evening. This may be increased, if necessary, at intervals of 4 weeks or more, up to 80 mg daily, in two divided doses or as a once-daily modified-release preparation; patients requiring a large reduction in LDL-cholesterol may be started on the 80 mg daily dose. A dose of 80 mg daily may also be used in patients who have had a percutaneous coronary intervention.

For the use of fluvastatin in children, see below.

References.
1. Langtry HD, Markham A. Fluvastatin: a review of its use in lipid disorders. *Drugs* 1999; 57: 583–606.
2. Corsini A, *et al.* Fluvastatin: clinical and safety profile. *Drugs* 2004; 64: 1305–23.
3. Winkler K, *et al.* Risk reduction and tolerability of fluvastatin in patients with the metabolic syndrome: a pooled analysis of thirty clinical trials. *Clin Ther* 2007; 29: 1987–2000.
4. McDonald KJ, Jardine AG. The use of fluvastatin in cardiovascular risk management. *Expert Opin Pharmacother* 2008; 9: 1407–14.

Administration in children. Fluvastatin may be used in the management of children aged 9 years and over (or from 10 years in the USA) with heterozygous familial hypercholesterolaemia.[1] Suitable oral doses range from 20 mg once daily to 80 mg daily in 2 divided doses or as a once-daily modified release preparation, adjusted according to severity and response. US licensed product information recommends that dosage adjustments should be made at 6-week intervals.

1. van der Graaf A, *et al.* Efficacy and safety of fluvastatin in children and adolescents with heterozygous familial hypercholesterolaemia. *Acta Paediatr* 2006; 95: 1461–6.

Adverse Effects and Precautions

As for Simvastatin, p. 1492.1 and p. 1494.1, respectively.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluvastatin as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions of statins with other drugs are described under simvastatin (p. 1494.2). Fluvastatin is metabolised mainly by the cytochrome P450 isoenzyme CYP2C9 and does not have the same interactions with CYP3A4 inhibitors as simvastatin, although caution has been advised when such combinations are used. However, interactions may occur with inhibitors of CYP2C9, such as fluconazole; use with rifampicin, a CYP2C9 inducer, may reduce the bioavailability of fluvastatin by about 50%.

Pharmacokinetics

Fluvastatin is rapidly and completely absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver, its primary site of action. Metabolism is mainly by the cytochrome P450 isoenzyme CYP2C9, with only a small amount metabolised by CYP3A4. An absolute bioavailability of about 24% has been reported. It is more than 98% bound to plasma proteins. About 90% is excreted in the faeces, mainly as metabolites, with only about 6% being excreted in the urine.

General reviews.
1. Scripture CD, Pieper JA. Clinical pharmacokinetics of fluvastatin. *Clin Pharmacokinet* 2001; 40: 263–81.
2. Neuvonen PJ, *et al.* Pharmacokinetic comparison of the potential over-the-counter statins simvastatin, lovastatin, fluvastatin and pravastatin. *Clin Pharmacokinet* 2008; 47: 463–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lescol; *Austral.*: Lescol; Vastin; *Austria*: Lescol; *Belg.*: Lescol; *Braz.*: Fluvastat; Lescol; *Canad.*: Lescol; *China*: Lescol (来适可); *Cz.*: Fluvakarav; Fuvatalip; Lescol; Vuyator; *Denm.*: Dortelwestin; Edemestized†; Fedivan†; Flustatin†; Flurisan†; Fluvactalin; Fluvacur†; Fluvamyl; Fluvanidda; Fluvaratio; Fluvastadig; Fluvastaham; Fluvastamil; Fluvastasof; Fluvatamed†; Fluvatifi†; Fluviatin; Fluxstatin; Imasemamed; Lavesten; Lescol; Luvastix; Luvinsta; Lyavinmed†; Stadifluven; Stavatin; *Fin.*: Lescol; *Fr.*: Fractal; Lescol; *Ger.*: Cranoc†; LOCOL; *Gr.*: Hovalin; Lescol; *Hong Kong*: Lescol; *Hung.*: Lescol; Locholl†; Stipatin; *India*: Lescol; *Indon.*: Lescol; *Irl.*: Fluvat; Lescol; Lochol; Luvinsta†; Statease; *Israel*: Lescol; *Ital.*: Lescol; Lipaxan; Primesin; *Jpn*: Lochol; *Malaysia*: Lescol; *Mex.*: Lescol; Vastaflux†; *Neth.*: Lescol; Vaditon†; *Norw.*: Lescol; *Philipp.*: Lescol; *Pol.*: Lescol; *Port.*: Canef; Cardiol; Fluvaphar†; Lescol; *Rus.*: Lescol (Лескол); *S.Afr.*: Lescol; *Singapore*: Lescol; *Spain*: Digaril; Lescol; Liposit; Lymetel†; Vaditon; *Swed.*: Lescol; *Switz.*: Lescol; *Thai.*: Lescol; *Turk.*: Lescol; *UK*: Dorisin; Lescol; Luvinsta; Sinfatix; *Ukr.*: Lescol (Лескол); *USA*: Lescol.

Pharmacopoeial Preparations
USP 36: Fluvastatin Capsules.

Fondaparinux Sodium *(BAN, USAN, rINN)*

Fondaparin Sodium; Fondaparinuks Sodyum; Fondaparinuuksinatrium; Fondaparinux sódico; Fondaparinux Sodique; Fondaparinuxnatrium; Fondaparinuxum Natricum; Fondaparinuxum Natrium; Org-31540; SR-90107A; Фондапаринукс Натрия.
CAS — 114870-03-0.
ATC — B01AX05.
ATC Vet — QB01AX05.
UNII — X0Q6N9USOZ.

Uses and Administration

Fondaparinux is a synthetic pentasaccharide anticoagulant that acts as a selective inhibitor of factor Xa (activated factor X). It is used as the sodium salt in the management of venous thromboembolism (p. 1274.1), unstable angina (p. 1254.3), and acute myocardial infarction (p. 1257.1). It has also been used in patients with heparin-induced thrombocytopenia (see Effects on the Blood under Adverse Effects of Heparin, p. 1399.1).

For *prophylaxis* of **venous thromboembolism** in abdominal and orthopaedic surgery, fondaparinux sodium is given by subcutaneous injection in a dose of 2.5 mg once daily, starting at least 6 to 8 hours after surgery and continued for at least 5 to 9 days, or up to 32 days in hip fracture. For prophylaxis in high-risk medical patients, the same dose is given once daily for 6 to 14 days.

In the initial *treatment* of venous thromboembolism, fondaparinux sodium is given by subcutaneous injection once daily at a dose of 5 mg for patients weighing less than 50 kg, 7.5 mg for weight 50 to 100 kg, and 10 mg for weight over 100 kg. Treatment is usually continued for 5 to 9 days, and at least until oral anticoagulation is established. In the treatment of superficial-vein thrombosis, fondaparinux sodium is given by subcutaneous injection in a dose of 2.5 mg once daily and continued for 30 to 45 days.

Fondaparinux is also used in **unstable angina** and acute ST-elevation **myocardial infarction**, but is only indicated in patients for whom urgent percutaneous coronary intervention is not planned. It is given in a dose of 2.5 mg subcutaneously once daily for up to 8 days, with the first dose given intravenously in acute ST-elevation myocardial infarction. Heparin should be given at the time of the procedure if percutaneous coronary intervention is performed and fondaparinux should be restarted when clinically appropriate.

Doses of fondaparinux may need to be reduced in patients with renal impairment (see p. 1386.1).

References.
1. The Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003; 349: 1695–1702.
2. Reynolds NA, *et al.* Fondaparinux sodium: a review of its use in the prevention of venous thromboembolism following major orthopaedic surgery. *Drugs* 2004; 64: 1575–96.
3. Büller HR, *et al.* Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med* 2004; 140: 867–73.
4. The OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006; 295: 1519–30.
5. Cohen AT, *et al.* ARTEMIS Investigators. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. Abridged version: *BMJ* 2006; 332: 325–9. Full version: http://www.bmj.com/cgi/reprint/332/7537/325 (accessed 14/05/08)
6. Yusuf S, *et al.* Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006; 354: 1464–76.
7. Mehta SR, *et al.* OASIS 5 and 6 Investigators. Antithrombotic therapy with fondaparinux in relation to interventional management strategy in patients with ST- and non-ST-segment elevation acute coronary syndromes: an individual patient-level combined analysis of the Fifth and Sixth Organization to Assess Strategies in Ischemic Syndromes (OASIS 5 and 6) randomized trials. *Circulation* 2008; 118: 2038–46.

8. Karthikeyan G, *et al.* Fondaparinux in the treatment of acute coronary syndromes: evidence from OASIS 5 and 6. *Expert Rev Cardiovasc Ther* 2009; 7: 241–9.
9. Blackmer AB, *et al.* Fondaparinux and the management of heparin-induced thrombocytopenia: the journey continues. *Ann Pharmacother* 2009; 43: 1636–46.
10. Decousus H, *et al.* CALISTO Study Group. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. *N Engl J Med* 2010; 363: 1222–32.
11. Sharma T, *et al.* Update on fondaparinux: role in management of thromboembolic and acute coronary events. *Cardiovasc Hematol Agents Med Chem* 2010; 8: 96–103.

Administration in renal impairment. Fondaparinux is eliminated renally and should be used with caution in patients with renal impairment. US licensed product information contra-indicates its use in patients with creatinine clearance (CC) below 30 mL/minute, and advises caution in those with CC between 30 and 50 mL/minute. In the UK, recommendations are based on indication, as follows:

- in the *treatment of acute coronary syndromes*: contra-indicated if CC is below 20 mL/min
- in the *treatment of venous thromboembolism*: contra-indicated if CC is below 30 mL/min
- in the *prophylaxis of venous thromboembolism and in the treatment of superficial-vein thrombosis*: contra-indicated if CC is below 20 mL/min; reduce dose to 1.5 mg daily if CC is between 20 and 50 mL/min

Adverse Effects

As for Heparin, p. 1398.3.

Treatment of Adverse Effects

If bleeding occurs fondaparinux should be stopped and appropriate therapy given. Unlike heparin, there is no specific antidote for fondaparinux (but see below).

Overdosage. Activated eptacog alfa (recombinant factor VIIa) given 2 hours after an injection of fondaparinux was found[1] in healthy subjects to normalise coagulation times and thrombin generation for up to 6 hours, suggesting that it may be useful to treat bleeding complications, or if acute surgery is needed. A subsequent review[2] concluded that activated eptacog alfa was of benefit in the management of bleeding associated with certain anticoagulants including fondaparinux. Although the lowest effective dose was uncertain, 90 micrograms/kg had been reported to be effective for fondaparinux reversal. Use of repeat doses of eptacog alfa was not recommended.

1. Bijsterveld NR, *et al.* Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation* 2002; 106: 2550–54.
2. Vavra KA, *et al.* Recombinant factor VIIa to manage major bleeding from newer parenteral anticoagulants. *Ann Pharmacother* 2010; 44: 718–26.

Precautions

As for Heparin, p. 1399.3.

Fondaparinux should be used cautiously in those with a history of heparin-induced thrombocytopenia, and it should not be given to patients who have developed thrombocytopenia with heparin and who also have a positive *in-vitro* platelet aggregation test (that is, cross-reactivity) in the presence of fondaparinux itself.

Fondaparinux is contra-indicated in severe renal impairment, and special care is required in patients with body-weight below 50 kg.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fondaparinux as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/10/11)

Interactions

As for Heparin, p. 1400.2.

Pharmacokinetics

After subcutaneous injection fondaparinux sodium is rapidly and completely absorbed, with bioavailability of 100%. It is extensively bound in plasma, mainly to antithrombin III. It is excreted in the urine, with 64 to 77% of a dose excreted unchanged. The elimination half-life is between 17 and 21 hours, but is prolonged in patients with renal impairment, in the elderly, and in those weighing less than 50 kg.

References.

1. Donat F, *et al.* The pharmacokinetics of fondaparinux sodium in healthy volunteers. *Clin Pharmacokinet* 2002; 41 (suppl 2): 1–9.
2. Paolucci F, *et al.* Fondaparinux sodium mechanism of action: identification of specific binding to purified and human plasma-derived proteins. *Clin Pharmacokinet* 2002; 41 (suppl 2): 11–18.
3. Turpie AG, *et al.* Pharmacokinetic and clinical data supporting the use of fondaparinux 1.5 mg once daily in the prevention of venous thromboembolism in renally impaired patients. *Blood Coag Fibrinol* 2009; 20: 114–21.
4. Delavenne X, *et al.* Population pharmacokinetics of fondaparinux administered at prophylactic doses after major orthopaedic surgery in everyday practice. *Thromb Haemost* 2010; 104: 252–60.

Pregnancy. Although an *in vitro* study[1] reported that fondaparinux does not cross the placenta, a small study[2] in pregnant women who had received fondaparinux found that anti-factor Xa activity was elevated in umbilical cord blood, suggesting that a small amount of placental transfer had taken place.

1. Lagrange P, *et al.* Fondaparinux sodium does not cross the placental barrier: study using the in-vitro human dually perfused cotyledon model. *Clin Pharmacokinet* 2002; 41 (suppl 2): 47–9.
2. Dempfle C-EH. Minor transplacental passage of fondaparinux in vivo. *N Engl J Med* 2004; 350: 1914–15.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Arixtra; *Austral.*: Arixtra; *Austria*: Arixtra; *Belg.*: Arixtra; *Braz.*: Arixtra; *Canad.*: Arixtra; *Chile*: Arixtra; *China*: Arixtra (安卓); *Cz.*: Arixtra; *Denm.*: Arixtra; *Fin.*: Arixtra; *Fr.*: Arixtra; *Ger.*: Arixtra; *Gr.*: Arixtra; *Hung.*: Arixtra; *India*: Arixtra; *Indon.*: Arixtra; *Irl.*: Arixtra; *Israel*: Arixtra; *Ital.*: Arixtra; *Jpn*: Arixtra; *Malaysia*: Arixtra; *Mex.*: Arixtra; *Neth.*: Arixtra; Quixidar†; *Norw.*: Arixtra; *Philipp.*: Arixtra; *Pol.*: Arixtra; *Port.*: Arixtra; *Rus.*: Arixtra (Арикстра); *S.Afr.*: Arixtra; *Singapore*: Arixtra; *Spain*: Arixtra; *Swed.*: Arixtra; *Switz.*: Arixtra; *Thai.*: Arixtra; *Turk.*: Arixtra; *UK*: Arixtra; *Ukr.*: Arixtra (Арикстра); *USA*: Arixtra.

Fosinopril Sodium *(BANM, USAN, rINNM)*

Fosinoprilinatrium; Fosinopril-Natrium; Fosinopril sódico; Fosinopril Sodique; Fosinopril Sodyum; Fosinoprilnatrium; Fosinoprilum natricum; Natrii Fosinoprilum; SQ-28555; Натрий Фозиноприл.

(4*S*)-4-Cyclohexyl-1-[[(*RS*)-2-methyl-1-(propionyloxy)propoxy]-(4-phenylbutyl)phosphinylacetyl]-L-proline sodium.

$C_{30}H_{45}NNaO_7P$=585.7

CAS — 97825-24-6 (fosinopril); 98048-97-6 (fosinopril); 88889-14-9 (fosinopril sodium).

ATC — C09AA09.

ATC Vet — QC09AA09.

UNII — NW2RTH6T2N.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Fosinopril Sodium). A white or almost white, crystalline powder. It shows polymorphism. Freely soluble in water; sparingly soluble in dehydrated alcohol; practically insoluble in hexane.

USP 36: (Fosinopril Sodium). Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Fosinopril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1) and heart failure (p. 1262.3).

Fosinopril owes its activity to fosinoprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after 2 to 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic action lasts for about 24 hours, allowing once-daily dosing. Fosinopril is given orally as the sodium salt.

In the treatment of **hypertension**, the initial dose of fosinopril sodium is 10 mg once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Usual maintenance doses range from 10 to 40 mg once daily. In patients already taking diuretic therapy the diuretic should be withdrawn if possible several days before starting fosinopril, and resumed later if necessary.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision. Fosinopril sodium is given in an initial dose of 10 mg once daily and, if well tolerated, increased to a maximum of 40 mg once daily. An initial dose of 5 mg may be given in patients at high risk of hypotension.

For doses in children, see below.

Reviews.

1. Murdoch D, McTavish D. Fosinopril: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in essential hypertension. *Drugs* 1992; 43: 123–40.
2. Wagstaff AJ, *et al.* Fosinopril: a reappraisal of its pharmacology and therapeutic efficacy in essential hypertension. *Drugs* 1996; 51: 777–91.
3. Davis R, *et al.* Fosinopril: a review of its pharmacology and clinical efficacy in the management of heart failure. *Drugs* 1997; 54: 103–16.

Administration in children. US licensed product information recommends that fosinopril sodium may be given to children weighing over 50 kg in the treatment of hypertension in an oral dose of 5 to 10 mg once daily.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fosinopril as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Fosinopril acts as a prodrug of the diacid fosinoprilat, its active metabolite. About 36% of an oral dose of fosinopril is absorbed. Fosinopril is rapidly and completely hydrolysed to fosinoprilat in both gastrointestinal mucosa and liver. Peak plasma concentrations of fosinoprilat occur about 3 hours after an oral dose of fosinopril. Fosinoprilat is more than 95% bound to plasma proteins. It is excreted both in urine and in the faeces via the bile; it has been detected in breast milk. The effective half-life for accumulation of fosinoprilat after multiple doses of fosinopril is about 11.5 hours in patients with hypertension and about 14 hours in patients with heart failure.

References.

1. Singhvi SM, *et al.* Disposition of fosinopril sodium in healthy subjects. *Br J Clin Pharmacol* 1988; 25: 9–15.
2. Kostis JB, *et al.* Fosinopril: pharmacokinetics and pharmacodynamics in congestive heart failure. *Clin Pharmacol Ther* 1995; 58: 660–5.

Renal impairment. Total body clearance of fosinoprilat, the active metabolite of fosinopril, is slower in patients with renal impairment. However, pharmacokinetic studies in patients with varying degrees of impairment,[1-5] including those requiring dialysis, indicate that decreases in renal clearance may be compensated for, at least in part, by increases in hepatic clearance.

1. Hui KK, *et al.* Pharmacokinetics of fosinopril in patients with various degrees of renal function. *Clin Pharmacol Ther* 1991; 49: 457–67.
2. Gehr TWB, *et al.* Fosinopril pharmacokinetics and pharmacodynamics in chronic ambulatory peritoneal dialysis patients. *Eur J Clin Pharmacol* 1991; 41: 165–9.
3. Sica DA, *et al.* Comparison of the steady-state pharmacokinetics of fosinopril, lisinopril and enalapril in patients with chronic renal insufficiency. *Clin Pharmacokinet* 1991; 20: 420–7.
4. Gehr TWB, *et al.* The pharmacokinetics and pharmacodynamics of fosinopril in haemodialysis patients. *Eur J Clin Pharmacol* 1993; 45: 431–6.
5. Greenbaum R, *et al.* Comparison of the pharmacokinetics of fosinoprilat with enalaprilat and lisinopril in patients with congestive heart failure and chronic renal insufficiency. *Br J Clin Pharmacol* 2000; 49: 23–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Fospril; Monace; Monopril; *Austria*: Fositens; *Belg.*: Fosinil; *Braz.*: Fospraz; Monopril; *Canad.*: Monopril; *Chile*: Monopril†; *China*: Monopril (蒙诗); *Cz.*: Apo-Fosinop; Fenosimed; Fosinogen; Monace; Monopril; *Fr.*: Fozitec; *Ger.*: Dynacil†; Fosinorm†; *Gr.*: Monopril; Sinopril; *Hong Kong*: Monopril†; *Hung.*: Monopril; Noviform; *India*: Fosinace; Fovas; *Indon.*: Acenor-M†; *Ital.*: Eliten; Fosipres; Tensogard; *Mex.*: Monopril; *Neth.*: NewAce†; *Philipp.*: BPNorm; *Pol.*: Monopril†; *Port.*: Fositen; *Rus.*: Fosicard (Фозикард); Monopril (Моноприл); *S.Afr.*: Monopril; *Spain*: Fositens; Hiperlex†; Tenso Stop; Tensocardil†; *Swed.*: Monopril†; *Switz.*: Fositen†; *Thai.*: Monopril†; *Turk.*: Forsace; *Monopril*; *UAE*: Fospril; *UK*: Staril†; *Ukr.*: Fosicard (Фозикард); *USA*: Monopril; *Venez.*: Monopril.

Multi-ingredient Preparations. *Austral.*: Fosetic; Hyforil; Monoplus; *Austria*: Fosicomb; *Braz.*: Monoplus; *Chile*: Monopril Plus†; *Cz.*: Foprin Plus H†; Monace Combi; *Fr.*: Foziretic; *Ger.*: Dynacil comp; Fosinorm comp†; *Gr.*: Fozide; Monoplus; *Hung.*: Duopril; Fosicard Plus; Noviform Plusz; *Ital.*: Fosicombi; Tenozide; *Neth.*: Diurace†; *Port.*: Fositen Plus; *Rus.*: Fosicard B (Фозикард Н); Fozide (Фозид); *S.Afr.*: Monozide†; *Spain*: Fositens Plus; Hiperlex Plus†; Tenso Stop Plus; *Switz.*: Fosicomp; *Thai.*: Monoplus; *Turk.*: Forsace Plus; Monopril Plus; *Ukr.*: Fosicard H (Фозикард Н); *USA*: Monopril-HCT; *Venez.*: Monopril Plus.

Pharmacopoeial Preparations

USP 36: Fosinopril Sodium and Hydrochlorothiazide Tablets; Fosinopril Sodium Tablets.

Furosemide (BAN, USAN, rINN) ⊗

Frusemide; Furosemid; Furosemida; Furosémide; Furosemidi; Furosemidum; Furoszemid; Furozemidas; LB-502; Dypoce-mid.

4-Chloro-*N*-furfuryl-5-sulphamoylanthranilic acid.

$C_{12}H_{11}ClN_2O_5S$=330.7

CAS — 54-31-9.

ATC — C03CA01.

ATC Vet — QC03CA01.

UNII — 7LXU5N7ZOS.

NOTE. Compounded preparations of furosemide may be represented by the following names:

- Co-amilofruse (*BAN*)—furosemide 8 parts and amiloride hydrochloride 1 part (w/w).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Furosemide). A white or almost white, crystalline powder. Practically insoluble in water and in dichloromethane; sparingly soluble in alcohol; soluble in acetone. It dissolves in dilute solutions of alkali hydroxides. Protect from light. It shows polymorphism.

USP 36: (Furosemide). A white to slightly yellow, odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone, in dimethylformamide, and in solutions of alkali hydroxides; very slightly soluble in chloroform; slightly soluble in ether; soluble in methyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Solutions for injection are prepared with the aid of sodium hydroxide, giving solutions with a pH of 8.0 to 9.3.

Incompatibility. Solutions of furosemide for injection are alkaline and should not be mixed or diluted with glucose injection or other acidic solutions.

Furosemide injection has been reported[1] to be visually incompatible with injections of diltiazem hydrochloride, dobutamine hydrochloride, dopamine hydrochloride, labetalol hydrochloride, midazolam hydrochloride, milrinone lactate, nicardipine hydrochloride, and vecuronium bromide. Incompatibility has also been noted with parenteral nutrient solutions,[2] with cisatracurium besilate,[3] with levofloxacin,[4] with phenylephrine,[5] and with vasopressin.[5]

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; 54: 64–5.
2. Trissel LA, *et al.* Compatibility of parenteral nutrient solutions with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; 54: 1295–1300.
3. Trissel LA, *et al.* Compatibility of cisatracurium besylate with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; 54: 1735–41.
4. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; 56: 1458–9.
5. Faria CE, *et al.* Visual compatibility of furosemide with phenylephrine and vasopressin. *Am J Health-Syst Pharm* 2006; 63: 906–8.

Stability. A study[1] showed that furosemide injection (10 mg/mL) in 25% human albumin solution was stable for 48 hours at room temperature when protected from light, and for 14 days under refrigeration. No bacterial or fungal growth was found.

1. Elwell RJ, *et al.* Stability of furosemide in human albumin solution. *Ann Pharmacother* 2002; 36: 423–6.

Uses and Administration

Furosemide is a potent diuretic with a rapid action. Like the other loop or high-ceiling diuretics it is used in the treatment of oedema associated with heart failure (p. 1388.1), including pulmonary oedema, and with renal and hepatic disorders (but see Precautions, p. 1389.2) and may be effective in patients unresponsive to thiazide diuretics. It is also used in high doses in the management of oliguria due to renal failure or insufficiency. Furosemide is also used in the treatment of hypertension (p. 1251.1), either alone or with other antihypertensives.

Furosemide inhibits the reabsorption of electrolytes mainly in the thick ascending limb of the loop of Henle and also in the distal renal tubules. It may also have a direct effect in the proximal tubules. Excretion of sodium, potassium, calcium, and chloride ions is increased and water excretion enhanced. It has no clinically significant effect on carbonic anhydrase. See Action, below, for further reference to its mechanism of action.

Administration and dosage. Furosemide's effects are evident within 30 minutes to 1 hour after an oral dose, peak at 1 to 2 hours, and last for about 6 hours; after intravenous injection its effects are evident in about 5 minutes and last for about 2 hours. It is given orally, usually in the morning. Alternatively it may be given intramuscularly or intravenously as the sodium salt; doses are expressed in terms of furosemide base. 10.7 mg of furosemide sodium is equivalent to about 10 mg of furosemide base. Licensed product information recommends that whether by direct intravenous injection or by infusion the rate of intravenous dosage should not exceed 4 mg/minute although the *BNF* advises that a single dose of up to 80 mg may be given more rapidly. In patients with renal impairment, a lower maximum infusion rate of 2.5 mg/minute has been suggested.

Unlike the thiazide diuretics where, owing to their flat dose-response curve, very little is gained by increasing the dose, furosemide has a steep dose-response curve, which gives it a wide therapeutic range.

In the treatment of **oedema**, the usual initial oral dose is 40 mg once daily, adjusted as necessary according to response. Mild cases may respond to 20 mg daily or 40 mg on alternate days. Some patients may need doses of 80 mg or more daily given as one or two doses daily, or intermittently. Severe cases may require gradual titration of the furosemide dosage up to 600 mg daily. In an emergency or when oral therapy cannot be given, 20 to 50 mg of furosemide may be given by slow intravenous injection; intramuscular injection may be given in exceptional cases but is not suitable for acute conditions. If necessary further doses may be given, increasing by 20-mg increments and not given more often than every 2 hours, up to a maximum daily dose of 1.5 g. If doses above 50 mg are required they should be given by slow intravenous infusion. For pulmonary oedema, if an initial slow intravenous injection of 40 mg does not produce a satisfactory response within one hour, a further 80 mg may be given slowly intravenously.

In the treatment of **hypertension**, furosemide is given in oral doses of 40 to 80 mg daily, either alone, or with other antihypertensives.

High-dose therapy. In the management of **oliguria** in acute or chronic renal failure where the glomerular filtration rate is less than 20 mL/minute but greater than 5 mL/minute, furosemide 250 mg diluted to 250 mL in a suitable diluent is infused over one hour. If urine output is insufficient within the next hour, this dose may be followed by 500 mg added to an appropriate infusion fluid, the total volume of which must be governed by the patient's state of hydration, and infused over about 2 hours. If a satisfactory urine output has still not been achieved within one hour of the end of the second infusion then a third dose of 1 g may be infused over about 4 hours. The rate of infusion should never exceed 4 mg/minute. In oliguric patients with significant fluid overload, the injection may be given without dilution directly into the vein, using a constant rate infusion pump with a micrometer screw-gauge adjustment; the rate should still never exceed 4 mg/minute. Patients who do not respond to a dose of 1 g probably require dialysis. If the response to either dosage method is satisfactory, the effective dose (of up to 1 g) may then be repeated every 24 hours. Dosage adjustments should subsequently be made according to the patient's response. Alternatively, oral treatment may be maintained; 500 mg should be given orally for each 250 mg required by injection.

When used in chronic renal impairment, an initial oral dose of 250 mg may be given, increased, if necessary in steps of 250 mg every 4 to 6 hours to a maximum of 1.5 g in 24 hours; in exceptional cases up to 2 g in 24 hours may be given. Dosage adjustments should subsequently be made according to the patient's response.

For doses in children, see below.

Action. The mechanism of action of furosemide is not fully understood.[1] It appears to act mainly by inhibiting active reabsorption of chloride ions in the ascending limb of the loop of Henle. Urinary excretion of sodium, chloride, potassium, hydrogen, calcium, magnesium, ammonium, bicarbonate, and possibly phosphate is increased; the chloride excretion exceeds that of sodium and there is an enhanced exchange of sodium for potassium leading to greater excretion of potassium. The resulting low osmolality of the medulla inhibits the reabsorption of water by the kidney. There is a possibility that furosemide may also act at a more proximal site.

In addition to its diuretic actions, furosemide has been shown to increase peripheral venous capacitance and reduce forearm blood flow. It also reduces renal vascular resistance with a resultant increase in renal blood flow the degree of which is proportional to the initial resistance.

Furosemide has been shown to increase plasma-renin activity, plasma-noradrenaline concentrations, and plasma-arginine-vasopressin concentrations. Alterations in the renin-angiotensin-aldosterone system may play a part in the development of acute tolerance. Furosemide increases renal-prostaglandin concentrations but it is unknown whether this is due to increased synthesis or inhibition of degradation or both. Prostaglandins appear to mediate the diuretic/natriuretic action. The primary effects appear to be alterations in renal haemodynamics with subsequent increases in electrolyte and fluid excretion.

The diuretic response to furosemide is related to the concentration in the urine, not to that in the plasma. Furosemide is delivered to the renal tubules by a non-specific organic acid pump in the proximal tubules.[1]

In some cases sodium intake may be sufficient to overcome the diuretic effect, and limiting sodium intake could restore responsiveness.[2]

1. Ponto LLB, Schaenwald RD. Furosemide (frusemide): a pharmacokinetic/pharmacodynamic review (part I). *Clin Pharmacokinet* 1990; 18: 381–408.
2. Brater DC. Resistance to loop diuretics: why it happens and what to do about it. *Drugs* 1985; 30: 427–43.

Administration. Continuous intravenous infusion of loop diuretics may be more effective than intermittent intravenous bolus injection and may provide a more consistent urine flow with fewer alterations in urine balance.[1,2] Bumetanide was more effective by continuous infusion than as bolus doses in 8 patients with severe chronic renal impairment.[3] In 20 patients with chronic heart failure requiring high-dose furosemide therapy, furosemide given by continuous infusion was more effective than the same dose by bolus injection.[4] The lower plasma concentrations associated with continuous infusion may also reduce the risk of toxicity.

1. Yelton SL, *et al.* The role of continuous infusion loop diuretics. *Ann Pharmacother* 1995; 29: 1010–14.
2. Gulbis BE, Spencer AP. Efficacy and safety of a furosemide continuous infusion following cardiac surgery. *Ann Pharmacother* 2006; 40: 1797–1803.
3. Rudy DW, *et al.* Loop diuretics for chronic renal insufficiency: a continuous infusion is more efficacious than bolus therapy. *Ann Intern Med* 1991; 115: 360–6.
4. Dormans TPJ, *et al.* Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. *J Am Coll Cardiol* 1996; 28: 376–82.

Administration in children. Furosemide has been given to neonates, infants, and children in the treatment of oedema and oliguria. For **oedema**, UK licensed product information allows an *oral* dose of 1 to 3 mg/kg daily in the morning, to a maximum of 40 mg daily, or an *intravenous* injection or infusion of 0.5 to 1.5 mg/kg daily, to a maximum of 20 mg daily. Alternatively, the *BNFC* suggests the following regimens, given according to age:

Oral

- neonate: 0.5 to 2 mg/kg every 12 to 24 hours (every 24 hours if postmenstrual age is under 31 weeks)
- 1 month to 12 years: 0.5 to 2 mg/kg given 2 or 3 times daily (every 24 hours if postmenstrual age is under 31 weeks); higher doses may be required in resistant oedema. Maximum daily dose is the smaller of 12 mg/kg or 80 mg
- 12 to 18 years: usually 20 to 40 mg daily; 80 to 120 mg daily is permitted in resistant oedema

Slow intravenous injection

- neonate: 0.5 to 1 mg/kg every 12 to 24 hours (every 24 hours if postmenstrual age under 31 weeks)
- 1 month to 12 years: 0.5 to 1 mg/kg (maximum 2 mg/kg or 40 mg, whichever is smaller) every 8 hours as necessary
- 12 to 18 years: 20 to 40 mg every 8 hours as necessary. Resistant oedema may require higher doses

Continuous intravenous infusion

- 1 month to 18 years: 0.1 to 2 mg/kg per hour. After cardiac surgery, the lower dose of 100 micrograms/kg per hour should be given initially, and doubled every 2 hours until urine output exceeds 1 mL/kg per hour

In the treatment of **oliguria**, the *BNFC* suggests the following doses:

Oral

- 12 to 18 years: an initial dose of 250 mg daily, adjusted if necessary by 250 mg increments given every 4 to 6 hours. A maximum single dose of 2 g is permitted.

Intravenous infusion

- 1 month to 12 years: 2 to 5 mg/kg up to 4 times daily (maximum 1 g daily)
- 12 to 18 years: an initial dose of 250 mg given over 1 hour. If a satisfactory urine output is not obtained, a further 500 mg may be given over 2 hours, then a further 1 g over 4 hours if necessary. If no response is obtained, dialysis is probably required. The effective dose (up to 1 g) may be repeated every 24 hours.

Ascites. Dietary sodium restriction and diuretics are mainstays of the management of cirrhotic ascites (p. 1276.2). Spironolactone is usually the diuretic of first choice, but furosemide may be added to therapy as necessary.

Bronchopulmonary dysplasia. Bronchopulmonary dysplasia is a major cause of chronic lung disease in infants. Treatment often involves the use of corticosteroids (see p. 1602.1). Additional supportive therapy may include the use of diuretics such as furosemide.

Alternate-day therapy with oral furosemide 4 mg/kg has produced modest benefits in pulmonary status in the absence of a diuretic effect, and few adverse effects.[1] Improved pulmonary function has occurred in infants

given furosemide 1 mg/kg parenterally after packed red blood cell transfusions, given to improve oxygen-carrying capacity.[2] The successful use of nebulised furosemide in a dose of 1 mg/kg has been reported;[3,4] again pulmonary status was improved without production of diuresis or renal adverse effects. However, a single inhaled dose of 1 mg/kg failed to improve pulmonary mechanics in another study involving older infants with more severe disease.[5] Systematic reviews of the use of intravenous or oral,[6] or nebulised[7] diuretics in preterm infants with chronic lung disease concluded that, although there were improvements in pulmonary function, there was insufficient evidence to recommend routine use.

1. Rush MG, *et al.* Double-blind, placebo-controlled trial of alternate-day furosemide therapy in infants with chronic bronchopulmonary dysplasia. *J Pediatr* 1990; 117: 112–18.
2. Stefano JL, Bhutani VK. Role of furosemide therapy after boosterpacked erythrocyte transfusions in infants with bronchopulmonary dysplasia. *J Pediatr* 1990; 117: 965–8.
3. Rastogi A, *et al.* Nebulized furosemide in infants with bronchopulmonary dysplasia. *J Pediatr* 1994; 125: 976–9.
4. Prabhu VG, *et al.* Pulmonary function changes after nebulised and intravenous frusemide in ventilated premature infants. *Arch Dis Child* 1997; 77: F32–F35.
5. Kugelman A, *et al.* Pulmonary effect of inhaled furosemide in ventilated infants with severe bronchopulmonary dysplasia. *Pediatrics* 1997; 99: 71–5.
6. Brion LP, Primhak RA. Intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 24/06/05).
7. Brion LP, *et al.* Aerosolized diuretics for preterm infants with (or developing) chronic lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 07/05/08).

Haemolytic-uraemic syndrome. Renal failure is a possible consequence of the haemolytic-uraemic syndrome (see Thrombotic Microangiopathies, p. 1159.1). Correction of any hypovolaemic state with adequate fluids and of oliguria by inducing diuresis with furosemide may be used to prevent this.

Of 54 children with haemolytic-uraemic syndrome given intravenous furosemide 2.5 to 4 mg/kg every 3 to 4 hours immediately after diagnosis 24% eventually required dialysis.[1] In contrast, a retrospective analysis of 39 patients treated conservatively showed that 82% had required dialysis. The results therefore suggested that high-dose furosemide could prevent the progression of oliguria to anuria in these patients by increasing urate clearance.

1. Rousseau E, *et al.* Decreased necessity for dialysis with loop diuretic therapy in hemolytic uremic syndrome. *Clin Nephrol* 1990; 34: 22–5.

Heart failure. Diuretics have been the mainstay in the treatment of heart failure (p. 1262.3) but drugs such as ACE inhibitors that have been shown to improve mortality are now generally recommended for first-line therapy along with diuretics. Diuretics provide very effective symptomatic control in patients with peripheral or pulmonary oedema and rapidly relieve dyspnoea. If symptoms of fluid retention are only mild, a thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide, may be adequate. However, in most cases, especially in moderate or severe fluid retention, a loop diuretic such as furosemide will be necessary. Combination treatment with diuretics that behave synergistically by acting at different sites (the principle of sequential nephron blockade), namely a loop diuretic with a thiazide or potassium-sparing diuretic, may be needed in some patients, especially when there is diuretic resistance.

Patients have been successfully treated using continuous intravenous infusions[1] or high doses (up to 8 g daily) of furosemide given by intravenous infusion[2,3] or orally.[3] A patient who was successfully maintained on intravenous furosemide at home has been described.[4] Combination of furosemide with thiazide diuretics[5] or metolazone[6,7] has been reported. There is a danger of overdiuresis with both of these strategies, and careful monitoring of electrolytes and renal function is essential.[8] Delivery of furosemide to the renal tubules may be enhanced by combined therapy with hydralazine[9] or captopril.[10] The use of captopril and furosemide may also correct hyponatraemia without fluid restriction.[11] In elderly patients not responding adequately to low-dose furosemide with optimum doses of ACE inhibitors, increasing the dose of furosemide (to an average of 297 mg daily orally) has been reported[12] to be of benefit. However, caution is necessary when using furosemide with antihypertensives and especially ACE inhibitors since these combinations can result in sudden and profound hypotension and renal toxicity. Low-dose dopamine infusion has been suggested as an alternative to high-dose furosemide infusion and may cause less toxicity. In a study[13] in patients with severe refractory heart failure given optimal therapy with ACE inhibitors, oral diuretics, nitrates, and digoxin, additional therapy with low-dose intravenous dopamine (4 micrograms/kg per minute) and low-dose oral furosemide (80 mg daily) was as effective as intravenous high-dose furosemide (10 mg/kg daily) but caused less hypokalaemia and renal impairment. Use of intravenous hypertonic saline has also been reported[14] to augment the effect of furosemide.

For the suggestion that torasemide may be a better choice of loop diuretic in patients with heart failure see p. 1516.3.

1. Lawson DH, *et al.* Continuous infusion of frusemide in refractory oedema. *BMJ* 1978; 2: 476.
2. O'Rourke MF, *et al.* High-dose furosemide in cardiac failure. *Arch Intern Med* 1984; 144: 2429.
3. Gerlag PGG, van Meijel JJM. High-dose furosemide in the treatment of refractory congestive heart failure. *Arch Intern Med* 1988; 148: 286–91.
4. Hattersley AT, *et al.* Home intravenous diuretic therapy for patient with refractory heart failure. *Lancet* 1989; I: 446.
5. Channer KS, *et al.* Thiazides with loop diuretics for severe congestive heart failure. *Lancet* 1990; 335: 922–3.
6. Aravot DJ, *et al.* Oral metolazone plus frusemide for home therapy in patients with refractory heart failure. *Lancet* 1989; I: 727.
7. Friedland JS, Ledingham JGG. Oral metolazone plus frusemide for home therapy in patients with refractory heart failure. *Lancet* 1989; I: 727–8.
8. Oster JR, *et al.* Combined therapy with thiazide-type and loop diuretic agents for resistant-sodium retention. *Ann Intern Med* 1983; 99: 405–6.
9. Nomura A, *et al.* Effect of furosemide in congestive heart failure. *Clin Pharmacol Ther* 1981; 30: 177–82.
10. Dzau VJ, Hollenberg NK. Renal response to captopril in severe heart failure: role of furosemide in natriuresis and reversal of hyponatremia. *Ann Intern Med* 1984; 100: 777–82.
11. Hamilton RW, Buckalew VM. Sodium, water, and congestive heart failure. *Ann Intern Med* 1984; 100: 902–4.
12. Waterer G, Donaldson M. High-dose frusemide for cardiac failure. *Lancet* 1995; 346: 254.
13. Cotter G, *et al.* Increased toxicity of high-dose furosemide versus low-dose dopamine in the treatment of refractory congestive heart failure. *Clin Pharmacol Ther* 1997; 62: 187–93.
14. Paterna S, *et al.* Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. *Eur J Heart Fail* 2000; 2: 305–13.

Hypercalcaemia. Hypercalcaemia (p. 1778.1) usually results from an underlying disease and long-term management involves treating the cause. However, if significant symptoms are present, treatment is necessary to reduce plasma-calcium concentrations. This mainly involves rehydration, but loop diuretics such as furosemide have traditionally been used after rehydration to promote urinary calcium excretion, a practice that has been questioned.[1-3] Drugs such as bisphosphonates that inhibit bone resorption are now generally considered first-line where specific therapy is warranted, although loop diuretics may still have a role in the prevention of fluid overload or heart failure. Licensed doses used for hypercalcaemia have ranged from 20 to 240 mg of furosemide daily, given intravenously.

1. LeGrand SB, *et al.* Narrative review. Furosemide for hypercalcemia: an unproven yet common practice. *Ann Intern Med* 2008; 149: 259–63.
2. Robey RB, *et al.* Does furosemide have a role in the management of hypercalcemia? *Ann Intern Med* 2009; 150: 146–7.
3. LeGrand SB. Does furosemide have a role in the management of hypercalcemia? *Ann Intern Med* 2009; 150: 147.

Obstructive airways disease. In patients with *asthma*, furosemide given by oral inhalation has been found to protect against bronchoconstriction induced by exercise[1] and external stimuli,[2,3] although it did not improve bronchial hyperresponsiveness in a 4-week study[4] and provided no additional benefit when added to salbutamol for the treatment of acute asthma in a small study in children.[5] Mechanisms have been suggested for the protective effect of furosemide, including inhibition of electrolyte transport across epithelium, inhibition of inflammatory mediators, or an effect on mast cell function.[6] The potential for clinical applications remains unclear[4] and furosemide is not a part of the accepted schedules for the treatment of asthma (p. 1195.2).

Small studies in patients with *chronic obstructive pulmonary disease* have reported improvements in dyspnoea[7,8] and exercise capacity[8] with inhaled furosemide.

Inhaled furosemide has also been used to relieve *dyspnoea in patients with terminal cancer*.[9]

1. Munyard P, *et al.* Inhaled frusemide and exercise-induced bronchoconstriction in children with asthma. *Thorax* 1995; 50: 677–9.
2. Bianco S, *et al.* Protective effect of inhaled furosemide on allergen-induced early and late asthmatic reactions. *N Engl J Med* 1989; 321: 1069–73.
3. Seidenberg J, *et al.* Inhaled frusemide against cold air induced bronchoconstriction in asthmatic children. *Arch Dis Child* 1992; 67: 214–17.
4. Yates DH, *et al.* Effect of acute and chronic inhaled furosemide on bronchial hyperresponsiveness in mild asthma. *Am J Respir Crit Care Med* 1995; 152: 2173–5.
5. González-Sánchez R, *et al.* Furosemide plus albuterol compared with albuterol alone in children with acute asthma. *Allergy Asthma Proc* 2002; 23: 181–4.
6. Floreani AA, Rennard SI. Experimental treatments for asthma. *Curr Opin Pulm Med* 1997; 3: 30–41.
7. Ong K-C, *et al.* Effects of inhaled furosemide on exertional dyspnea in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 169: 1028–33.
8. Jensen D, *et al.* Mechanisms of dyspnoea relief and improved exercise endurance after furosemide inhalation in COPD. *Thorax* 2008; 63: 606–13.
9. Kallet RH. The role of inhaled opioids and furosemide for the treatment of dyspnea. *Respir Care* 2007; 52: 900–10.

Patent ductus arteriosus. The usual initial treatment for a haemodynamically significant ductus is reduction of fluid intake, correction of anaemia, support of respiration, and giving a diuretic. If that fails to control symptoms then indometacin is generally given to promote closure of the ductus (see p. 72.2).

Furosemide is often the diuretic chosen. It is effective and widely used but there has been concern that it might delay closure (and even increase the incidence of patent ductus arteriosus in infants treated for respiratory distress syndrome — see Effects in Infants and Neonates under Adverse Effects, p. 1389.1). A systematic review[1] of those treated for patent ductus concluded that this did not seem to be the case, and that the diuretic might reduce adverse renal effects of indometacin; however, the evidence for this was limited and it was felt that there was not enough evidence to support the use of furosemide in infants treated with indometacin.

1. Brion LP, Campbell DE. Furosemide for prevention of morbidity in indomethacin-treated infants with patent ductus arteriosus. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley, 2001 (accessed 12/07/05).

Raised intracranial pressure. Osmotic diuretics such as mannitol are first-line drugs for the management of raised *intracranial* pressure (p. 1271.3) but loop diuretics such as furosemide may be used as adjuncts.

Tinnitus. Furosemide is one of many drugs that have been tried in tinnitus (p. 1994.1), but although reported to be effective in some patients, it is rarely used because of problems with adverse effects.

Adverse Effects

Most adverse effects of furosemide occur with high doses, and serious effects are uncommon. The most common adverse effect is fluid and electrolyte imbalance including hyponatraemia, hypokalaemia, and hypochloraemic alkalosis, particularly after large doses or prolonged use. Signs of electrolyte imbalance include headache, hypotension, muscle cramps, dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, oliguria, cardiac arrhythmias, and gastrointestinal disturbances. Hypovolaemia and dehydration may occur, especially in the elderly. The risk of hypokalaemia may be less with loop diuretics such as furosemide, which have a short duration of action, than with thiazide diuretics. Unlike the thiazides, furosemide increases the urinary excretion of calcium and nephrocalcinosis has been reported in preterm infants.

Furosemide may cause hyperuricaemia and precipitate gout in some patients. It may provoke hyperglycaemia and glycosuria, but probably to a lesser extent than the thiazide diuretics.

Pancreatitis and cholestatic jaundice seem to occur more often than with the thiazides. Other adverse effects include blurred vision, yellow vision, dizziness, headache, and orthostatic hypotension. Other adverse effects occur rarely. Rashes and photosensitivity reactions may be severe; hypersensitivity reactions include interstitial nephritis and vasculitis; fever has also been reported. Bone marrow depression may occur: there have been reports of agranulocytosis, thrombocytopenia, and leucopenia. Tinnitus and deafness may occur, in particular during rapid high-dose parenteral furosemide. Deafness may be permanent, especially in patients taking other ototoxic drugs.

Incidence of adverse effects. In a survey of 553 hospital inpatients[1] receiving furosemide 220 patients (40%) had 480 adverse reactions. Electrolyte disturbances occurred in 130 (23.5%) patients and extracellular volume depletion in 50 (9%). Adverse reactions were more common in those with liver disease, and hepatic coma occurred in 20 patients with hepatic cirrhosis. A similar survey in 585 hospital inpatients[2] revealed 177 adverse effects in 123 (21%). These included volume depletion in 85 patients (14.5%), hypokalaemia in 21 (3.6%), and hyponatraemia in 6 (1%). Hypokalaemia was considered to be life-threatening in 2 patients. Hyperuricaemia occurred in 54 patients (9.2%), of whom 40 also had volume depletion, and clinical gout developed in 2.

1. Naranjo CA, *et al.* Frusemide-induced adverse reactions during hospitalization. *Am J Hosp Pharm* 1978; 35: 794–8.
2. Lowe J, *et al.* Adverse reactions to frusemide in hospital inpatients. *BMJ* 1979; 2: 360–2.

Carcinogenicity. See under Hydrochlorothiazide, p. 1404.2.

Dementia. Licensed product information states that more deaths were seen in elderly patients with dementia who were taking risperidone and furosemide than in those taking either drug alone; use of risperidone with other diuretics (mainly low-dose thiazides) was not associated with such findings. See also under Risperidone, p. 1105.1.

Effects on bone. The hypercalciuria caused by loop diuretics may alter bone metabolism, but the clinical significance of this is unknown. Results of studies have been conflicting: some have failed to show an adverse effect on bone mineral density[1] or risk of fracture[2] with loop diur-

etics, while others have reported a greater degree of bone loss[2,3] and an increased risk of fractures[4,5] in both men and women taking loop diuretics. However, the magnitude of effect has, at best, been modest, and interpretation of results has been complicated by confounding factors.

For mention of effects on bone in children (possibly associated with secondary hyperparathyroidism) see Effects in Infants and Neonates, below.

1. Lim LS, *et al.* Diuretic use and bone mineral density in older USA men: the osteoporotic fractures in men (MrOS) study. *Age Ageing* 2005; 34: 504–7.
2. Lim LS, *et al.* Loop diuretic use and rates of hip bone loss and risk of falls and fractures in older women. *J Am Geriatr Soc* 2009; 57: 855–62.
3. Lim LS, *et al.* Osteoporotic Fractures in Men (MrOS) Study Group. Loop diuretic use and increased rates of hip bone loss in older men: the Osteoporotic Fractures in Men Study. *Arch Intern Med* 2008; 168: 735–40.
4. Rejnmark L, *et al.* Fracture risk in patients treated with loop diuretics. *J Intern Med* 2006; 259: 117–24.
5. Carbone LD, *et al.* Loop diuretic use and fracture in postmenopausal women: findings from the Women's Health Initiative. *Arch Intern Med* 2009; 169: 132–40.

Effects on the ears. Ototoxicity and deafness during furosemide therapy is most frequently associated with elevated blood concentrations resulting from rapid intravenous infusion[1] or delayed excretion in patients with renal impairment.[2] Of 29 cases of furosemide-induced deafness reported to the FDA[3] in the USA, most patients had renal disease or had received the drug intravenously. Eight patients had also received another ototoxic drug. However, deafness occurred in 11 patients after oral use, and in 4 of these hearing loss occurred in the absence of renal disease or other ototoxic drugs. Hearing loss was generally transient, lasting from one-half to 24 hours, but permanent hearing loss occurred in 3 patients, one of whom had taken furosemide orally. Deafness was not always associated with high doses; six patients had received a total of 200 mg or less of furosemide.

See also Precautions, below.

1. Heidland A, Wigand ME. Einfluss hoher Furosemiddosen auf die Gehörfunktion bei Urämie. *Klin Wochenschr* 1970; 48: 1052–6.
2. Schwartz GH, *et al.* Ototoxicity induced by furosemide. *N Engl J Med* 1970; 282: 1413–14.
3. Gallagher KL, Jones JK. Furosemide-induced ototoxicity. *Ann Intern Med* 1979; 91: 744–5.

Effects on electrolyte balance. *CALCIUM.* Furosemide increases renal calcium excretion. There is a danger of hypocalcaemic tetany during furosemide use in hypoparathyroid patients[1] and it has also been reported[2] in a patient with latent hypoparathyroidism following thyroidectomy.

The decrease in serum-calcium concentrations could also induce hyperparathyroidism. In a study involving 36 patients with heart failure, furosemide was associated with elevations in both parathyroid hormone and alkaline phosphatase concentrations, possibly indicating accelerated bone remodelling such as that found in primary hyperparathyroidism.[3]

For the suggestion that hypercalciuria in those taking loop diuretics may affect bone metabolism, see Effects on Bone, p. 1388.3. For reports of hypercalciuria, rickets, renal calculi, and hyperparathyroidism in neonates given furosemide, see Effects in Infants and Neonates, below.

1. Gabow PA, *et al.* Furosemide-induced reduction in ionized calcium in hypoparathyroid patients. *Ann Intern Med* 1977; 86: 579–81.
2. Beshey A, MacNee W. Tetany induced by frusemide in latent hypoparathyroidism. *BMJ* 1987; 295: 960–1.
3. Elmgreen J, *et al.* Elevated serum parathyroid hormone concentration during treatment with high ceiling diuretics. *Eur J Clin Pharmacol* 1980; 18: 363–4.

MAGNESIUM, POTASSIUM, AND SODIUM. For discussions of the effects of diuretics on these electrolytes see under the Adverse Effects of Hydrochlorothiazide, p. 1404.2 and p. 1404.3.

Effects in infants and neonates. Furosemide is commonly used in the treatment of cardiac and pulmonary disorders in premature infants and neonates. This age group appears to be particularly susceptible to adverse effects arising from the increase in urinary calcium excretion which occurs during long-term use. Increases in parathyroid hormone concentration[1,2] and evidence of bone resorption[1,3] support the suggestion that the increased calcium loss causes secondary hyperparathyroidism. There have been reports of decreased mineral content of bone,[1,3] rickets,[4] fractures,[3] and renal calcification.[1,5–7] An observation[5] that renal calcification could be reversed by the addition of a thiazide diuretic was supported by other workers.[6] There is evidence[8] that furosemide-related renal calcifications in very low birth-weight infants might be associated with long-term renal impairment. Renal calcification has also been reported after furosemide use in older infants.[9]

It has been suggested[10] that a sodium deficit in infants given furosemide for heart failure may contribute to a failure to thrive.

Concern has been expressed over the finding[11] that furosemide use in premature infants with respiratory distress syndrome increases the incidence of patent ductus arteriosus. The mechanism is thought to be connected with stimulation of renal prostaglandin E_2. However, the increased incidence of patent ductus arteriosus did not adversely affect the mortality in infants given furosemide, and a subsequent study[12] failed to find any increase in the incidence of patent ductus arteriosus in infants treated with furosemide compared with a control group. Paradoxically, furosemide has been used in the management of delayed closure of ductus (see Patent Ductus Arteriosus under Uses and Administration, p. 1388.2). There is a possibility that furosemide may not be effective in infants given indometacin[13] but it can prevent the decline in urine output that occurs during indometacin use.[14,15]

1. Venkataraman PS, *et al.* Secondary hyperparathyroidism and bone disease in infants receiving long-term furosemide therapy. *Am J Dis Child* 1983; 137: 1157–61.
2. Vileisis RA. Furosemide effect on mineral status of parenterally nourished premature neonates with chronic lung disease. *Pediatrics* 1990; 85: 316–22.
3. Morgan MEI, Evans SE. Osteopenia in very low birthweight infants. *Lancet* 1986; ii: 1399–1400.
4. Chudley AE, *et al.* Nutritional rickets in 2 very low birthweight infants with chronic lung disease. *Arch Dis Child* 1980; 55: 687–90.
5. Hufnagle KG, *et al.* Renal calcifications: a complication of long-term furosemide therapy in preterm infants. *Pediatrics* 1982; 70: 360–3.
6. Noe HN, *et al.* Urolithiasis in pre-term neonates associated with furosemide therapy. *J Urol (Baltimore)* 1984; 132: 93–4.
7. Pearse DM, *et al.* Sonographic diagnosis of furosemide-induced nephrocalcinosis in newborn infants. *J Ultrasound Med* 1984; 3: 553–6.
8. Downing GJ, *et al.* Kidney function in very low birth weight infants with furosemide-related renal calcifications at ages 1 to 2 years. *J Pediatr* 1992; 120: 599–604.
9. Alon US, *et al.* Nephrocalcinosis and nephrolithiasis in infants with congestive heart failure treated with furosemide. *J Pediatr* 1994; 125: 149–51.
10. Salmon AP, *et al.* Sodium balance in infants with severe congestive heart failure. *Lancet* 1989; ii: 875.
11. Green TP, *et al.* Furosemide promotes patent ductus arteriosus in premature infants with respiratory-distress syndrome. *N Engl J Med* 1983; 308: 743–8.
12. Yeh TF, *et al.* Early furosemide therapy in premature infants (≤ 2000 gm) with respiratory distress syndrome: a randomized controlled trial. *J Pediatr* 1984; 105: 603–9.
13. Friedman Z, *et al.* Urinary excretion of prostaglandin E following the administration of furosemide and indomethacin to sick low-birth-weight infants. *J Pediatr* 1978; 93: 512–15.
14. Yeh TF, *et al.* Furosemide prevents the renal side effects of indomethacin therapy in premature infants with patent ductus arteriosus. *J Pediatr* 1982; 101: 433–7.
15. Nahata MC, *et al.* Furosemide can prevent decline in urine output in infants receiving indomethacin for patent ductus closure: a multidose study. *Infusion* 1988; 12: 11–12 and 15.

Effects on lipid metabolism. Most studies into the effects of diuretics on blood-lipid concentrations have used thiazides (see Hydrochlorothiazide, p. 1405.2). The few studies into the effects of furosemide suggest that, like thiazides, it may adversely influence blood-lipid concentrations during short-term use.[1]

1. Ames RP. The effects of antihypertensive drugs on serum lipids and lipoproteins I: diuretics. *Drugs* 1986; 32: 260–78.

Precautions

Precautions and contra-indications for furosemide that are dependent on its effects on fluid and electrolyte balance are similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1406.1). Although furosemide is used in high doses for oliguria due to chronic or acute renal impairment it should not be given in anuria or in renal failure caused by nephrotoxic or hepatotoxic drugs nor in renal failure associated with hepatic coma. Furosemide should not be given in pre-comatose states associated with hepatic cirrhosis. It should be used with care in patients with prostatic hyperplasia or impairment of micturition since it can precipitate acute urinary retention.

To reduce the risk of ototoxicity, licensed product information recommends that furosemide should not be injected intravenously at a rate exceeding 4 mg/minute although the *BNF* advises that a single dose of up to 80 mg may be given more rapidly.

Furosemide should be used with caution during pregnancy and breast feeding since it crosses the placenta and also appears in breast milk. Furosemide may compromise placental perfusion by reducing maternal blood volume; it may also inhibit lactation.

Hepatic impairment. In patients with chronic heart failure and moderate liver congestion, high-dose furosemide therapy could produce increases in liver enzymes suggestive of hepatitis.[1] Special care should be taken in such patients to avoid severe ischaemic liver damage caused by a drop in systemic blood pressure.

As with the thiazides, furosemide should be avoided in patients with severe hepatic impairment.

1. Lang I, *et al.* Furosemide and increases in liver enzymes. *Ann Intern Med* 1988; 109: 845.

Hypersensitivity. Furosemide is a sulfa-containing diuretic and hypersensitivity reactions may occur, although they are rare; cross-reactivity with other sulfa-containing drugs is also possible. However, 2 patients who had in the distant past shown serious adverse reactions to sulfa-containing diuretics were successfully treated[1] with furosemide using a rechallenge protocol. They were given an initial dose of 50 micrograms which was increased gradually each day to 20 mg by day 10, and were discharged from hospital on a maintenance dose of 40 mg twice daily. Another patient[2] with a history of sulfonamide-induced pancreatitis developed pancreatitis with furosemide, which recurred with bumetanide and torasemide and on rechallenge with furosemide. She underwent a rapid desensitisation regimen and was subsequently successfully stabilised on oral furosemide. Others have also described rapid desensitisation protocols.[3] For further information on cross-reactivity between sulfa-containing drugs see under Sulfamethoxazole, p. 365.3.

1. Earl G, *et al.* Furosemide challenge in patients with heart failure and adverse reactions to sulfa-containing diuretics. *Ann Intern Med* 2003; 138: 358–9.
2. Juang P, *et al.* Probable loop diuretic-induced pancreatitis in a sulfonamide-allergic patient. *Ann Pharmacother* 2006; 40: 128–34.
3. Alim N, Patel JY. Rapid oral desensitization to furosemide. *Ann Allergy Asthma Immunol* 2009; 103: 538.

Hypoparathyroidism. For comments on the possibility of hypocalcaemic tetany in hypoparathyroid patients taking furosemide, see Effects on Electrolyte Balance, above.

Infants and neonates. Caution must be exercised in using furosemide in infants, particularly for long periods. The immaturity of the renal system can result in unexpectedly high blood concentrations and extended half-lives. **Fluid and electrolyte balances** should therefore be monitored carefully. Neonates appear to be particularly susceptible to increases in urinary calcium concentrations after long-term use. There have also been reports[1] of an increased incidence of patent ductus arteriosus in infants given furosemide, although this did not adversely affect mortality.

Secondly, several studies[2–4] have shown furosemide to be a potent displacer of **bilirubin** from albumin binding sites and it should be used with caution in jaundiced infants. On a molar basis chlorothiazide, furosemide, and etacrynic acid were at least as potent as sulfafurazole in displacing bilirubin from albumin.[3] Doses of furosemide 1 mg/kg probably do not produce a significant increase in free bilirubin in most jaundiced infants,[3,4] although doses greater than 1.5 mg/kg or repeated dosing could potentially do so.[4] Chlorothiazide 15 to 20 mg/kg would not be an appropriate alternative to furosemide[3] since it could produce higher plasma bilirubin concentrations in jaundiced infants.

In addition, there is some evidence from an *in vitro* study[5] that bilirubin may displace furosemide from binding sites to a greater extent in neonates than in adults. The clearance of furosemide is much slower in neonates than in adults, with an eightfold prolongation in plasma half-life, and this should be taken into account during repeat dosing.[4]

1. Green TP, *et al.* Furosemide promotes patent ductus arteriosus in premature infants with the respiratory-distress syndrome. *N Engl J Med* 1983; 308: 743–8.
2. Shankaran S, Poland RL. The displacement of bilirubin from albumin by furosemide. *J Pediatr* 1977; 90: 642–6.
3. Wennberg RP, *et al.* Displacement of bilirubin from human albumin by three diuretics. *J Pediatr* 1977; 90: 647–50.
4. Aranda JV, *et al.* Pharmacokinetic disposition and protein binding of furosemide in newborn infants. *J Pediatr* 1978; 93: 507–11.
5. Viani A, Pacifici GM. Bilirubin displaces furosemide from serum protein: the effect is greater in newborn infants than adult subjects. *Dev Pharmacol Ther* 1990; 14: 90–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies furosemide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions of furosemide that are due to its effects on fluid, electrolyte, and carbohydrate balance are similar to those of hydrochlorothiazide (see p. 1406.1).

Furosemide may enhance the nephrotoxicity of cephalosporin antibacterials such as cefalotin and can enhance the ototoxicity of aminoglycoside antibacterials and other ototoxic drugs.

Aliskiren. Licensed product information for aliskiren states that it may decrease furosemide and torasemide concentrations.

Antiepileptics. The diuretic effect of furosemide has been shown to be substantially reduced by mixed antiepileptic therapy that included *phenytoin*.[1,2] The mean diuretic effect of furosemide 20 mg or 40 mg orally in patients on such therapy was 68% and 51% that of healthy controls respectively.[1]

For the effect of furosemide on *phenobarbital*, see p. 538.1.

Symptomatic hyponatraemia has been associated with the use of furosemide or hydrochlorothiazide with *carbamazepine*.[3]

1. Ahmad S. Renal insensitivity to frusemide caused by chronic anticonvulsant therapy. *BMJ* 1974; 3: 657–9.
2. Fine A, *et al.* Malabsorption of frusemide caused by phenytoin. *BMJ* 1977; 2: 1061–2.
3. Yassa R, *et al.* Carbamazepine, diuretics, and hyponatremia: a possible interaction. *J Clin Psychiatry* 1987; 48: 281–3.

Diuretics. Severe electrolyte disturbances may occur in patients given *metolazone* with furosemide.

Hypnotics. A syndrome of flushing, tachycardia, elevated blood pressure, and severe diaphoresis was reported after intravenous dosage of furosemide in 6 patients who had taken *cloral hydrate* orally during the preceding 24 hours.[1] The reaction recurred in 1 patient on a subsequent occasion when given both drugs but not when furosemide was used without cloral hydrate. A subsequent retrospective study[2] among 43 patients who had received both cloral hydrate and furosemide showed that 1 patient had suffered a similar reaction; of 2 further patients who had possibly been affected, 1 had subsequently taken both drugs without adverse effects. A similar interaction has been reported in an 8-year-old child.[3]

1. Malach M, Berman N. Furosemide and chloral hydrate: adverse drug interaction. *JAMA* 1975; 232: 638–9.
2. Pevonka MP, *et al.* Interaction of chloral hydrate and furosemide: a controlled retrospective study. *Drug Intell Clin Pharm* 1977; 11: 332–5.
3. Dean RP, *et al.* Interaction of chloral hydrate and intravenous furosemide in a child. *Clin Pharm* 1991; 10: 385–7.

Lithium. For reports of a possible increase in plasma-lithium concentrations in patients receiving loop diuretics, see p. 432.2.

NSAIDs. NSAIDs may antagonise the diuretic effect of furosemide and other diuretics.[1] Use of NSAIDs with diuretics may increase the risk of nephrotoxicity, although it has also been suggested that furosemide may protect against the renal effects of *indometacin* in infants (see Effects in Infants and Neonates, p. 1389.1).

1. Webster J. Interactions of NSAIDs with diuretics and β-blockers: mechanisms and clinical implications. *Drugs* 1985; 30: 32–41.

Probenecid. Probenecid has been shown[1-4] to reduce the renal clearance of furosemide, and to reduce the diuretic effect.[2,3]

1. Honari J, *et al.* Effects of probenecid on furosemide kinetics and natriuresis in man. *Clin Pharmacol Ther* 1977; 22: 395–401.
2. Odlind B, Beermann B. Renal tubular secretion and effects of furosemide. *Clin Pharmacol Ther* 1980; 27: 784–90.
3. Smith DE, *et al.* Preliminary evaluation of furosemide-probenecid interaction in humans. *J Pharm Sci* 1980; 69: 571–5.
4. Vree TB, *et al.* Probenecid inhibits the renal clearance of frusemide and its acyl glucuronide. *Br J Clin Pharmacol* 1995; 39: 692–5.

Tobacco. The effects of tobacco smoking on the pharmacokinetics of furosemide have been reviewed.[1,2] Nicotine inhibits diuresis and diminishes the diuretic effect of furosemide. However, this effect is attenuated in habitual smokers.

1. Miller LG. Recent developments in the study of the effects of cigarette smoking on clinical pharmacokinetics and clinical pharmacodynamics. *Clin Pharmacokinet* 1989; 17: 90–108.
2. Miller LG. Cigarettes and drug therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharm* 1990; 9: 125–35.

Xanthines. For the effect of furosemide on *theophylline*, see Diuretics, p. 1236.1.

Pharmacokinetics

Furosemide is fairly rapidly absorbed from the gastrointestinal tract; bioavailability has been reported to be about 60 to 70% but absorption is variable and erratic. The half-life of furosemide is up to about 2 hours although it is prolonged in neonates and in patients with renal and hepatic impairment. Furosemide is up to 99% bound to plasma albumin, and is mainly excreted in the urine, largely unchanged. There is also some excretion via the bile and non-renal elimination is considerably increased in renal impairment. Furosemide crosses the placental barrier and is distributed into breast milk. The clearance of furosemide is not increased by haemodialysis.

The pharmacokinetics of furosemide have been extensively reviewed.[1-6] The development of an analytical method using HPLC with fluorescence has produced greater sensitivity and more consistent results. Absorption after oral use is erratic and is subject to large inter- and intra-individual variation. It is influenced by the dosage form, underlying disease processes, and by the presence of food. Furosemide absorption in patients with heart failure has been reported to be even more erratic than in healthy subjects. The bioavailability of furosemide from oral dosage forms is also highly variable with reported values ranging from 20 to 100%. It is influenced by factors affecting absorption but the poor solubility of furosemide does not appear to have a major influence on bioavailability and *in vitro* dissolution data may not reflect *in vivo* bioavailability. Bioavailability tends to be decreased by about 10% in patients with renal disease, and slightly increased in liver disease. Values are erratic in patients with heart disease.

Furosemide is highly bound to plasma proteins, almost exclusively to albumin. The proportion of free (unbound) furosemide is higher in patients with heart disease, renal impairment, and cirrhosis of the liver. Patients with liver disease also have an increased apparent volume of distribution which is proportionally greater than the decrease seen in protein binding. Patients with nephrotic syndrome have significant proteinuria and secondary hypoalbuminaemia. This results in reduced protein binding in the blood, particularly at higher blood concentrations, and binding to proteins present in the urine, which may account for the resistance to furosemide therapy reported in these patients.

A glucuronide metabolite of furosemide is produced in varying amounts. The site of metabolism is unknown at present. There is debate over another potential metabolite, 4-chloro-5-sulfamoyl anthranilic acid (CSA). It has been argued[5] that it is an artefact produced during the extraction procedures although there is some evidence to refute this.[6]

A half-life for furosemide in healthy subjects has generally been reported in the range of 30 to 120 minutes. In patients with end-stage renal disease the average half-life is 9.7 hours. The half-life may be slightly longer in patients with hepatic dysfunction and a range of 50 to 327 minutes has been reported in patients with heart failure. In severe multi-organ failure the half-life may range from 20 to 24 hours.

Furosemide clearance is influenced by age, underlying disease state, and drug interactions. Clearance reduces with increasing age, probably due to declining renal function. Renal impairment in renal or cardiac disease reduces renal clearance, although this may be compensated for by increases in non-renal clearance. Hepatic impairment has little impact on clearance. Renal and non-renal clearance may be reduced by probenecid and indometacin.

The efficacy of furosemide as a diuretic depends upon it reaching its site of action, the renal tubules, unchanged. About one-half to two-thirds of an intravenous dose or one-quarter to one-third of an oral dose are excreted unchanged, the difference being largely due to the poor bioavailability from the oral route. The effect of furosemide is more closely related to its urinary excretion than to the plasma concentration. Urinary excretion may be reduced in renal impairment due to reduced renal blood flow and reduced tubular secretion.

1. Cutler RE, Blair AD. Clinical pharmacokinetics of frusemide. *Clin Pharmacokinet* 1979; 4: 279–96.
2. Benet LZ. Pharmacokinetics/pharmacodynamics of furosemide in man: a review. *J Pharmacokinet Biopharm* 1979; 7: 1–27.
3. Hammarlund-Udenaes M, Benet LZ. Furosemide pharmacokinetics and pharmacodynamics in health and disease—an update. *J Pharmacokinet Biopharm* 1989; 17: 1–46.
4. Ponto LLB, Schoenwald RD. Furosemide (frusemide): a pharmacokinetic/pharmacodynamic review (part I). *Clin Pharmacokinet* 1990; 18: 381–408.
5. Ponto LLB, Schoenwald RD. Furosemide (frusemide): a pharmacokinetic/pharmacodynamic review (part II). *Clin Pharmacokinet* 1990; 18: 460–71.
6. Vrhovac B, *et al.* Pharmacokinetic changes in patients with oedema. *Clin Pharmacokinet* 1995; 28: 405–18.

Infants and neonates. The half-life of furosemide in term and preterm neonates is markedly prolonged compared with that in adults.[1,2] Half-lives of 4.5 to 46 hours have been reported and it has been suggested that the prolongation may be greater in preterm than in term neonates. This effect is due mainly to immature renal function and if repeated doses are necessary over a short period accumulation may occur.[1]

1. Besunder JB, *et al.* Principles of drug biodisposition in the neonate: a critical evaluation of the pharmacokinetic-pharmacodynamic interface (part II). *Clin Pharmacokinet* 1988; 14: 261–86.
2. Aranda JV, *et al.* Pharmacokinetic disposition and protein binding of furosemide in newborn infants. *J Pediatr* 1978; 93: 507–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Errolon; Fabofurox; Puragrand; Furital; Purix; Purotral; Pursemida; Furtenk; Kolkin; Lasix; Nuriban; Retep; *Austral.*: Prusehexal†; Prusid; Lasix; Uremide; Urex; *Austria*: Purohexal; Puron; Purostad; Lasix; *Belg.*: Docfurose†; Furotop†; Lasix; *Braz.*: Closenid; Diuremida; Fluxil; Puresin†; Puromida; Furosan; Purosantisa; Puroseni†; Purosemin; Purosetron; Purosix; Purozix; Pursemida; Lasix; Neosemid; Rovelan; Urasix; *Canad.*: Lasix; Novo-Semide†; *Chile*: Asax; *China*: A Xi Ya (阿西亚); Ai Ge (艾格); *Cz.*: Puron; Furorese; *Denm.*: Diural; Purix; Lasix; *Fin.*: Puresis; Puromin†; Lasix; Vesix; *Fr.*: Lasilix; *Ger.*: Diurapid†; Puranthril; Furo-Puren†; Puro†; Purobeta; Purogamma; Furorese†; Purosal†; Pusid†; Jufurix†; Lasix†; *Gr.*: Pudesix; Puranthril; Hydroflux; Inzury; Lasix; Riomid; Semid; *Hong Kong*: CP-Puro; Diurex†; Lasix; Naqua†; Urex; *Hung.*: Puron; *India*: Fru; Frusemix; Frusenex; Prusim; Prusix; Lasix; *Indon.*: Cetasix†; Classic; Diurefo†; Diuvar; Edemin; Parsix; Purosix; Impugan; Lasix; Naclex; Silax; Uresix; *Irl.*: Pruside; Lasix; *Israel*: Furovenir; Fusid; Miphar; *Ital.*: Lasix; *Malaysia*: Akoset; Dirine; Pruside; Lasix; Rasitol; Suopinchon; *Mex.*: Biomisen; Butosall; Diurmessel; Edenol; Purosan; Henexal†; Klimyn; Lasix; Luzamida; Osemin; Selectofur†; Zafimida; *Neth.*: Lasiletten; Lasix; *Norw.*: Diural; Purix; Lasix; *NZ*: Diurin; Frusid; Lasix; Urex; *Philipp.*: Diuril†; Diuspec; Edemann; Flexamide; Premid; Pretic; Pruserna; Puride; Purolink; Puroscan; Pusimex; Lasix; Pharmix†; Pisamor; Rasitol; Rofunil; *Port.*: Lasix; Naqua†; *Rus.*: Lasix (Лазикс); *S.Afr.*: Aquarid; Beuresis; Beurises; Dino-Retic; Diuresix; Lasix; Puresis; Uretic†; *Singapore*: Dirine; Purmide; Lasix; Rasitol; Sunmide; *Spain*: Seguril; *Swed.*: Purix; Impugan; Lasix; *Switz.*: Purodrix; Pursol; Lasix; Oedemex; *Thal.*: Dema; Dirine; Femide; Frusil; Pudirine; Puretic; Furide; Purine; Puromed; Puromide; Purozide; Fuseride; Pusesian; H-Mide; Hawkmide; Lasiven; Lasix; Prosix; Rosemide†; *Turk.*: Desal; Puromid; Lasix; Lizik; Urever; Urex; *UAE*: Salurin; *UK*: Froop; Prusid; Frusol; Lasix; Rusyde; *Ukr.*: Lasix (Лазикс); *USA*: Lasix; *Venez.*: Biosemida; Edemid; Inciens; Lasix; Lifurox; Salca; Terysol.

Multi-ingredient Preparations. *Arg.*: Aldactone-D; Diflux; Errolon A; Lasilacton; Lasiride; Nuriban A; *Austria*: Puro-Spirobene; Lasilacton; Lasitace; Spirono comp; *Belg.*: Frusamil; *Braz.*: Diurana; Diurisa; Furosemide Composto; Hidrion; Lasilactona; *Chile*: Furdiuren; Hidrium; Hidropid†; *China*: Puluobi (福洛必); *Denm.*: Frusamil; *Fin.*: Furesis comp; *Fr.*: Aldalix; Logirene; *Ger.*: Betasemid; Diaphal; Puro-Aldopur†; Furorese Comp†; Osyrol Lasix†; Spiro comp; Spiro-D†; *Gr.*: Prumil; *India*: Aldostix; Amifru-S; Amifru; Amimide; Aquamide; Diucontin-K; Exna-K; Frumil; Fruselac; Frusemene; Lasilactone; Lasiride; Minilactone; Spiromide; *Irl.*: Diumide-K Continus†; Fru-Co; Frumil; *Ital.*: Fluss; Lasitone; Spirofur; *Mex.*: Lasilacton; *NZ*: Frumil; *Philipp.*: Diumide-K; *Switz.*: Furospir; Lasilactone; *UK*: Aridil; Pru-Co; Frumil; Frusene; Komil; Lasikal; Lasilactone; *Venez.*: Purdiuren.

Pharmacopoeial Preparations

BP 2014: Co-amilofruse Tablets; Furosemide Injection; Furosemide Tablets;

USP 36: Furosemide Injection; Furosemide Oral Solution; Furosemide Tablets.

Gallopamil Hydrochloride *(BANM, rINNM)*

D-600 (gallopamil); Gallopamil, Chlorhydrate de; Gallopamilhydrokloridi; Gallopamilli Hydrochloridum; Gallopamilli-hydrokloridi; Galopamilo, hidrocloruro de; Hidrocloruro de galopamilo; Methoxyverapamil Hydrochloride; Галлопамила Гидрохлорид.

5-[*N*-(3,4-Dimethoxyphenethyl)-*N*-methylamino]-2-(3,4,5-trimethoxyphenyl)-2-isopropylvaleronitrile hydrochloride.

$C_{28}H_{40}N_2O_5$,HCl=521.1

CAS — 16662-47-8 (gallopamil); 16662-46-7 (gallopamil hydrochloride).

ATC — C08DA02.

ATC Vet — QC08DA02.

UNII — VT4VR32A0T.

Profile

Gallopamil is a calcium-channel blocker (see p. 1244.2) with antiarrhythmic activity and is chemically related to verapamil. It is used in the management of angina pectoris (p. 1254.3), cardiac arrhythmias (p. 1266.1), and hypertension (p. 1251.1). Gallopamil hydrochloride is given orally in doses of 25 to 50 mg every 6 to 12 hours up to a maximum total dose of 200 mg daily. Modified-release preparations are also available and are given once or twice daily in similar total daily doses.

Reviews.

1. Brogden RN, Benfield P. Gallopamil: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in ischaemic heart disease. *Drugs* 1994; 47: 93–115.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Procorum; *China*: Procorum (普可佳); *Ger.*: Gallobeta†; Procorum; *Hung.*: Procorum†; *Ital.*: Algocor; Procorum; *Mex.*: Procorum†; *Philipp.*: Procorum†; *Thai.*: Procorum†.

Gemfibrozil *(BAN, USAN, rINN)*

CI-719; Gemfibrotsilli; Gemfibrozilo; Gemfibrozilum; Gemfibrozyl; Гемфиброзил.

2,2-Dimethyl-5-(2,5-xylyloxy)valeric acid.

$C_{15}H_{22}O_3$=250.3

CAS — 25812-30-0.

ATC — C10AB04.

ATC Vet — QC10AB04.

UNII — Q8X02627X3.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Gemfibrozil). A white or almost white, waxy, crystalline powder. M.p. 58 degrees to 61 degrees. Practically insoluble in water; freely soluble in dehydrated

alcohol and in methyl alcohol; very soluble in dichloromethane. Protect from light.

USP 36: (Gemfibrozil). A white waxy crystalline solid. M.p. 58 degrees to 61 degrees. Practically insoluble in water; soluble in alcohol, in methyl alcohol, and in chloroform. Store in airtight containers.

Uses and Administration

Gemfibrozil, a fibric acid derivative, is a lipid regulating drug with actions on plasma lipids similar to those of bezafibrate (p. 1323.2).

Gemfibrozil is used to reduce total cholesterol and triglycerides in the management of hyperlipidaemias (p. 1248.1), including type IIa, type IIb, type III, type IV, and type V hyperlipoproteinaemias. It is also indicated for the primary prevention of ischaemic heart disease (see Cardiovascular Risk Reduction, p. 1246.1) in hyperlipidaemic men: in the USA this use is restricted to type IIb patients who also have low HDL-cholesterol concentrations and who have not responded to dietary and other measures. The usual oral dose is 1.2 g daily in 2 divided doses given 30 minutes before the morning and evening meals. Alternatively, a single daily dose of 900 mg has been given 30 minutes before the evening meal.

Reviews.

1. Spencer CM, Barradell LB. Gemfibrozil: a reappraisal of its pharmacological properties and place in the management of dyslipidaemia. *Drugs* 1996; 51: 982–1018.

Administration in renal impairment. Gemfibrozil is contra-indicated in patients with severe renal impairment. However, UK licensed prescribing information allows its use in patients with mild to moderate impairment (glomerular filtration rate 30 to 80 mL/minute per 1.73 m^2); the initial dose should be reduced to 900 mg daily and renal function should be assessed before increasing the dose.

In a study[1] of the pharmacokinetics of gemfibrozil in 17 patients with stable chronic renal failure the mean plasma half-life was 1.8 and 1.9 hours after multiple and single doses respectively, which was comparable with that reported in patients with normal renal function. Gemfibrozil clearance was independent of renal function, but the kinetics of gemfibrozil metabolites were not evaluated.

Beneficial responses[2] were seen in lipid and lipoprotein concentrations in 5 of 6 uraemic patients treated with gemfibrozil 1.2 g daily for six months and in 6 nephrotic patients given gemfibrozil 800 mg daily for 4 months. No significant adverse effects or signs of organ toxicity were seen. Results of a secondary prevention study[3] also suggested that gemfibrozil at a dose of 1.2 g daily was safe and effective in patients with mild to moderate renal impairment.

1. Evans JR, *et al.* The effect of renal function on the pharmacokinetics of gemfibrozil. *J Clin Pharmacol* 1987; 27: 994–1000.
2. Manninen V, *et al.* Gemfibrozil treatment of dyslipidaemias in renal failure with uraemia or in the nephrotic syndrome. *Ren Clin Forums* 1982; 4: 113–18.
3. Tonelli M, *et al.* for the Veterans' Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) Investigators. Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. *Kidney Int* 2004; 66: 1123–30.

Adverse Effects and Precautions

As for Bezafibrate, p. 1324.2.

Incidence of adverse effects. In the Helsinki Heart Study,[1] 11.3% of 2051 patients taking gemfibrozil reported various moderate to severe upper gastrointestinal tract symptoms during the first year of treatment compared with 7% of 2030 patients taking placebo. No differences were seen between gemfibrozil and placebo groups in haemoglobin concentrations, urinary-protein, or urinary-sugar concentrations.

There was no significant difference in the total number of cancers between the gemfibrozil and placebo groups nor in the number of operations for gallstones or for cataract surgery. A higher number of deaths in the gemfibrozil group was mainly due to accident or violence and intracranial haemorrhage.

A follow-up study[2] reported that gastrointestinal symptoms remained more common in patients taking gemfibrozil. Although there was no significant difference between the gemfibrozil and placebo groups cholecystectomies were consistently more common in those receiving gemfibrozil during the entire 8.5-year observation period. Cancer occurred equally in both groups, but there was increased mortality attributable to cancer in the gemfibrozil group, mainly during the last 1.5 years of follow-up; this difference was no longer apparent after 18 years.[3]

1. Frick MH, *et al.* Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; 317: 1237–45.
2. Huttunen JK, *et al.* The Helsinki Heart Study: an 8.5-year safety and mortality follow-up. *J Intern Med* 1994; 235: 31–9.
3. Tenkanen L, *et al.* Gemfibrozil in the treatment of dyslipidemia: an 18-year mortality follow-up of the Helsinki Heart Study. *Arch Intern Med* 2006; 166: 743–8.

Effects on the skin. Psoriasis was exacerbated in a patient within 2 weeks of starting gemfibrozil therapy and recurred when gemfibrozil was subsequently reintroduced.[1]

1. Fisher DA, *et al.* Exacerbation of psoriasis by the hypolipidemic agent, gemfibrozil. *Arch Dermatol* 1988; 124: 854–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gemfibrozil as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Bezafibrate, p. 1325.2.

Gemfibrozil is an inhibitor of several cytochrome P450 isoenzymes, including CYP2C8, CYP2C9, CYP2C19, and CYP1A2 and may increase the plasma concentration of drugs metabolised by these isoenzymes; it also inhibits some UDP-glucuronosyltransferases. Increased plasma concentration of bexarotene (see p. 749.1), pioglitazone (see p. 494.2), and rosiglitazone (see p. 499.1) have been reported with gemfibrozil, and use of gemfibrozil in patients receiving repaglinide is contra-indicated due to the risk of serious hypoglycaemia (see p. 496.1).

Pharmacokinetics

Gemfibrozil is readily absorbed from the gastrointestinal tract; bioavailability is close to 100% and is highest when gemfibrozil is taken 30 minutes before food. Peak concentrations in plasma occur within 1 to 2 hours; the half-life is about 1.5 hours. Plasma protein binding of gemfibrozil is about 98%. About 70% of a dose is excreted in the urine mainly as glucuronide conjugates of gemfibrozil and its metabolites; little is excreted in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Gedun; Hipolixan; Lopid; ***Austral.***: Ausgem; Gemhexal; Jezil; Lipazil; Lipigem; Lopid; ***Austria***: Gevilon; ***Braz.***: Lopid; Lozil; ***Canad.***: Lopid; ***Chile***: Grifogemzilo; Lipotril; Lopid; ***China***: Chang Heng Lin (常衡林); Luo Ping (洛平); Uragem (尤瑞吉); Weijiangzhi (维绛知); Xin Si Da (新斯达); ***Denm.***: Lopid; ***Fin.***: Lopid; ***Fr.***: Lipur; ***Ger.***: Gemfi†; Gevilon; ***Gr.***: Adrotan; Amedran; Antilipid; Cholhepan; Clipostat; Dosamont; Drisofal; Eklipid; Entianthe; Fibrolip; Fibrospes; Gebrozil; Gedizil; Gemfolid; Gemlipid; Gineton; Hobatolex; Leptokin; Lisolip; Lopid; Noxobran; Parnoxil; Prelisin; Renolip; Solulip; Terostrant; Tiazam; ***Hong Kong***: Fibrozo; Gemzil†; Gen-Fibro†; Ipolipid; Lipison; Lipistorol; Lipofor; Lopid; Lowin†; Marbrozil†; Qualipid; Ronox†; Saffid†; Synbrozil†; ***Hung.***: Innogem; Minilip; ***India***: Gempar; Lipizyl; Lopid; Losterol; Normolip; ***Indon.***: Detrichol; Fetinor; Fibrallp†; Hypofil; Inobes†; Lapibroz; Lifibron; Lipira; Lipitrop; Lokoles; Lopid; Lowlip†; Mersikol; Nufalemzil; Progemzal†; Renabrazin; Scantipid; Zenibroz; Zilop; ***Irl.***: Lopid; ***Ital.***: Gemlipid†; Genlip; Lopid; ***Malaysia***: Brozil; Ipolipid; Lipofor†; ***Mex.***: Apo-Fide; Lopid; Raypid; ***Neth.***: Lopid; ***NZ***: Lipazil; ***Philipp.***: Eogem; Lipigem; Lipison†; Lipizile; Lipozid†; Lopid; Reducel; ***Port.***: Lipoite; Lopid; ***Rus.***: Ipolipid (Ипомид); ***S.Afr.***: Lopid; ***Singapore***: Brozil; Gemd†; Hidil; Ipolipid; Lipison; Lipistorol; Lipofor; Recozil; ***Spain***: Lopid; Pilder†; Trialmin; ***Swed.***: Lopid; ***Switz.***: Gevilon; ***Thai.***: Bisil; Delipid; Dropid; Fibropid; Gembropac; Gemfibril; Gemox; GFB; Gozid; Hidil; Lespid; Lipidys†; Lipison; Lipolo; Lipozil†; Locholes†; Lodil; Lopicare; Lopid; Lopol; Manobrozil; Mariston†; Milpid; Norpid; Pharzil†; Poli-Fibrozil; Polyxit; Ronox; Tiba†; Tolip; U-Pid; ***Turk.***: Lopid; ***UK***: Lopid; ***USA***: Lopid; ***Venez.***: Lipontal; Lopid.

Pharmacopoeial Preparations
BP 2014: Gemfibrozil Capsules; Gemfibrozil Tablets;
USP 36: Gemfibrozil Capsules; Gemfibrozil Tablets.

Glyceryl Trinitrate

Gliceriin trinitrát; Glicerolio trinitratas; Gliseril Trinitrat; Glonoin; Glyceroli Trinitras; Glyceroli Trinitratis; Glycerol trinitrát; Glycéryle trinitrate de; Glycerytrinitrat; Glyseryltrinitraattia; GTN; Nitrato de glicerilo; Nitroglicerina; Nitroliserin; Nitroglycerin; Nitroglycerol; NTG; Trinitrato de glicerilo; Trinitrin; Trinitroglicerina; Trinitroglycerin; Тринитроглицерин; Trinitrotol.

Propane-1,2,3-triol trinitrate.

$C_3H_5(NO_3)_3$ = 227.1

CAS — 55-63-0.

ATC — C01DA02; C05AE01.

ATC Vet — QC01DA02; QC05AE01.

UNII — GS9M75OWS3.

Pharmacopoeias. *Chin.*, *Eur.* (see p. vii), *US*, and *Viet.* include glyceryl trinitrate as diluted solutions.

Ph. Eur. 8: (Glyceryl Trinitrate Solution). An ethanolic solution containing 1 to 10% w/w of glyceryl trinitrate. It is a clear, colourless or slightly yellow solution. Miscible with dehydrated alcohol and with acetone.

Pure glyceryl trinitrate is practically insoluble in water; freely soluble in dehydrated alcohol; miscible with acetone.

Protect from light. Diluted solutions (1%) should be stored at 2 degrees to 15 degrees; more concentrated solutions may be stored at 15 degrees to 20 degrees.

USP 36: (Diluted Nitroglycerin). A mixture of glyceryl trinitrate with lactose, glucose, alcohol, propylene glycol, or other suitable inert excipient, usually containing not more than 10% glyceryl trinitrate. When diluted in either alcohol or propylene glycol it is a clear, colourless, or pale yellow liquid. When diluted with lactose, it is a white odourless powder. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Prevent exposure to temperatures above 40 degrees. Protect from light.

Undiluted glyceryl trinitrate is a white to pale yellow, thick, flammable, explosive liquid. Slightly soluble in water; soluble in alcohol, in acetone, in carbon disulfide, in chloroform, in dichloromethane, in ether, in ethyl acetate, in glacial acetic acid, in methyl alcohol, in benzene, in toluene, in nitrobenzene, and in phenol.

Handling. Undiluted glyceryl trinitrate can be exploded by percussion or excessive heat and only exceedingly small amounts should be isolated.

Incompatibility. Studies have found glyceryl trinitrate to be incompatible with phenytoin,[1] alteplase,[2] and levofloxacin.[3]

1. Klamerus KJ, *et al.* Stability of nitroglycerin in intravenous admixtures. *Am J Hosp Pharm* 1984; 41: 303–5.
2. Lee CY, *et al.* Visual and spectrophotometric determination of compatibility of alteplase and streptokinase with other injectable drugs. *Am J Hosp Pharm* 1990; 47: 606–8.
3. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; 56: 1458–9.

Stability. *INTRAVENOUS SOLUTIONS.* The loss of glyceryl trinitrate from solution by adsorption or absorption into some plastics of intravenous giving sets has been recognised for some years,[1,2] although adsorption does not appear to occur to any great extent with polyolefin[3,4] or polyethylene.[5-7] It is not only infusion containers and plastic tubing that may be involved; some in-line filters can adsorb glyceryl trinitrate.[8,9]

1. Grouthamel WG, *et al.* Loss of nitroglycerin from plastic intravenous bags. *N Engl J Med* 1978; 299: 262.
2. Roberts MS, *et al.* The availability of nitroglycerin from parenteral solutions. *J Pharm Pharmacol* 1980; 32: 237–44.
3. Wagenknecht DM, *et al.* Stability of nitroglycerin solutions in polyolefin and glass containers. *Am J Hosp Pharm* 1984; 41: 1807–11.
4. Trissel LA, *et al.* Drug compatibility with new polyolefin infusion solution containers. *Am J Health-Syst Pharm* 2006; 63: 2379–82.
5. Schaber DE, *et al.* Nitroglycerin adsorption to a combination polyvinyl chloride, polyethylene intravenous administration set. *Drug Intell Clin Pharm* 1985; 19: 572–5.
6. Tracy TS, *et al.* Nitroglycerin delivery through a polyethylene-lined intravenous administration set. *Am J Hosp Pharm* 1989; 46: 2031–5.
7. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; 47: 369–73.
8. Baaske DM, *et al.* Nitroglycerin compatibility with intravenous fluid filters, containers, and administration sets. *Am J Hosp Pharm* 1980; 37: 201–5.
9. Kanke M, *et al.* Binding of selected drugs to a "treated" inline filter. *Am J Hosp Pharm* 1983; 40: 1323–8.

TABLETS. Many studies have shown that glyceryl trinitrate tablets are unstable and subject to considerable loss of potency in contact with packaging components such as adhesive labels, cotton and rayon fillers, and plastic bottles and caps. Both the Council of the Royal Pharmaceutical Society of Great Britain and the FDA in the USA have issued packaging and dispensing guidelines. Glyceryl trinitrate tablets should be dispensed only in glass containers sealed with a foil lined cap and containing no cotton wool wadding. In addition, the Council of the Royal Pharmaceutical Society of Great Britain recommends that no more than 100 tablets should be supplied and that the container should be labelled with an indication that any tablets should be discarded after 8 weeks in use.

Uses and Administration

Glyceryl trinitrate is a nitrovasodilator used in the management of angina pectoris (p. 1254.3), heart failure (p. 1262.3), and myocardial infarction (p. 1392.3). Other indications include inducing hypotension and controlling hypertension during surgery.

Glyceryl trinitrate is believed to exert its vasodilator effect through release of nitric oxide, which causes stimulation of guanylate cyclase in the vascular smooth muscle cells; this results in an increase in cyclic guanosine monophosphate. This nucleotide induces relaxation, probably by lowering the free calcium concentration in the cytosol. In its action on vascular muscle, venous dilatation predominates over dilatation of the arterioles. Venous dilatation decreases venous return as a result of venous pooling, and lowers left ventricular diastolic volume and pressure (termed a reduction in preload). The smaller or less important dilatation of arterioles reduces both peripheral vascular resistance and left ventricular pressure at systole (termed a reduction in afterload). The consequent effect is a reduction in the primary determinants of myocardial oxygen demand. The effect on preload is not shared by beta blockers or calcium-channel blockers. Glyceryl trinitrate also has a coronary vasodilator effect, which improves regional coronary blood flow to ischaemic areas resulting in improved oxygen supply to the myocardium.

Glyceryl trinitrate may be given by the sublingual, buccal, oral, transdermal, or intravenous route. The dose and choice of formulation depend upon the clinical situation.

In the management of **acute angina** glyceryl trinitrate is given as sublingual tablets, a sublingual aerosol spray, or buccal tablets, which all produce a rapid onset of therapeutic effect and provide rapid relief of anginal pain. These dosage forms may also be used before an activity or stress which might provoke an attack. One sublingual tablet (usual strength 300 to 600 micrograms) is placed under the tongue. The dose may be repeated as required but patients should be advised to seek medical care if pain persists after a total of 3 doses within 15 minutes. If an aerosol spray is used one or two sprays of 400 micrograms each are directed onto or under the tongue, then the mouth is closed; three sprays may be used if necessary. Buccal tablets of glyceryl trinitrate are placed between the upper lip and gum (see below for precautions to be observed during use). The usual dose is 2 mg when required, increased to 3 mg if necessary; a dose of 5 mg may be given in severe angina.

In the long-term management of **stable angina** glyceryl trinitrate is given as modified-release tablets or capsules, transdermal formulations, or buccal tablets, which all provide a long duration of action. Dosage varies according to the specific formulation. In the USA, for example, modified-release oral capsules may be taken in a usual starting dose of 2.5 to 6.5 mg three or four times daily, increased up to 26 mg four times daily if needed. The transdermal formulations available are ointments and patches. With the ointment a measured amount (½ to 2 inches of glyceryl trinitrate ointment 2%) is applied 2 to 4 times daily, or every 3 to 4 hours if necessary, to a hairless area of the chest, arm, thigh, or back. Transdermal patches applied to the chest, upper arm, or shoulder are more convenient. Patches are generally designed to release glyceryl trinitrate at a constant rate; they are available in a range of sizes, releasing about 100 to 800 micrograms/hr (equivalent to about 2.5 to 20 mg in 24 hours, although the patches are generally removed for part of this period to prevent tolerance developing). A maximum daily dose of 20 mg has been suggested. Glyceryl trinitrate ointment and patches should be applied to a fresh area of skin and several days should elapse before re-application to formerly used sites. Buccal tablets are used in doses of 2 to 5 mg three times daily. The tablets are retained in the buccal cavity; the rate of dissolution of the tablet can be increased by touching the tablet with the tongue or drinking hot liquids. It is common practice to remove the tablets at bedtime because of the risk of aspiration. Also patients using buccal tablets should be advised to alternate placement sites and pay close attention to oral hygiene to reduce the risk of dental caries. The tablets are not intended to be chewed; if the buccal tablet is inadvertently swallowed, another may be placed in the buccal cavity.

Tolerance tends to develop in the majority of patients on continuous nitrate therapy and nitrate-free intervals are often employed to avoid this problem (see p. 1394.1 under Precautions, Nitrate Tolerance for further details).

In the management of **unstable angina** glyceryl trinitrate may be given by intravenous infusion. Manufacturers' guidelines for dilution of glyceryl trinitrate injection specify glucose 5% or sodium chloride 0.9% as the diluent. During intravenous use of glyceryl trinitrate there should be haemodynamic monitoring of the patient with the dose being adjusted gradually to produce the desired response. The plastic used in the infusion equipment may adsorb glyceryl trinitrate (see Stability, p. 1391.3) and allowance may have to be made for this. The usual initial dose for unstable angina is 5 to 10 micrograms/minute. Most patients respond to doses between 10 and 200 micrograms/minute. The sublingual and buccal routes may also be used; doses of up to 5 mg as buccal tablets may be required to relieve pain in patients with unstable angina.

In the management of acute **heart failure** glyceryl trinitrate is given intravenously in an initial dose of 5 to 25 micrograms/minute. Buccal tablets have been used in doses of 5 mg repeated as needed until symptoms are controlled. In chronic heart failure buccal tablets may be given in doses of 5 to 10 mg three times daily.

Glyceryl trinitrate is also used intravenously in acute **myocardial infarction**, and to induce hypotension or control hypertension during **surgery**. The initial dose is 5 to 25 micrograms/minute, adjusted according to response. The usual range is 10 to 200 micrograms/minute but some surgical patients may require up to 400 micrograms/minute.

Glyceryl trinitrate has also been used as transdermal patches in the prophylactic treatment of **phlebitis and extravasation** secondary to venous cannulation. One 5-mg patch is applied distal to the intravenous site; the patch should be replaced at a different skin site either daily or after 3 to 4 days, depending on the patch. This treatment should continue only as long as the intravenous infusion is maintained.

Glyceryl trinitrate may also be used as a 0.4% ointment for the relief of pain due to chronic **anal fissure** (below). A measured amount equivalent to about 1.5 mg is applied intra-anally every 12 hours for up to 8 weeks.

Administration in children. Although such use is unlicensed in children in the UK, the *BNFC* suggests that an intravenous infusion of glyceryl trinitrate may be used to produce vasodilatation in neonates, infants, and children in an initial dose of 200 to 500 nanograms/kg per minute, adjusted according to response to a usual dose of 1 to 3 micrograms/kg per minute. The dose should not exceed 10 micrograms/kg per minute, or 200 micrograms/minute.

In the management of anal fissures in children, the *BNFC* suggests the application of a glyceryl trinitrate 0.05 or 0.1% ointment.

Anal fissure. Nitrates such as glyceryl trinitrate are used for the treatment of chronic anal fissure (p. 2017.3) because of their ability to relax the anal sphincter. Topical application of glyceryl trinitrate ointment in concentrations of 0.2 to 0.8% has relieved pain and aided healing of anal fissures both in uncontrolled[1-3] and controlled studies,[4,5] although only the effect on pain appears to be significant.[4] One study[5] found that a concentration of 0.6% had no additional benefit over 0.2%. Follow-up[5,7] of some of the patients indicated that after 6 to 38 months most had not had further problems or had had occasional recurrences (relapses of about one-quarter to one-third) which in the majority of cases had responded to further topical treatment. A small placebo-controlled study specifically in children, however, did not find topical glyceryl trinitrate to be of benefit in this patient population.[8]

There is evidence that application of a glyceryl trinitrate patch may be as effective as topical application of a 0.2% ointment.[9]

Encouraging results have also been obtained in an uncontrolled study using a 1% ointment of isosorbide dinitrate.[10]

1. Gorfine SR. Topical nitroglycerin therapy for anal fissures and ulcers. *N Engl J Med* 1995; 333: 1156–7.
2. Lund JN *et al.* Use of glyceryl trinitrate ointment in the treatment of anal fissure. *Br J Surg* 1996; 83: 776–7.
3. Watson SJ, *et al.* Topical glyceryl trinitrate in the treatment of chronic anal fissure. *Br J Surg* 1996; 83: 771–5.
4. Lund JN, Scholefield JH. A randomised, prospective, double-blind, placebo-controlled trial of glyceryl trinitrate ointment in treatment of anal fissure. *Lancet* 1997; 349: 11–14. Correction. *ibid.*: 656.
5. Carapeti EA, *et al.* Randomised controlled trial shows that glyceryl trinitrate heals anal fissures, higher doses are not more effective, and there is a high recurrence rate. *Gut* 1999; 44: 727–30.
6. Penton C, *et al.* 0.4% Nitroglycerin ointment: in the treatment of chronic anal fissure pain. *Drugs* 2006; 66: 343–9.
7. Lund JN, Scholefield JH. Follow-up of patients with chronic anal fissure treated with topical glyceryl trinitrate. *Lancet* 1998; 352: 1681.
8. Kenny SE, *et al.* Double blind randomised controlled trial of topical glyceryl trinitrate in anal fissure. *Arch Dis Child* 2001; 85: 404–7.
9. Zuberi BF, *et al.* A randomized trial of glyceryl trinitrate ointment and nitroglycerin patch in healing of anal fissures. *Int J Colorectal Dis* 2000; 15: 243–5.
10. Schouten WR, *et al.* Pathophysiological aspects and clinical outcome of intra-anal application of isosorbide dinitrate in patients with chronic anal fissure. *Gut* 1996; 39: 465–9.

Erectile dysfunction. Erectile dysfunction (p. 2348.2) is usually managed with oral or intracavernosal vasodilators. Several studies have investigated topical alternatives, mostly glyceryl trinitrate applied either as ointment or as a transdermal patch to the penis.[1-5] Nitrates are believed to act by providing the smooth muscle relaxation and vasodilatation necessary for penile erection, and such treatment can produce erections in some subjects, although response rates vary.

Topical application of a cream containing isosorbide dinitrate, codergocrine mesilate, and aminophylline produced satisfactory erections in 21 of 36 men with erectile dysfunction due to various causes.[6] Eight out of 9 men with erectile dysfunction of psychogenic origin reported a satisfactory response. However, another study[7] was abandoned after the cream produced no effect in 10 consecutive patients. A further study in 14 patients who used a total of 77 applications of the cream reported no benefit over placebo.[8] Topical treatment with a cream containing isosorbide dinitrate, codergocrine mesilate, and testosterone has also been tried for erectile dysfunction; in a study in 42 men with low sexual interest and low or slightly depressed testosterone levels, 28 reported beneficial results.[9]

It has been recommended that a condom be worn to prevent drug transfer to the partner,[4] although the effects of the ointment on condom integrity do not seem to have been studied.

Topical nitrates should be avoided in those already taking phosphodiesterase type-5 inhibitors—see under Interactions, p. 1394.2.

1. Heaton JPW, *et al.* Topical glyceryl trinitrate causes measurable penile arterial dilation in impotent men. *J Urol (Baltimore)* 1990; 143: 729–31.
2. Meyhoff HH, *et al.* Non-invasive management of impotence with transcutaneous nitroglycerin. *Br J Urol* 1992; 69: 88–90.
3. Nunez BD, Anderson DC. Nitroglycerin ointment in the treatment of impotence. *J Urol (Baltimore)* 1993; 150: 1241–3.
4. Anderson DC, Seifert CF. Topical nitrate treatment of impotence. *Ann Pharmacother* 1993; 27: 1203–5.
5. Gramkow J, *et al.* Transcutaneous nitroglycerine in the treatment of erectile dysfunction: a placebo controlled clinical trial. *Int J Impot Res* 1999; 11: 35–9.
6. Gomaa A, *et al.* Topical treatment of erectile dysfunction: randomised double blind placebo controlled trial of cream containing aminophylline, isosorbide dinitrate, and co-dergocrine mesylate. *BMJ* 1996; 312: 1512–15.
7. Naude JH, Le Roux PJ. Topical treatment of erectile dysfunction did not show results. *BMJ* 1998; 316: 1318.
8. Le Roux PJ, Naude JH. Topical vasoactive cream in the treatment of erectile failure: a prospective, randomized placebo-controlled trial. *BJU Int* 1999; 83: 810–11.
9. Gomaa A, *et al.* The effect of topically applied vasoactive agents and testosterone versus testosterone in the treatment of erectile dysfunction in aged men with low sexual interest. *Int J Impot Res* 2001; 13: 93–9.

Gallstones. Endoscopic removal of gallstones (p. 2639.1) in a small series of 15 patients was facilitated by glyceryl trinitrate 1.2 to 3.6 mg applied as a spray to the tongue. Glyceryl trinitrate 1.2 mg was shown to relax the sphincter of Oddi to about 30% of its normal pressure.[1] The ability of glyceryl trinitrate to relax smooth muscle has also been used to relieve biliary colic (p. 6.3) in 3 patients with gallstones;[2] in one of these patients standard managements for the pain such as oral opioids had been only moderately effective.

1. Staritz M, *et al.* Nitroglycerine dilatation of sphincter of Oddi for endoscopic removal of bileduct stones. *Lancet* 1984; i: 956.
2. Hassel B. Treatment of biliary colic with nitroglycerin. *Lancet* 1993; 342: 1305.

Migraine. Although use of glyceryl trinitrate may precipitate or exacerbate migraine (p. 670.3) inhalation of glyceryl trinitrate at the onset of a migraine aura aborted attacks in a patient at risk of permanent neurological damage from migraine. Standard prophylactic therapy had previously been unsuccessful.[1]

1. Mitchell GK. Nitroglycerine by inhaler as treatment for migraine causing cerebral ischaemia. *Med J Aust* 1999; 171: 336.

Myocardial infarction. Intravenous nitrates are widely used in acute myocardial infarction (p. 1257.1), although evidence to support their use in patients undergoing reperfusion is limited. An overview of studies carried out before reperfusion (thrombolysis or percutaneous coronary intervention) became routine found that the use of intravenous nitrates (glyceryl trinitrate or sodium nitroprusside) within 24 hours of the onset of pain was associated with a reduction in mortality,[1] but whether they are of benefit in addition to reperfusion is less clear. However, empirical use of intravenous glyceryl trinitrate appears to be safe, and it should therefore be given where clinically indicated for ongoing ischaemic pain. In the GISSI-3 study,[2] glyceryl trinitrate was given by intravenous infusion during the first 24 hours, starting at 5 micrograms/minute and increasing by 5 to 20 micrograms/minute every 5 minutes for the first half hour until systolic blood pressure fell by at least 10% provided it remained above 90 mmHg; after 24 hours it was replaced by a transdermal patch providing 10 mg daily.

Long-term use of nitrates after myocardial infarction may be indicated in patients with myocardial ischaemia or poor left ventricular function, but there is no evidence to support their routine use. In the GISSI-3 study there was no significant benefit from the use of transdermal glyceryl trinitrate when assessed 6 weeks[2] and 6 months[3] post-infarction and in the ISIS-4 study[4] oral isosorbide mononitrate apparently had no effect on 35-day mortality.

1. Yusuf S, *et al.* Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomised trials. *Lancet* 1988; i: 1088–92.
2. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994; 343: 1115–22.
3. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. Six-month effects of early treatment with lisinopril and transdermal glyceryl trinitrate singly and together withdrawn six weeks

after myocardial infarction: the GISSI-3 trial. *J Am Coll Cardiol* 1996; 27: 337–44.
4. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995; 345: 669–85.

Obstetrics and gynaecology. The smooth muscle relaxant properties of glyceryl trinitrate have been used in various obstetric or gynaecological situations although most reports are anecdotal or include small numbers of patients. The intravenous injection of glyceryl trinitrate 50 to 100 micrograms repeated to a total dose of 200 micrograms if necessary has produced sufficient uterine relaxation in postpartum women for the manual extraction of retained placentas.[1,2] Use as a sublingual spray has also successfully aided breech extraction in a set of twins.[3]

Glyceryl trinitrate has been given as a sublingual spray to relax the cervix before IUD insertion. In a series of over 100 patients one or two doses of 400 micrograms sublingually were usually adequate.[4]

Beneficial results have been reported in women with possible premature labour (p. 2131.1) after application of glyceryl trinitrate patches to the abdomen.[5,6] In one study[7] this was as effective as ritodrine infusion, but another[8] found transdermal glyceryl trinitrate to be less effective than beta agonists. A study[9] comparing glyceryl trinitrate and magnesium sulfate, both given intravenously, found that glyceryl trinitrate was associated with a higher failure rate and a greater reduction in maternal blood pressure. A systematic review[10] concluded that there was insufficient evidence to support the routine use of glyceryl trinitrate.

Transdermal glyceryl trinitrate has been tried for controlling pain in severe and moderate-to-severe dysmenorrhoea[11,12] (p. 8.2).

Glyceryl trinitrate has been given in the management of pre-eclampsia (see under Hypertension, p. 1251.1). Intravenous use was reported to reduce blood pressure without compromising uterine blood flow,[13] but a systematic review of nitric oxide donors (given by any route) considered the evidence insufficient to draw conclusions about efficacy.[14]

Isosorbide mononitrate given vaginally has been found to produce cervical ripening[15] and although there is some evidence[16] that it is less effective, it may be an alternative to standard treatments such as prostaglandins (see Termination of Pregnancy p. 2131.3). Isosorbide dinitrate has been used similarly after missed abortion.[17]

1. DeSimone CA, *et al.* Intravenous nitro-glycerin aids manual extraction of a retained placenta. *Anesthesiology* 1990; 73: 787.
2. Lowenwirt IP, *et al.* Safety of intravenous glyceryl trinitrate in management of retained placenta. *Aust N Z J Obstet Gynaecol* 1997; 37: 20–4.
3. Greenspoon JS, Kovacic A. Breech extraction facilitated by glyceryl trinitrate sublingual spray. *Lancet* 1991; 338: 124–5.
4. Yadava RP. Sublingual glyceryl trinitrate spray facilitates IUD insertion. *Br J Sex Med* 1990; 17: 217.
5. Lees C, *et al.* Arrest of preterm labour and prolongation of gestation with glyceryl trinitrate, a nitric oxide donor. *Lancet* 1994; 343: 1325–6.
6. Smith GN, *et al.* Randomised, double-blind, placebo controlled pilot study assessing nitroglycerin as a tocolytic. *Br J Obstet Gynaecol* 1999; 106: 736–9.
7. Lees CC, *et al.* Glyceryl trinitrate and ritodrine in tocolysis: an international multicenter randomized study. *Obstet Gynecol* 1999; 94: 403–8.
8. Bisits A, *et al.* The Randomized Nitric Oxide Tocolysis Trial (RNOTT) for the treatment of preterm labor. *Am J Obstet Gynecol* 2004; 191: 683–90.
9. El-Sayed YY, *et al.* Randomized comparison of intravenous nitroglycerin and magnesium sulfate for treatment of preterm labor. *Obstet Gynecol* 1999; 93: 79–83.
10. Duckitt K, Thornton S. Nitric oxide donors for the treatment of preterm labour. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2002 (accessed 28/11/07).
11. Pittrof R, *et al.* Crossover study of glyceryl trinitrate patches for controlling pain in women with severe dysmenorrhoea. *BMJ* 1996; 312: 884.
12. The Transdermal Nitroglycerine/Dysmenorrhoea Study Group. Transdermal nitroglycerine in the management of pain associated with primary dysmenorrhoea: a multinational pilot study. *J Int Med Res* 1997; 25: 41–4.
13. Grunewald C, *et al.* Effects of nitroglycerin on the uterine and umbilical circulation in severe preeclampsia. *Obstet Gynecol* 1995; 86: 600–4.
14. Meher S, Duley L. Nitric oxide for preventing pre-eclampsia and its complications. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2007 (accessed 30/03/10).
15. Thomson AJ, *et al.* Randomised trial of nitric oxide donor versus prostaglandin for cervical ripening before first-trimester termination of pregnancy. *Lancet* 1998; 352: 1093–6.
16. Chen FC-K, *et al.* Isosorbide mononitrate vaginal gel versus misoprostol vaginal gel versus Dilapan-S for cervical ripening before first trimester curettage. *Eur J Obstet Gynecol Reprod Biol* 2008; 138: 176–9.
17. Arteaga-Troncoso G, *et al.* Intracervical application of the nitric oxide donor isosorbide dinitrate for induction of cervical ripening: a randomised controlled trial to determine clinical efficacy and safety prior to first trimester surgical evacuation of retained products of conception. *BJOG* 2005; 112: 1615–19.

Oesophageal motility disorders. Achalasia is obstruction caused by failure of the lower oesophageal sphincter to relax and permit passage of food into the stomach. Nitrates such as isosorbide dinitrate have been reported to produce effective relaxation and to reduce symptoms when given sublingually. They have a role when mechanical dilatation of the sphincter or surgery are not feasible (see Oesophageal Motility Disorders, p. 1816.2).

Nitrates may also be employed in oesophageal disorders such as variceal haemorrhage (see below).

Pain. Nitrates have been tried topically in the management of pain. Beneficial results have been reported with glyceryl trinitrate, applied as patches[1] or as a spray,[2] and isosorbide dinitrate spray,[3] in patients with painful diabetic neuropathy. Glyceryl trinitrate has also been used topically in musculoskeletal disorders[4] (see also Soft-tissue Rheumatism, below), and in surgical pain,[5,6] and intravenously as an adjunct to regional anaesthesia.[7]

Glyceryl trinitrate is also used topically to relieve pain in patients with anal fissure (p. 1392.2). For reference to its use in biliary colic, see Gallstones, p. 1392.3.

1. Rayman G, *et al.* Glyceryl trinitrate patches as an alternative to isosorbide dinitrate spray in the treatment of chronic painful diabetic neuropathy. *Diabetes Care* 2003; 26: 2697–8.
2. Agrawal RP, *et al.* Glyceryl trinitrate spray in the management of painful diabetic neuropathy: a randomized double blind placebo controlled cross-over study. *Diabetes Res Clin Pract* 2007; 77: 161–7.
3. Yuen KCJ, *et al.* Treatment of chronic painful diabetic neuropathy with isosorbide dinitrate spray: a double-blind placebo-controlled cross-over study. *Diabetes Care* 2002; 25: 1699–1703.
4. Paoloni JA, *et al.* Topical nitric oxide application in the treatment of chronic extensor tendinosis at the elbow: a randomized, double-blinded, placebo-controlled clinical trial. *Am J Sports Med* 2003; 31: 915–20.
5. McCabe JE, *et al.* A randomized controlled trial of topical glyceryl trinitrate before transrectal ultrasonography-guided biopsy of the prostate. *BJU Int* 2007; 100: 536–8.
6. Karanlik H, *et al.* The effect of glyceryl trinitrate ointment on posthemorrhoidectomy pain and wound healing: results of a randomized, double-blind, placebo-controlled study. *Dis Colon Rectum* 2009; 52: 280–5.
7. Sen S, *et al.* The analgesic effect of nitroglycerin added to lidocaine on intravenous regional anesthesia. *Anesth Analg* 2006; 102: 916–20.

Peripheral vascular disease. Nitrates have been used as vasodilators and smooth muscle relaxants to improve resting blood flow in vasospastic arterial disorders (p. 1275.3) and atherosclerotic peripheral vascular disorders (p. 1272.3). Some benefit has been reported with topical glyceryl trinitrate in atherosclerotic distal limb ischaemia,[1] and in Raynaud's syndrome,[2-4] but its use is not established.

1. Fletcher S, *et al.* Locally applied transdermal nitrate patches for the treatment of ischaemic rest pain. *Int J Clin Pract* 1997; 51: 324–5.
2. Franks AG. Topical glyceryl trinitrate as adjunctive treatment in Raynaud's disease. *Lancet* 1982; i: 76–7.
3. Coppock JS, *et al.* Objective relief of vasospasm by glyceryl trinitrate in secondary Raynaud's phenomenon. *Postgrad Med J* 1986; 62: 15–18.
4. Teh LS, *et al.* Sustained-release transdermal glyceryl trinitrate patches as a treatment for primary and secondary Raynaud's phenomenon. *Br J Rheumatol* 1995; 34: 636–41.

Pulmonary hypertension. Glyceryl trinitrate reduces total pulmonary resistance in most patients with pulmonary arterial hypertension (p. 1278.2),[1,2] including when given by inhalation.[3] However, other vasodilators such as calcium-channel blockers, epoprostenol, or bosentan are generally preferred for long-term treatment.

1. Pearl RG, *et al.* Acute hemodynamic effects of nitroglycerin in pulmonary hypertension. *Ann Intern Med* 1983; 99: 9–13.
2. Weir EK, *et al.* The acute administration of vasodilators in primary pulmonary hypertension. *Am Rev Respir Dis* 1989; 140: 1623–30.
3. Goyal P, *et al.* Efficacy of nitroglycerin inhalation in reducing pulmonary arterial hypertension in children with congenital heart disease. *Br J Anaesth* 2006; 97: 208–14.

Quinine oculotoxicity. Intravenous nitrate has been suggested for the management of quinine oculotoxicity (p. 667.3) and its benefit may be due to an increase in retinal vascular bed flow.[1]

1. Moore D, *et al.* Research into quinine ocular toxicity. *Br J Ophthalmol* 1992; 76: 703.

Soft-tissue rheumatism. There is evidence from *animal* studies that nitric oxide plays an important role in tendon healing, and randomised studies in patients with tennis elbow (epicondylitis), Achilles tendinosis (tendinitis), and supraspinatus tendinosis showed enhanced subjective and objective recovery when a glyceryl trinitrate patch (releasing 1.25 mg over 24 hours) was applied over the area of tenderness once daily.[1] The benefits of such treatment appeared to be sustained on 3-year follow-up,[2] suggesting that it was not just an analgesic effect; however, the same group found that a different glyceryl trinitrate patch was ineffective in another group of patients.[3] Glyceryl trinitrate patches have also been tried in rotator cuff disease, and a systematic review[4] considered that there may be some evidence for a reduction in acute symptoms, although insufficient evidence of a longer-term efficacy. Glyceryl trinitrate has also been tried in musculoskeletal pain (see Pain, above). For the general management of soft-tissue rheumatism see p. 14.2.

1. Murrell GAC. Using nitric oxide to treat tendinopathy. *Br J Sports Med* 2007; 41: 227–31.
2. Paoloni JA, Murrell GAC. Three-year followup study of topical glyceryl trinitrate treatment of chronic noninsertional Achilles tendinopathy. *Foot Ankle Int* 2007; 28: 1064–8.
3. Paoloni JA, *et al.* Randomised, double-blind, placebo-controlled clinical trial of a new topical glyceryl trinitrate patch for chronic lateral epicondylosis. *Br J Sports Med* 2009; 43: 299–302.
4. Cumpston M, *et al.* Topical glyceryl trinitrate for rotator cuff disease. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2009 (accessed 30/03/10).

Variceal haemorrhage. The usual treatment in variceal haemorrhage (p. 2563.1) is injection sclerotherapy or banding ligation which may be performed during the emergency endoscopy procedure. Where endoscopy is unavailable drug therapy may be used; it may also have a role when sclerotherapy fails and some have suggested that initial drug therapy may be preferable to sclerotherapy. Vasoconstrictors that are used include vasopressin and its analogue terlipressin, given with glyceryl trinitrate which counteracts the adverse cardiac effects of vasopressin while potentiating its beneficial effects on portal pressure; somatostatin is also used.

Prophylaxis of a first bleed in patients with portal hypertension is controversial since about 70% of patients who have varices will never bleed. It is postulated that a reduction in portal pressure to below 12 mmHg is necessary to reduce the incidence of variceal bleeding and that treatment with beta blockers alone does not achieve this. More effective drugs are being sought and isosorbide mononitrate (as adjunctive therapy with a beta blocker) has been investigated, both for prophylaxis of a first bleed[1,2] and in the prevention of rebleeding.[3] Early emergency treatment (before endoscopy) with terlipressin given intravenously and glyceryl trinitrate transdermally controlled bleeding and lowered mortality rates in patients with gastrointestinal bleeding and a history or clinical signs of cirrhosis.[4] However, use of oral isosorbide mononitrate with somatostatin infusion for acute variceal bleeding was less effective than somatostatin alone and induced more adverse effects.[5]

1. Angelico M, *et al.* Isosorbide-5-mononitrate versus propranolol in the prevention of first bleeding in cirrhosis. *Gastroenterology* 1993; 104: 1460–5.
2. Merkel C, *et al.* Randomised trial of nadolol alone or with isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. *Lancet* 1996; 348: 1677–81.
3. Villanueva C, *et al.* Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal rebleeding. *N Engl J Med* 1996; 334: 1624–9.
4. Levacher S, *et al.* Early administration of terlipressin plus glyceryl trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. *Lancet* 1995; 346: 865–8.
5. Junquera F, *et al.* Somatostatin plus isosorbide 5-mononitrate versus somatostatin in the control of acute gastro-oesophageal variceal bleeding: a double blind, randomised, placebo controlled clinical trial. *Gut* 2000; 46: 127–32.

Venepuncture. Glyceryl trinitrate patches applied to skin adjacent to intravenous infusion sites are used in the prophylactic treatment of phlebitis and extravasation.[1]

Local application of glyceryl trinitrate 1 to 2 mg as ointment was found to be a useful aid to venepuncture in a study of 50 patients undergoing surgery,[2] but conflicting results have been reported in children and neonates.[3,4]

1. Ijon JA, Ansani NT. Transdermal nitroglycerin for the prevention of intravenous infusion failure due to phlebitis and extravasation. *Ann Pharmacother* 2000; 34: 1189–92.
2. Hecker JF, *et al.* Nitroglycerine ointment as an aid to venepuncture. *Lancet* 1983; i: 332–3.
3. Vaksmann G, *et al.* Nitroglycerine ointment as aid to venous cannulation in children. *J Pediatr* 1987; 111: 89–91.
4. Maynard EC, Oh W. Topical nitroglycerin ointment as an aid to insertion of peripheral venous catheters in neonates. *J Pediatr* 1989; 114: 474–6.

Adverse Effects

Glyceryl trinitrate may cause flushing of the face, dizziness, tachycardia, and throbbing headache. Large doses cause vomiting, restlessness, blurred vision, hypotension (which can be severe), syncope, and rarely cyanosis, and methaemoglobinaemia; impairment of respiration and bradycardia may ensue. Contact dermatitis has been reported in patients using topical glyceryl trinitrate preparations; local irritation and erythema may also occur. Preparations applied to the oral mucosa frequently produce a localised burning sensation.

Chronic poisoning may occur in industry but tolerance develops when glyceryl trinitrate is regularly handled and nitrate dependence can lead to severe withdrawal symptoms in subjects abruptly removed from chronic exposure. Loss of such tolerance is rapid and may cause poisoning on re-exposure. Tolerance may occur during clinical use and is usually associated with preparations that produce sustained plasma concentrations.

Effects on the heart. Tachycardia, hypotension, and bradycardia are recognised adverse cardiac effects of glyceryl trinitrate. Rarely reported adverse effects include asystole[1] and complete heart block.[2]

1. Ong EA, *et al.* Nitroglycerin-induced asystole. *Arch Intern Med* 1985; 145: 954.
2. Lancaster L, Penster PE. Complete heart block after sublingual nitroglycerin. *Chest* 1983; 84: 111–12.

Effects on taste. A 61-year-old man experienced loss of bitter and salty taste sensations 2 weeks after addition of glyceryl trinitrate patches to his post-myocardial infarction

drug regimen.[1] The patient had complete loss of taste after 6 weeks; his taste sensation returned to normal within 1 week of stopping glyceryl trinitrate patches. Taste sensation was again altered on rechallenge.

1. Ewing RC, *et al.* Ageusia associated with transdermal nitroglycerin. *Clin Pharm* 1989; 8: 146–7.

Hypersensitivity. Contact dermatitis has been reported in patients using glyceryl trinitrate ointment and patches.[1] Both glyceryl trinitrate and formulation components may be involved in these reactions.

1. Carmichael AJ. Skin sensitivity and transdermal drug delivery: a review of the problem. *Drug Safety* 1994; 10: 151–9.

Intravenous administration. Some formulations of glyceryl trinitrate for intravenous use may contain substantial quantities of alcohol in the solvent. There have been several reports of alcohol intoxication occurring in patients during high-dose intravenous glyceryl trinitrate infusion.[1-3] In a patient[3] who required glyceryl trinitrate 2 mg/minute, a blood-alcohol concentration of 2.67 mg/mL was reported. PVC tubing had been used for the infusion and it was suggested that adsorption of glyceryl trinitrate onto the tubing may have increased the dose requirement and thus the amount of alcohol given.

Propylene glycol is also used as a solvent in some formulations of glyceryl trinitrate. Infusion of solutions with propylene glycol can lead to hyperosmolarity: see under Propylene Glycol, p. 2205.3, for details.

1. Shook TL, *et al.* Ethanol intoxication complicating intravenous nitroglycerin therapy. *Ann Intern Med* 1984; 101: 498–9.
2. Daly TJ, *et al.* "Cocktail"-coronary care. *N Engl J Med* 1984; 310: 1123.
3. Korn SH, Comer JB. Intravenous nitroglycerin and ethanol intoxication. *Ann Intern Med* 1985; 102: 274.

Treatment of Adverse Effects

Syncope and hypotension should be treated by keeping the patient in a recumbent position with the head lowered; pressor agents may be necessary in extreme hypotension. Oxygen, with assisted respiration, may be needed in severe poisoning and infusion of plasma expanders or suitable electrolyte solutions may be required to maintain the circulation. If methaemoglobinaemia occurs methylthioninium chloride may be given intravenously. In the case of severe poisoning with tablets the stomach may be emptied by lavage. If large amounts have been ingested within 1 hour, activated charcoal may be considered.

Precautions

Glyceryl trinitrate should not be used in patients with severe hypotension, hypovolaemia, marked anaemia, heart failure due to obstruction (including constrictive pericarditis), or raised intracranial pressure due to head trauma or cerebral haemorrhage. Although it has been suggested that glyceryl trinitrate may increase intra-ocular pressure in patients with angle-closure glaucoma and should be avoided in such patients there appears to be no evidence for such a contra-indication.

Glyceryl trinitrate should be used with caution in patients with severe renal or severe hepatic impairment, hypothyroidism, malnutrition, or hypothermia. Metal-containing transdermal patches should be removed before cardioversion or diathermy. Buccal administration has rarely been associated with dental caries; patients should be advised to alternate the site of application and maintain good dental hygiene. Those with xerostomia should moisten the mouth before using buccal tablets; however, the sublingual spray may be a more suitable formulation in such patients.

Nitrate tolerance. Although organic nitrates are effective anti-anginal drugs, their use is limited by the development of tolerance and the loss or attenuation of their anti-anginal and anti-ischaemic effects.[1,2] This can occur with all of the organic nitrates, particularly if frequent or continuous dosing is used.[1-3]

The mechanisms of nitrate tolerance are incompletely understood. The vasodilator effect of organic nitrates may depend on their conversion to nitric oxide, a process which requires the presence of a sulfhydryl donor such as cysteine or another thiol. Repeated doses of a nitrate exhaust tissue stores of sulfhydryl groups and this is one mechanism that may account for the development of tolerance.[1,2] The activation of neurohormonal systems, which releases vasoconstrictor hormones that counteract the effects of organic nitrates, has also been proposed as a mechanism.[1,2] An increase in free-radical production during nitrate therapy has also been suggested,[1] and may inhibit bioactivation of the nitrate.[3] Nitrate-induced expansion of plasma volume may also contribute, leading to reversal of the effects of nitrates on ventricular preload.[1,2]

The method most commonly used to avoid the development of tolerance is to provide a nitrate-free interval.[1,2] The optimum duration is not clear, but a nitrate-free period of 10 to 12 hours has been suggested.[1,2] With transdermal glyceryl trinitrate systems, the patch can be removed at night. For oral, buccal, and ointment preparations, the dose given at the end of the day can be omitted. However, rebound myocardial ischaemia may occur during this time,[1] and may require the use of short-acting nitrate preparations.[2] Whether a nitrate-free interval is necessary for all patients is unknown as many patients using continuous nitrates do not show clinical tolerance. A transdermal patch with a higher release rate during the first part of a 24-hour period has been found not to prevent the development of tolerance.[4]

Various drugs have been reported to reduce the development of nitrate tolerance, including sulfhydryl donors and drugs with antioxidant properties, but none has an established role.[1,3]

1. Parker JD, Parker JO. Nitrate therapy for stable angina pectoris. *N Engl J Med* 1998; 338: 520–31.
2. Rutherford JD. Nitrate tolerance in angina therapy: how to avoid it. *Drugs* 1995; 49: 196–9.
3. Münzel T, *et al.* Explaining the phenomenon of nitrate tolerance. *Circ Res* 2005; 97: 618–28.
4. Wiegand A, *et al.* Pharmacodynamic and pharmacokinetic evaluation of a new transdermal delivery system with a time-dependent release of glyceryl trinitrate. *J Clin Pharmacol* 1992; 32: 77–84.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glyceryl trinitrate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Transdermal patches. An explosion occurred during defibrillation in a patient with a glyceryl trinitrate transdermal patch on the left side of the chest.[1] There was no visible injury to the patient. Subsequent studies suggested that this was caused by an electrical arc between the defibrillator paddle and the aluminium backing of the patch rather than explosion of the glyceryl trinitrate.

Although removal of transdermal patches before diathermy is usually recommended, a maximum rise in patch temperature of only 2.2 degrees was reported when patches were exposed to power densities up to 800 watts/m^2. It was considered that exposure of transdermal patches to microwave diathermy, for example as part of physiotherapy treatment, was unlikely to cause direct thermal injury to the wearer.[2]

1. Babka JC. Does nitroglycerin explode? *N Engl J Med* 1983; 309: 379.
2. Moseley H, *et al.* The influence of microwave radiation on transdermal delivery systems. *Br J Dermatol* 1990; 122: 361–3.

Interactions

The hypotensive effects of glyceryl trinitrate may be enhanced by alcohol, and by vasodilators and other drugs with hypotensive actions. The efficacy of sublingual and buccal tablet preparations may be reduced by drugs that cause dry mouth (such as tricyclic antidepressants and other antimuscarinics) since dissolution may be delayed (see also Precautions, above).

Anticoagulants. For the effects of glyceryl trinitrate on the activity of *heparin*, see p. 1400.2.

Ergot alkaloids. For the effects of glyceryl trinitrate on *dihydroergotamine*, see under Interactions of Ergotamine, p. 675.3.

Phosphodiesterase type-5 inhibitors. The concurrent use of nitrates and phosphodiesterase type-5 inhibitors such as sildenafil is contra-indicated. Significant hypotension may occur due to potentiation of the vasodilator actions of nitrates.[1] Deaths due to a possible interaction have been reported.[2]

1. Webb DJ, *et al.* Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. *J Am Coll Cardiol* 2000; 36: 25–31.
2. Cheitlin MD, *et al.* Use of sildenafil (Viagra) in patients with cardiovascular disease. *J Am Coll Cardiol* 1999; 33: 273–82. Correction. *ibid.*; 34: 1850.

Thrombolytics. For the effects of glyceryl trinitrate and *alteplase* when given together, see p. 1298.2.

Pharmacokinetics

Glyceryl trinitrate is rapidly absorbed from the oral mucosa. It is also well absorbed from the gastrointestinal tract and through the skin. Bioavailability is less than 100% when given by any of these routes due to pre-systemic clearance; bioavailability is further reduced after oral use owing to extensive first-pass metabolism in the liver.

Therapeutic effect is apparent within 1 to 3 minutes of use of sublingual tablets, sublingual spray, or buccal tablets; within 30 to 60 minutes of applying an ointment or transdermal patch; and within 1 to 2 minutes after intravenous doses.

Duration of action is about 30 to 60 minutes with sublingual tablets or spray and 3 to 5 hours with modified release buccal tablets. Transdermal patches are designed to release a stated amount of drug over 24 hours, while therapeutic effects after application of glyceryl trinitrate ointment 2% persist for up to 8 hours. Duration of action after intravenous dosage is about 3 to 5 minutes.

Glyceryl trinitrate is widely distributed with a large apparent volume of distribution. It is taken up by smooth muscle cells of blood vessels and the nitrate group is cleaved to inorganic nitrite and then to nitric oxide. This reaction requires the presence of cysteine or another thiol. Glyceryl trinitrate also undergoes hydrolysis in plasma and is rapidly metabolised in the liver by glutathione-organic nitrate reductase to dinitrates and mononitrates. The dinitrates are less potent vasodilators than glyceryl trinitrate; the mononitrates may have some vasodilator activity.

References.
1. Bogaert MG. Clinical pharmacokinetics of glyceryl trinitrate following the use of systemic and topical preparations. *Clin Pharmacokinet* 1987; 12: 1–11.
2. Thadani U, Whitsett T. Relationship of pharmacokinetic and pharmacodynamic properties of the organic nitrates. *Clin Pharmacokinet* 1988; 15: 32–43.
3. Ridout G, *et al.* Pharmacokinetic considerations in the use of newer transdermal formulations. *Clin Pharmacokinet* 1988; 15: 114–31.
4. Hashimoto S, Kobayashi A. Clinical pharmacokinetics and pharmacodynamics of glyceryl trinitrate and its metabolites. *Clin Pharmacokinet* 2003; 42: 205–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dauxona; Enetege; Minitran; Niglinar; Nitradisc; Nitro-Dur; Nitroderm TTS; Nitrodom; Nitrogray; ***Austral.***: Anginine; Lycinate; Minitran; Nitro-Dur; Nitrolingual; Rectogesic; Transiderm-Nitro; ***Austria***: Deponit; Nitro Mack†; Nitro Pohl; Nitro-Dur†; Nitroderm; Nitrolingual; Perlinganit; ***Belg.***: Deponit; Diafusor; Minitran; Nitroderm; Nitrolingual; Nitropohl†; Nysconitrine†; Rectogesic; Trinipatch; Willlong†; ***Braz.***: Nitradisc; Nitroderm TTS; Tridil; ***Canad.***: Gen-Nitro†; Minitran; Mylan-Nitro; Nitro-Dur; Nitroject; Nitrol; Nitrolingual; Nitrostat; Rho-Nitro; Transderm-Nitro; Trinipatch; ***Chile***: Angiolingual; Nitrocor†; Nitroderm; ***China***: Deponit (帖保吖); Nitrocine (异述欣); Nitrolingual; Nitrostat (耐较吖); Pailuo (派洛); Ruo Bi Xun (若必獯); Ruo Xin Lai (若欣莱); XinShu (信舒); ***Cz.***: Nit-Ret†; Nitro Pohl; Nitromint; Perlinganit; Rectogesic; ***Denm.***: Discotrine; Glytrin; Nitrolingual; Nitromex†; Rectogesic; ***Fin.***: Deponit; Minitran; Nitro; Nitromex†; Perlinganit; Rectogesic; Transiderm-Nitro; ***Fr.***: Cordipatch; Diafusor; Discotrine; Epinitril; Natispray; Nitriderm TTS; Nitronal; Rectogesic; Trinipatch; ***Ger.***: Aquo-Trinitrosan†; Corangin Nitrospray†; Deponit†; MinitranS; Nitrangin†; Nitro Carino; Nitroderm TTS; Nitrolingual; Perlinganit†; Rectogesic; Trinitrosan†; ***Gr.***: Apirol; Cardiplast; Carina; Epinitril; Glyconitron; Nilmadin; Nitro Mack; Nitrocerin; Nitrodyl; Nitrolingual; Nitronal; Nitrong; Nitroretard; Nitrosylon; Pancoran; Rectogesic; Sodemethin; Solinitrina; Supranitrin; Trinipatch; Trinitrine Simple Laleuf; ***Hong Kong***: Angised; Deponit; Nitro Mack†; Nitro-Dur†; Nitrocine; Nitroderm TTS; Nitrolingual; ***Hung.***: Nitro Pohl; Nitro-Dur; Nitroderm TTS; Nitrolingual; Nitromint; Rectogesic; Sustac; ***India***: Angised; Angispan-TR; Glynit; GTN Sorbitrate; Leonite; Millisrol†; Myonit; Myovin; NG-Care; NGLong; NGTel; Nig; Nitrocerin; Nitrocin; Nitrocontin; Nitrocure; Nitroday; Nitroderm TTS; Nitrofast; Nitrogesic; Nitroglyn; Nitroject; Nitrolife; Nitrolingual†; Nitroplus; Nitrosol; Nitrovir; Nizo; ***Indon.***: Nitrocine†; Nitrokaf; ***Irl.***: Deponit†; Dermatrans; Epinitril; Glytrin; Nitro-Dur; Nitrocine; Nitrolingual; Nitromin†; Nitronal†; Rectogesic; Suscard; Sustac†; Transiderm-Nitro; ***Israel***: Deponit; Nitrocine; Nitroderm TTS; Nitrolingual; Rectogesic; ***Ital.***: Adesitrin; Deponit; Dermatrans; Epinitril; Keritrina; Minitran; Natispray; Nitraket; Nitro-Dur; Nitrocor; Nitroderm TTS; Nitrosylon; Perganit; Rectogesic; Top-Nitro; Triniplas; Trinitrina; Venitrin; ***Jpn***: Meditrans; Millisrol; Vasolator; ***Malaysia***: Deponit; Nitrocine; Nitroderm; ***Mex.***: Angiopohl; Anglix; Cardinit; Minitran; Nitradisc; Nitro-Dur; Nitroder; Nitroderm TTS; ***Neth.***: Deponit; Glytrin; Minitran; Nitro Pohl; Nitro-Dur; Nitrolingual; Rectogesic†; Transiderm TTS; Transiderm-Nitro; Trinipatch; ***Norw.***: Minitran; Nitro-Dur; Nitrolingual; Nitromex†; Nitroven; Rectogesic; Transiderm-Nitro; ***NZ***: Glytrin; Lycinate; Minitran; Nitroderm; Nitrolingual; Nitronal; Rectogesic; ***Philipp.***: Deponit; Minitran; Nitrolingual; Nitronal; Nitrostat; Nyserin; Perlinganit; Transderm-Nitro; ***Pol.***: Nitracor; Nitrocard; Nitroderm; Nitromint; Perlinganit; Rectogesic†; Sustonit; Trimonit; ***Port.***: Dermatrans; Diafusor†; Discotrine†; Epinitril; Glytrin; Nitradisc; Nitro-Dur; Nitroderm TTS; Nitromint; Plastranit; Rectogesic; ***Rus.***: Deponit (Депонит); Nirmin (Нирмин)†; Nitro (Нитро); Nitrocor (Нитрокор); Nitrogranulong (Нитрогранулонг); Nitroject (Нитроджект); Nitromint (Нитромент); Nitrong (Нитронг); Nitrospray (Нитроспрей); Perlinganit (Перлинганит); Sustac (Сустак); Sustonit (Сустонит); Trinitrolong (Тринитролонг); ***S.Afr.***: Angised; Nitrocine; Nitrolingual; Tridil†; ***Singapore***: Angised; Deponit†; Glytrin; Nitrocine; Nitrolingual; Rectogesic; ***Spain***: Cordiplast; Dermatrans; Diafusor; Epinitril; Minitran; Nitradisc; Nitro-Dur; Nitroderm; Nitrofix; Nitroplast; Rectogesic; Solinitrina; Trinipatch; Trinispray; Vernies; ***Swed.***: Glytrin; Minitran; Nitrolingual; Nitromex†; Rectogesic; Suscard†; Transiderm-Nitro; ***Switz.***: Deponit; Minitran; Nitro-Dur; Nitroderm TTS; Nitrolingual; Nitronal†; Perlinganit; Trinitrine; ***Thai.***: Glytrin†; Nitrocine†; Nitroderm; Nitroject; Nitromint; ***Turk.***: Deponit; Nitroderm

TTS; Nitrolingual†; Nitronal; Perlinganit; *UK*: Coro-Nitro; Deponit; Glytrin; Minitran; Nitro-Dur; Nitrocine; Nitrolingual; Nitromin; Nitronal; Percutol; Rectogesic; Suscard†; Transiderm-Nitro; Trinitek†; *Ukr.*: Nitro (Нитро); Nitromint (Нитромінт)†; Nitrong (Нитронг); Sustac (Сустак)†; *USA*: Minitran; Nitrek; Nitro-Bid; Nitro-Derm†; Nitro-Dur; Nitro-Time; Nitrodisc†; Nitrogard†; Nitrolingual; NitroMist; NitroQuick†; Nitrostat; Rectiv; Transderm-Nitro†; Transdermal-NTG†; *Venez.*: Nitro Mack; Nitrocor; Nitroderm.

Multi-ingredient Preparations. *Arg.*: Trinitron; *Gr.*: Trinitrine Cafein Dubois; *Pol.*: Pentaerythritol Compositum; *Rus.*: Carniland (Карнилонд); *Spain*: Cafinitrina; *USA*: Emergent-Ez.

Homoeopathic Preparations. *Austria*: Cactus compositum; Rytmopasc; *Canad.*: Headache & Migraine; Homeo-Form *MI*†; HPB Complex†; Menopause L122; Travel Sickness; *Cz.*: Glonoinum; Ypsiloheel; *Fr.*: Actheane; Agnus Castus Complexe No 2†; Cocculus Complexe No 73; Crataegus Complexe No 15; Lachesis Complexe No 122; Sclero-Drainol†; *Ger.*: Arte-cyl Ho-Len-Complex; Cefangipect†; Cefavora Cor; Homviocorin spezial; Lowe-Komplex Nr 3; Migrane Hevert†; Migrane Hevert; Naranocor HM; Neuro-Do; Otio-cyl Ho-Len-Complex; Oto-cyl Ho-Len-Complex; Pectapas SL; Rytmopasc; Schworocard; Strophanthus comp; Vertigo-Hevert; Viscum-Entoxin N; Ypsiloheel N; *Neth.*: Gletar; *Rus.*: Tonginal (Тонгинал); *Ukr.*: Tonginal (Тонгінал).

Pharmacopoeial Preparations
BP 2014: Glyceryl Trinitrate Ointment; Glyceryl Trinitrate Sublingual Spray; Glyceryl Trinitrate Tablets; Glyceryl Trinitrate Transdermal Patches;
USP 36: Nitroglycerin Injection; Nitroglycerin Ointment; Nitroglycerin Tablets.

Guanabenz Acetate *(USAN, rINNM)*

Acetato de guanabenzo; Guanabenz, Acétate de; Guanabenzi Acetas; Guanabenzo, acetato de; NSC-68982 (guanabenz); Wy-8678 (guanabenz); Гуанабенза Ацетат.

(2,6-Dichlorobenzylideneamino)guanidine acetate

$C_8H_8Cl_2N_4.C_2H_4O_2$=291.1

CAS — 5051-62-7 (guanabenz); 23256-50-0 (guanabenz acetate).

UNII — 443O19GK1A.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Guanabenz Acetate). A white or almost white powder with not more than a slight odour. Sparingly soluble in water and in 0.1N hydrochloric acid; soluble in alcohol and in propylene glycol. A 0.7% solution in water has a pH of 5.5 to 7.0. Store in airtight containers. Protect from light.

Uses and Administration

Guanabenz is an alpha$_2$-adrenoceptor agonist with actions and uses similar to those of clonidine (p. 1339.2). It is used in the management of hypertension (p. 1251.1), either alone or with other antihypertensives, particularly thiazide diuretics.

Guanabenz is given orally as the acetate, but doses are usually expressed in terms of the base. Guanabenz acetate 5 mg is equivalent to about 4 mg of guanabenz.

In hypertension, the usual dose is 4 mg twice daily initially; the daily dose may be increased by amounts of 4 to 8 mg every 1 to 2 weeks according to response. Doses of up to 32 mg twice daily have been used.

Adverse Effects and Precautions

As for Clonidine Hydrochloride, p. 1341.2.

Overdosage. Overdosage with guanabenz has been reported.[1] The main symptoms were lethargy, drowsiness, bradycardia, and hypotension. A 45-year-old woman who had taken 200 to 240 mg of guanabenz with alcohol recovered after gastric lavage and intravenous fluids; a 3-year-old child who had taken 12 mg of guanabenz responded to atropine and dopamine. Naloxone had little effect in either patient.

1. Hall AH, *et al.* Guanabenz overdose. *Ann Intern Med* 1985; 102: 787–8.

Interactions

As for Clonidine Hydrochloride, p. 1342.1.

Pharmacokinetics

About 75% of an oral dose of guanabenz is absorbed and undergoes extensive first-pass metabolism. Peak plasma concentrations occur about 2 to 5 hours after a dose. It is about 90% bound to plasma proteins. Guanabenz is mainly excreted in urine, almost entirely as metabolites, with less than 1% as unchanged drug; about 10 to 30% is excreted in faeces. The average elimination half-life is reported to range from 4 to 14 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Lisapres; *USA*: Wytensin†.

Pharmacopoeial Preparations
USP 36: Guanabenz Acetate Tablets.

Guanadrel Sulfate *(USAN, rINNM)*

CL-1388R; Guanadrel, Sulfate de; Guanadrel, sulfato de; Guanadrel Sulphate; Guanadrell Sulfas; Sulfato de guanadrel; U-28288D; Гуанадрела Сульфат.

1-(Cyclohexanespiro-2′-[1′,3′]dioxolan-4′-ylmethyl)guanidine sulfate; 1-(1,4-Dioxaspiro[4.5]dec-2-ylmethyl)guanidine sulfate.

$(C_{10}H_{19}N_3O_2)_2.H_2SO_4$=524.6

CAS — 40580-59-4 (guanadrel); 22195-34-2 (guanadrel sulfate).

UNII — MT147RMO9T.

Pharmacopoeias. In *US*.

USP 36: (Guanadrel Sulfate). A white to off-white crystalline powder. Soluble in water; slightly soluble in alcohol and in acetone; sparingly soluble in methyl alcohol.

Profile

Guanadrel is an antihypertensive with properties similar to those of guanethidine (below). After oral administration, guanadrel acts within 2 hours with the maximum effect after 4 to 6 hours. The hypotensive effect is reported to last for 4 to 14 hours after a single dose. It has been given orally as the sulfate in the management of hypertension, although it has largely been superseded by other drugs less likely to cause orthostatic hypotension.

Preparations

Pharmacopoeial Preparations
USP 36: Guanadrel Sulfate Tablets.

Guanethidine Monosulfate

(BANM, USAN, rINNM)

Guanéthidine, Monosulfate de; Guanethidine Monosulphate; Guanethidini Monosulfas; Guanethidini Monosulfas; Guanethidin-monosulfát; Guanetidilnimonosulfaatti; Guanetidina, monosulfato de; Guanetidinmonosulfat; Guanetidinmonozulfát; Guanetidino monosulfatas; Monosulfato de guanetidina; NSC-29863 (guanethidine hemisulfate); Su-5864 (guanethidine hemisulfate); Гуанетидина Моносульфат.

1-[2-(Perhydroazocin-1-yl)ethyl]guanidine monosulfate.

$C_{10}H_{22}N_4.H_2SO_4$=296.4

CAS — 55-65-2 (guanethidine); 60-02-6 (guanethidine hemisulfate); 645-43-2 (guanethidine monosulfate).

ATC — C02CC02; S01EX01.

ATC Vet — QC02CC02; QS01EX01.

UNII — SU8Y8Y002G.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Chin. includes the hemisulfate.

Ph. Eur. 8: (Guanethidine Monosulfate). A colourless crystalline powder. Freely soluble in water; practically insoluble in alcohol. A 2% solution in water has a pH of 4.7 to 5.5. Protect from light.

USP 36: (Guanethidine Monosulfate). A white to off-white crystalline powder. Very soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform. A 2% solution in water has a pH of 4.7 to 5.7.

Uses and Administration

Guanethidine is an antihypertensive that acts by selectively inhibiting transmission in postganglionic adrenergic nerves. It is believed to act mainly by preventing the release of noradrenaline at nerve endings. Guanethidine causes the depletion of noradrenaline stores in peripheral sympathetic nerve terminals but does not prevent the secretion of catecholamines by the adrenal medulla.

When given orally its maximal effects may take 1 to 3 weeks to appear on continued dosing and persist for 1 to 3 weeks after treatment has been stopped. It causes an initial reduction in cardiac output but its main hypotensive effect is to cause peripheral vasodilatation; it reduces the vasoconstriction which normally results from standing up and which is the result of reflex sympathetic nervous activity. In the majority of patients it reduces standing blood pressure but has a lesser effect on supine blood pressure. When applied topically to the eye guanethidine reduces the production of aqueous humour.

Guanethidine is used in the management of hypertension (p. 1251.1). Eye drops of guanethidine have been used for open-angle glaucoma (p. 1999.1) and for lid retraction associated with hyperthyroidism. Guanethidine has also been used in the management of neuropathic pain syndromes (see below).

Guanethidine is used in the treatment of hypertension when other drugs have proved inadequate, but it has largely been superseded by other drugs less likely to cause orthostatic hypotension. Tolerance to guanethidine has occurred in some patients; this may be countered by concomitant diuretic therapy.

In **hypertension**, the usual initial oral dose of guanethidine monosulfate has been 10 mg daily. This is increased by increments of 10 to 12.5 mg, not more often than every 5 to 7 days, according to response. The usual maintenance dose has been 25 to 50 mg once daily.

Guanethidine monosulfate has been given intramuscularly in the treatment of hypertensive crises, including severe pre-eclampsia, but more suitable drugs are available. An intramuscular dose of 10 to 20 mg is reported to produce a fall in blood pressure within 30 minutes.

Eye drops containing guanethidine monosulfate have been used in the treatment of open-angle **glaucoma** (usually combined with adrenaline), and for the lid retraction that may accompany hyperthyroidism.

Pain syndromes. Sympathetic nerve blocks may be used in the management of acute or chronic pain associated with a well-defined anatomical site. Guanethidine is one of several drugs that have been used for intravenous regional sympathetic block in the management of neuropathic pain (see Complex Regional Pain Syndrome, p. 8.1), to reduce pain and to maintain blood flow. However, reviews and some studies[1,2] in patients with reflex sympathetic dystrophy failed to find any benefit from guanethidine.

1. Jadad AR, *et al.* Intravenous regional sympathetic blockade for pain relief in reflex sympathetic dystrophy: a systematic review and a randomized, double-blind crossover study. *J Pain Symptom Manage* 1995; 10: 13–20.
2. Livingstone JA, Atkins RM. Intravenous regional guanethidine blockade in the treatment of post-traumatic complex regional pain syndrome type 1 (algodystrophy) of the hand. *J Bone Joint Surg Br* 2002; 84: 380–6.

Adverse Effects

The commonest adverse effects of guanethidine are severe postural and exertional hypotension and diarrhoea which may be particularly troublesome during the initial stages of therapy and during dose adjustment. Dizziness, syncope, muscle weakness, and lassitude are liable to occur, especially on rising from sitting or lying. Orthostatic hypotension may be severe enough to provoke angina, renal impairment, and transient cerebral ischaemia. Other frequent adverse effects are bradycardia, failure of ejaculation, fatigue, headache, and salt and water retention and oedema, which may be accompanied by breathlessness and may occasionally precipitate overt heart failure.

Nausea, vomiting, dry mouth, nasal congestion, parotid tenderness, blurring of vision, depression, myalgia, muscle tremor, paraesthesias, hair loss, dermatitis, disturbed micturition, priapism, aggravation or precipitation of asthma, and exacerbation of peptic ulcer disease have also been reported. Guanethidine may possibly cause anaemia, leucopenia, and thrombocytopenia.

When guanethidine is used as eye drops, common adverse effects are conjunctival hyperaemia and miosis. Burning sensations and ptosis have also occurred. Superficial punctate keratitis has been reported particularly after prolonged use of high doses.

Treatment of Adverse Effects

Withdrawal of guanethidine or dose reduction reverses many adverse effects. Diarrhoea may also be controlled by giving codeine phosphate or antimuscarinics. If overdosage occurs the benefit of gastric decontamination is uncertain, but activated charcoal may be given if the patient presents within 1 hour. Hypotension may respond to placing the patient in the supine position with the feet raised. If hypotension is severe it may be necessary to give intravenous fluid replacement and small doses of vasopressors may be given cautiously. The patient must be monitored for several days.

Precautions

Guanethidine should not be given to patients with phaeochromocytoma, as it may cause a hypertensive crisis, or to patients with heart failure not caused by hypertension.

It should be used with caution in patients with renal impairment, cerebrovascular disorders, or ischaemic heart disease, or with a history of peptic ulcer disease or asthma. Exercise and heat may increase the hypotensive effect of guanethidine, and dosage requirements may be reduced in patients who develop fever.

There may be an increased risk of cardiovascular collapse or cardiac arrest in patients undergoing surgery while taking guanethidine, but authorities have differed as to whether the drug should be stopped before elective surgery. Former US licensed product information recommended stopping up to 2 or 3 weeks beforehand. In patients undergoing emergency procedures or where treatment has not been interrupted large doses of atropine should be given before induction of anaesthesia.

Patients undergoing treatment with eye drops containing guanethidine should be examined regularly for signs of conjunctival damage.

Interactions

Patients taking guanethidine may show increased sensitivity to the action of adrenaline, amfetamine, and other sympathomimetics, resulting in exaggerated pressor effects. The hypotensive effects may also be antagonised by tricyclic antidepressants, MAOIs, and phenothiazine derivatives and related antipsychotics (although phenothiazines may also exacerbate orthostatic hypotension, which may be more relevant clinically). In the UK licensed product information suggests that MAOIs should be stopped at least 14 days before beginning guanethidine, although in the USA a minimum of a week has been recommended as adequate. It has been reported that oral contraceptives may reduce the hypotensive action of guanethidine. Use of digoxin or other digitalis derivatives with guanethidine may cause excessive bradycardia.

The hypotensive effects of guanethidine may be enhanced by thiazide diuretics, other antihypertensives, and levodopa. Alcohol may cause orthostatic hypotension in patients taking guanethidine.

Pharmacokinetics

Guanethidine is variably and incompletely absorbed from the gastrointestinal tract with less than 50% of the dose reaching the systemic circulation. It is actively taken up into adrenergic neurones by the mechanism responsible for noradrenaline reuptake. A plasma concentration of 8 nanograms/mL is reported to be necessary for adrenergic blockade, but the dose required to achieve this varies between individuals due to differences in absorption and metabolism. Guanethidine is partially metabolised in the liver, and is excreted in the urine as metabolites and unchanged guanethidine. It has a terminal half-life of about 5 days. Guanethidine does not penetrate the blood-brain barrier significantly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Ismelin†; *Gr.*: Ismelin; *UK*: Ismelin†.

Multi-ingredient Preparations. *Ger.*: Thilodigon†; *Gr.*: Thilodigon; *India*: Optex; *Irl.*: Ganda†; *USA*: Esimil.

Pharmacopoeial Preparations
BP 2014: Guanethidine Tablets;
USP 36: Guanethidine Monosulfate Tablets.

Guanfacine Hydrochloride

(BANM, USAN, rINNM)

BS-100-141; Guanfacina, hidrocloruro de; Guanfacine Chlorhydrate de; Guanfacini Hydrochloridum; Hidrocloruro de guanfacina; LON-798; Гуанфацина гидрохлорид

N-Amidino-2-(2,6-dichlorophenyl)acetamide hydrochloride

$C_9H_9Cl_2N_3O,HCl$=282.5

CAS — 29110-47-2 (guanfacine); 29110-48-3 (guanfacine hydrochloride).
ATC — C02AC02.
ATC Vet — QC02AC02.
UNII — PML56A1600.

Pharmacopoeias. In *US*.

USP 36: (Guanfacine Hydrochloride). Store in airtight containers. Protect from light.

Uses and Administration

Guanfacine is a centrally acting alpha$_2$-adrenoceptor agonist with actions and uses similar to those of clonidine (p. 1339.2). It is used in the management of hypertension (p. 1251.1), although other drugs are usually preferred. It may be used alone or with other antihypertensives, particularly thiazide diuretics. It is also used in the management of attention deficit hyperactivity disorder in children and adolescents (see Administration in Children, below) and has been tried in the management of opioid withdrawal.

Guanfacine is given orally as the hydrochloride, but doses are usually expressed in terms of the base. Guanfacine hydrochloride 1.15 mg is equivalent to about 1 mg of guanfacine. In hypertension the usual initial dose is 1 mg daily increasing after 3 to 4 weeks to 2 mg daily if necessary.

Reviews.
1. Cornish LA. Guanfacine hydrochloride: a centrally acting antihypertensive agent. *Clin Pharm* 1988; 7: 187–97.

Administration in children. For the treatment of attention deficit hyperactivity disorder (below) guanfacine may be given to children aged 6 years and above. It is given orally as a modified-release tablet in an initial dose of 1 mg once daily, increased if necessary by increments of 1 mg at intervals of no less than 1 week to a maximum of 4 mg once daily.

Hyperactivity. Drug treatment of attention deficit hyperactivity disorder (ADHD, p. 2314.1) is usually begun with a central stimulant. Alpha$_{2A}$-agonists such as clonidine and guanfacine have also been used, and guanfacine has been shown to be a safe and effective treatment in children (for recommended doses see above).

References.
1. Posey DJ, McDougle CJ. Guanfacine and guanfacine extended release: treatment for ADHD and related disorders. *CNS Drug Rev* 2007; 13: 465–74.
2. Biederman J, *et al.* SPD503 Study Group. A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics* 2008; 121: e73–e84.
3. Strange BC. Once-daily treatment of ADHD with guanfacine: patient implications. *Neuropsychiatr Dis Treat* 2008; 4: 499–506.
4. Biederman J, *et al.* Long-term, open-label extension study of guanfacine extended release in children and adolescents with ADHD. *CNS Spectr* 2008; 13: 1047–55.
5. Sallee FR, *et al.* Long-term safety and efficacy of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2009; 19: 215–26.
6. Sallee FR, *et al.* SPD503 STUDY GROUP. Guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder: a placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 2009; 48: 155–65.
7. Faraone SV, Glatt SJ. Effects of extended-release guanfacine on ADHD symptoms and sedation-related adverse events in children with ADHD. *J Atten Disord* 2010; 13: 532–8.
8. Connor DF, Rubin J. Guanfacine extended release in the treatment of attention deficit hyperactivity disorder in children and adolescents. *Drugs Today* 2010; 46: 299–314.

Tourette's syndrome. Guanfacine may be used as an alternative to clonidine in the management of patients with mild to moderate symptoms of Tourette's syndrome (see Tics, p. 1030.1). First-line use of these drugs is increasingly favoured in such patients because of a relative lack of serious adverse effects when compared with the commonly used antipsychotics.

Adverse Effects and Precautions

As for Clonidine Hydrochloride, p. 1341.2. Rebound hypertension may occur but is delayed due to the longer half-life.

References.
1. Jerie P. Clinical experience with guanfacine in long-term treatment of hypertension, part II: adverse reactions to guanfacine. *Br J Clin Pharmacol* 1980; 10 (suppl 1): 157S–164S.
2. Board AW, *et al.* A postmarketing evaluation of guanfacine hydrochloride in mild to moderate hypertension. *Clin Ther* 1988; 10: 761–75.
3. Horrigan JP, Barnhill LJ. Guanfacine and secondary mania in children. *J Affect Disord* 1999; 54: 309–14.
4. McGrath JC, Klein-Schwartz W. Epidemiology and toxicity of pediatric guanfacine exposures. *Ann Pharmacother* 2002; 36: 1698–1703.
5. Boreman CD, Arnold LE. Hallucinations associated with initiation of guanfacine. *J Am Acad Child Adolesc Psychiatry* 2003; 42: 1387.
6. Minns AB, *et al.* Guanfacine overdose resulting in initial hypertension and subsequent delayed, persistent orthostatic hypotension. *Clin Toxicol* 2010; 48: 146–8.

Withdrawal. Rapid reduction of the guanfacine dosage resulted in rebound hypertension leading to generalised seizures and coma in a 47-year-old patient with renal failure who was receiving haemodialysis.[1] Use with phenobarbital may have enhanced the metabolism of guanfacine and contributed to the development of the withdrawal effect.

1. Kiechel JR, *et al.* Pharmacokinetic aspects of guanfacine withdrawal syndrome in a hypertensive patient with chronic renal failure. *Eur J Clin Pharmacol* 1983; 25: 463–6.

Interactions

As for Clonidine Hydrochloride, p. 1342.1. The metabolism of guanfacine may be altered by strong inhibitors and inducers of the cytochrome P450 isoenzyme CYP3A4.

Pharmacokinetics

Guanfacine is rapidly absorbed after oral doses and peak plasma concentrations occur 1 to 4 hours after ingestion of an immediate-release dosage form. The oral bioavailability is reported to be about 80%. It is about 70% bound to plasma proteins. It is excreted in urine as unchanged drug and metabolites; about 50% of a dose is reported to be eliminated unchanged. The normal elimination half-life ranges from 10 to 30 hours, tending towards the upper range in older patients.

Renal impairment. A study[1] in patients with normal or impaired renal function found that guanfacine clearance and serum concentrations were not significantly different in the 2 groups, suggesting that non-renal elimination plays an important role in patients with renal impairment.

1. Kirch W, *et al.* Elimination of guanfacine in patients with normal and impaired renal function. *Br J Clin Pharmacol* 1980; 10 (suppl 1): 33S–35S.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Estulic; *Fr.*: Estulic†; *Hung.*: Estulic; *Rus.*: Estulic (Эстулик); *Ukr.*: Estulic (Эстулик); *USA*: Intuniv; Tenex.

Pharmacopoeial Preparations
USP 36: Guanfacine Tablets.

Heparin *(BAN)*

Eparina; Heparíini; Heparina; Heparine; Héparine; Heparinum; Heparyna; Гепарин.

CAS — 9005-49-6.
ATC — B01AB01; C05BA03; S01XA14.
ATC Vet — QB01AB01; QC05BA03; QS01XA14.
UNII — T2410KM04A.

Description. Heparin is an anionic polysaccharide of mammalian origin with irregular sequence. It consists principally of alternating iduronate and glucosamine residues, most of which are sulfated. It may be described as a sulfated glucosaminoglycan. Heparin has the characteristic property of delaying the clotting of freshly shed blood. It may be prepared from the lungs of oxen or the intestinal mucosa of oxen, pigs, or sheep.

Heparin is often described in the literature as **standard heparin** or **unfractionated heparin** to distinguish it from low-molecular-weight heparins.

Heparin Calcium *(BANM)*

Calcium Heparin; Hepariinikalsium; Heparin-Calcium; Heparin Kalsiyum; Heparin Sodyum; Heparin vápenatá sůl; Heparina cálcica; Héparine calcique; Heparinkalcium; Heparino kalcio druska; Heparinum calcicum; Heparyna wapniowa; Гепарин Кальция.

CAS — 37270-89-6.
ATC — B01AB01; C05BA03; S01XA14.
ATC Vet — QB01AB01; QC05BA03; QS01XA14.
UNII — M4F288ZCTR.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.*

Ph. Eur. 8: (Heparin Calcium). The calcium salt of a sulfated glycosaminoglycan present in mammalian tissues. It is prepared either from lungs of cattle or from the intestinal mucosa of pigs, cattle, or sheep. It has a potency of not less than 180 international units per mg calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers.

Incompatibility. See Heparin Sodium, p. 1397.1.

Heparin Sodium *(BANM, rINN)*

Heparíininatrium; Heparin-Natrium; Heparin sodná sůl; Heparina sódica; Héparine Sodique; Heparinnatrium; Heparino natrio druska; Heparinum Natricum; Heparyna sodowa; Sodium Heparin; Soluble Heparin; Гепарин Натрий.

CAS — 9041-08-1.
ATC — B01AB01; C05BA03; S01XA14.
ATC Vet — QB01AB01; QC05BA03; QS01XA14.
UNII — ZZ45AB24CA.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Heparin Sodium). The sodium salt of a sulfated glycosaminoglycan present in mammalian tissues. It is prepared either from lungs of cattle or from the intestinal mucosa of pigs, cattle, or sheep. It has a potency of not less than 180 international units per mg calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers.

USP 36: (Heparin Sodium). The sodium salt of heparin with a potency, calculated on the dried basis, of not less than 180 USP units in each mg. USP heparin units are not equivalent to international units. The source of the material is usually the intestinal mucosa or other suitable tissues of domestic mammals used for food by man and should be stated on the label. A white or pale-coloured amorphous, odourless or almost odourless, hygroscopic powder. Soluble 1 in 20 of water. A 1% solution in water has a pH of 5.0 to 7.5. Store in

airtight containers at temperatures below 40 degrees, preferably between 15 and 30 degrees.

Incompatibility. Licensed product information states that incompatibility has been reported between heparin calcium or sodium and alteplase, amikacin sulfate, amiodarone hydrochloride, ampicillin sodium, aprotinin, benzylpenicillin potassium or sodium, cefalotin sodium, ciprofloxacin lactate, cisatracurium besilate, cytarabine, dacarbazine, daunorubicin hydrochloride, diazepam, dobutamine hydrochloride, doxorubicin hydrochloride, droperidol, erythromycin lactobionate, gentamicin sulfate, haloperidol lactate, hyaluronidase, hydrocortisone sodium succinate, kanamycin sulfate, labetalol hydrochloride meticillin sodium, nicardipine hydrochloride, netilmicin sulfate, some opioid analgesics, oxytetracycline hydrochloride, some phenothiazines, polymyxin B sulfate, reteplase, streptomycin sulfate, tetracycline hydrochloride, tobramycin sulfate, vancomycin hydrochloride, and vinblastine sulfate. Heparin sodium has also been reported to be incompatible with levofloxacin[1] and vinorelbine tartrate.[2] Although visually compatible,[3] cefmetazole sodium is reported to inactivate heparin sodium.

Glucose can have variable effects,[4,5] but glucose-containing solutions are generally considered suitable diluents for heparin. Incompatibility has also been reported between heparin and fat emulsion.

1. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; 56: 1458–9.
2. Balthasar JP. Concentration-dependent incompatibility of vinorelbine tartrate and heparin sodium. *Am J Health-Syst Pharm* 1999; 56: 1891.
3. Hutching SR, *et al.* Compatibility of cefmetazole sodium with commonly used drugs during Y-site delivery. *Am J Health-Syst Pharm* 1996; 53: 2185–8.
4. Anderson W, Harthill JE. The anticoagulant activity of heparins in dextrose solutions. *J Pharm Pharmacol* 1982; 34: 90–6.
5. Wright A, Hecker JNLong term stability of heparin in dextrose-saline intravenous fluids. *Int J Pharm Pract* 1995; 3: 253–5.

Units

The fifth International Standard for unfractionated heparin was established in 1998. The USP 36 states that USP and international units are not equivalent, although doses expressed in either appear to be essentially the same.

Uses and Administration

Heparin is an anticoagulant used mainly in the treatment and prophylaxis of thromboembolic disorders (p. 1273.2). It is often described as standard heparin or unfractionated heparin to distinguish it from low-molecular-weight heparins (p. 1426.1).

Heparin inhibits clotting of blood *in vitro* and *in vivo* by enhancing the action of antithrombin III. Antithrombin III, which is present in plasma, inhibits the activity of activated clotting factors including thrombin (factor IIa) and activated factor X (factor Xa). Heparin increases the rate of this inhibition, but in a manner that is dependent on its dose. With normal therapeutic doses heparin has an inhibitory effect on both thrombin and factor Xa. The inhibition of thrombin blocks the conversion of fibrinogen to fibrin, and the inhibition of factor Xa blocks the conversion of prothrombin to thrombin. The low doses that are given subcutaneously for the prophylaxis of thromboembolism have a selective effect on inhibition of factor Xa. Very high doses are reported to reduce the activity of antithrombin III. Heparin also has some effect on platelet function, inhibits the formation of a stable fibrin clot, and has an antilipidaemic effect. For an explanation of the coagulation cascade, see Haemostasis and Fibrinolysis, p. 1124.3.

Heparin is used in the treatment and prophylaxis of venous thromboembolism (deep-vein thrombosis and pulmonary embolism, p. 1274.1), especially prophylaxis in surgical patients and in those pregnant women at particular risk. It is also used in the management of arterial thromboembolism including that associated with unstable angina pectoris (p. 1254.3), myocardial infarction (p. 1257.1), and acute peripheral arterial thromboembolism (p. 1273.3). It is often used as a precursor to oral anticoagulation and is withdrawn once the oral anticoagulant is exerting its full effect.

Heparin has been tried in the treatment of disseminated intravascular coagulation. It is also used to prevent coagulation during haemodialysis and other extracorporeal circulatory procedures such as cardiopulmonary bypass. Other uses include the anticoagulation of blood for transfusion or blood samples and the flushing of catheters and cannulas to maintain patency.

Heparin and its salts are constituents of many topical preparations for the treatment of various inflammatory disorders.

Administration and dosage. Heparin is given intravenously, preferably by continuous infusion, or by subcutaneous injection. It may be given as the calcium or sodium salt and it is generally accepted that there is little difference in their effects. Oral formulations of heparin are under investigation.

Doses of heparin for treatment (sometimes termed 'full-dose' heparin), and in some cases prophylaxis, of thromboembolism should be monitored and determined as discussed below under Control of Heparin Therapy. The subcutaneous doses of heparin commonly used for prophylaxis (often termed 'low-dose') do not require routine monitoring. A test dose has been recommended for patients with a history of allergy. Although international and USP units are not strictly equivalent, doses expressed in either appear to be essentially the same.

For **treatment of venous thromboembolism**, an intravenous loading dose of 75 to 80 units/kg or 5000 units is given (10 000 units may be required in severe pulmonary embolism). This is followed by a continuous intravenous infusion of 18 units/kg per hour (usually in the range of 1000 to 2000 units/hour), adjusted according to response. Alternatively, a similar maintenance dose may be given by intermittent subcutaneous injection: ranges of 15 000 to 20 000 units every 12 hours or 8000 to 10 000 units every 8 hours have been suggested. Another alternative is an intermittent intravenous injection of 5000 to 10 000 units given every 4 to 6 hours.

For **prophylaxis of postoperative venous thromboembolism**, subcutaneous doses used are 5000 units 2 hours before surgery then every 8 to 12 hours for 7 days or until the patient is ambulant. Similar doses are used to prevent thromboembolism during pregnancy in women with a history of deep-vein thrombosis or pulmonary embolism; the dosage may need to be increased to 10 000 units every 12 hours during the third trimester.

In the management of **unstable angina** or acute **peripheral arterial embolism**, heparin may be given by continuous intravenous infusion in the same doses as those recommended for the treatment of venous thromboembolism. For the prevention of re-occlusion of the coronary arteries after thrombolytic therapy in **myocardial infarction**, intravenous doses of 60 units/kg (maximum 4000 units) are recommended, or a bolus of 5000 units if streptokinase was used. This is followed by 12 units/kg per hour (maximum 1000 units/hour) with a duration of treatment of 48 hours.

For administration in children, see below. Treatment doses for children may also be considered in small adults.

Control of heparin therapy. Treatment with full-dose heparin must be monitored to ensure that the dose is providing the required effect on antithrombin III. The most commonly used test to monitor the action of heparin is the activated partial thromboplastin time (APTT). The APTT of patients on full-dose heparin should generally be maintained at 1.5 to 2.5 times the control value although the optimum therapeutic range varies between individual laboratories depending on the APTT reagent in use. Regular monitoring is essential, preferably on a daily basis. Prophylaxis with low-dose subcutaneous heparin is not routinely monitored; the APTT is not significantly prolonged in these patients. Other tests used include the activated clotting time (ACT). The value of measuring heparin concentration in the blood is uncertain.

General references to anticoagulation with heparin.

1. Hirsh J. Heparin. *N Engl J Med* 1991; 324: 1565–74.
2. Freedman MD. Pharmacodynamics, clinical indications, and adverse effects of heparin. *J Clin Pharmacol* 1992; 32: 584–96.
3. Hyers TM. Heparin therapy: regimens and treatment considerations. *Drugs* 1992; 44: 738–49.
4. Hirsh J, Fuster V. Guide to anticoagulant therapy part 1: heparin. *Circulation* 1994; 89: 1449–68.
5. Baglin T, *et al.* for the British Committee for Standards in Haematology. Guidelines on the use and monitoring of heparin. *Br J Haematol* 2006; 133: 19–34. Also available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2005.05953.x/pdf (accessed 21/10/11)
6. Hirsh J, *et al.* Parenteral anticoagulants: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133 (suppl): 141S–159S. Also available at: http://www.chestjournal.org/content/133/6_suppl/141S.full.pdf (accessed 27/08/09)
7. Vardi M, *et al.* Subcutaneous unfractionated heparin for the initial treatment of venous thromboembolism. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 03/06/10).
8. Gray E, *et al.* Heparin and low-molecular-weight heparin. *Thromb Haemost* 2008; 99: 807–18.

Action. Heparin is well established as an anticoagulant and antithrombotic and acts mainly by binding to, and enhancing the activity of, antithrombin III. However, it has other actions and the physiological role of endogenous heparin has not been clearly defined, despite its presence in mast cells, its ability to interact with many proteins, and its close structural similarity to heparan sulfate (suleparoid), the ubiquitous cell-surface glycosaminoglycan.[1-3] Endogenous heparin activity may have a role in protecting against atherosclerosis.[4] Non-anticoagulant properties of heparin or low-molecular-weight heparins have been reported to include anti-inflammatory activity,[5] with a possible application in, for example, asthma[6-8] or inflammatory bowel disease; however, studies in patients with active ulcerative colitis have not found any benefit.[9] For mention of the use of aerosolised heparin alternating with acetylcysteine to treat inhalation injury, see Burns, under Acetylcysteine, p. 1653.1. The risk of bleeding is a major obstacle to the use of heparin for non-anticoagulant purposes.

1. Lane DA, Adams L. Non-anticoagulant uses of heparin. *N Engl J Med* 1993; 329: 129–30.
2. Page CP. Proteoglycans: the "Teflon" of the airways? *Thorax* 1997; 52: 924–5.
3. Ludwig RJ. Therapeutic use of heparin beyond anticoagulation. *Curr Drug Discov Technol* 2009; 6: 281–9.
4. Engelberg H. Actions of heparin in the atherosclerotic process. *Pharmacol Rev* 1996; 48: 327–52.
5. Young E. The anti-inflammatory effects of heparin and related compounds. *Thromb Res* 2008; 122: 743–52.
6. Martineau P, Vaughan LM. Heparin inhalation for asthma. *Ann Pharmacother* 1995; 29: 71–2.
7. Ahmed T, *et al.* Prevention of exercise-induced bronchoconstriction by inhaled low-molecular-weight heparin. *Am J Respir Crit Care Med* 1999; 160: 576–81.
8. Steinach I, *et al.* The effect of inhaled heparin on airway responsiveness to histamine and leukotriene D4. *Allergy Asthma Proc* 2003; 24: 59–65.
9. Chande N, *et al.* Unfractionated or low-molecular weight heparin for induction of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 10. Chichester: John Wiley; 2010 (accessed 21/10/11).

Administration. The activated partial thromboplastin time (APTT) is the test most commonly used to monitor intravenous full-dose heparin therapy.[1] Heparin dosing algorithms have been developed[2,3] so that the time taken to achieve a therapeutic APTT and maintain it in the therapeutic range (usually 1.5 to 2.5 times the control value) is shortened and thus the risk of recurrent thrombosis and major bleeding complications is reduced. An automated method of monitoring and regulation has been tried.[4] Although use of ideal body-weight for dosage calculation in obese patients has been suggested, actual body-weight may be more appropriate,[5,6] but maximum bolus doses and infusion rates should be set, to avoid overdosage in morbidly obese patients. A weight-based algorithm for treatment doses of subcutaneous heparin in deep-vein thrombosis has also been proposed.[7]

However, the therapeutic ranges used in such algorithms are not applicable to all APTT reagents because the latter vary in their sensitivity to heparin.[8] The optimum therapeutic range therefore varies between individual laboratories depending on the APTT reagent used. Dosing algorithms may be adapted by calibrating the therapeutic APTT with plasma-heparin concentrations.[8,9]

Anti-factor Xa monitoring,[10] and the activated clotting time (ACT) have been used as alternatives to APTT monitoring.

1. Eikelboom JW, Hirsh J. Monitoring unfractionated heparin with the aPTT: time for a fresh look. *Thromb Haemost* 2006; 96: 547–52.
2. Cruickshank MK, *et al.* A standard heparin nomogram for the management of heparin therapy. *Arch Intern Med* 1991; 151: 333–7.
3. Raschke RA, *et al.* The weight-based heparin dosing nomogram compared with a "standard care" nomogram: a randomized controlled trial. *Ann Intern Med* 1993; 119: 874–81.
4. Newby LK, *et al.* An automated strategy for bedside aPTT determination and unfractionated heparin infusion adjustment in acute coronary syndromes: insights from FARAGON A. *J Thromb Thrombolysis* 2002; 14: 33–42.
5. Yee WP, Norton LL. Optimal weight base for a weight-based heparin dosing protocol. *Am J Health-Syst Pharm* 1998; 55: 159–62.
6. Yee WP, Norton LL. Clarification of weight-based heparin protocol. *Am J Health-Syst Pharm* 2002; 59: 1788.
7. Prandoni P, *et al.* Use of an algorithm for administering subcutaneous heparin in the treatment of deep venous thrombosis. *Ann Intern Med* 1998; 129: 299–302.
8. Brill-Edwards P, *et al.* Establishing a therapeutic range for heparin therapy. *Ann Intern Med* 1993; 119: 104–9.
9. Volles DF, *et al.* Establishing an institution-specific therapeutic range for heparin. *Am J Health-Syst Pharm* 1998; 55: 2002–6.
10. Smith ML, Wheeler KE. Weight-based heparin protocol using antifactor Xa monitoring. *Am J Health-Syst Pharm* 2010; 67: 371–4.

Administration in children. Heparin may be given to children for the *treatment* of venous thromboembolism. An intravenous loading dose of 50 units/kg may be followed by an intravenous infusion of 15 to 25 units/kg per hour, or a subcutaneous injection of 250 units/kg twice daily. Alternatively, the *BNFC* suggests the following doses, adjusted according to activated partial thromboplastin time (APTT):

- neonates and infants aged up to 1 year: an initial intravenous injection of 75 units/kg (or 50 units/kg if under 35 weeks post-menstrual age), followed by an intravenous infusion of 25 units/kg per hour
- children aged 1 to 18 years: an initial intravenous injection of 75 units/kg, followed by an intravenous infusion of 20 units/kg per hour

Although unlicensed in the UK for the *prophylaxis* of venous thromboembolism in children, the *BNFC* suggests that those aged 1 month to 18 years may be given a dose of 100 units/kg (to a maximum of 5000 units) twice daily by subcutaneous injection, adjusted according to APTT.

The pharmacokinetics and activity of heparin appear to be age dependent; infants may require relatively larger doses and higher infusion rates to achieve therapeutic anticoagulation and similar prolongation of thromboplastin time than do older children and adults. A review[1] of the

topic considered that current management strategies for heparin therapy in infants and children were suboptimal.

1. Newall F, *et al.* Unfractionated heparin therapy in infants and children. Abstract: *Pediatrics* 2009; 123: 896. Full version: http://pediatrics.aappublications.org/cgi/reprint/123/3/e510.pdf (accessed 13/10/09)

Catheters and cannulas. Solutions of heparin sodium 10 or 100 units/mL in sodium chloride 0.9% are used for flushing intravenous catheters, cannulas, and other indwelling intravenous infusion devices used for intermittent dosing (heparin locks). A meta-analysis[1] of controlled studies was, however, unable to show any major advantage of either strength of heparin sodium solution over sodium chloride 0.9% alone in maintaining peripheral cannula patency or reducing the incidence of thrombophlebitis, and sodium chloride 0.9% is therefore recommended for cannulas intended to be in place for 48 hours or less. Less use of heparin flush solutions could minimise the risk of adverse effects such as thrombocytopenia and reduce the risk of incompatibilities with intravenous drugs.

Use of heparin-bonded catheters or the addition of heparin to intravenous fluids such as total parenteral nutrition solutions has also been tried in an attempt to maintain indwelling intravenous infusion devices (but see Catheters and Cannulas under Precautions, p. 1400.1). Continuous infusion of heparin-containing fluids may prolong the patency of peripheral arterial catheters.[1] To maintain the patency of umbilical artery catheters in neonates, US guidelines[2] suggest continuous infusion of heparin at a concentration of 0.25 to 1 unit/mL.

Central venous catheters are also subject to thrombus formation and their use may be complicated by vascular thrombosis and systemic infection. A meta-analysis[3] found that the use of unfractionated heparin, low-molecular-weight heparin, or low-dose warfarin reduced the risk of venous thromboembolism in patients with central venous catheters, but the effect on outcomes was unclear. The benefits seen in early studies might have diminished in part due to improvements in catheter technology, placement, and aftercare,[4] although this has been disputed.[3] More specific systematic reviews have found that continuous infusion of heparin reduces the incidence of catheter occlusion in neonates with peripherally-placed central venous catheters,[5] and that heparin-bonded catheters may reduce the risk of catheter occlusion in children with central venous catheters.[6] Very low doses of warfarin (typically 1 mg daily) have been used to prevent thrombosis in cancer patients with central venous catheters; however, results from studies have been conflicting.[4,7-11] Guidelines[12] do not currently recommend the use of low-dose warfarin or low-molecular-weight heparin for the prevention of central venous catheter-related thrombosis in cancer patients. Malignancy itself carries a risk of thrombosis—see below.

1. Randolph AG, *et al.* Benefit of heparin in peripheral venous and arterial catheters: systematic review and meta-analysis of randomised controlled trials. *BMJ* 1998; 316: 969–75.
2. Monagle P, *et al.* Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133 (suppl): 887S–968S. Also available at: http://www.chestjournal.org/content/133/6_suppl/887S.full.pdf (accessed 27/08/09)
3. Kirkpatrick A, *et al.* Prevention of central venous catheter-associated thrombosis: a meta-analysis. *Am J Med* 2007; 120: 901–10.
4. Young AM, *et al.* WARP Collaborative Group, UK. Warfarin thromboprophylaxis in cancer patients with central venous catheters (WARP): an open-label randomised trial. *Lancet* 2009; 373: 567–74.
5. Shah PS, Shah VS. Continuous heparin infusion to prevent thrombosis and catheter occlusion in neonates with peripherally placed percutaneous central venous catheters. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 15/05/08).
6. Shah PS, Shah N. Heparin-bonded catheters for prolonging the patency of central venous catheters in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 15/05/08).
7. Bern MM, *et al.* Very low doses of warfarin can prevent thrombosis in central venous catheters: a randomized prospective trial. *Ann Intern Med* 1990; 112: 423–8.
8. Couban S, *et al.* Randomized placebo-controlled study of low-dose warfarin for the prevention of central venous catheter-associated thrombosis in patients with cancer. *J Clin Oncol* 2005; 23: 4063–9.
9. Boraks P, *et al.* Prevention of central venous catheter associated thrombosis using minidose warfarin in patients with haematological malignancies. *Br J Haematol* 1998; 101: 483–6.
10. Magagnoli M, *et al.* Prophylaxis of central venous catheter-related thrombosis with minidose warfarin in patients treated with high-dose chemotherapy and peripheral-blood stem-cell transplantation: retrospective analysis of 228 cancer patients. *Am J Hematol* 2006; 81: 1–4.
11. Chan A, *et al.* Systemic anticoagulant prophylaxis for central catheter-associated venous thrombosis in cancer patients. *Ann Pharmacother* 2007; 41: 635–41.
12. Geerts WH, *et al.* American College of Chest Physicians. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest* 2008; 133 (suppl): 381S–453S. Also available at: http://www.chestjournal.org/content/133/6_suppl/381S.full.pdf (accessed 27/08/09)

Disseminated intravascular coagulation. Heparin has been used with some success in disseminated intravascular coagulation (p. 1126.1) associated with a variety of conditions. This use has been considered by some to be controversial and is usually reserved for specific situations where the risk of bleeding is relatively minor in comparison with the possible beneficial effect on formation of microthromboses. Guidelines[1] suggest that in cases where thrombosis predominates, *therapeutic* doses of heparin should be considered. If there is a co-existing high risk of bleeding, a continuous infusion of heparin in a weight-adjusted dose (10 units/kg per hour is suggested) may be used with careful monitoring. *Prophylactic* doses of heparin or low-molecular-weight heparin are recommended in critically ill, non-bleeding patients.

1. Levi M, *et al.* Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. *Br J Haematol* 2009; 145: 24–33.

Extracorporeal circulation. Anticoagulation with heparin is necessary during procedures such as cardiopulmonary bypass and haemodialysis and haemofiltration. In the case of bypass, heparin is added to the crystalloid solution and any stored blood used for priming the bypass machine and is given intravenously before cannulation of the heart and major blood vessels. Activated clotting time (ACT) is monitored throughout. After bypass is stopped, anticoagulation can be reversed with protamine but caution is advised because of potential toxicity on the cardiopulmonary circulation.

At the start of haemodialysis sessions patients generally get a loading dose of heparin followed by continuous infusion into the exit line of the extracorporeal circuit until about one hour before the end of dialysis. The dose of heparin varies widely depending on body-weight, volume of the extracorporeal circulation, dialysis membrane biocompatibility, and pump speed.

Malignant neoplasms. Cancer is a risk factor for thromboembolism and anticoagulants are often used in patients with malignant neoplasms. There is some evidence that outcomes are improved in patients treated with heparin, and both unfractionated and low-molecular-weight heparins have therefore been studied in patients with malignant neoplasms but no other indication for anticoagulation. Systematic reviews[1,2] have found that there may be a clinically significant improvement in survival, although the risk of bleeding is also increased. However, further study is needed and current guidelines do not recommend the use of anticoagulants in cancer patients without other risk factors.[3,4]

1. Akl EA, *et al.* Oral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. Available in The Cochrane Database of Systematic Reviews; Issue 6. Chichester: John Wiley; 2011 (accessed 21/10/11).
2. Lazo-Langner A, *et al.* The effect of low-molecular-weight heparin on cancer survival. A systematic review and meta-analysis of randomized trials. *J Thromb Haemost* 2007; 5: 729–37.
3. Geerts WH, *et al.* American College of Chest Physicians. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest* 2008; 133 (suppl): 381S–453S. Also available at: http://chestjournal.chestpubs.org/content/133/6_suppl/381S.full.pdf (accessed 03/08/10)
4. Mandalà M, *et al.* ESMO Guidelines Working Group. Venous thromboembolism in cancer patients: ESMO Clinical Practice Guidelines for the management. *Ann Oncol* 2010; 21 (suppl 5): v274–v276.

Pregnancy. Heparin or low-molecular-weight heparins are the anticoagulants of choice for use in pregnancy although they are not without risk for the fetus (see Pregnancy, under Precautions, p. 1400.1), and for the mother.

Guidelines on thrombosis associated with pregnancy have been published.[1-3] Pregnant women may require anticoagulation for the treatment or prophylaxis of venous thromboembolism (p. 1274.1), or for the prevention of systemic thromboembolism associated with prosthetic heart valves (p. 1264.3). Patients with a history of thromboembolism or a thrombophilic abnormality such as inherited deficiencies of antithrombin III, protein C, or protein S or acquired antiphospholipid antibodies may be at particular risk. Women with antiphospholipid antibodies may also be at increased risk of fetal loss (see Systemic Lupus Erythematosus, p. 1613.3) and prophylaxis with low-dose aspirin is usually recommended.[3] Addition of heparin has been reported to further reduce the risk,[4-6] and treatment with heparin or low-molecular-weight heparin, in addition to aspirin, has therefore also been recommended.[2] However, a systematic review[7] concluded that there was inadequate evidence to support extrapolation of such use to prevent miscarriages without apparent cause other than inherited thrombophilia. Another systematic review[8] noted that in contrast to unfractionated heparin the efficacy of low-molecular-weight heparins plus aspirin in increasing live births in women with antiphospholipid syndromes remained unproven, and that large controlled studies were urgently needed.

1. Royal College of Obstetricians and Gynaecologists. Thromboembolic disease in pregnancy and the puerperium: acute management (February 2007). Available at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT28ThromboembolicDisease2007.pdf (accessed 03/08/10)
2. Bates SM, *et al.* Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133 (suppl): 844S–886S. Also available at: http://www.chestjournal.org/content/133/6_suppl/844S.full.pdf (accessed 27/08/09)
3. Royal College of Obstetricians and Gynaecologists. Reducing the risk of thrombosis and embolism during pregnancy and the puerperium (November 2009). Available at: http://www.rcog.org.uk/files/rcog-corp/GT37ReducingRiskThrombo.pdf (accessed 03/08/10)
4. Rai R, *et al.* Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ* 1997; 314: 253–7.
5. Empson M, *et al.* Recurrent pregnancy loss with antiphospholipid antibody: a systematic review of therapeutic trials. *Obstet Gynecol* 2002; 99: 135–44.
6. Ziakas PD, *et al.* Heparin treatment in antiphospholipid syndrome with recurrent pregnancy loss: a systematic review and meta-analysis. *Obstet Gynecol* 2010; 115: 1256–62.
7. Kaandorp S, *et al.* Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 15/04/09).

Reperfusion and revascularisation procedures. Heparin has an established role as an adjunct to percutaneous vascular interventions and bypass surgery, to prevent perioperative thrombosis of the target artery, and is usually given with aspirin or other antiplatelet drugs (see Reperfusion and Revascularisation Procedures, p. 1259.2). High doses are used, particularly in patients undergoing bypass surgery with extracorporeal circulation, and bleeding is a common problem. Although heparin may have an antiproliferative effect, treatment with systemic heparin (unfractionated or low-molecular-weight) appears to have no effect on restenosis;[1] however, a study using local application of enoxaparin suggested that restenosis was reduced.[2] Heparin-coated intracoronary stents have also been used; they improve outcomes compared with balloon angioplasty,[3] but have not been shown to be superior to bare-metal stents[4] or to have any additional effect on restenosis.[5,6] Heparin-coated stents have also been used successfully in cerebrovascular interventions.[7]

1. Grassman ED, *et al.* A randomized trial of the low-molecular-weight heparin certoparin to prevent restenosis following coronary angioplasty. *J Invasive Cardiol* 2001; 13: 723–8.
2. Kiesz RS, *et al.* Local delivery of enoxaparin to decrease restenosis after stenting: results of initial multicenter trial: Polish-American Local Lovenox NIR Assessment study (The POLONIA study). *Circulation* 2001; 103: 26–31.
3. Serruys PW, *et al.* Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* 1998; 352: 673–81. Correction. *ibid.*; 1478.
4. Mehran R, *et al.* An Internet-based registry examining the efficacy of heparin coating in patients undergoing coronary stent implantation. *Am Heart J* 2005; 150: 1171–6.
5. Wöhrle J, *et al.* Comparison of the heparin coated vs the uncoated Jostent—no influence on restenosis or clinical outcome. *Eur Heart J* 2001; 22: 1808–16.
6. Semiz E, *et al.* Comparison of initial efficacy and long-term follow-up of heparin-coated Jostent with conventional NIR stent. *Jpn Heart J* 2003; 44: 889–98.
7. Parkinson RJ, *et al.* Use of heparin-coated stents in neurovascular interventional procedures: preliminary experience with 10 patients. *Neurosurgery* 2006; 59: 812–21.

Adverse Effects

Heparin can give rise to haemorrhage as a consequence of its action. It can also cause thrombocytopenia, either through a direct effect or through an immune effect producing a platelet-aggregating antibody. Consequent platelet aggregation and thrombosis may therefore exacerbate the condition being treated. The incidence of thrombocytopenia is reported to be greater with bovine than porcine heparin.

Hypersensitivity reactions may occur, as may local irritant effects, and skin necrosis. Alopecia and osteoporosis resulting in spontaneous fractures have occurred after prolonged use of heparin.

When used to flush intravenous devices, the low levels of heparin that reach the systemic circulation are unlikely to cause adverse effects; however, immune-mediated thrombocytopenia and thrombosis have been reported rarely.

Effects on the adrenal glands. Heparin inhibits the secretion of aldosterone and so may cause **hyperkalaemia.**[1] Although all patients treated with heparin may develop reduced aldosterone concentrations, most are able to compensate through the renin-angiotensin system. Patients on prolonged heparin therapy or those unable to compensate, such as patients with diabetes mellitus or renal impairment or those also receiving potassium-sparing drugs such as ACE inhibitors, may present with symptoms of hyperkalaemia. The UK CSM suggests[2] that plasma-potassium concentration should be monitored in all patients with risk factors, particularly those receiving heparin for more than 7 days. The hyperkalaemia is usually transient or resolves when heparin is stopped and treatment is not generally required; fludrocortisone was successfully used to treat resistant hyperkalaemia in a patient in whom continued heparin therapy was necessary.[3]

Adrenal insufficiency secondary to adrenal haemorrhage has also been associated with heparin; heparin-induced thrombocytopenia may be implicated.[4]

1. Oster JR, *et al.* Heparin-induced aldosterone suppression and hyperkalemia. *Am J Med* 1995; 98: 575–86.
2. CSM/MCA. Suppression of aldosterone secretion by heparin. *Current Problems* 1999; 25: 6. Also available at: http://www.mhra.gov.uk/home/

idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)
3. Sherman DS, *et al.* Fludrocortisone for the treatment of heparin-induced hyperkalemia. *Ann Pharmacother* 2000; 34: 606–10.
4. Dahlberg PJ, *et al.* Adrenal insufficiency secondary to adrenal hemorrhage: two case reports and a review of cases confirmed by computed tomography. *Arch Intern Med* 1990; 150: 905–9.

Effects on the blood. *Haemorrhage* is a recognised risk with heparin. The risk of major bleeding may be lower with continuous intravenous infusion than with intermittent intravenous injection; risk may increase with heparin dose and patient age.[1] It is unclear whether the risk is lower with *low-molecular-weight heparins*, see p. 1426.3.

Heparin has been associated with the development of *thrombocytopenia*, which may be of two types. The first is a common, acute, but usually mild, fall in platelet count occurring within 1 to 4 days of starting therapy and which often resolves without stopping treatment.[2] A direct effect of heparin on platelet aggregation appears to be responsible. The second type of thrombocytopenia (heparin-induced thrombocytopenia; HIT) is a more serious, immune-mediated reaction. In about a fifth of heparin-treated patients, antibodies are seen against a complex formed between heparin and platelet factor-4 (found on platelets and endothelial cells). In a small subset of these patients, a cycle of platelet activation, thrombocytopenia, and life- and limb-threatening venous or arterial thrombosis develops; bleeding has also occurred.[2-4] HIT usually occurs after 5 to 14 days although its onset may be more rapid in patients previously exposed to heparin;[3,4] delayed presentation up to 40 days after stopping heparin has also been reported.[5,6] The reaction is independent of dose or route; there have been reports of thrombocytopenia after use of heparin flushes[7] or heparin-coated catheters.[8]

The incidence of HIT varies considerably between different patient populations.[9] It is more common in surgical patients than medical, and less common in obstetric patients. It occurs more often with bovine heparin than porcine, and less often with low-molecular-weight heparins. Duration of exposure is a factor, as is recent exposure. Patients with lupus anticoagulant may also be more susceptible.[10] Based on these factors, patients can be classified according to their risk of developing HIT: high (>1%), medium (0.1 to 1%), and low (<0.1%); and this may be used to decide if platelet-count **monitoring** is necessary.[9] A baseline platelet count has been recommended in all patients who are to receive any type of heparin.[11] A second count should then be taken after 24 hours in patients who have received unfractionated heparin within the last 100 days; otherwise, counts should be repeated every 2 days in those at high risk or every 2 or 3 days in those at medium risk, from day 4 to 14 of therapy or until heparin is stopped.[9] Regular monitoring is not considered necessary in those at low risk.[9,11]

HIT should be suspected in any patient who develops new thrombosis or a drop in platelets during or shortly after heparin therapy. This includes thrombosis in those whose platelet count appears to be normal, since thrombosis may occasionally precede thrombocytopenia.[2,9] Testing for HIT antibodies may be used to exclude a diagnosis, but false positive results are common.[4,9]

Management of HIT involves stopping heparin and replacing it immediately with a suitable *non-heparin* anticoagulant.[2,4,9]

- The direct thrombin inhibitors lepirudin, argatroban, and bivalirudin are recommended licensed choices,[9] although bivalirudin is currently licensed to treat HIT only in those undergoing PCI.
- Danaparoid, a heparinoid, is another recommended choice. Because it may very rarely produce cross-reactivity, licensed product information suggests the use of *in-vitro* testing before use; however, current guidelines[9] do not consider this to be of value.
- The pentasaccharide fondaparinux has been used; however, it is not licensed for the treatment of HIT, and evidence of benefit is not yet considered adequate to make firm recommendations.[2,9]
- Other drugs that have been tried in the acute treatment of HIT include: the anticoagulant dermatan;[12] aspirin and dipyridamole or normal immunoglobulin to correct severe thrombocytopenia;[13] and thrombolytics for occlusive thrombosis.[14,15]
- A coumarin may be given for longer-term treatment of thrombosis caused by HIT. Use should be postponed until the platelet count has recovered since coumarins have caused microvascular thrombosis and venous limb gangrene if given earlier.[2,4,9] A non-heparin parenteral anticoagulant should be started first and overlapped with the coumarin for at least 5 days and until the INR is stable.[9] The coumarin may then be continued for 3 to 6 months.[2]

HIT antibodies usually clear within about 100 days in most individuals. Since the risks associated with re-exposure are uncertain, future avoidance is generally considered prudent.[2]

The principles of monitoring and treatment in **children** are similar to those in adults.[16]

There may be a relationship between heparin-induced thrombocytopenia and skin necrosis (see below).

1. Schulman S, *et al.* Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133 (suppl): 257S–298S.
2. Shantsila E, *et al.* Heparin-induced thrombocytopenia: a contemporary clinical approach to diagnosis and management. *Chest* 2009; 135: 1651–64.
3. Hassell K. Heparin-induced thrombocytopenia: diagnosis and management. *Thromb Res* 2008; 123 (suppl 1): S16–S21.
4. Greinacher A, *et al.* Heparin-induced thrombocytopenia. *Hamostaseologie* 2010; 30: 17–28.
5. Warkentin TE, Kelton JG. Delayed-onset heparin-induced thrombocytopenia and thrombosis. *Ann Intern Med* 2001; 135: 502–6.
6. Rice L, *et al.* Delayed-onset heparin-induced thrombocytopenia. *Ann Intern Med* 2002; 136: 210–15.
7. Heeger PS, Backstrom JT. Heparin flushes and thrombocytopenia. *Ann Intern Med* 1986; 105: 143.
8. Laster JL, *et al.* Thrombocytopenia associated with heparin-coated catheters in patients with heparin-associated antiplatelet antibodies. *Arch Intern Med* 1989; 149: 2285–7.
9. Warkentin T, *et al.* American College of Chest Physicians. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133 (suppl): 340S–380S. Also available at: http://chestjournal.chestpubs.org/content/139/5/1261.full.pdf (accessed 25/10/11) Correction. *ibid.* 2011; 139: 1261. [dose]
10. Auger WR, *et al.* Lupus anticoagulant, heparin use, and thrombocytopenia in patients with chronic thromboembolic pulmonary hypertension: a preliminary report. *Am J Med* 1995; 99: 392–6.
11. Keeling D, *et al.* on behalf of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. The management of heparin induced thrombocytopenia. *Br J Haematol* 2006; 133: 259–69. Also available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2006.06018.x/pdf (accessed 21/10/11)
12. Taliani MR, *et al.* Dermatan sulphate in patients with heparin-induced thrombocytopenia. *Br J Haematol* 1999; 104: 87–9.
13. Frame JN, *et al.* Correction of severe heparin-associated thrombocytopenia with intravenous immunoglobulin. *Ann Intern Med* 1989; 111: 946–7.
14. Krueger SK, *et al.* Thrombolysis in heparin-induced thrombocytopenia with thrombosis. *Ann Intern Med* 1985; 103: 159.
15. Clifton GD, Smith MD. Thrombolytic therapy in heparin-associated thrombocytopenia with thrombosis. *Clin Pharm* 1986; 5: 597–601.
16. Risch L, *et al.* Heparin-induced thrombocytopenia in paediatrics: clinical characteristics, therapy and outcomes. *Intensive Care Med* 2004; 30: 1615–24.

Effects on the bones. Osteoporosis is a rare complication of long-term heparin therapy. Treatment and prophylaxis of thromboembolism in pregnancy is one of the few indications for long term use of heparin, so most reports and studies of heparin-induced osteoporosis have been in pregnant women.[1] The incidence of symptomatic osteoporosis in patients given heparin long term has been estimated to be about 2%.[1,2] Subclinical reduction in bone density occurs in up to one-third of patients,[2,3] but it is not possible to predict which of these patients will develop osteoporotic fractures. Pregnancy normally causes reversible bone demineralisation, so the combination of pregnancy and heparin therapy may therefore result in symptomatic osteoporosis in susceptible individuals.[1,4] Bone changes may be reversible.[1] Although some evidence suggests that bone demineralisation is dose- and duration-dependent, this has not been conclusively established.[1,4] Use of low-molecular-weight heparins seems to be associated with a lower risk of heparin-induced osteoporosis,[2,3,5] and there is some evidence that while heparin both reduces bone formation and increases resorption, the low-molecular-weight heparins act only in the former manner.[3]

1. Nelson-Piercy C. Heparin-induced osteoporosis. *Scand J Rheumatol* 1998; 27 (suppl 107): 68–71.
2. Bates SM, *et al.* Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133 (suppl): 844S–886S. Also available at: http://www.chestjournal.org/content/133/6_suppl/844S.full.pdf (accessed 27/08/09)
3. Rajgopal R, *et al.* The effects of heparin and low molecular weight heparins on bone. *Thromb Res* 2008; 122: 293–8.
4. Farquharson RG. Heparin, osteoporosis and pregnancy. *Br J Hosp Med* 1997; 58: 205–7.
5. Lefkou E, *et al.* Review: low-molecular-weight heparin-induced osteoporosis and osteoporotic fractures: a myth or an existing entity? *Lupus* 2010; 19: 3–12.

Effects on electrolyte balance. See Effects on the Adrenal Glands, p. 1398.3.

Effects on lipid metabolism. Use of heparin leads to the release of lipoprotein lipase into the plasma. Postprandial lipidaemia is reduced due to increased hydrolysis of triglycerides into free fatty acids and glycerol. Raised concentrations of free fatty acids have been reported after heparin use but the magnitude of this effect may have been overestimated.[1] Rebound hyperlipidaemia may occur when heparin is withdrawn. With long-term use reserves of lipoprotein lipase may be depleted; severe hypertriglyceridaemia reported in a pregnant woman was attributed to long-term heparin prophylaxis that was thought to have resulted in lipoprotein lipase deficiency.[2]

1. Riemersma RA, *et al.* Heparin-induced lipolysis, an exaggerated risk. *Lancet* 1981; ii: 471.
2. Watts GF, *et al.* Lipoprotein lipase deficiency due to long-term heparinization presenting as severe hypertriglyceridaemia in pregnancy. *Postgrad Med J* 1991; 67: 1062–4.

Effects on the liver. Increases in transaminase values, usually reversible on stopping therapy, have been reported in patients given therapeutic[1-3] or prophylactic[3] doses of heparin. A prospective study[4] found increased transaminases that were assessed as probably due to heparin in 8 of 54 patients; the reaction seemed to occur more frequently with therapeutic doses. Increased transaminases have also been reported[5,6] in patients receiving low-molecular-weight heparins (enoxaparin).

1. Sonnenblick M, *et al.* Hyper-transaminasemia with heparin therapy. *BMJ* 1975; 3: 77.
2. Dukes GE, *et al.* Transaminase elevations in patients receiving bovine or porcine heparin. *Ann Intern Med* 1984; 100: 646–50.
3. Monreal M, *et al.* Adverse effects of three different forms of heparin therapy: thrombocytopenia, increased transaminases, and hyperkalaemia. *Eur J Clin Pharmacol* 1989; 37: 415–18.
4. Guevara A, *et al.* Heparin-induced transaminase elevations: a prospective study. *Int J Clin Pharmacol Ther Toxicol* 1993; 31: 137–41.
5. Kui C-K, *et al.* Low molecular weight heparin-induced liver toxicity. *J Clin Pharmacol* 2001; 41: 691–4.
6. Baker EL, *et al.* Probable enoxaparin-induced hepatotoxicity. *Am J Health-Syst Pharm* 2009; 66: 638–41.

Effects on sexual function. Priapism has been associated with the use of heparin.[1,2] The prognosis is poor, impotence following more often than in priapism of other aetiologies. The mechanism of heparin-induced priapism is unclear. Priapism has also been reported[3] with low-molecular-weight heparins (dalteparin).

1. Baños JE, *et al.* Drug-induced priapism: its aetiology, incidence and treatment. *Med Toxicol* 1989; 4: 46–58.
2. Bschleipfer TH, *et al.* Heparin-induced priapism. *Int J Impot Res* 2001; 13: 357–9.
3. Lin PH, *et al.* Low molecular weight heparin induced priapism. *J Urol (Baltimore)* 2004; 172: 263.

Effects on the skin. Skin necrosis is a rare complication of heparin use.[1,2] It may be a localised reaction at the site of subcutaneous injection or possibly be related to heparin-induced thrombocytopenia (see Effects on the Blood, above). An immune mechanism may be responsible.

More common is a delayed (type IV) hypersensitivity reaction to subcutaneous heparin, characterised by erythema or eczema around the injection site.[3] This type of hypersensitivity shows a high cross-reactivity with low-molecular-weight heparins, heparinoids such as danaparoid and pentosan, and fondaparinux. Hirudins such as lepirudin, bivalirudin and argatroban are reported to be safe alternatives. The risk of a generalised reaction to intravenous heparin appears to be minimal, although its safety in patients with type IV hypersensitivity to subcutaneous heparin is uncertain.

Recurrent fixed eczematous lesions have been attributed to heparin used intravenously during haemodialysis.[4]

1. Ulrick PJ, Manoharan A. Heparin-induced skin reaction. *Med J Aust* 1984; 140: 287–9.
2. Fowlie J, *et al.* Heparin-associated skin necrosis. *Postgrad Med J* 1990; 66: 573–5.
3. Trautmann A, Seitz CS. Heparin allergy: delayed-type non-IgE-mediated allergic hypersensitivity to subcutaneous heparin injection. *Immunol Allergy Clin North Am* 2009; 29: 469–80.
4. Mohammed KN. Symmetric fixed eruption to heparin. *Dermatology* 1995; 190: 91.

Hypersensitivity. An increased incidence of severe hypersensitivity reactions, including fatalities, was reported with some heparin preparations in early 2008;[1] it has been confirmed that the presence of an over-sulfated chondroitin sulfate contaminant was responsible.[1-3]

See Effects on the Blood and Effects on the Skin, above, for further hypersensitivity reactions associated with heparin.

1. FDA. Update to healthcare facilities and healthcare professionals about heparin and heparin-containing medical products. Available at: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm135355.htm (accessed 03/08/10)
2. Blossom DB, *et al.* Outbreak of adverse reactions associated with contaminated heparin. *N Engl J Med* 2008; 359: 2674–84.
3. McKee J, *et al.* Structure elucidation and biological activity of the oversulfated chondroitin sulfate contaminant in Baxter heparin. *J Clin Pharmacol* 2010; 50: 1159–70.

Treatment of Adverse Effects

Asymptomatic overdosage can usually be managed by stopping heparin. Protamine can be used as described on p. 1572.1 to reverse the effects of heparin if large doses have been given or if there is evidence of haemorrhage. Further management is symptomatic; hypovolaemia is treated with intravenous fluids and blood transfusion as needed.

Thrombocytopenia. For reference to the treatment of heparin-induced thrombocytopenia and associated thromboembolic complications, see Effects on the Blood, above.

Precautions

Heparin should not be given to patients who are haemorrhaging. In general it should not be given to

patients at serious risk of haemorrhage, although it has been used with very careful control; patients at risk include those with haemorrhagic blood disorders, thrombocytopenia, peptic ulcer disease, cerebrovascular disorders, bacterial endocarditis, severe hypertension, oesophageal varices, or patients who have recently undergone surgery at sites where haemorrhage would be an especial risk. Caution is required in hepatic and renal impairment; severe hepatic impairment may be a contra-indication. Heparin should not be given by intramuscular injection. Since heparin has caused thrombocytopenia with severe thromboembolic complications, platelet counts should be monitored in certain patients (see Effects on the Blood, p. 1399.1). Heparin should be stopped if thrombocytopenia develops. A test dose has been recommended for patients with a history of allergy.

Dosage of heparin may need to be reduced in the elderly; elderly women appear to be especially susceptible to haemorrhage after use of heparin.

Catheters and cannulas. Serum concentrations of sodium and potassium could be falsely elevated in samples obtained through heparin-bonded umbilical catheters due to release of benzalkonium chloride used in the manufacturing process of some catheters.[1] It was unknown if the amount released would be toxic to small premature neonates.

1. Gaylord MS, *et al.* Release of benzalkonium chloride from a heparin-bonded umbilical catheter with resultant factitious hypernatremia and hyperkalemia. *Pediatrics* 1991; 87: 631–5.

Hyperkalaemia. For recommendations concerning the monitoring of patients susceptible to developing hyperkalaemia, such as those with diabetes mellitus or renal impairment, see Effects on the Adrenal Glands under Adverse Effects, p. 1398.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies heparin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/10/11)

Pregnancy. Heparin does not cross the placenta, and therefore adverse effects on the fetus would not be expected.[1,2] A review[1] of the literature, however, indicated 2 spontaneous abortions and 17 still-births in 135 pregnancies exposed to heparin; 29 infants were premature, 10 of whom died. Another literature review[2] found adverse outcomes in 21.7% of heparin-treated patients, but this dropped to 10.4% when pregnancies with comorbid conditions were excluded. A further drop to 3.6% was seen when cases of prematurity with normal outcome were also excluded. The death rate of 2.5% and prematurity rate of 6.8% in heparin-treated patients was similar to that found in the normal population. It was concluded that heparin appears safer for the fetus than warfarin when used during pregnancy. Similar results have also been reported with low-molecular-weight heparins; a systematic review[3] found an adverse outcome in 9.3% of 486 pregnancies in which low-molecular-weight heparin was used, but this dropped to 3.1% in women without comorbid conditions.

Some heparin preparations contain the preservative benzyl alcohol and should be used with caution, if at all, in pregnant women—see below.

For further details on the use of heparin and low-molecular-weight heparins in pregnancy, see under Uses and Administration, p. 1398.2.

1. Hall JG, *et al.* Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 1980; 68: 122–40.
2. Ginsberg JS, Hirsh J. Optimum use of anticoagulants in pregnancy. *Drugs* 1988; 36: 505–12.
3. Sanson B-J, *et al.* Safety of low-molecular-weight heparin in pregnancy: a systematic review. *Thromb Haemost* 1999; 81: 668–72.

Preservative. The preservatives used in heparin preparations have been implicated in unwanted effects. Benzyl alcohol in heparinised flushing solutions has been suspected of causing toxicity in neonates (see p. 1740.3), and therefore any heparin preparation containing it should be used with caution, if at all, in susceptible patients such as premature babies, neonates, and pregnant women.

Chlorobutanol present in another heparin preparation caused a sharp fall in blood pressure (see Effects on the Cardiovascular System under Chlorobutanol, p. 1748.3).

Spinal anaesthesia. Spinal and epidural haematomas, sometimes leading to paralysis, have occurred after spinal or epidural anaesthesia or analgesia (Central Nerve Block, p. 1981.2) in patients given heparin or low-molecular-weight heparins. The risk of haematoma appears to be higher in patients with indwelling epidural catheters, and in those with coagulopathies or who have also been given other drugs that affect haemostasis. Age may also be a risk factor.[1]

Recommendations[1] to avoid this vary depending on the type of heparin used and the dosing regimen.

- Central nerve blocks are not considered to be contra-indicated in those receiving *unfractionated heparin* in prophylactic doses (5000 units twice daily subcutaneously).
- Safety with higher or more frequent dosing of unfractionated heparin is unknown. In patients receiving high doses for vascular surgery, it is recommended that
  - pre-operative doses of heparin are given no sooner than 1 hour after placement of the catheter for anaesthesia
  - that the catheter is removed no sooner than 2 to 4 hours after the last heparin dose
  - and that postoperative heparin is given no sooner than 1 hour after catheter removal
- For those taking prophylactic doses of a *low-molecular-weight heparin*, placement of the catheter for anaesthesia should occur no sooner than 10 to 12 hours after the last dose.
- Patients given once-daily prophylactic doses of a low-molecular-weight heparin should be re-heparinised 6 to 8 hours after the operation, with the second postoperative dose given no sooner than 24 hours after the first. Indwelling catheters may be maintained; removal should occur no sooner than 10 to 12 hours after the last dose of heparin, and at least 2 hours before the next dose.
- Twice-daily prophylactic dosing of low-molecular-weight heparin carries a greater risk of haematoma, and catheter removal should occur before re-heparinisation. The first postoperative heparin dose should be delayed for 24 hours and at least 2 hours after removal of the catheter.
- The safety of indwelling catheters in patients taking treatment doses of a low-molecular-weight heparin is less clear, and alternative methods of anaesthesia might be preferable.

1. Horlocker TT, *et al.* Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med* 2010; 35: 64–101.

Interactions

Heparin should be used with care with oral anticoagulants or drugs, such as aspirin and dipyridamole, that affect platelet function. NSAIDs may also increase the risk of haemorrhage. Other drugs that affect the coagulation process and which may therefore increase the risk of haemorrhage include dextrans, thrombolytic enzymes such as streptokinase, high doses of penicillins and some cephalosporins, some contrast media, asparaginase, and epoprostenol; for use of heparin with drotrecogin alfa (activated) see p. 1161.3. Estimations of oral anticoagulant control may be modified by heparin's action on prothrombin.

ACE inhibitors. For reference to hyperkalaemia in patients on heparin and ACE inhibitors, see Effects on the Adrenal Glands, p. 1398.3.

Alcohol. Heavy drinkers were found to be at greater risk of major heparin-associated bleeding than moderate drinkers or non-drinkers.[1]

1. Walker AM, Jick H. Predictors of bleeding during heparin therapy. *JAMA* 1980; 244: 1209–12.

Aprotinin. For comment on the use of heparin with aprotinin, see Effects on Coagulation Tests under Aprotinin, p. 1134.2.

Glyceryl trinitrate. Glyceryl trinitrate has been reported to reduce the activity of heparin when both drugs are given simultaneously by the intravenous route.[1] This effect has been seen even with low doses of glyceryl trinitrate.[2] Propylene glycol present in the glyceryl trinitrate formulation may[3] or may not[1] contribute to the effect. No interaction was reported when glyceryl trinitrate was given immediately after heparin.[4]

1. Habbab MA, Haft JI. Heparin resistance induced by intravenous nitroglycerin. *Arch Intern Med* 1987; 147: 857–60.
2. Brack MJ, *et al.* The effect of low dose nitroglycerine on plasma heparin concentrations and activated partial thromboplastin times. *Blood Coag Fibrinol* 1993; 4: 183–6.
3. Col J, *et al.* Propylene glycol-induced heparin resistance during nitroglycerin infusion. *Am Heart J* 1985; 110: 171–3.
4. Bode V, *et al.* Absence of drug interaction between heparin and nitroglycerin. *Arch Intern Med* 1990; 150: 2117–19.

Palifermin. For precautions when giving heparin to patients also receiving palifermin, see p. 2579.2.

Tobacco. Reduced half-life and increased elimination of heparin have been reported in smokers compared with non-smokers.[1]

1. Cipolle RJ, *et al.* Heparin kinetics: variables related to disposition and dosage. *Clin Pharmacol Ther* 1981; 29: 387–93.

Pharmacokinetics

Heparin is not absorbed from the gastrointestinal tract. After intravenous or subcutaneous injection heparin is extensively bound to plasma proteins. It does not cross the placenta and it is not distributed into breast milk. The half-life of heparin depends on its dose and route as well as the method of calculation and is subject to wide inter- and intra-individual variation; a range of 1 to 6 hours with an average of 1.5 hours has been cited. It may be slightly prolonged in renal impairment, decreased in patients with pulmonary embolism, and either increased or decreased in patients with liver disorders. Heparin is taken up by the reticuloendothelial system. It is excreted in the urine, mainly as metabolites, although after large doses up to 50% may be excreted unchanged.

References.

1. Estes JW. Clinical pharmacokinetics of heparin. *Clin Pharmacokinet* 1980; 5: 204–20.
2. Kandrotas RJ. Heparin pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 1992; 22: 359–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Calciparine; Cervep; Cronepanna; Cycloparin; Hepatriet; Parinix; Riveparin; Serianor; Sobrius; Sodiparin; *Austria*: Lioton; Thrombophob-S; Thrombophob; Venoruton Heparin; Viatromb; *Braz.*: Actparin; Alimax; Disotron; Hemofol; Hepamax; Heptar; Liquemine; Trombofol; *Canad.*: Hepalean-Lok†; Hepalean†; *China*: Hepudiod (海普林; Jipailin (吉派林); Kai Rui (凯瑞); Mei De Xi (美得喜); Sai Lu Xi Ping (赛络喜平); *Cz.*: Lioton; Viatromb; *Fin.*: Hepaflex; *Fr.*: Calciparine; *Ger.*: Calciparin†; Essaven 60 000†; Exhirud Heparin; Hepa-Gel; Hepa-Salbe; Hepathromb; Hepathrombir; Parin-POS; Sportino†; Thrombareduct†; Thrombophob; Venalitan†; Venoruton Emulgel†; Vetren; *Gr.*: Calciparine; Cronepana; Hepsal; Monoparin; Multiparin; *Hong Kong*: Liotor; Multiparin†; *Hung.*: Heparibene; Lioton; *India*: Beparine; Beprin; Bioclot; Blockasol; Caprin; Cathflush; Declot; Hep; Heparen; Hepgel; Heplock; Ignava; Inhep; Keparin; Line Flush; No-Clot; Nuparin; Thrombophob; *Indon.*: Hico; Inviclot Thrombophob; *Irl.*: Hepsal†; Monoparin†; Multiparin†; *Ital.*: Ateroclar†; Calciparina; Clarisco; Disebrin; Ecafast; Ecasolv Emoklar; Eparinlider; Eparinovis; Eparven; Epsoclar; Epsodilave; Flusolv; Isoclar†; Normoparin†; Pharepa; Reoflus; Sosefluss; Trombolisin; Veracer; Zepac; *Malaysia*: Unihepa; *Mex.*: Hep-Tec; Proparin; *Norw.*: Hepaflex; *NZ*: Multiparin; *Philipp.*: Hemastat; Heprin; Heptin; Lioton; Lipactin; Meparin; Nuparin; *Pol.*: Coaparin; Heparizen; Lioton; Lipohep; *Rus.*: Lavenum (Лавенум); Lioton (Лиотон); Trombless (Тромблесс); *S.Afr.*: Calciparine†; Thrombophob†; *Spain*: Menaven; *Switz.*: Calciparine; Demovarin; Gelparin; HepaGel; Hepasol Lipogel†; Lioton; Liquemine; Lyman Mono; Sportium uno; *Turk.*: Calciparine; Liparin-S; Liquemine; Nevparin; *UK*: Canusal†; Hepsal†; Monoparin†; Multiparin†; *Ukr.*: Heparil (Гепарил) Lioton (Лиотон); Lyogel (Лиогель); *USA*: Hep-Lock; Hepflush; *Venez.*: Hirox; Riveparin.

Multi-ingredient Preparations. *Arg.*: Contractubex; Integrum Venostasin; *Austria*: Ambenat†; Contractubex; Derivon; Dolo Menthoneurin; Dolobene; Etrat; Heparin Comp; Ichthalgan forte; Lipactin; Pasta Cool; Sensicutan; Thrombophob; Venobene; Vetren; *Belg.*: Lipactin; *Braz.*: Contractubex; Dolobene†; Trombofob; Venalot H; *Canad.*: Lipactin; *China*: Contractubex (康瑞保); Dolobene (瑞乐平); *Cz.*: Contractubex; Dolobene Sensicutan; *Fin.*: Lipactin; Trombosol; *Fr.*: Cirkan a la Prednacinolone; Esberiven; Flector Tissugel Heparine; *Ger.*: Contractubex; Dolobene†; Lipactin; Sensicutan; *Gr.*: Contractubex; *Hong Kong*: Contractubex; Dolobene†; *Hung.*: Contractubex; Dolobene; Pasta Cool; *India*: Beparine; Contractubex; Hexilak Proctosedyl; Thrombophob; *Indon.*: Thrombophob; *Ital.*: Flebs Idracemi Eparina; Luxazone Eparina; Proctosoll; Venoplant Viamal Trauma; Viteparin; Xantervit Eparina; *Mex.*: Contractubex; *Philipp.*: Contractubex; *Pol.*: Alcepalan†; Biherpan†; Cepan; Contractubex; Dolobene†; Savarix; Tointex†; *Port.*: DM Gel; *Rus.*: Contractubex (Контрактубекс); Dolobene (Долобене); Heparin Ointment (Гепариновая Мазь); Hepatrombir (Гепатромбин); Hepatrombin H (Гепатромбин Г); Hepazolon (Гепазолон); Nigepan (Нигепан); Proctosedyl (Проктоседил); Venitan Forte (Венитан Форте); Venolife (Венолайф); *Spain*: Essavenon†; Venacol†; *Switz.*: Assan thermo; Assan; Butaparin†; Contractubex; Dolo-Arthrosenex; Dolobene; Flectoparin Gorgonium; Heparinol†; Keli-med; Keppur; Keppur; Lipactin Lyman; Sportium; Sportusal assan thermo; Sportusal; Venucreme; Venugel; *Turk.*: Contractubex; *Ukr.*: Contractubex (Контрактубекс); Dolobene (Долобене); Hepathrombin (Гепатромбин); Hepathrombin H (Гепатромбин Г); Phytobene (Фитобене); Proctosedyl (Проктоседил); Venitan Forte (Венитан); Venohepanol (Веногепанол); Venosan (Веносан).

Homoeopathic Preparations. *Ger.*: NeyGeront Vitalkapsein A.

Pharmacopoeial Preparations
BP 2014: Heparin Injection;
USP 36: Anticoagulant Heparin Solution; Heparin Lock Flush Solution; Heparin Sodium Injection.

Heparinoids

Heparinoide; Heparinoides; Гепариноиды.

Profile

The term heparinoid includes heparin derivatives and has also been used more loosely to include naturally occurring and synthetic highly-sulfated polysaccharides of similar structure. Such compounds have been described in many ways; some of the terms used include sulfated glucosaminoglycans; glycosaminoglycan polysulfate compounds; or sulfated mucopolysaccharides.

The following anticoagulants may be described as heparinoids:

- Danaparoid Sodium, p. 1349.2
- Dermatan Sulfate, p. 1350.3
- Pentosan Polysulfate Sodium, p. 1465.1
- Sodium Apolate, p. 1497.1
- Suleparoid, p. 1507.2
- Sulodexide, p. 1507.3

Heparinoid preparations are available with uses ranging from anticoagulation to the alleviation of inflammation (applied topically); some are claimed to have hypolipidaemic properties.

The proprietary names listed in this monograph refer to preparations containing undefined or less readily defined heparinoids that are used in a range of conditions including musculoskeletal and joint disorders, haemorrhoids, lipid disorders, and thromboembolic disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fleboderma; Hirudoid; *Austral.*: Hirudoid; Lasonil†; *Austria*: Hemeran; Hirudoid; *Belg.*: Hemeran; Hirudoid; *Braz.*: Hirudoid; Topcoid; *Chile*: Hirudoid†; *China*: Hirudoid (喜辽妥); *Cz.*: Heparoid; Hirudoid; *Denm.*: Hirudoid; *Fin.*: Hirudoid; *Ger.*: Hirudoid; *Gr.*: Arteparon†; Hemeran; Hirudoid; Lasonil N; *Hong Kong*: Hepacare; Hirudoid; *Hung.*: Hirudoid; *India*: Hirudoid; *Indon.*: Hirudoid†; *Ital.*: Ateroid; Condral; Hirudoid; Matrix†; *Neth.*: Hirudoid; *Norw.*: Hirudoid; *NZ*: Hirudoid; Lasonil; *Philipp.*: Hirudoid; *Pol.*: Hirudoid; *Port.*: Hemeran; Hirudoid; Lasonil†; *Rus.*: Balarpan (Балярпан); Heparoid (Гепароид); *Singapore*: Hirudoid; *Spain*: Dinoven†; Hirudoid; *Swed.*: Hirudoid; *Switz.*: Hemeran; Hirudoid; *Thai.*: Hirudoid; Varidoid; *Turk.*: Hirudoid; Lasonil; *UK*: Bruiseze; Hirudoid; *Ukr.*: Heparoid (Гепароид)†; *Venez.*: Hirudoid.

Multi-ingredient Preparations. *Arg.*: Mantus; *Austria*: Mobilat; Mobilisin plus; Mobilisin; Moviflex; *Belg.*: Mobilat; Mobilisin; *Braz.*: Mobilat; Mobilisin Composto; *Chile*: Mobilat†; Reparinven; *Cz.*: Ibu-Hepa; Mobilat; *Fin.*: Mobilat; *Gr.*: Bayolin; Lasonil; Movilisin; *Hung.*: Mobilat N; *India*: Movelisin; *Ital.*: Flebs; Mobilisin; Momendol; *Mex.*: Mobilat; *Neth.*: Mobilat; *Philipp.*: Hiruscar; Mobilat; *Pol.*: Helason; Ibalgin Sport; Lumbolin†; Mobilat; *Port.*: Anacal; Mobilat; Mobilisin; Movilisin; Rimanal; *Singapore*: Hiruscar; *Spain*: Movilat; Movilisin†; *Switz.*: Mobilat Intense; Mobilat; Mobilisin†; *Thai.*: Mobilat; *UK*: Anacal; Movelat; *Venez.*: Bargonil; Permucal.

Hexobendine *(BAN, USAN, rINN)*

Hexobendina; Hexobendinum; Гексобендин.
$C_{30}H_{44}N_2O_{10}$=592.7
CAS — 54-03-5.
ATC — C01DX06.
ATC Vet — QC01DX06.
UNII — B6X4SYR93B.

Hexobendine Hydrochloride *(BANM, rINNM)*

Hexobendina, hidrocloruro de; Hexobendine, Chlorhydrate d'; Hexobendini Hydrochloridum; Hidrocloruro de hexobendina; ST-7090; Гексобендина гидрохлорид.
NN'-Ethylenebis(3-methylaminopropyl 3,4,5-trimethoxybenzoate) dihydrochloride.
$C_{30}H_{44}N_2O_{10}$,2HCl=665.6
CAS — 50-62-4.
ATC — C01DX06.
ATC Vet — QC01DX06.

Profile

Hexobendine hydrochloride is a vasodilator that has been used in ischaemic heart disease. It is also included in multi-ingredient preparations used in cerebrovascular disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hong Kong*: Instenon; *Rus.*: Instenon (Инстенон); *Ukr.*: Instenon (Инстенон).

Hirudin

Hirudiini; Hirudina; Hirudine; Hirudyna; Гирудин.

Profile

Hirudin is a 65-amino-acid protein that is a direct inhibitor of thrombin (see Lepirudin, p. 1418.2). It has been extracted from leeches (p. 1418.1) and this form is used in various topical preparations for peripheral vascular disorders. Recombinant hirudins, such as desirudin (p. 1351.1) and lepirudin (p. 1418.2) and analogues of hirudin, such as bivalirudin (p. 1326.2), are used as anticoagulants.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Exhirud†; *Fr.*: Hirucreme.

Hydralazine Hydrochloride

(BANM, rINNM)

Apressinum; Hidralazina, hidrocloruro de; Hidralazin-hidroklorid; Hidralazino hidrochloridas; Hidrocloruro de hidralazina; Hydralatsiinihydrokloridi; Hydralazin hydrochlorid; Hydralazin Hydrochloridum; Hydralazine, chlorhydrate d'; Hydralazinhydrochlorid; Hydralazinhydroklorid; Hydralazini hydrochloridum; Hydrallazine Hydrochloride; Idralazina; Гидралазина гидрохлорид.
1-Hydrazinophthalazine hydrochloride.
$C_8H_8N_4$,HCl=196.6
CAS — 86-54-4 (hydralazine); 304-20-1 (hydralazine hydrochloride).
ATC — C02DB02.
ATC Vet — QC02DB02.
UNII — FD1718778Y.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Hydralazine Hydrochloride). A white or almost white, crystalline powder. Soluble in water; slightly soluble in alcohol; very slightly soluble in dichloromethane. A 2% solution in water has a pH of 3.5 to 4.2. Protect from light.

USP 36: (Hydralazine Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble 1 in 25 of water and 1 in 500 of alcohol; very slightly soluble in ether. A 2% solution in water has a pH of 3.5 to 4.2. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Stability. Discoloration of hydralazine injection was seen on several occasions after storage in a syringe for up to 12 hours.[1] Hydralazine reacts with metals and therefore the injection should be prepared using a nonmetallic filter and should be used as quickly as possible after being drawn through a needle into a syringe.

A study of the rate of degradation of hydralazine hydrochloride, 1 mg/mL in sweetened, aqueous oral liquids showed that glucose, fructose, lactose, and maltose reduced the stability of the drug.[2] In solutions containing mannitol or sorbitol, there was less than 10% degradation of hydralazine after 3 weeks. UK licensed product information states that contact with glucose causes hydralazine to be rapidly broken down and that hydralazine injection is therefore not compatible with glucose solutions.

1. Enderlin G. Discoloration of hydralazine injection. *Am J Hosp Pharm* 1984; 41: 634.
2. Das Gupta V, *et al.* Stability of hydralazine hydrochloride in aqueous vehicles. *J Clin Hosp Pharm* 1986; 11: 215–23.

Uses and Administration

Hydralazine is a direct-acting vasodilator that acts mainly on the arterioles. It reduces blood pressure and peripheral resistance but produces fluid retention. Tachycardia and an increase in cardiac output occur mainly as a reflex response to the reduction in peripheral resistance. Hydralazine tends to improve renal and cerebral blood flow and its effect on diastolic pressure is more marked than on systolic pressure.

Hydralazine hydrochloride is given orally for the treatment of hypertension (p. 1251.1), usually with a beta blocker and a thiazide diuretic. In addition to an additive antihypertensive effect, this combination reduces the reflex tachycardia and fluid retention caused by hydralazine. Hydralazine may be given intravenously in hypertensive crises. It is also used with isosorbide dinitrate in the management of heart failure (but see Precautions, p. 1402.3). For further discussion of this use of hydralazine, see below.

The dose of hydralazine should be reduced or the dosage interval prolonged in patients with hepatic or renal impairment.

In **hypertension**, the usual initial oral dose of hydralazine hydrochloride is 40 to 50 mg daily in divided doses, increased according to response. In the UK it is recommended that the dose should not be increased above 100 mg daily without checking acetylator status, although the recommended maximum dose for hypertension is 200 mg daily; doses above 100 mg daily are associated with an increased incidence of lupus erythematosus, particularly in women and in slow acetylators.

In hypertensive crises, hydralazine hydrochloride is given by intravenous or intramuscular injection. In the UK, a dose of 5 to 10 mg is given by slow intravenous injection, repeated if necessary after 20 to 30 minutes. Alternatively, a continuous intravenous infusion is given in an initial dose of 200 to 300 micrograms/minute; the usual maintenance dose range is 50 to 150 micrograms/minute. In the USA, higher doses are used; a dose of 20 to 40 mg is given by rapid intravenous or intramuscular injection, repeated as necessary.

For chronic **heart failure**, hydralazine hydrochloride is given (with a nitrate) in a usual initial oral dose of 25 mg 3 or 4 times daily, increased to a usual maintenance dose of 50 to 75 mg 4 times daily. Lower doses and slower titration may be necessary if adverse effects occur. In self-identified black patients, hydralazine may also be given as an oral combination preparation with isosorbide dinitrate; the dose is 37.5 mg of hydralazine hydrochloride with 20 mg of isosorbide dinitrate three times daily, and may be doubled if necessary.

Administration in children. Hydralazine hydrochloride has been used for hypertension in children. The usual oral dose is 750 micrograms/kg daily initially in four divided doses, increased gradually over 3 to 4 weeks to a maximum of 7.5 mg/kg or 200 mg daily. An intravenous or intramuscular dose of 1.7 to 3.5 mg/kg daily is given in 4 to 6 divided doses.

In the UK, the *BNFC* suggests that hydralazine hydrochloride may be given to neonates and children in the treatment of hypertension in the following doses:

- orally: 250 to 500 micrograms/kg every 8 to 12 hours, increased if necessary to a maximum of 2 to 3 mg/kg every 8 hours (neonates) or 7.5 mg/kg (maximum 200 mg) daily (those aged 1 month and over). Those aged 12 years and over may be given the usual adult dose (see above)
- slow intravenous injection: 100 to 500 micrograms/kg, repeated every 4 to 6 hours as necessary (maximum 3 mg/kg or 60 mg daily). Those aged 12 years and over may be given 5 to 10 mg, repeated every 4 to 6 hours as necessary
- continuous intravenous infusion (the preferred route in cardiac patients): 12.5 to 50 micrograms/kg per hour, to a maximum of 2 mg/kg daily (neonates) or 3 mg/kg daily (1 month to 12 years). Those aged 12 years and over may be given 3 to 9 mg/hour (maximum 3 mg/kg daily)

Heart failure. Hydralazine with isosorbide dinitrate may have a role[1] in the management of patients with heart failure (p. 1262.3) who remain symptomatic despite standard therapy or in whom standard therapy is contra-indicated or not tolerated. Although a meta-analysis of studies[2] of vasodilator therapy for heart failure failed to show a benefit in terms of improved functional status or reduced mortality in patients given hydralazine alone, there is evidence from the Veterans Administration Cooperative Study[3] of reduced mortality from the use of hydralazine with nitrates. This has been confirmed in a second study (V-HeFTII),[4] although hydralazine with isosorbide dinitrate was less effective than enalapril. Subgroup analysis suggested that the effect might be greater in black patients, and a later study[5] in black patients found that addition of isosorbide dinitrate and hydralazine to standard therapy improved both morbidity and mortality.

Hydralazine has also been tried in children with heart failure,[6,7] but experience is limited.

1. Thadani U, Jacob RG. Isosorbide dinitrate/hydralazine: its role in the treatment of heart failure. *Drugs Today* 2008; 44: 925–37.
2. Mulrow CD, *et al.* Relative efficacy of vasodilator therapy in chronic congestive heart failure: implications of randomized trials. *JAMA* 1988; 259: 3422–6.
3. Cohn JN, *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration cooperative study. *N Engl J Med* 1986; 314: 1547–52.
4. Cohn JN, *et al.* A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991; 325: 303–10.
5. Taylor AL, *et al.* Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004; 351: 2049–57. Correction. *ibid.* 2005; 352: 1276.

6. Artman M, *et al.* Hemodynamic effects of hydralazine in infants with idiopathic dilated cardiomyopathy and congestive heart failure. *Am Heart J* 1987; 113: 144–50.
7. Rao PS, Andaya WG. Chronic afterload reduction in infants and children with primary myocardial disease. *J Pediatr* 1986; 108: 530–4.

Adverse Effects

Adverse effects are common with hydralazine, particularly tachycardia, palpitations, angina pectoris, severe headache, and gastrointestinal disturbances such as anorexia, nausea, vomiting, and diarrhoea. These adverse effects, and flushing, dizziness, and nasal congestion, which occur less often, may be seen at the start of treatment, especially if the dose is increased quickly. They generally subside with continued treatment. Other less common adverse effects include orthostatic hypotension, fluid retention with oedema and weight gain, conjunctivitis, lachrymation, tremor, and muscle cramps.

Hydralazine may deplete pyridoxine in the body, and can produce peripheral neuropathy with numbness and tingling of the extremities. Occasionally, hepatotoxicity, blood dyscrasias, haemolytic anaemia, difficulty in urinating, glomerulonephritis, constipation, paralytic ileus, depression, and anxiety occur.

Hypersensitivity reactions including fever, chills, pruritus, and rashes have been reported, and eosinophilia may occur.

Antinuclear antibodies may develop after prolonged use of large doses, and a condition resembling SLE may occur. The incidence is greater in slow acetylators, patients with renal impairment, women, and patients taking more than 100 mg of hydralazine daily. The symptoms usually disappear when the drug is withdrawn; some patients may require treatment with corticosteroids.

Acute overdosage may produce hypotension, tachycardia, myocardial ischaemia, arrhythmias, shock, and coma.

Carcinogenicity. Although earlier reports suggested that hydralazine might be carcinogenic, there was no evidence from a survey of 1978 patients with lung or colorectal cancer and 6807 controls that there was an increased risk of these neoplasms.[1]

1. Kaufman DW, *et al.* Hydralazine use in relation to cancers of the lung, colon, and rectum. *Eur J Clin Pharmacol* 1989; 36: 259–64.

Effects on the blood. Three cases of thrombocytopenia were reported[1] in neonates whose mothers had been treated with hydralazine for some months before delivery. The thrombocytopenia and bleeding was transient with full recovery occurring within a few weeks. No adverse effects were noticed in the mothers.

1. Widerlöv E, *et al.* Hydralazine-induced neonatal thrombocytopenia. *N Engl J Med* 1980; 303: 1235.

Effects on the cardiovascular system. Paradoxical severe hypertension developed after oral or intramuscular hydralazine on 3 occasions in a patient with renal artery stenosis.[1]

1. Webb DB, White JP. Hypertension after taking hydrallazine. *BMJ* 1980; 280: 1582.

Effects on the kidneys. Rapidly progressive glomerulonephritis with focal and segmental lesions, usually accompanied by necrosis and crescent formation, has been reported in patients given hydralazine.[1-4] The condition is reported to be associated with the presence of antinuclear antibodies[3] and slow acetylator status,[2] factors associated with the development of hydralazine-induced lupus erythematosus.[5] However, renal involvement is much less common in drug-induced lupus,[5] and in a report of 15 such cases men and women and fast and slow acetylators were equally affected;[3] in addition the criteria for SLE were not usually fulfilled in these patients and it was suggested that the condition should be distinguished from lupus nephritis. A report[4] commented that glomerulonephritis represents an ANCA-positive hydralazine-induced vasculitis, and that patients with such symptoms typically have a more severe course than those with hydralazine-induced lupus, and require more aggressive treatment. Immediate withdrawal of hydralazine generally results in some improvement in renal function but complete recovery is uncommon; severe cases may require immunosuppressive therapy.[3]

1. Björck S, *et al.* Rapidly progressive glomerulonephritis after hydralazine. *Lancet* 1983; ii: 42.
2. Kincaid-Smith P, Whitworth JA. Hydralazine-associated glomerulonephritis. *Lancet* 1983; ii: 348.
3. Björck S, *et al.* Hydralazine-induced glomerulonephritis. *Lancet* 1985; i: 392.
4. Dobre M, *et al.* Hydralazine-induced ANCA-positive pauci-immune glomerulonephritis: a case report and literature review. *Ren Fail* 2009; 31: 745–8.
5. Hughes GRV. Recent developments in drug-associated systemic lupus erythematosus. *Adverse Drug React Bull* 1987; (Apr.): 460–3.
6. Yokogawa N, Vivino FB. Hydralazine-induced autoimmune disease: comparison to idiopathic lupus and ANCA-positive vasculitis. *Mod Rheumatol* 2009; 19: 338–47.

Effects on the skin. Pruritus and rashes have been reported with hydralazine use.

A 59-year-old woman who had been taking hydralazine 25 mg three times daily for 6 months developed symptoms of Sweet's syndrome (erythematous plaques and nodules and haemorrhagic blisters).[1] Symptoms began to subside on withdrawal of the drug but recurred on rechallenge. The condition resolved when hydralazine was stopped and prednisolone given.

1. Gilmour E, *et al.* Drug-induced Sweet's syndrome (acute febrile neutrophilic dermatosis) associated with hydralazine. *Br J Dermatol* 1995; 133: 490–1.

Lupus erythematosus. Lupus erythematosus is a well-documented adverse effect of hydralazine. Onset is typically delayed from 1 month to 5 years from the start of treatment, and the most common symptoms are arthralgia or arthritis, usually non-deforming, in up to 95% of patients, fever and myalgia in about 50%, and pleuropulmonary involvement, manifesting as pleurisy, pleural effusions, or pulmonary infiltrates in up to 30%.[1-4] Renal involvement is reported to be less common than in idiopathic SLE and there is some uncertainty as to whether the glomerulonephritis sometimes seen in patients receiving hydralazine should be considered lupus nephritis (see Effects on the Kidneys, above). Nonetheless, a 20% incidence of renal involvement has been reported.[1] Other complications and symptoms associated with lupus erythematosus in patients taking hydralazine include cutaneous vasculitis,[5-7] orogenital and cutaneous ulceration,[8] bilateral retinal vasculitis,[9] reactive hypoglycaemia (although the attribution is uncertain),[10] life-threatening cardiac tamponade,[11] and hoarseness and stridor secondary to vocal cord palsy, which progressed to respiratory arrest.[12] Rashes are reported to be less prominent than with the idiopathic form of the disease.[1] Fatalities have occurred,[13,14] but appear to be rare. A lupus-like syndrome was also reported[15] in a neonate whose mother was given hydralazine during pregnancy.

Estimates of the overall incidence of hydralazine-associated lupus erythematosus vary from about 1.2 to 5% or more.[16-19] The syndrome appears to occur only in patients who develop antinuclear antibodies while receiving hydralazine, but the incidence of positive antinuclear antibody tests is much higher than that of lupus, at up to 60%, so the presence of antinuclear antibodies alone is not diagnostic.[18] There is a strong relationship with drug dose,[17,19] acetylator status,[16,18,19] and patient gender,[19] the syndrome being more common in slow acetylators and women, and in patients receiving 100 mg daily or more.

Although it has been reported that hydralazine-associated lupus was more frequent in patients with the HLA-DR4 antigen[20] this was not confirmed by others[21] and subsequent work has suggested that the association is rather with the non-expressing or null forms of the adjacent complement C4 gene.[22] Hydralazine can inactivate complement C4 *in vitro*[23] and might exacerbate complement deficiency (which is known to be associated with idiopathic SLE) in patients with an already low level of C4 due to a null allele.[22]

1. Hughes GRV. Recent developments in drug-associated systemic lupus erythematosus. *Adverse Drug React Bull* 1987; (Apr.): 460–3.
2. Cohen MG, Prowse MV. Drug-induced rheumatic syndromes: diagnosis, clinical features and management. *Med Toxicol Adverse Drug Exp* 1989; 4: 199–218.
3. Price EJ, Venables PJW. Drug-induced lupus. *Drug Safety* 1995; 12: 283–90.
4. Pinks SW, *et al.* Hydralazine-induced lupus: maintaining vigilance with increased use in patients with heart failure. *South Med J* 2006; 99: 18–22.
5. Bernstein RM, *et al.* Hydrallazine-induced cutaneous vasculitis. *BMJ* 1980; 280: 156–7.
6. Peacock A, Weatherall D. Hydralazine-induced necrotising vasculitis. *BMJ* 1981; 282: 1121–2.
7. Finlay AY, *et al.* Hydrallazine-induced necrotising vasculitis. *BMJ* 1981; 282: 1703–4.
8. Neville E, *et al.* Orogenital ulcers, SLE and hydrallazine. *Postgrad Med J* 1981; 57: 378–9.
9. Doherty M, *et al.* Hydralazine induced lupus syndrome with eye disease. *BMJ* 1985; 290: 675.
10. Blackshear PJ, *et al.* Reactive hypoglycaemia and insulin autoantibodies in drug-induced lupus erythematosus. *Ann Intern Med* 1983; 99: 182–4.
11. Anandadas JA, Simpson P. Cardiac tamponade, associated with hydralazine therapy, in a patient with rapid acetylator status. *Br J Clin Pract* 1986; 40: 305–6.
12. Chong WK, *et al.* Acute laryngeal stridor with respiratory arrest in drug induced systemic lupus erythematosus. *BMJ* 1988; 297: 660–1.
13. Sturman SG, *et al.* Fatal hydralazine-induced systemic lupus erythematosus. *Lancet* 1988; ii: 1304.
14. Birobaum B, *et al.* Pulminating hydralazine-induced lupus pneumonitis. *Arthritis Rheum* 2006; 55: 501–6.
15. Yemini M, *et al.* Lupus-like syndrome in a mother and newborn following administration of hydralazine; a case report. *Eur J Obstet Gynecol Reprod Biol* 1989; 30: 193–7.
16. Bing RF, *et al.* Hydrallazine in hypertension: is there a safe dose? *BMJ* 1980; 281: 353–4.
17. Freestone S, *et al.* Incidence of hydrallazine-associated autoimmune disease. *Br J Clin Pharmacol* 1982; 13: 291P–292P.
18. Mansilla-Tinoco R, *et al.* Hydralazine, antinuclear antibodies, and the lupus syndrome. *BMJ* 1982; 284: 936–9.
19. Cameron HA, Ramsay LE. The lupus syndrome induced by hydralazine: a common complication with low dose treatment. *BMJ* 1984; 289: 410–12.
20. Batchelor JR, *et al.* Hydralazine-induced systemic lupus erythematosus: influence of HLA-DR and sex on susceptibility. *Lancet* 1980; i: 1107–9.
21. Brand C, *et al.* Hydralazine-induced lupus: no association with HLA-DR4. *Lancet* 1984; i: 462.
22. Speirs C, *et al.* Complement system protein C4 and susceptibility to hydralazine-induced systemic lupus erythematosus. *Lancet* 1989; i: 922–4.
23. Sim E, *et al.* Drugs that induce systemic lupus erythematosus inhibit complement component C4. *Lancet* 1984; ii: 422–4.

Treatment of Adverse Effects

Withdrawal of hydralazine or dosage reduction reverses many of the adverse effects. Peripheral neuropathy has been reported to be alleviated by pyridoxine.

If overdosage occurs the benefit of gastric decontamination is uncertain, but activated charcoal may be given if the patient presents within 1 hour of ingestion. Symptomatic and supportive treatment, including plasma expanders for shock and a beta blocker for tachycardia, should be given as necessary. Hypotension may respond to placing the patient in the supine position with the feet raised. If possible, pressor drugs should be avoided. If a pressor is necessary, one should be chosen that will not cause tachycardia or exacerbate arrhythmias; adrenaline should not be used.

Precautions

Hydralazine is contra-indicated in patients with severe tachycardia, dissecting aortic aneurysm, heart failure with high cardiac output, cor pulmonale, or myocardial insufficiency due to mechanical obstruction, for example aortic or mitral stenosis or constrictive pericarditis. Hydralazine is also contra-indicated in patients with idiopathic SLE and related disorders.

Hydralazine-induced vasodilatation produces myocardial stimulation. It should therefore be used with caution in patients with ischaemic heart disease since it can increase angina and it should not be given after myocardial infarction until the patient's condition has stabilised. Patients with suspected or confirmed ischaemic heart disease should be given hydralazine under cover of a beta blocker, which should be started a few days before hydralazine, in order to prevent myocardial stimulation. If given to patients with heart failure they should be monitored for orthostatic hypotension and tachycardia during the initial stages of therapy, preferably in hospital. If treatment with hydralazine is to be stopped in patients with heart failure it should generally be withdrawn gradually. Hydralazine should be used with caution in patients with cerebrovascular disorders.

The dose of hydralazine should be reduced or the dosage interval prolonged in patients with hepatic or renal impairment. Complete blood counts and antinuclear antibody determinations should be carried out about every 6 months during long-term therapy. Urine analysis (for microhaematuria and proteinuria) is also recommended.

Hydralazine is teratogenic in some species of *animals* and UK licensed product information recommends that hydralazine be avoided during the first two trimesters of pregnancy.

Patients may have impaired reactions, especially at the start of therapy, and should not drive or operate machinery if affected.

Breast feeding. Hydralazine is distributed into breast milk in small amounts (see under Pharmacokinetics, p. 1403.2) but no adverse effects have been seen in infants and the American Academy of Pediatrics therefore considers[1] hydralazine to be usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/09/05)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hydralazine as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pregnancy. For reports of thrombocytopenia and a lupus-like syndrome occurring in neonates after maternal treatment with hydralazine during pregnancy, see Effects on the Blood and Lupus Erythematosus respectively, under Adverse Effects, above.

Interactions

The hypotensive effect of hydralazine may be enhanced by other drugs with a hypotensive action. Severe hypotension may occur if hydralazine and diazoxide are given together. However, some interactions with antihypertensives may be beneficial: thiazide diuretics also counteract the fluid

retention caused by hydralazine, and beta blockers diminish the cardiac-accelerating effects.

Indometacin. A study[1] in 9 healthy subjects found that indometacin 100 mg daily did not lessen the hypotensive effect of hydralazine. However, another study[2] showed that indometacin 200 mg daily, while having no effect on heart rate, renal or limb blood flow, or plasma-catecholamine concentration, did reduce the hypotensive effect of hydralazine.

1. Jackson SHD, Pickles H. Indomethacin does not attenuate the effects of hydralazine in normal subjects. *Eur J Clin Pharmacol* 1983; 25: 303–5.
2. Cinquegrani MP, Liang C. Indomethacin attenuates the hypotensive action of hydralazine. *Clin Pharmacol Ther* 1986; 39: 564–70.

Pharmacokinetics

Hydralazine given orally is rapidly absorbed from the gastrointestinal tract but undergoes considerable first-pass metabolism by acetylation in the gastrointestinal mucosa and liver. The rate of metabolism is genetically determined and depends upon the acetylator status of the individual. The bioavailability of hydralazine has been reported to be about 35% in slow acetylators and less in fast acetylators; thus plasma concentrations after a given dose are higher in slow acetylators. Peak plasma concentrations have been reported to occur after about one hour.

Hydralazine is chiefly present in plasma as a hydrazone conjugate with pyruvic acid. Plasma protein binding is about 90%. The drug is widely distributed, notably into arterial walls.

Systemic metabolism in the liver is by hydroxylation of the ring system and conjugation with glucuronic acid; most sources suggest that *N*-acetylation is not of major importance in systemic clearance and that therefore acetylator status does not affect elimination. Hydralazine is excreted mainly in urine as metabolites.

The apparent average half-life for hydralazine has been reported to vary from about 45 minutes to about 8 hours, with several sources giving the average as about 2 to 4 hours. Some of the variation may be due to problems with the analytical procedures—see below. The half-life is prolonged in renal impairment and may be up to 16 hours in patients with a creatinine clearance of less than 20 mL/minute.

Hydralazine crosses the placenta and is distributed into breast milk.

Attempts to describe the pharmacokinetics of hydralazine have been complicated by the instability of the drug itself in plasma and in alkaline solutions, and the instability of its circulating metabolites during analysis. This has meant that many techniques for the measurement of hydralazine have proved non-selective and yield overestimates of unchanged drug.[1] Studies using less selective methods have yielded an apparent bioavailability for oral hydralazine of 38 to 69% in slow acetylators and 22 to 32% in fast acetylators; in contrast, more selective assays have yielded values of 31 to 35% and 10 to 16% for slow and rapid acetylators respectively. Similarly, hydralazine plasma clearance is lower and the half-life longer when based upon the results of non-selective assay procedures; mean elimination half-life has ranged from 2.2 to 3.6 hours based upon these methods compared with 0.67 to 0.96 hours using a more selective assay. Improved pharmacokinetic data have indicated that while the first-pass effect is dependent upon acetylator phenotype, systemic clearance is only minimally dependent upon acetylation. The formation of the pyruvic acid hydrazone, which is without significant vasodilator activity, contributes to extrahepatic phenotype-independent clearance.

Although some workers have correlated the hypotensive effect of hydralazine with concentrations,[2] others have been unable to do so.[3] Moreover, the duration of hypotensive effect has been shown to exceed considerably that predicted from the rate of elimination.[4,5] Possible explanations are the accumulation of hydralazine at its sites of action in the arterial walls[6] or the existence of active metabolites.[7-9]

Concurrent intake of food has been found to enhance considerably the bioavailability of hydralazine[10] but food-related reductions in plasma-hydralazine concentrations with reduced vasodilator effect have also been reported.[11] The discrepancy was thought to be due to the greater specificity of the assay used in the latter study and to differences in the timing of food and hydralazine administration in the two studies.[12,13]

1. Ludden TM, *et al.* Clinical pharmacokinetics of hydralazine. *Clin Pharmacokinet* 1982; 7: 185–205.
2. Zacest R, Koch-Weser J. Relation of hydralazine plasma concentration to dosage and hypotensive action. *Clin Pharmacol Ther* 1972; 13: 420–5.
3. Talseth T, *et al.* Hydralazine slow-release: observations on serum profile and clinical efficacy in man. *Curr Ther Res* 1977; 21: 157–68.
4. O'Malley K, *et al.* Duration of hydralazine action in hypertension. *Clin Pharmacol Ther* 1973; 18: 581–6.
5. Shepherd AMM, *et al.* Hydralazine kinetics after single and repeated oral doses. *Clin Pharmacol Ther* 1980; 28: 804–11.
6. Moore-Jones D, Perry HM. Radioautographic localization of hydralazine-1-C_{14} in arterial walls. *Proc Soc Exp Biol Med* 1966; 122: 576–9.
7. Barron K, *et al.* Comparative evaluation of the in vitro effects of hydralazine and hydralazine acetonide on arterial smooth muscle. *Br J Pharmacol* 1977; 61: 345–9.
8. Haegele KD, *et al.* Identification of hydrallazine and hydrallazine hydrazone metabolites in human body fluids and quantitative in vitro comparisons of their smooth muscle relaxant activity. *Br J Clin Pharmacol* 1978; 5: 489–94.
9. Reece PA, *et al.* Interference in assays for hydralazine in humans by a major plasma metabolite, hydralazine pyruvic acid hydrazone. *J Pharm Sci* 1978; 67: 1150–3.
10. Melander A, *et al.* Enhancement of hydralazine bioavailability by food. *Clin Pharmacol Ther* 1977; 22: 104–7.
11. Shepherd AMM, *et al.* Effect of food on blood hydralazine levels and response in hypertension. *Clin Pharmacol Ther* 1984; 36: 14–18.
12. Melander A, *et al.* Concomitant food intake does enhance the bioavailability and effect of hydralazine. *Clin Pharmacol Ther* 1985; 38: 475.
13. Shepherd AMM, *et al.* Concomitant food intake does enhance the bioavailability and effect of hydralazine. *Clin Pharmacol Ther* 1985; 38: 475–6.

Pregnancy and breast feeding. Hydralazine concentrations were found to be similar in maternal and umbilical-cord blood in a study of 6 women being treated with hydralazine for pronounced hypertension during pregnancy.[1] Hydralazine was determined in the breast milk of 1 mother, but amounts detected were unlikely to produce clinically relevant concentrations in the infant.

1. Liedholm H, *et al.* Transplacental passage and breast milk concentrations of hydralazine. *Eur J Clin Pharmacol* 1982; 21: 417–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Hidral; Hydrapres; *Austral.*: Alphapress; Apresoline; *Braz.*: Apresolina; Nepresol; *Canad.*: Apresoline; Novo-Hylazin†; Nu-Hydral; *Hong Kong*: Alphapress†; *Irl.*: Apresoline; *Mex.*: Apresolina; Bionobal; *Norw.*: Apresolin; *NZ*: Apresoline; *Philipp.*: Apresoline; Aprezin; *S. Afr.*: Apresoline†; Hyperphen; *Singapore*: Apresoline; *Spain*: Hydrapres; *Swed.*: Apresolin; *Thai.*: Apresoline; Cesoline; *UK*: Apresoline; *USA*: Apresoline†.

Multi-ingredient Preparations. *Austria*: Polinorm†; Triloc†; *Ger.*: Pertenso N; TRI-Normin; *India*: Corbetazine; *Indon.*: Ser-Ap-Es; *Spain*: Neatenol Diuvas†; *Thai.*: Hydrares; Mano-Ap-Es; Reser; Ser-Ap-Es†; *USA*: BiDil; Hydra-zide; Marpres.

Pharmacopoeial Preparations

BP 2014: Hydralazine Injection; Hydralazine Tablets;
USP 36: Hydralazine Hydrochloride Injection; Hydralazine Hydrochloride Oral Solution; Hydralazine Hydrochloride Tablets; Reserpine, Hydralazine Hydrochloride, and Hydrochlorothiazide Tablets.

Hydrochlorothiazide *(BAN, rINN)* ⊗

Hidroclorotiazidas; Hidroclorotiazida; Hidroklorotiazid; Hydrochlorothiazid; Hydrochlorothiazidum; Hydroklorotiazyd; Hydrokloortiatsiidi; Hydroklortiazid; Гидрохлоротиазид.

6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_7H_8ClN_3O_4S_2$=297.7

CAS — 58-93-5.

ATC — C03AA03.

ATC Vet — QC03AA03.

UNII — 0J48LPH2TH.

NOTE. Compounded preparations of hydrochlorothiazide may be represented by the following names:

- Co-amilozide (*BAN*)—hydrochlorothiazide 10 parts and amiloride hydrochloride 1 part (w/w)
- Co-amilozide (*PEN*)—amiloride hydrochloride and hydrochlorothiazide
- Co-spironozide (*PEN*)—spironolactone and hydrochlorothiazide
- Co-triamterzide (*BAN*)—triamterene 2 parts and hydrochlorothiazide 1 part (w/w)
- Co-triamterzide (*PEN*)—triamterene and hydrochlorothiazide
- Co-zidocapt (*BAN*)—hydrochlorothiazide 1 part and captopril 2 parts (w/w).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Hydrochlorothiazide). A white or almost white, crystalline powder. It exhibits polymorphism. Very slightly soluble in water; sparingly soluble in alcohol; soluble in acetone. It dissolves in dilute solutions of alkali hydroxides.

USP 36: (Hydrochlorothiazide). A white or practically white, practically odourless crystalline powder. Very slightly soluble in water; insoluble in chloroform, in ether, and in dilute mineral acids; freely soluble in dimethylformamide, in *n*-butylamine, and in sodium hydroxide solution; sparingly soluble in methyl alcohol.

Uses and Administration

Hydrochlorothiazide and the other thiazide diuretics are used in the treatment of hypertension (p. 1251.1), either alone or with other antihypertensives such as ACE inhibitors and beta blockers. They are also used to treat oedema associated with heart failure (p. 1262.3) and with renal and hepatic disorders. Other indications have included the treatment of oedema accompanying the premenstrual syndrome (p. 2272.3), the prevention of water retention associated with corticosteroids and oestrogens, the treatment of diabetes insipidus (p. 1404.1), and the prevention of renal calculus formation in patients with hypercalciuria (p. 1404.1).

Thiazides are moderately potent diuretics and exert their diuretic effect by reducing the reabsorption of electrolytes from the renal tubules, thereby increasing the excretion of sodium and chloride ions, and consequently of water. They act mainly at the beginning of the distal tubules. The excretion of other electrolytes, notably potassium and magnesium, is also increased. The excretion of calcium is reduced. They also reduce carbonic-anhydrase activity so that bicarbonate excretion is increased, but this effect is generally small compared with the effect on chloride excretion and does not appreciably alter the pH of the urine. They may also reduce the glomerular filtration rate.

Their hypotensive effect is probably partly due to a reduction in peripheral resistance; they also enhance the effects of other antihypertensives. Paradoxically, thiazides have an antidiuretic effect in patients with diabetes insipidus.

Administration and dosage. Thiazides are usually given in the morning so that sleep is not interrupted by diuresis. Diuresis starts in about 2 hours after oral doses of hydrochlorothiazide, reaches a peak in about 4 hours, and lasts for 6 to 12 hours.

The dosage of thiazides should be adjusted to the minimum effective dose. In general lower doses are required for the treatment of hypertension than for oedema, although the maximum therapeutic effect may not be seen for several weeks.

They may be given to patients with mild renal impairment, but thiazides are generally not effective at a creatinine clearance of less than 30 mL/minute.

Hydrochlorothiazide is given orally.

In the treatment of **hypertension** an initial dose of 12.5 mg may be sufficient, increasing to 25 to 50 mg daily if necessary, either alone or with other antihypertensives. Doses of up to 100 mg have been suggested but are rarely necessary.

In the treatment of **oedema** the usual dose is 25 to 100 mg daily, reduced to a dose of 25 to 50 mg daily or intermittently; in severe cases initial doses of up to 200 mg daily have been suggested, but the more powerful loop diuretics (see Furosemide, p. 1387.1) are preferred in such patients.

In the treatment of nephrogenic **diabetes insipidus** an initial dose of up to 100 mg daily may be used.

For doses in children, see below.

For discussion of potassium supplementation in patients taking thiazide diuretics see Effects on Electrolyte Balance, under Adverse Effects, p. 1404.2.

General references.

1. Ellison DH, Loffing J. Thiazide effects and adverse effects: insights from molecular genetics. *Hypertension* 2009; 54: 196–202.
2. Moser M, Peig PU. Fifty years of thiazide diuretic therapy for hypertension. *Arch Intern Med* 2009; 169: 1851–6.
3. Ernst ME, Moser M. Use of diuretics in patients with hypertension. *N Engl J Med* 2009; 361: 2153–64.
4. Neff KM, Nawarskas JJ. Hydrochlorothiazide versus chlorthalidone in the management of hypertension. *Cardiol Rev* 2010; 18: 51–6.

Administration in children. Hydrochlorothiazide has been given to infants and children for the treatment of hypertension or oedema in an oral dose of 1 to 2 mg/kg daily in single or 2 divided doses. Infants aged under 6 months may need up to 3 mg/kg daily in 2 divided doses. The total daily dose should not exceed 37.5 mg in those aged under 2 years, or 100 mg in those aged from 2 to 12 years.

Bronchopulmonary dysplasia. Bronchopulmonary dysplasia (p. 1602.1) is a major cause of chronic lung disease in infants. Treatment often involves the use of corticosteroids. Additional supportive therapy has included the use of diuretics such as furosemide (p. 1387.3); results with hydrochlorothiazide or spironolactone have been more ambiguous. No beneficial effects on lung function or oxygenation were found in a study of 12 infants after 1 week of treatment with hydrochlorothiazide and spironolactone.[1] However, hydrochlorothiazide and spironolactone therapy was found to improve total respiratory system compliance with decreased lung damage and increased survival rate in 34 premature infants with bronchopulmonary dysplasia after 8 weeks of therapy.[2] In the latter study furosemide was also given if clinically indicated.

1. Engelhardt B, *et al.* Effect of spironolactone-hydrochlorothiazide on lung function in infants with chronic bronchopulmonary dysplasia. *J Pediatr* 1989; 114: 619–24.
2. Albersheim SG, *et al.* Randomized, double-blind, controlled trial of long-term diuretic therapy for bronchopulmonary dysplasia. *J Pediatr* 1989; 115: 615–20.

Diabetes insipidus. Thiazide diuretics are used in nephrogenic diabetes insipidus (p. 2348.2), sometimes with potassium-sparing diuretics. For instance, hydrochlorothiazide with amiloride was effective in controlling nephrogenic diabetes insipidus in 5 boys and compared favourably with treatment with hydrochlorothiazide and indometacin.[1] Treatment was well tolerated in 4 patients. Abdominal pain and anorexia necessitated withdrawal of amiloride in the fifth patient after 6 months. The use of hydrochlorothiazide with amiloride avoided the need for potassium supplements, which were required with hydrochlorothiazide and indometacin. The use of hydrochlorothiazide with amiloride was also effective and well tolerated in a group of 4 children with nephrogenic diabetes insipidus who were treated for up to 5 years.[2]

1. Knoers N, Monnens LAH. Amiloride-hydrochlorothiazide versus indomethacin-hydrochlorothiazide in the treatment of nephrogenic diabetes insipidus. *J Pediatr* 1990; 117: 499–502.
2. Kirchlechner V, *et al.* Treatment of nephrogenic diabetes insipidus with hydrochlorothiazide and amiloride. *Arch Dis Child* 1999; 80: 548–52.

Hypoparathyroidism. In hypoparathyroidism (p. 1171.2), treatment is usually with oral vitamin D compounds to correct the hypocalcaemia. Thiazides may be useful in some patients. Beneficial effects on serum-calcium concentrations in patients with hypoparathyroidism have been reported after chlortalidone plus dietary salt restriction,[1] and with bendroflumethiazide.[2] However, chlortalidone has not been found to be effective in all patients,[3] and the reduction in urinary calcium excretion by thiazides has been shown to be diminished in patients with hypoparathyroidism,[4] suggesting that this effect may be dependent on the presence of active parathyroid hormone. Care should be taken when giving diuretics to hypoparathyroid patients with co-existing adrenal insufficiency[5] or metabolic alkalosis.[5]

1. Porter RH, *et al.* Treatment of hypoparathyroid patients with chlorthalidone. *N Engl J Med* 1978; 298: 577–81.
2. Newman GH, *et al.* Effect of bendrofluazide on calcium reabsorption in hypoparathyroidism. *Eur J Clin Pharmacol* 1984; 27: 41–6.
3. Gertner JM, Genel M. Chlorthalidone for hypoparathyroidism. *N Engl J Med* 1978; 298: 1478.
4. Middler S, *et al.* Thiazide diuretics and calcium metabolism. *Metabolism* 1973; 22: 139–45.
5. Barzel US. Chlorthalidone for hypoparathyroidism. *N Engl J Med* 1978; 289: 1478.

Ménière's disease. In Ménière's disease (p. 611.2) there is an excess of endolymph fluid in the ear and diuretics such as hydrochlorothiazide have been used in attempts to relieve symptoms by reducing the amount of fluid.

Osteoporosis. Although some epidemiological studies have indicated beneficial effects of thiazides on bone (reduced rates of bone loss[1] and a reduced risk of hip fracture[2-5]) a comprehensive analysis involving 9704 women over the age of 65 years[6] showed only a small effect on bone mass, no effect on the risk for falls, and no overall protective effect against fractures. A further prospective study[7] reported a reduction in forearm fracture, but hip fracture was only reduced in postmenopausal women. Randomised, controlled studies[8,9] have confirmed that hydrochlorothiazide reduces bone loss, but again the effects were small. Thus, thiazides have no established role in the prevention or treatment of osteoporosis (p. 1168.1). They might, however, be useful to reduce hypercalciuria in patients taking glucocorticoids[10] but serum-potassium concentrations should be monitored closely.

1. Wasnich R, *et al.* Effect of thiazide on rates of bone mineral loss: a longitudinal study. *BMJ* 1990; 301: 1303–5. Correction. *ibid.* 1991; 302: 218.
2. Ray WA, *et al.* Long-term use of thiazide diuretics and risk of hip fracture. *Lancet* 1989; i: 687–90.
3. LaCroix AZ, *et al.* Thiazide diuretic agents and the incidence of hip fracture. *N Engl J Med* 1990; 322: 286–90.
4. Felson DT, *et al.* Thiazide diuretics and the risk of hip fracture: results from the Framingham Study. *JAMA* 1991; 265: 370–3.
5. Schoofs MWCJ, *et al.* Thiazide diuretics and the risk for hip fracture. *Ann Intern Med* 2003; 139: 476–82.
6. Cauley JA, *et al.* Effects of thiazide diuretic therapy on bone mass, fractures, and falls. *Ann Intern Med* 1993; 118: 666–73.
7. Feskanich D, *et al.* A prospective study of thiazide use and fractures in women. *Osteoporosis Int* 1997; 7: 79–84.
8. Reid IR, *et al.* Hydrochlorothiazide reduces loss of cortical bone in normal postmenopausal women: a randomized controlled trial. *Am J Med* 2000; 109: 362–70.
9. LaCroix AZ, *et al.* Low-dose hydrochlorothiazide and preservation of bone mineral density in older adults: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000; 133: 516–26.
10. Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. *Ann Intern Med* 1990; 112: 352–64.

Renal calculi. A thiazide diuretic may be given to prevent the recurrence of calcium-containing renal calculi (p. 2350.3) in patients with hypercalciuria.[1,2]

1. Pearle MS, *et al.* Meta-analysis of randomized trials for medical prevention of calcium oxalate nephrolithiasis. *J Endourol* 1999; 13: 679–85.
2. Tiselius H-G, *et al.* European Association of Urology. Guidelines on urolithiasis (issued March 2008). Available at: http://www.uroweb.org/fileadmin/cx_eauguidelines/2008/Full/17%20Urolithiasis.pdf (accessed 24/07/08)

Adverse Effects

Hydrochlorothiazide and other thiazide diuretics may cause metabolic disturbances especially at high doses. They may provoke hyperglycaemia and glycosuria in diabetic and other susceptible patients. They may cause hyperuricaemia and precipitate attacks of gout in some patients. Thiazide diuretics may be associated with electrolyte imbalances including hypochloraemic alkalosis, hyponatraemia, and hypokalaemia. Hypokalaemia intensifies the effect of digitalis on cardiac muscle and treatment with digitalis or its glycosides may have to be temporarily suspended. Patients with cirrhosis of the liver are particularly at risk from hypokalaemia. Hyponatraemia may occur in patients with severe heart failure who are very oedematous, particularly with large doses used with restricted salt in the diet. The urinary excretion of calcium is reduced. Hypomagnesaemia has also occurred. Adverse changes in plasma lipids have also been noted but their clinical significance is unclear.

Signs of electrolyte imbalance include dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain and cramps, seizures, oliguria, hypotension, and gastrointestinal disturbances.

Other adverse effects include anorexia, gastric irritation, nausea, vomiting, constipation, diarrhoea, sialadenitis, headache, dizziness, photosensitivity reactions, orthostatic hypotension, paraesthesia, impotence, and yellow vision. Hypersensitivity reactions include rashes, fever, pulmonary oedema, pneumonitis, anaphylaxis, and toxic epidermal necrolysis. Cholestatic jaundice, pancreatitis, and blood dyscrasias including thrombocytopenia and, more rarely, granulocytopenia, leucopenia, and aplastic and haemolytic anaemia have been reported.

Intestinal ulceration has occurred after the use of tablets containing thiazides with an enteric-coated core of potassium chloride (see also under Potassium, p. 1796.3).

Carcinogenicity. Several studies have suggested that long-term diuretic therapy may be associated with the development of cancer. A meta-analysis[1] of 9 case control studies and 3 cohort studies found an increased risk of renal cell carcinoma in patients receiving diuretics, and a further retrospective study[2] found that the risk of colon cancer was also increased. While the risk is probably not significant in most patients, it was suggested[1,2] that it should be taken into consideration when choosing long-term therapy for younger patients.

1. Grossman E, *et al.* Does diuretic therapy increase the risk of renal cell carcinoma? *Am J Cardiol* 1999; 83: 1090–3.
2. Tenenbaum A, *et al.* Is diuretic therapy associated with an increased risk of colon cancer? *Am J Med* 2001; 110: 143–5.

Effects on the blood. There have been case reports of intravascular immune haemolysis in patients taking hydrochlorothiazide and methyldopa.[1-3] In each of these 3 cases the hydrochlorothiazide was identified as the probable cause of haemolysis on serological data, although methyldopa could have been a contributory factor. One of these patients died[3] during the haemolytic episode although post-mortem examination failed to reveal a cause of death.

1. Vila JM, *et al.* Thiazide-induced immune hemolytic anemia. *JAMA* 1976; 236: 1723–4.
2. Garraty G, *et al.* Acute immune intravascular hemolysis due to hydrochlorothiazide. *Am J Clin Pathol* 1981; 76: 73–8.
3. Beck ML, *et al.* Fatal intravascular immune hemolysis induced by hydrochlorothiazide. *Am J Clin Pathol* 1984; 81: 791–4.

Effects on electrolyte balance. *MAGNESIUM AND POTASSIUM.* The clinical **consequences** of diuretic-induced hypokalaemia have been controversial.[1-3] Of major concern has been the possibility that diuretic-induced hypokalaemia could predispose to cardiac arrhythmias and sudden cardiac death in some patients, and it has been suggested that this could explain the lower than expected reduction in deaths due to ischaemic heart disease found in some hypertension studies. Indeed, some case-control studies[4,5] have suggested an association between an increased risk of sudden cardiac death and the use of thiazides or other non-potassium-sparing diuretics; the addition of a potassium supplement had little effect on this risk, whereas addition of a potassium-sparing diuretic to the thiazide lowered the risk.[4] However, no reduction in cardiac arrhythmias after the correction of hypokalaemia has been seen[6] nor any evidence of increased arrhythmias associated with diuretic-induced hypokalaemia.[7] Several reviews[8,9] have argued that there is no proof of a causal relationship between hypokalaemia and serious dysrhythmias and this was endorsed by a randomised study.[10]

It is generally agreed that routine potassium **supplementation** in patients taking diuretics is unnecessary; however, supplementation will be required if the serum-potassium concentration falls below 3.0 mmol/litre. Potassium replacement or conservation is also likely to be necessary in patients at risk from the cardiac effects of hypokalaemia[11] such as those with severe heart disease, those taking digitalis preparations or high doses of diuretics and in patients with severe liver disease.

The amount of potassium in fixed combination diuretic and potassium preparations has long been considered insufficient to correct hypokalaemia and the efficacy of oral potassium supplements in increasing body stores of potassium has been questioned.[12-14] Hypokalaemia may be overcome by adding a potassium-sparing diuretic such as amiloride or triamterene[15] to the regimen, but there is a danger of hyperkalaemia if they are used indiscriminately. The *routine* use of fixed-dose combination preparations of a thiazide or loop diuretic with a potassium-sparing diuretic is considered unnecessary.[16] Potassium-sparing diuretics will not correct the potassium deficit unrelated to diuretic therapy in patients with severe heart failure.[17] When thiazides are given with drugs that may induce hyperkalaemia, such as beta blockers, ACE inhibitors, or angiotensin II receptor antagonists, the diuretic-induced hypokalaemia may be ameliorated, but not necessarily corrected completely. Hypokalaemia has been reported[18-20] in patients taking fixed-dose combinations of thiazides and beta blockers.

Potassium supplementation alone may not be sufficient to correct hypokalaemia in patients who are also deficient in magnesium,[21] although it is unlikely to be of clinical significance.[22]

Magnesium depletion has also been implicated as a risk factor for arrhythmias.[9,23]

1. Materson BJ. Diuretic-associated hypokalemia. *Arch Intern Med* 1985; 145: 1966–7.
2. Kaplan NM, *et al.* Potassium supplementation in hypertensive patients with diuretic-induced hypokalemia. *N Engl J Med* 1983; 312: 746–9.
3. Kassirer JP, Harrington JT. Fending off the potassium pushers. *N Engl J Med* 1985; 312: 785–7.
4. Siscovick DS, *et al.* Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med* 1994; 330: 1852–7.
5. Hoes AW, *et al.* Diuretics, β-blockers, and the risk for sudden cardiac death in hypertensive patients. *Ann Intern Med* 1995; 123: 481–7.
6. Papademetriou V, *et al.* Diuretic-induced hypokalemia in uncomplicated systemic hypertension: effect of plasma potassium correction on cardiac arrhythmias. *Am J Cardiol* 1983; 52: 1017–22.
7. Papademetriou V, *et al.* Thiazide therapy is not a cause of arrhythmia in patients with systemic hypertension. *Arch Intern Med* 1988; 148: 1272–6.
8. Harrington JT, *et al.* Our national obsession with potassium. *Am J Med* 1982; 73: 155–9.
9. Freis ED. Critique of the clinical importance of diuretic-induced hypokalemia and elevated cholesterol level. *Arch Intern Med* 1989; 149: 2640–8.
10. Siegel D, *et al.* Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. *JAMA* 1992; 267: 1083–9.
11. Anonymous. Potassium-sparing diuretics—when are they really needed? *Drug Ther Bull* 1985; 23: 17–20.
12. Jackson PR, *et al.* Relative potency of spironolactone, triamterene and potassium chloride in thiazide-induced hypokalaemia. *Br J Clin Pharmacol* 1982; 14: 257–63.
13. Shenfield GM. Fixed combination drug therapy. *Drugs* 1982; 23: 462–80.
14. Papademetriou V, *et al.* Effectiveness of potassium chloride or triamterene in thiazide hypokalemia. *Arch Intern Med* 1985; 145: 1986–90.
15. Kohvakka A. Maintenance of potassium balance during long-term diuretic therapy in chronic heart failure patients with thiazide-induced hypokalemia: comparison of potassium supplementation with potassium chloride and potassium-sparing agents, amiloride and triamterene. *Int J Clin Pharmacol Ther Toxicol* 1988; 26: 273–7.
16. Anonymous. Routine use of potassium-sparing diuretics. *Drug Ther Bull* 1991; 29: 85–7.
17. Davidson C, *et al.* The effects of potassium supplements, spironolactone or amiloride on the potassium status of patients with heart failure. *Postgrad Med J* 1978; 54: 405–9.
18. Skehan JD, *et al.* Hypokalaemia induced by a combination of a beta-blocker and a thiazide. *BMJ* 1982; 284: 83.
19. Odugbesan O, *et al.* Hazards of combined beta-blocker/diuretic tablets. *Lancet* 1985; i: 1221–2.
20. Jacobs L. Hypokalaemia with beta-blocker/thiazide combinations. *J R Coll Gen Pract* 1986; 36: 39.
21. Dyckner T. Relation of cardiovascular disease to potassium and magnesium deficiencies. *Am J Cardiol* 1990; 65: 44–6.
22. Papademetriou V. Magnesium depletion and thiazide hypokalemia. *Arch Intern Med* 1986; 146: 1026.
23. Ryan MP. Diuretics and potassium/magnesium depletion: directions for treatment. *Am J Med* 1987; 82 (suppl 3A): 38–47.

SODIUM. Diuretics are a common cause of hyponatraemia;[1-6] of 307 reports of hyponatraemia received by the Australian Adverse Drug Reactions Advisory Committee (ADRAC)[6] between May 2005 and October 2008, 126 involved a diuretic as the single suspected cause. Dilutional hyponatraemia may occur in patients with heart failure, but hyponatraemia may also result from sodium depletion[1] or inappropriate antidiuretic hormone secretion.[7] Other suggested mechanisms include decreased renal clearance of free water, hypomagnesaemia, and intracellular potassium depletion.[3,8] There have been reports suggesting that hyponatraemia may be a particular problem with combinations of hydrochlorothiazide and potassium-sparing diuretics,[9-11] especially in elderly patients. The effect may be exacerbated by the relatively high doses of thiazide present in some fixed-dose preparations.[12] The symptoms of hyponatraemia may be non-specific and include nausea, lethargy, weakness, mental confusion, and anorexia,[1,2] but it may be an important cause of morbidity.[2,8] Severe sequelae of hyponatraemia include tonic-clonic seizures[13] and clinical features resembling subarachnoid haemorrhage.[14,15] Some patients, especially the elderly, may be particularly susceptible to the hyponatraemic effects of thiazides, possibly as

a result of inappropriate secretion of antidiuretic hormone.[7] Plasma electrolyte concentrations should be monitored in patients taking long-term diuretic therapy.[3,13] Measurement of serum-sodium concentration and bodyweight after a single dose of thiazide could be useful in identifying patients at increased risk of developing hyponatraemia.[8]

1. Roberts CJC, *et al.* Hyponatraemia: adverse effect of diuretic treatment. *BMJ* 1977; 1: 210.
2. Kennedy PGE, *et al.* Severe hyponatraemia in hospital inpatients. *BMJ* 1978; 2: 1251–3.
3. Walters EG, *et al.* Hyponatraemia associated with diuretics. *Br J Clin Pract* 1987; 41: 841–4.
4. Spital A. Diuretic-induced hyponatremia. *Am J Nephrol* 1999; 19: 447–52.
5. Mann SJ. The silent epidemic of thiazide-induced hyponatremia. *J Clin Hypertens (Greenwich)* 2008; 10: 477–84.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Drug-induced hyponatraemia. *Aust Adverse Drug React Bull* 2008; 27: 19–20. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0810.htm (accessed 18/02/10)
7. Sonnenblick M, *et al.* Thiazide-induced hyponatremia and vasopressin release. *Ann Intern Med* 1989; 110: 751.
8. Friedman E, *et al.* Thiazide-induced hyponatremia: reproducibility by single dose rechallenge and an analysis of pathogenesis. *Am Intern Med* 1989; 110: 24–30.
9. Strykers PEL *et al.* Hyponatremia induced by a combination of amiloride and hydrochlorothiazide. *JAMA* 1984; 252: 389.
10. Roberts CJC, *et al.* Hyponatraemia induced by a combination of hydrochlorothiazide and triamterene. *BMJ* 1984; 288: 1962.
11. Millson D, *et al.* Hyponatraemia and Moduretic (amiloride plus hydrochlorothiazide). *BMJ* 1984; 289: 1308–9.
12. Bayer AJ, *et al.* Plasma electrolytes in elderly patients taking fixed combination diuretics. *Postgrad Med J* 1986; 62: 159–62.
13. Johnston C, *et al.* Hyponatraemia and Moduretic-grand mal seizures: a review. *J R Soc Med* 1989; 82: 479–83.
14. Benfield GFA, *et al.* Dilutional hyponatraemia masquerading as subarachnoid haemorrhage in patient on hydrochlorothiazide/amiloride/timolol combined drug. *Lancet* 1986; ii: 341.
15. Bain PG, *et al.* Thiazide-induced dilutional hyponatraemia masquerading as subarachnoid haemorrhage. *Lancet* 1986; ii: 634.

Effects on the gallbladder. There is an increased risk of cholecystitis in patients taking thiazides,[1] with some indication that risk increases with the duration of use;[2,3] some workers concluded that this increased risk was confined to patients with pre-existing gallstones.[3] In a study in 10 healthy subjects,[4] hydrochlorothiazide was found to induce modest changes in biliary lipid concentrations although it was not associated with supersaturation of the bile. These changes could not wholly explain any increase in gallbladder disease in patients taking thiazides. However, evidence is conflicting; other studies[5,6] have found no association between thiazides and cholecystitis, except possibly in women who are not overweight.[6]

1. González-Pérez A, García Rodríguez LA. Gallbladder disease in the general population: association with cardiovascular morbidity and therapy. *Pharmacoepidemiol Drug Safety* 2007; 16: 524–31.
2. Rosenberg L, *et al.* Thiazides and acute cholecystitis. *N Engl J Med* 1980; 303: 546–8.
3. van der Linden W, *et al.* Acute cholecystitis and thiazides. *BMJ* 1984; 289: 654–5.
4. Angelin B. Effect of thiazide treatment on biliary lipid composition in healthy volunteers. *Eur J Clin Pharmacol* 1989; 37: 95–6.
5. Porter JB, *et al.* Acute cholecystitis and thiazides. *N Engl J Med* 1981; 304: 954–5.
6. Kakar F, *et al.* Thiazide use and the risk of cholecystectomy in women. *Am J Epidemiol* 1986; 124: 428–33.

Effects on glucose metabolism. The adverse effects of thiazides on glucose metabolism, such as insulin resistance, impaired glucose tolerance, precipitation of overt diabetes, and worsening of diabetic control, are well established but appear to be dose-related and may not be significant at lower doses (for example, hydrochlorothiazide 6.25 or 12.5 mg).[1] A study[2] in 16 non-diabetic hypertensive patients found that bendroflumethiazide, in a dose of 1.25 mg daily, had no effect on insulin sensitivity whereas a daily dose of 5 mg produced hepatic insulin resistance. Similarly, the high doses, for example bendroflumethiazide 5 mg twice daily, used in the Medical Research Council Study on Mild to Moderate Hypertension[3] resulted in an incidence of glucose intolerance that led to withdrawal from the study of 9.38 per 1000 patient-years in men and 6.01 per 1000 patient-years in women compared with 2.51 and 0.82 per 1000 patient-years respectively in patients taking placebo. A later prospective study[4] in non-diabetic hypertensive patients found that those taking thiazides [doses not specified] were at no greater risk for developing diabetes than those not receiving antihypertensive therapy. However, a prospective cohort study[5] in men aged between 50 and 60 found that those taking antihypertensive treatment (mainly thiazides, beta blockers, or both) showed an increase in blood-glucose concentrations which was an independent risk factor for myocardial infarction, even when baseline insulin resistance was accounted for. Another prospective study[6] of 3 cohorts of men or women also found that use of thiazides was independently associated with a higher risk of diabetes.

It has been suggested[7] that the effect of thiazides on glucose metabolism is related to their effect on potassium and that control of hypokalaemia may prevent the development of diabetes, but this remains to be confirmed.

1. Neutel JM. Metabolic manifestations of low-dose diuretics. *Am J Med* 1996; 101 (suppl 3A): 71S–82S.
2. Harper R, *et al.* Effects of low dose versus conventional dose thiazide diuretic on insulin action in essential hypertension. *BMJ* 1994; 309: 226–30.
3. Greenburg G. Adverse reactions to bendroflumethiazide and propranolol for the treatment of mild hypertension: report of Medical Research Council Working Party on Mild to Moderate Hypertension. *Lancet* 1981; ii: 539–43.
4. Gress TW, *et al.* Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med* 2000; 342: 905–12.
5. Dunder K, *et al.* Increase in blood glucose concentration during antihypertensive treatment as a predictor of myocardial infarction: population based cohort study. *BMJ* 2003; 326: 681–4.
6. Taylor EN, *et al.* Antihypertensive medications and the risk of incident type 2 diabetes. *Diabetes Care* 2006; 29: 1065–70.
7. Zillich AJ, *et al.* Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension* 2006; 48: 219–24.

Effects on the kidneys. Thiazides can produce acute renal failure either from over-enthusiastic use producing sodium depletion and hypovolaemia or, occasionally, as a result of a hypersensitivity reaction.[1] Acute interstitial nephritis has been reported.[2,3] They can occasionally cause the formation of non-opaque urate calculi.[4]

1. Curtis JR. Diseases of the urinary system: drug-induced renal disorders: I. *BMJ* 1977; 2: 242–4.
2. Linton AL, *et al.* Acute interstitial nephritis due to drugs: review of the literature with a report of nine cases. *Ann Intern Med* 1980; 93: 735–41.
3. Anonymous. Case records of the Massachusetts General Hospital: case 42-1983. *N Engl J Med* 1983; 309: 970–8.
4. Curtis JR. Diseases of the urinary system: drug-induced renal disorders: II. *BMJ* 1977; 2: 375–7.

Effects on lipid metabolism. Thiazides have been reported to adversely affect the plasma-lipid profile in the short term by increasing concentrations of low-density and very-low-density lipoprotein cholesterol, as well as of triglycerides, but not of high-density lipoprotein cholesterol.[1] These effects are probably dose-related[2] and it has been argued that changes in plasma lipids are likely to be slight at the relatively low doses now used in hypertension. There is some evidence to suggest that these lipid changes may not persist long-term.[3] In the Treatment of Mild Hypertension Study (TOMHS),[4] plasma total cholesterol concentrations were increased after 12 months in patients receiving chlortalidone but this effect was no longer present after 24 months. Although there has been concern that any hyperlipidaemic effect might offset the benefits of treating hypertension in patients at risk of ischaemic heart disease, studies such as ALLHAT[5] have shown that thiazide-like diuretics (in this case chlortalidone) are as effective as other antihypertensives in reducing the incidence of cardiovascular events in patients with hypertension and at least one other risk factor for ischaemic heart disease.

1. Ames R. Effects of diuretic drugs on the lipid profile. *Drugs* 1988; 36 (suppl 2): 33–40.
2. Carlsen JE, *et al.* Relation between dose of bendroflumethiazide, antihypertensive effect, and adverse biochemical effects. *BMJ* 1990; 300: 975–8.
3. Freis ED. Critique of the clinical importance of diuretic-induced hypokalemia and elevated cholesterol level. *Arch Intern Med* 1989; 149: 2640–8.
4. Grimm RH, *et al.* Long-term effects on plasma lipids of diet and drugs to treat hypertension. *JAMA* 1996; 275: 1549–56.
5. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2981–97. Correction. *ibid.* 2003; 289: 178.

Effects on the nervous system. A 40-year old woman appeared sleepy and confused 1 week after starting hydrochlorothiazide.[1] Although her plasma-potassium concentrations had fallen they were still in the normal range, and it was concluded that her symptoms were due to an adverse reaction to the drug itself.

1. Daugherty KK, Subramanian J. Cognitive and neurologic impairment with hydrochlorothiazide. *Am J Health-Syst Pharm* 2005; 62: 2630–3.

Effects on respiratory function. Acute interstitial pneumonitis and acute pulmonary oedema are rare but potentially dangerous complications of thiazides and may be due to a hypersensitivity reaction. Several cases have been reported,[1-7] frequently after a single dose of hydrochlorothiazide or chlorothiazide. The presenting symptoms could be mistakenly attributed to myocardial infarction.

1. Steinberg AD. Pulmonary edema following ingestion of hydrochlorothiazide. *JAMA* 1968; 204: 167–9.
2. Beaudry C, Laplante L. Severe allergic pneumonitis from hydrochlorothiazide. *Ann Intern Med* 1973; 78: 251–3.
3. Parfrey NA, Herlong HF. Pulmonary oedema after hydrochlorothiazide. *BMJ* 1984; 288: 1880.
4. Watrigant Y, *et al.* Pneumopathie à l'hydrochlorothiazide d'évolution subaiguë: etude cytologique du lavage broncho-alvéolaire. *Rev Mal Respir* 1986; 4: 227–9.
5. Klein MD. Noncardiogenic pulmonary edema following hydrochlorothiazide ingestion. *Ann Emerg Med* 1987; 16: 901–3.
6. Bowden FJ. Non-cardiogenic pulmonary oedema after ingestion of chlorothiazide. *BMJ* 1989; 298: 605.
7. Bernal C, Pataca R. Hydrochlorothiazide-induced pulmonary edema and associated immunologic changes. *Ann Pharmacother* 1999; 33: 172–4.

Effects on sexual function. Adverse effects on sexual function have been reported in hypertensive patients given thiazides and other antihypertensives but it is not clear how much this is due to the underlying disease and how much is due to the drugs. In the Treatment of Mild Hypertension Study (TOMHS),[1] a double-blind randomised controlled study that allocated patients to treatment with one of five groups of antihypertensives, the incidence of erectile dysfunction in men was relatively low but was highest in the diuretic group (chlortalidone treatment). The incidence was significantly higher in chlortalidone recipients than in placebo recipients at 24 months (17.1 and 8.1% respectively), but the difference was no longer significant at 48 months (18.3 and 16.7% respectively).

1. Grimm RH, *et al.* Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women: Treatment of Mild Hypertension Study (TOMHS). *Hypertension* 1997; 29: 8–14.

Effects on the skin. Rashes and skin reactions have been reported in patients taking thiazides. *Photosensitivity* reactions are among the most frequently reported skin reactions. In Australia[1] co-amilozide was the preparation most commonly implicated in photosensitivity reactions in reports to the Australian Drug Reactions Advisory Committee, although this may reflect the high usage of this preparation. The most likely mechanism is thought to be phototoxicity[1,2] involving mainly UVA radiation although UVB may be involved in some cases.[2] Chronic photosensitivity does not usually occur after stopping the drug[2] although photosensitivity may persist for longer in some patients than in others.[2,3] Eruptions resembling *lichen planus*[4] and *subacute cutaneous lupus erythematosus*[5-7] may be due to photosensitivity reactions.

Other reported skin reactions include *vasculitis*,[8,9] *erythema multiforme*,[9] and *pseudoporphyria*.[10]

1. Stone K. Photosensitivity reactions to drugs. *Aust J Pharm* 1985; 66: 415–18.
2. Addo HA, *et al.* Thiazide-induced photosensitivity: a study of 33 subjects. *Br J Dermatol* 1987; 116: 749–60.
3. Robinson HN, *et al.* Thiazide diuretic therapy and chronic photosensitivity. *Arch Dermatol* 1985; 121: 522–4.
4. Graham-Brown R. Lichen planus and lichen-planus-like reactions. *Br J Hosp Med* 1986; 36: 281–4.
5. Jones SK, *et al.* Thiazide diuretic-induced subacute cutaneous lupus-like syndrome. *Br J Dermatol* 1985; 113 (suppl 29): 25.
6. Reed BR, *et al.* Subacute cutaneous lupus erythematosus associated with hydrochlorothiazide therapy. *Ann Intern Med* 1985; 103: 49–51.
7. Darken M, McBurney EI. Subacute cutaneous lupus erythematosus-like drug eruption due to combination diuretic hydrochlorothiazide and triamterene. *J Am Acad Dermatol* 1988; 18: 38–42.
8. Björnberg A, Gissén H. Thiazides: a cause of necrotising vasculitis? *Lancet* 1965; ii: 982–3.
9. Hardwick N, Saxe N. Patterns of dermatology referrals in a general hospital. *Br J Dermatol* 1986; 115: 167–76.
10. Motley RS. Pseudoporphyria due to Dyazide in a patient with vitiligo. *BMJ* 1990; 300: 1468.

Gout. Thiazides have been associated with hyperuricaemia and gout in some patients. In a single-blinded study,[1] men taking bendroflumethiazide had higher incidences of gout than those receiving placebo (12.23 and 1.03 per 1000 patient-years, respectively). The risk appears to be dose-related; in a retrospective study[2] in patients aged 65 or older receiving antihypertensive therapy, there was a significantly increased risk of starting anti-gout therapy in patients taking the equivalent of 25 mg hydrochlorothiazide or more daily, but not in those on lower doses.

1. Greenburg G. Adverse reactions to bendroflumethiazide and propranolol for the treatment of mild hypertension: report of Medical Research Council Working Party on Mild to Moderate Hypertension. *Lancet* 1981; ii: 539–43.
2. Gurwitz JH, *et al.* Thiazide diuretics and the initiation of anti-gout therapy. *J Clin Epidemiol* 1997; 50: 953–9.

Withdrawal. For a report of oedema after abrupt withdrawal of thiazides, see under Precautions, p. 1406.1.

Treatment of Adverse Effects

Hypokalaemia in patients treated with thiazides may be avoided or treated by use with potassium or a potassium-sparing diuretic (but see the discussion on potassium supplements, under Effects on Electrolyte Balance in Adverse Effects, p. 1404.2). Hypokalaemia can also be reduced by moderate sodium restriction. With the exception of patients with conditions such as hepatic failure or renal disease, chloride deficiency is usually mild and does not require specific treatment. Apart from the rare occasions when it is life-threatening, dilutional hyponatraemia is best treated with water restriction rather than salt therapy; in true hyponatraemia, appropriate replacement is the treatment of choice (see p. 1780.1).

In massive overdosage, treatment should be symptomatic and directed at fluid and electrolyte replacement. Use of activated charcoal should be considered if the patient presents within 1 hour of ingestion.

Precautions

All diuretics produce changes in fluid and electrolyte balance (see Adverse Effects, p. 1404.2). They should be used with caution in patients with existing fluid and electrolyte disturbances or who are at risk from changes in fluid and electrolyte balance, such as the elderly. They should be avoided in patients with severe hepatic impairment, in whom encephalopathy may be precipitated. Patients with hepatic cirrhosis are also more likely to develop hypokalaemia. Hyponatraemia may occur in patients with severe heart failure who are very oedematous, particularly with large doses of thiazides and restricted salt intake. All patients should be carefully observed for signs of fluid and electrolyte imbalance, especially in the presence of vomiting or during parenteral fluid therapy. Thiazides should not be given to patients with Addison's disease.

Diuretics should also be given with caution in renal impairment since they can further reduce renal function. Most thiazides are not effective in patients with a creatinine clearance of less than 30 mL/minute. They should not be used in patients with severe renal impairment or anuria.

Thiazides may precipitate attacks of gout in susceptible patients. They may cause hyperglycaemia and aggravate or unmask diabetes mellitus. Blood-glucose concentrations should be monitored in patients taking antidiabetics, since requirements may change. Thiazides can reduce urinary excretion of calcium, sometimes resulting in mild hypercalcaemia; they should not be given to patients with pre-existing hypercalcaemia. There is a possibility that thiazides may exacerbate or activate SLE in susceptible patients. For a suggestion that thiazides may increase the risk of developing gallstones, see Effects on the Gallbladder, p. 1405.1.

Thiazides cross the placenta and there have been reports of neonatal jaundice, thrombocytopenia, and electrolyte imbalances after maternal use. Reductions in maternal blood volume could also adversely affect placental perfusion. Treatment with large doses can inhibit lactation.

Breast feeding. Hydrochlorothiazide has been shown to pass into breast milk. In a woman taking 50 mg hydrochlorothiazide daily, peak milk concentrations were found[1] 5 to 10 hours after a dose and were about 25% of peak blood concentrations. No drug could be detected in the infant's blood, and his serum electrolytes, blood glucose, and blood urea nitrogen were normal. The American Academy of Pediatrics considers[2] that hydrochlorothiazide is usually compatible with breast feeding.

1. Miller ME, *et al.* Hydrochlorothiazide disposition in a mother and her breast-fed infant. *J Pediatr* 1982; 101: 789–91.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Hyperparathyroidism. Hypertension is a complication of primary hyperparathyroidism but thiazides have often been withheld for fear of exacerbating hypercalcaemia. However, no differences in plasma-calcium concentrations were found in 13 patients given thiazides intermittently for up to 18 months. It was therefore concluded that thiazides are not contra-indicated in such patients.[1] They should, however, be stopped before parathyroid function is tested.

1. Farquhar CW, *et al.* Failure of thiazide diuretics to increase plasma calcium in mild primary hyperparathyroidism. *Postgrad Med J* 1990; 66: 714–16.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hydrochlorothiazide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Withdrawal. In patients with mild hypertension whose blood pressure is consistently controlled, reduction in dosage or withdrawal of antihypertensive drugs may be possible. Serious oedema occurred in 8 patients with controlled hypertension within 2 weeks of abrupt withdrawal of thiazide diuretics.[1] Thiazides were resumed and gradually tapered without recurrence of oedema.

1. Brandspigel K. Diuretic-withdrawal edema. *N Engl J Med* 1986; 314: 515.

Interactions

Many of the interactions of hydrochlorothiazide and other thiazides are due to their effects on fluid and electrolyte balance. Diuretic-induced hypokalaemia may enhance the toxicity of digitalis glycosides and increase the risk of arrhythmias with drugs that prolong the QT interval, such as astemizole, terfenadine, halofantrine, pimozide, and sotalol. Thiazides may also enhance the neuromuscular blocking action of competitive neuromuscular blockers, such as atracurium, probably by their hypokalaemic effect.

The potassium-depleting effect of diuretics may be enhanced by corticosteroids, corticotropin, beta$_2$ agonists such as salbutamol, carbenoxolone, amphotericin B, or reboxetine.

Diuretics can enhance the effect of other antihypertensives, particularly the first-dose hypotension that occurs with alpha blockers or ACE inhibitors. Orthostatic hypotension associated with diuretics may be enhanced by alcohol, barbiturates, or opioids. The antihypertensive effects of diuretics may be antagonised by drugs that cause fluid retention, such as corticosteroids, NSAIDs, or carbenoxolone; the nephrotoxicity of NSAIDs may also be enhanced. Thiazides have been reported to diminish the response to pressor amines, such as noradrenaline, but the clinical significance of this effect is uncertain.

Thiazides should not usually be used with lithium since the association may lead to toxic blood concentrations of lithium. Other drugs for which increased toxicity has been reported when given with thiazides include allopurinol and tetracyclines. Thiazides may alter the requirements for hypoglycaemics in diabetic patients.

Antibacterials. Severe hyponatraemia has been reported in patients taking *trimethoprim* with co-amilozide[1] and hydrochlorothiazide.[2]

1. Eastell R, Edmonds CJ. Hyponatraemia associated with trimethoprim and a diuretic. *BMJ* 1984; 289: 1658–9.
2. Hart TL, *et al.* Hyponatremia secondary to thiazide-trimethoprim interaction. *Can J Hosp Pharm* 1989; 42: 243–6.

Antiepileptics. There has been a report of symptomatic hyponatraemia associated with the use of hydrochlorothiazide or furosemide and *carbamazepine*.[1]

1. Yassa R, *et al.* Carbamazepine, diuretics, and hyponatremia: a possible interaction. *J Clin Psychiatry* 1987; 48: 281–3.

Bile-acid binding resins. Gastrointestinal absorption of both chlorothiazide and hydrochlorothiazide has been reported to be reduced by *colestipol* and *colestyramine*.[1-3] In a study in healthy subjects[2] colestyramine had the greatest effect on hydrochlorothiazide, decreasing absorption by 85% compared with a decrease of 43% with colestipol. Even when colestyramine was given 4 hours after hydrochlorothiazide[3] reductions of absorption of at least 30 to 35% could be expected.

1. Kauffman RE, Azarnoff DL. Effect of colestipol on gastrointestinal absorption of chlorothiazide in man. *Clin Pharmacol Ther* 1973; 14: 886–90.
2. Hunninghake DB, *et al.* The effect of cholestyramine and colestipol on the absorption of hydrochlorothiazide. *Int J Clin Pharmacol Ther Toxicol* 1982; 20: 151–4.
3. Hunninghake DB, Hibbard DM. Influence of time intervals for cholestyramine dosing on the absorption of hydrochlorothiazide. *Clin Pharmacol Ther* 1986; 39: 329–34.

Calcium salts. The milk-alkali syndrome, characterised by hypercalcaemia, metabolic alkalosis, and renal failure, developed in a patient taking chlorothiazide and moderately large doses of calcium carbonate.[1] Patients taking thiazides may be at increased risk of developing the syndrome because of their reduced ability to excrete excess calcium. Hypercalcaemia may also occur in patients taking thiazides with drugs that increase calcium levels, such as vitamin D.

1. Gora ML, *et al.* Milk-alkali syndrome associated with use of chlorothiazide and calcium carbonate. *Clin Pharm* 1989; 8: 227–9.

Dopaminergics. For a report of increased *amantadine* toxicity associated with hydrochlorothiazide and triamterene, see p. 892.2.

NSAIDs. NSAIDs cause fluid retention and may antagonise the diuretic actions of thiazides.[1]

1. Webster J. Interactions of NSAIDs with diuretics and β-blockers: mechanisms and clinical implications. *Drugs* 1985; 30: 32–41.

Sex hormones. For a discussion of the possible interaction between hydrochlorothiazide and *drospirenone*, see Diuretics, p. 2269.3.

Pharmacokinetics

Hydrochlorothiazide is fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 65 to 70%. It has been estimated to have a plasma half-life of between about 5 and 15 hours and appears to be preferentially bound to red blood cells. It is excreted mainly unchanged in the urine. Hydrochlorothiazide crosses the placental barrier and is distributed into breast milk.

References.
1. Beermann B, *et al.* Absorption, metabolism, and excretion of hydrochlorothiazide. *Clin Pharmacol Ther* 1976; 19: 531–7.
2. Beermann B, Groschinsky-Grind M. Pharmacokinetics of hydrochlorothiazide in man. *Eur J Clin Pharmacol* 1977; 12: 297–303.
3. Beermann B, Groschinsky-Grind M. Pharmacokinetics of hydrochlorothiazide in patients with congestive heart failure. *Br J Clin Pharmacol* 1979-7: 579–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Diural; Diurex; Tandiur; ***Austral.***: Dithiazide; ***Braz.***: Clorana; Clorizin; Diurepina†; Diuretic; Diuretil; Diurezin; Diurix; Drenol; Hidrazim; Hidroclorozil†; Hidrolan; Hidromed; Hidrosan; Neo Hidroclor; ***Canad.***: Apo-Hydro; Novo-Hydrazide†; Nu-Hydro; Urozide; ***Chile***: Hidroronol; ***Cz.***: Losathia†; ***Denm.***: Hydromed; ***Fin.***: Hydrex; ***Fr.***: Esidrex; ***Ger.***: Disalunil; Esidrix; HCT-Beta; HCT-gamma; HCT-ISIS†; HCT; HCTad†; ***Gr.***: Diuren; Esidrex; ***Hong Kong***: Apo-Hydro†; Hydrozide; ***Hung.***: Hypothiazid; ***India***: Aquazide; BPzide; Esidrex; Hydrazide; Hydride; Hyzide; Klorzide; Selopres; ***Indon.***: HCT; Lodoz; ***Israel***: Disothiazide; ***Ital.***: Esidrex; ***Malaysia***: Apo-Hydro; Hydrozide; ***Mex.***: Rofucal; Top-K; ***Norw.***: Esidrex; ***Philipp.***: Cotrazid; Diuzid; Diuzide; Hytaz; Lorzan; Urilzid; ***Pol.***: Rasilez HCT; ***Rus.***: Hypothiazid (Гипотиазид); Lodoz (Лодоз); ***S.Afr.***: Hexazide; Ridaq; ***Singapore***: Apo-Hydro; Di-Ertride; Didralin; Hydrochlorzide; Hydrotride; Hydrozide; ***Spain***: Acuretic†; Esidrex; Hidrosaluretil; ***Swed.***: Esidrex; ***Switz.***: Esidrex; ***Thai.***: Dichlotride; Diric; Diuret-P; Dragotab; HCTZ; Hychlozide; Hydrozide; Urazide; ***Ukr.***: Hypothiazid (Гипотиазид); ***USA***: HydroDiuril; Microzide; Mictrin; ***Venez.***: Di-Eudrin.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Co-amilozide Oral Solution; Co-amilozide Tablets; Co triamterzide Tablets; Hydrochlorothiazide Tablets;

USP 36: Amiloride Hydrochloride and Hydrochlorothiazide Tablets; Bisoprolol Fumarate and Hydrochlorothiazide Tablets; Captopril and Hydrochlorothiazide Tablets; Enalapril Maleate and Hydrochlorothiazide Tablets; Fosinopril Sodium and Hydrochlorothiazide Tablets; Hydrochlorothiazide Capsules; Hydrochlorothiazide Tablets; Irbesartan and Hydrochlorothiazide Tablets; Lisinopril and Hydrochlorothiazide Tablets; Losartan Potassium and Hydrochlorothiazide Tablets; Methyldopa and Hydrochlorothiazide Tablets; Metoprolol Tartrate and Hydrochlorothiazide Tablets; Propranolol Hydrochloride and Hydrochlorothiazide Extended-release Capsules; Propranolol Hydrochloride and Hydrochlorothiazide Tablets; Quinapril and Hydrochlorothiazide Tablets; Reserpine and Hydrochlorothiazide Tablets; Reserpine, Hydralazine Hydrochloride, and Hydrochlorothiazide Tablets; Spironolactone and Hydrochlorothiazide Oral Suspension; Spironolactone and Hydrochlorothiazide Tablets; Telmisartan and Hydrochlorothiazide Tablets; Timolol Maleate and Hydrochlorothiazide Tablets; Triamterene and Hydrochlorothiazide Capsules; Triamterene and Hydrochlorothiazide Tablets; Valsartan and Hydrochlorothiazide Tablets.

Hydroflumethiazide *(BAN, rINN)* ⊗

Hidroflumetiazida; Hydroflumethiazide; Hydroflumethiazidum; Hydroflumetiatsidi; Hydroflumetiazid; Trifluoromethylhydrothiazide; Гидрофлуметиазид.

3,4-Dihydro-6-trifluoromethyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_8H_8F_3N_3O_4S_2$=331.3

CAS — 135-09-1.

ATC — C03AA02.

ATC Vet — QC03AA02.

UNII — 501CFL162R.

NOTE. Compounded preparations of hydroflumethiazide may be represented by the following names:

- Co-flumactone (*BAN*)—hydroflumethiazide and spironolactone in equal parts (w/w).

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Hydroflumethiazide). White or almost white, odourless or almost odourless, glistening crystals or crystalline powder. Practically insoluble in water; soluble in alcohol; practically insoluble in chloroform and in ether.

USP 36: (Hydroflumethiazide). A white to cream-coloured, odourless, finely divided crystalline powder. Very slightly soluble in water and in chloroform; soluble 1 in 39 of alcohol and 1 in 2500 of ether; freely soluble in acetone. A 1% dispersion in water has a pH of 4.5 to 7.5. Store in airtight containers.

Uses and Administration

Hydroflumethiazide is a thiazide diuretic with actions and uses similar to those of hydrochlorothiazide (p. 1403.2). It is given orally for oedema, including that associated with heart failure (p. 1262.3), and for hypertension (p. 1251.1).

Diuresis begins about 2 hours after an oral dose and has been reported to last for up to 24 hours.

In the treatment of **oedema** the usual initial dose is 50 to 200 mg daily, in one or two divided doses, reduced to a dose of 25 to 50 mg on alternate days or intermittently. In the treatment of **hypertension** the usual dose is 25 to 50 mg daily either alone, or with other antihypertensives. An initial dose of 12.5 mg has been used.

For doses in children, see p. 1407.1.

Administration in children. Hydroflumethiazide may be given to children in the treatment of hypertension and oedema at an initial dose of 1 mg/kg daily, reduced for maintenance.

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p. 1404.2.

Interactions

As for Hydrochlorothiazide, p. 1406.1.

Pharmacokinetics

Hydroflumethiazide is incompletely but fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a beta-phase biological half-life of about 17 hours and a metabolite with a longer half-life that is extensively bound to red blood cells. Hydroflumethiazide is excreted in the urine; its metabolite has also been detected in the urine.

References.

1. Broen O, *et al.* Pharmacokinetics of a single dose of hydroflumethiazide in health and in cardiac failure. *Eur J Clin Pharmacol* 1978; 14: 29–37.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Saluron.

Multi-ingredient Preparations. *India*: Aldactide; *Irl.*: Aldactide†; *S.Afr.*: Protensin-M†; *UK*: Aldactide.

Pharmacopoeial Preparations
BP 2014: Hydroflumethiazide Tablets;
USP 36: Hydroflumethiazide Tablets.

Hydroquinidine Hydrochloride

Dihydrochinidin Hydrochloride; Dihydroquinidine Hydrochloride; Hidrocloruro de dihidroquinidina; Hidroquinidina, hidrocloruro de; Hydroconchinine Hydrochloride; Гидрохинидина Гидрохлорид.

(8*R*,9*S*)-10,11-Dihydro-6′-methoxycinchonan-9-ol hydrochloride.

$C_{20}H_{26}N_2O_2$,HCl=362.9

CAS — 1435-55-8 (hydroquinidine); 1476-98-8 (hydroquinidine hydrochloride).

UNII — 6BR4G8VAHM.

Pharmacopoeias. In *Fr.*

Profile

Hydroquinidine is a class Ia antiarrhythmic with actions and uses similar to those of quinidine (p. 1481.1). It is given orally as the hydrochloride in a usual maintenance dose of 600 mg daily in divided doses.

Hydroquinidine alginate and quinalbital (the hydroquinidine salt of amobarbital) have also been used in the treatment of cardiac arrhythmias.

References.

1. Hermida J-S, *et al.* Hydroquinidine therapy in Brugada syndrome. *J Am Coll Cardiol* 2004; 43: 1853–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Serecor; *Gr.*: Ydroquinidine; *Spain*: Lentoquine.

Ibopamine *(BAN, USAN, rINN)* ⊗

Ibopamina; Ibopaminum; SB-7505; SKF-100168; Ибопамин.

4-(2-Methylaminoethyl)-o-phenylene di-isobutyrate.

$C_{17}H_{25}NO_4$=307.4

CAS — 66195-31-1.

ATC — C01CA16; S01FB03.

ATC Vet — QC01CA16; QS01FB03.

UNII — 8ZCA2I2L11.

Ibopamine Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de Ibopamina; Ibopaminihydrokloridi; Ibopamina, hidrocloruro de; Ibopamine, Chlorhydrate d'; Ibopaminhydroklorid; Ibopamini Hydrochloridum; Ибопамина Гидрохлорид.

$C_{17}H_{25}NO_4$,HCl=343.8

ATC — C01CA16; S01FB03.

ATC Vet — QC01CA16; QS01FB03.

UNII — 3VXW2HU8GS.

Uses and Administration

Ibopamine is a prodrug and is rapidly converted to its active metabolite, epinine, which is a peripheral dopamine agonist and sympathomimetic (p. 1507.3). At low doses its dopaminergic effects predominate, leading to vasodilatation and a weak positive inotropic effect; at high concentrations it has a stimulant action on alpha and beta adrenoceptors.

Ibopamine is used in the management of mild heart failure (p. 1262.3). It is given as the hydrochloride but doses are often expressed in terms of the base; 111.9 mg of hydrochloride is equivalent to about 100 mg of base. Doses of 100 to 200 mg orally two or three times daily have been used.

Ibopamine is also used topically as a mydriatic (p. 2000.2) in the form of eye drops containing ibopamine hydrochloride 2%.

Adverse Effects and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3. Ibopamine should not be used in patients with severe heart failure as it has been reported to increase the risk of death.

Effects on the cardiovascular system. A multicentre study (PRIME II) of the use of ibopamine in patients with severe (NYHA class III or IV) heart failure was stopped early when it was found that the drug was associated with an increased risk of death.[1] Subgroup analysis found that use of an antiarrhythmic drug was independently predictive of an adverse effect in ibopamine-treated patients. Excess mortality in heart failure has also been reported with dobutamine and xamoterol, and with the phosphodiesterase inhibitors amrinone, enoximone, milrinone, and vesnarinone, all of which produce positive inotropic effects through catecholamine-receptor stimulation or post-receptor pathway stimulation.[2] The association with antiarrhythmic therapy in the ibopamine study might reflect an interaction with amiodarone, the most commonly used antiarrhythmic in this study, or might simply be a marker for patients at risk of ibopamine-induced tachyarrhythmias.

1. Hampton JR, *et al.* Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. *Lancet* 1997; 349: 971–7.
2. Niebauer J, Coats AJS. Treating chronic heart failure: time to take stock. *Lancet* 1997; 349: 966–7.

Interactions

As for Sympathomimetics, p. 1508.3. It has been recommended that ibopamine should not be given to patients taking amiodarone in the light of the increased mortality seen in the PRIME II study in patients given both drugs (see above), although it is not clear that this represents a genuine interaction.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Scandine; *Ital.*: Scandine; Trazyl†; *Neth.*: Inopamil†.

Ibutilide Fumarate *(BANM, USAN, rINNM)*

Fumarato de ibutilida; Ibutilida, fumarato de; Ibutilide, Fumarate d'; Ibutilidi Fumaras; U-70226E; Ибутилида Фумарат.

(±)-4′-[4-(Ethylheptylamino)-1-hydroxybutyl]methanesulfonanilide fumarate (2:1).

$(C_{20}H_{36}N_2O_3S)_2C_4H_4O_4$=885.2

CAS — 122647-31-8 (ibutilide); 122647-32-9 (ibutilide fumarate).

ATC — C01BD05.

ATC Vet — QC01BD05.

UNII — 9L5X4M5L6I.

Uses and Administration

Ibutilide is a class III antiarrhythmic (p. 1243.1) used for the acute treatment of atrial fibrillation or flutter (p. 1266.1).

Ibutilide is given intravenously as the fumarate. For the termination of atrial fibrillation or flutter, ibutilide fumarate is given as a single dose of 1 mg in patients weighing 60 kg and over, or 10 micrograms/kg in patients weighing less than 60 kg, infused over 10 minutes; the infusion should be stopped as soon as the arrhythmia is terminated. If the arrhythmia persists 10 minutes after completion of the infusion, a second infusion of the same dose may be given.

References.

1. Foster RH, *et al.* Ibutilide: a review of its pharmacological properties and clinical potential in the acute management of atrial flutter and fibrillation. *Drugs* 1997; 54: 312–30.
2. Granberry MC. Ibutilide: a new class III antiarrhythmic agent. *Am J Health-Syst Pharm* 1998; 55: 255–60.
3. Howard PA. Ibutilide: an antiarrhythmic agent for the treatment of atrial fibrillation or flutter. *Ann Pharmacother* 1999; 33: 38–47.
4. Doggrell SA, Hancox JC. Ibutilide—recent molecular insights and accumulating evidence for use in atrial flutter and fibrillation. *Expert Opin Invest Drugs* 2005; 14: 655–69.
5. Kafkas NV, *et al.* Conversion efficacy of intravenous ibutilide compared with intravenous amiodarone in patients with recent-onset atrial fibrillation and atrial flutter. *Int J Cardiol* 2007; 118: 321–5.
6. Hoyer AW, Balaji S. The safety and efficacy of ibutilide in children and in patients with congenital heart disease. *Pacing Clin Electrophysiol* 2007; 30: 1003–8.
7. Giudici MC, *et al.* Ibutilide therapy for atrial fibrillation: 5-year experience in a community hospital. *J Cardiovasc Nurs* 2008; 23: 484–8.
8. Pragakis N, *et al.* Acute beta-adrenoceptor blockade improves efficacy of ibutilide in conversion of atrial fibrillation with a rapid ventricular rate. *Europace* 2009; 11: 70–4.

Adverse Effects

Adverse cardiovascular effects associated with ibutilide include heart block, hypotension, hypertension, and bradycardia. It prolongs the QT interval and, like other antiarrhythmics, can cause arrhythmias, including torsade de pointes. Other adverse effects include nausea and vomiting.

Effects on the heart. Ibutilide prolongs the QT interval and has been associated with torsade de pointes, particularly in women.[1] A small study[2] suggested that this effect could be prevented by magnesium sulfate (p. 1790.1), which might therefore be suitable for use as prophylaxis. Although magnesium could theoretically reduce the antiarrhythmic effect of ibutilide as well as the proarrhythmic effect, a retrospective study[3] found that the rate of cardioversion was higher in patients given both ibutilide and magnesium than in those given ibutilide alone, an effect confirmed in a later study.[4] An episode of asystole lasting for 7 seconds in an elderly woman given ibutilide for cardioversion[5] was thought to be caused by the drug unmasking and exacerbating latent sick sinus syndrome.

1. Gowda RM, *et al.* Female preponderance in ibutilide-induced torsade de pointes. *Int J Cardiol* 2004; 95: 219–22.
2. Caron MF, *et al.* Effects of intravenous magnesium sulfate on the QT interval in patients receiving ibutilide. *Pharmacotherapy* 2003; 23: 296–300.
3. Kalus JS, *et al.* Impact of prophylactic i.v. magnesium on the efficacy of ibutilide for conversion of atrial fibrillation or flutter. *Am J Health-Syst Pharm* 2003; 60: 2308–12.
4. Tercius AJ, *et al.* Intravenous magnesium sulfate enhances the ability of intravenous ibutilide to successfully convert atrial fibrillation or flutter. *Pacing Clin Electrophysiol* 2007; 30: 1331–5.
5. Neumayr G, *et al.* Ibutilide and sinus arrest. *Herz* 2007; 32: 342.

Effects on the kidneys. Acute renal failure with biopsy evidence of acute tubular necrosis developed in a 52-year-old man shortly after he received 2 doses of ibutilide for an episode of atrial flutter.[1] Renal function returned to normal after 4 sessions of haemodialysis.

1. Franz M, *et al.* Acute renal failure after ibutilide. *Lancet* 1999; 353: 467.

Precautions

ECG monitoring should be carried out during, and for at least 4 hours after, ibutilide infusion, and the infusion should be stopped if the QT interval becomes markedly prolonged. Electrolyte abnormalities should be corrected before treatment is started.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ibutilide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

Use of ibutilide with other antiarrhythmics or drugs that prolong the QT interval should be avoided.

Magnesium. For the synergistic effect of magnesium and ibutilide in producing cardioversion, see Effects on the Heart, above.

Pharmacokinetics

Ibutilide is widely distributed in the body after intravenous infusion. It has low plasma protein binding (about 40%) and undergoes extensive metabolism in the liver to form several metabolites. Ibutilide is excreted mainly in the urine, as metabolites and a small amount of unchanged drug (about 7%), with about 19% being excreted in the faeces. The elimination half-life is reported to range from 2 to 12 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Corvert; *Canad.*: Corvert; *Fin.*: Corvert; *Fr.*: Corvert†; *Gr.*: Corvert; *Ital.*: Corvert; *Neth.*: Corvert; *Norw.*: Corvert; *Rus.*: Corvert (Корверт); *Swed.*: Corvert; *Switz.*: Corvert; *USA*: Corvert.

Idraparinux Sodium *(USAN, rINN)*

Idraparinux sódico; Idraparinux Sodique; Idraparinuxum Natricum; Org-34006; SANORG-34006; SR-34006; Идрапаринукс Натрия.

Methyl 6-O-2,3,4-tri-O-methyl-6-O-sulfo-α-D-glucopyranosyl-(1→4)-O-2,3-di-O-methyl-β-D-glucopyranuronosyl-(1→4)-O-2,3,6-tri-O-sulfo-α-D-glucopyranosyl-(1→4)-O-2,3-di-O-methyl-α-L-idopyranuronosyl-(1→4)-2,3,6-tri-O-sulfo-α-D-glucopyranoside nonasodium.

$C_{38}H_{55}Na_9O_{49}S_7$=1727.1

CAS — 162610-12-5 (idraparinux); 149920-56-9 (idraparinux sodium).

UNII — H84IXP29FN.

Profile

Idraparinux is a pentasaccharide inhibitor of factor Xa that acts in a similar manner to fondaparinux (p. 1385.3). It has a long half-life and has been investigated in once-weekly doses for the management of venous thromboembolism; however, results have been disappointing, with bleeding being a particular problem. A biotinylated version, idrabiotaparinux, whose action may be reversed by the glycoprotein avidin, is under development in an attempt to improve the safety profile of the drug.

References.

1. Buller HR, *et al.* Idraparinux versus standard therapy for venous thromboembolic disease. *N Engl J Med* 2007; 357: 1094–1104.
2. Buller HR, *et al.* Extended prophylaxis of venous thromboembolism with idraparinux. *N Engl J Med* 2007; 357: 1105–12.
3. Bousser MG, *et al.* Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. *Lancet* 2008; 371: 315–21.
4. Prandoni P, *et al.* Idraparinux: review of its clinical efficacy and safety for prevention and treatment of thromboembolic disorders. *Expert Opin Invest Drugs* 2008; 17: 773–7.
5. Harenberg J. Development of idraparinux and idrabiotaparinux for anticoagulant therapy. *Thromb Haemost* 2009; 102: 811–15.
6. van Doormaal FF, *et al.* Idraparinux versus standard therapy in the treatment of deep venous thrombosis in cancer patients: a subgroup analysis of the Van Gogh DVT trial. *Thromb Haemost* 2010; 104: 86–91.
7. Paty I, *et al.* Reversibility of the anti-FXa activity of idrabiotaparinux (biotinylated idraparinux) by intravenous avidin infusion. *J Thromb Haemost* 2010; 8: 722–9.
8. Equinox Investigators. Efficacy and safety of once weekly subcutaneous idrabiotaparinux in the treatment of patients with symptomatic deep venous thrombosis. *J Thromb Haemost* 2011; 9: 92–9.

Ifenprodil Tartrate *(rINNM)*

Ifenprodil, Tartrate d'; Ifenprodil, tartrato de; Ifenprodili Tartras; RC-61-91; Tartrato de ifenprodil; Ифенпродила Тартрат.

(±)-2-(4-Benzylpiperidino)-1-(4-hydroxyphenyl)propan-1-ol tartrate.

$(C_{21}H_{27}NO_2)_2C_4H_6O_6$=801.0

CAS — 23210-56-2 (ifenprodil); 23210-58-4 (ifenprodil tartrate).

ATC — C04AX28.

ATC Vet — QC04AX28.

UNII — 89CTB4XUF7.

Pharmacopoeias. In *Jpn*.

Profile

Ifenprodil tartrate is a vasodilator, with alpha-adrenoceptor blocking properties, used in peripheral vascular disorders (p. 1272.3). It is given in usual oral doses of 40 to 60 mg daily, and has also been given by deep intramuscular injection, slow intravenous injection, or intravenous infusion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Vadilex; *Gr.*: Vadilex.

Iloprost *(BAN, USAN, rINN)*

Ciloprost; E-1030; Iloprosti; Iloprostum; SH-401; ZK-00036374; ZK-36374; Илопрост.

(*E*)-(3a*S*,4*R*,5*R*,6a*S*)-Hexahydro-5-hydroxy-4-[(*E*)-(3*S*,4*RS*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-Δ$^{2(1H)\Delta}$-pentalenevaleric acid.

$C_{22}H_{32}O_4$=360.5

CAS — 73873-87-7; 78919-13-8.

ATC — B01AC11.

ATC Vet — QB01AC11.

UNII — JED5K35YGL.

Iloprost Trometamol *(BANM, rINNM)*

Ciloprost Tromethamine; Iloprost Trometamol; Iloprost Tromethamine; Iloprostum Trometamolum; Илопрост Трометамол.

$C_{22}H_{32}O_4.C_4H_{11}NO_3$=481.6

ATC — B01AC11.

ATC Vet — QB01AC11.

Uses and Administration

Iloprost, a vasodilator and platelet aggregation inhibitor, is a stable analogue of the prostaglandin epoprostenol (prostacyclin). It is given as the trometamol salt in the treatment of peripheral vascular disease and pulmonary hypertension but doses are described in terms of iloprost; 1.3 nanograms of iloprost trometamol is equivalent to about 1 nanogram of iloprost.

The usual dose for **peripheral vascular disease** is the equivalent of iloprost 0.5 to 2 nanograms/kg per minute for 6 hours daily by intravenous infusion. The course of treatment may be up to 4 weeks. For **pulmonary hypertension**, the dose is 1 to 8 nanograms/kg per minute for 6 hours daily; alternatively, iloprost may be given by nebulised solution at a dose of 2.5 or 5 micrograms inhaled 6 to 9 times daily. Doses should be reduced in patients with hepatic or renal impairment (see below).

Oral iloprost is under investigation.

Reviews.

1. Grant SM, Goa KL. Iloprost: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peripheral vascular disease, myocardial ischaemia and extracorporeal circulation procedures. *Drugs* 1992; 43: 889–924.

Administration in children. Although iloprost is unlicensed in the UK for use in children, the *BNFC* suggests that it may be given intravenously to children aged 12 years and over in the treatment of **Raynaud's syndrome**, and by nebulisation to those aged 8 years and over in the treatment of **pulmonary hypertension**, in the usual adult doses (see above), although treatment duration should be limited to 3 to 5 days in Raynaud's syndrome.

References.

1. Zulian F, *et al.* Safety and efficacy of iloprost for the treatment of ischaemic digits in paediatric connective tissue diseases. *Rheumatology (Oxford)* 2004; 43: 229–33.
2. Ivy DD, *et al.* Short- and long-term effects of inhaled iloprost therapy in children with pulmonary arterial hypertension. *J Am Coll Cardiol* 2008; 51: 161–9.
3. Tissot C, Beghetti M. Review of inhaled iloprost for the control of pulmonary artery hypertension in children. *Vasc Health Risk Manag* 2009; 5: 325–31.

Administration in hepatic or renal impairment. The dose of intravenous iloprost should be reduced, and may need to be halved, in patients with liver cirrhosis or renal impairment requiring dialysis. In hepatic impairment, the initial dose of inhaled iloprost should be 2.5 micrograms given at intervals of at least 3 hours to a maximum of 6 times daily; the dose may be cautiously increased or given more frequently according to patient response.

Peripheral vascular disease. Prostaglandins, including iloprost,[1-10] have been used in the treatment of peripheral vascular disorders (p. 1272.3), although their role remains unclear. They may be of benefit in severe Raynaud's syndrome (see Vasospastic Arterial Disorders, p. 1275.3), that is complicated by ulceration. Systematic review[10] suggests that intravenous iloprost produces prolonged benefit in Raynaud's phenomenon secondary to scleroderma. The benefits of oral iloprost are less clear. It is also unclear whether iloprost infusion is of benefit in occlusive peripheral arterial disease due to atherosclerosis: although a meta-analysis of (conflicting) controlled studies did suggest an effect,[6] firm conclusions are difficult.

1. Waller PC, *et al.* Placebo controlled trial of iloprost in patients with stable intermittent claudication. *Br J Clin Pharmacol* 1986; 21: 562P–563P.
2. Rademaker M, *et al.* Comparison of intravenous infusions of iloprost and oral nifedipine in treatment of Raynaud's phenomenon in patients with systemic sclerosis: a double blind randomised study. *BMJ* 1989; 298: 561–4.
3. Flessinger JN, Schäfer M. Trial of iloprost versus aspirin treatment for critical limb ischaemia of thromboangiitis obliterans. *Lancet* 1990; 335: 555–7.
4. Zahavi J, *et al.* Ischaemic necrotic toes associated with antiphospholipid syndrome and treated with iloprost. *Lancet* 1993; 342: 862.
5. Tait IS, *et al.* Management of intra-arterial injection injury with iloprost. *Lancet* 1994; 343: 419.
6. Loosemore TM, *et al.* A meta-analysis of randomized placebo control trials in Fontaine stages III and IV peripheral occlusive arterial disease. *Int Angiol* 1994; 13: 133–42.
7. Wigley FM, *et al.* Oral iloprost treatment in patients with Raynaud's phenomenon secondary to systemic sclerosis: a multicenter, placebo-controlled, double-blind study. *Arthritis Rheum* 1998; 41: 670–7.
8. Black CM, *et al.* Oral iloprost in Raynaud's phenomenon secondary to systemic sclerosis: a multicentre, placebo-controlled, dose-comparison study. *Br J Rheumatol* 1998; 37: 952–60.
9. Scorza R, *et al.* Effects of long-term cyclic iloprost therapy in systemic sclerosis with Raynaud's phenomenon: a randomized, controlled study. *Clin Exp Rheumatol* 2001; 19: 503–8.
10. Pope J, *et al.* Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 16/06/05).

Pulmonary hypertension. Epoprostenol is an accepted part of the management of pulmonary hypertension (p. 1278.2) and the use of iloprost, a stable analogue, has been studied. Inhaled iloprost may have a role;[1,2] it was found[3] to improve walking-test distances, reduce severity of heart failure, and stabilise haemodynamic measures in a 12-week study of patients with severe pulmonary hypertension, while long-term treatment of at least 1 year has been reported to have sustained beneficial effects.[4,5] It has been used for management in children.[6] Iloprost has also been used successfully in a few cases to manage pulmonary hypertension in pregnant women.[7] There are also reports of effective combination therapy using inhaled iloprost with intravenous epoprostenol,[8] oral sildenafil,[9] or oral bosentan.[10] Continuous intravenous infusion[11] has also been tried with beneficial results over several weeks, and short-term intravenous infusion for 7 days[12] has been successfully used for pulmonary hypertension after pulmonary thromboendarterectomy.

1. Baker SE, Hockman RH. Inhaled iloprost in pulmonary arterial hypertension. *Ann Pharmacother* 2005; 39: 1265–73.
2. Krug S, *et al.* Inhaled iloprost for the control of pulmonary hypertension. *Vasc Health Risk Manag* 2009; 5: 465–74.
3. Olschewski H, *et al.* Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002; 347: 322–9.
4. Hoeper MM, *et al.* Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. *N Engl J Med* 2000; 342: 1866–70.
5. Olschewski H, *et al.* Long-term therapy with inhaled iloprost in patients with pulmonary hypertension. *Respir Med* 2010; 104: 731–40.
6. Tissot C, Beghetti M. Review of inhaled iloprost for the control of pulmonary artery hypertension in children. *Vasc Health Risk Manag* 2009; 5: 325–31.
7. Elliot CA, *et al.* The use of iloprost in early pregnancy in patients with pulmonary arterial hypertension. *Eur Respir J* 2005; 26: 168–73.
8. Petkov V, *et al.* Aerosolised iloprost improves pulmonary haemodynamics in patients with primary pulmonary hypertension receiving continuous epoprostenol treatment. *Thorax* 2001; 56: 734–6.
9. Ghofrani HA, *et al.* Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med* 2002; 136: 515–22.
10. McLaughlin VV, *et al.* Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2006; 174: 1257–63.
11. Higenbottam TW, *et al.* Treatment of pulmonary hypertension with the continuous infusion of a prostacyclin analogue, iloprost. *Heart* 1998; 79: 175–9.
12. Hsu H-H, *et al.* Short-term intravenous iloprost for treatment of reperfusion lung oedema after pulmonary thromboendarterectomy. *Thorax* 2007; 62: 459–61.

Thrombotic microangiopathies. For reports of the use of iloprost in patients with thrombotic microangiopathies such as thrombotic thrombocytopenic purpura, see under Epoprostenol, p. 1375.3.

Adverse Effects and Precautions

As for Epoprostenol, p. 1375.3. Inhaled iloprost may cause cough.

Effects on the cardiovascular system. Hypotension was seen[1] in 2 of 6 patients given iloprost. Both patients recovered rapidly when iloprost was stopped, although one required intravenous atropine to correct sinus bradycardia.

Evidence of myocardial ischaemia was reported in 4 of 33 patients with coronary artery disease during iloprost infusion.[2] The same authors[3] noted a similar effect in 4 of 28 patients with stable angina in a subsequent study. According to one study,[4] there might be an increased risk of thromboembolism in some patients given iloprost, due to platelet activation and enhanced coagulation.

1. Upward JW, *et al.* Hypotension in response to iloprost, a prostacyclin analogue. *Br J Clin Pharmacol* 1986; 21: 241–3.
2. Bugiardini R, *et al.* Myocardial ischemia induced by prostacyclin and iloprost. *Clin Pharmacol Ther* 1985; 38: 101–8.
3. Bugiardini R, *et al.* Effects of iloprost, a stable prostacyclin analog, on exercise capacity and platelet aggregation in stable angina pectoris. *Am J Cardiol* 1986; 58: 453–9.
4. Kovacs IB, *et al.* Infusion of a stable prostacyclin analogue, iloprost, to patients with peripheral vascular disease: lack of antiplatelet effect but risk of thromboembolism. *Am J Med* 1991; 90: 41–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies iloprost as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pregnancy. For reference to the successful use of iloprost in pregnancy see Pulmonary Hypertension, under Uses and Administration, above.

Interactions

Iloprost may increase the effect of other vasodilators and antihypertensives. The use of iloprost with other inhibitors of platelet aggregation may increase the risk of bleeding.

Pharmacokinetics

On intravenous infusion iloprost is rapidly cleared from the plasma by oxidation. About 80% of the metabolites are excreted in urine and 20% in the bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ventavis; *Austral.*: Ventavis; *Austria*: Ilomedin; Ventavis; *Belg.*: Ventavis; *Chile*: Ventavis; *China*: Ventavis (万他维); *Cz.*: Ilomedin†; Ventavis; *Denm.*: Ilomedin; Ventavis; *Fin.*: Ilomedin; Ventavis; *Fr.*: Ilomedine; Ventavis; *Ger.*: Ilomedin; Ventavis; *Gr.*: Ilomedin; Ventavis; *Hong Kong*: Ilomedin; Ventavis; *Hung.*: Ilomedin; Ventavis; *Indon.*: Ventavis; *Irl.*: Ventavis; *Israel*: Ilomedin; Ventavis; *Ital.*: Endoprost; Ventavis; *Malaysia*: Ilomedin; Ventavis; *Mex.*: Ventavis; *Neth.*: Ilomedine; Ventavis; *Norw.*: Ilomedin; Ventavis; *NZ*: Ilomedin; Ventavis; *Pol.*: Ilomedin; Ventavis; *Port.*: Ilomedin; Ventavis; *Rus.*: Ilomedin (Иломедин); Ventavis (Вентавис); *Singapore*: Ventavis; *Spain*: Ilomedin; Ventavis; *Swed.*: Ilomedin; Ventavis; *Switz.*: Ilomedin; Ventavis; *Thai.*: Ilomedin; Ventavis; *Turk.*: Ilomedin: Ventavis; *UK*: Ventavis; *USA*: Ventavis.

Imidapril Hydrochloride *(BANM, rINNM)*

EG-006; Hidrocloruro de imidapril; Imidapriilihydrokloridi; Imidapril; Chlorhydrate d'; Imidapril, hidrocloruro de; Imidaprilhydroklorid; Imidaprili Hydrochloridum; TA-6366; Имидаприла Гидрохлорид.

(*S*)-3-[*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-1-methyl-2-oxoimidazoline-4-carboxylic acid hydrochloride.

$C_{20}H_{27}N_3O_6$,HCl=441.9

CAS — 89371-37-9 (imidapril); 89396-94-1 (imidapril hydrochloride).

ATC — C09AA16.

ATC Vet — QC09AA16.

UNII — 7NSF9GG1NU.

NOTE. The name Vitor has been used as a trade mark for imidapril.

Uses and Administration

Imidapril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1). Imidapril owes its activity to imidaprilat, to which it is converted after oral doses. The maximum haemodynamic effect occurs 6 to 8 hours after a dose, although the full effect may not develop for several weeks during chronic dosing. Imidapril is given orally as the hydrochloride.

In the treatment of hypertension, the usual initial dose of imidapril hydrochloride is 5 mg once daily, before food. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. An initial dose of 2.5 mg daily should be used in the elderly, in patients with renal or hepatic impairment, or in those receiving a *diuretic*; if possible, the diuretic should be withdrawn 2 or 3 days before imidapril is started and resumed later if necessary. The usual maintenance dose is 10 mg daily, although up to 20 mg daily may be given if required. The maximum dose for elderly patients is 10 mg daily.

Imidapril is being investigated for the treatment of cachexia in cancer patients.

Reviews.

1. Robinson DM, *et al.* Imidapril: a review of its use in essential hypertension, type 1 diabetic nephropathy and chronic heart failure. *Drugs* 2007; 67: 1359–78.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Imidapril acts as a prodrug of the diacid imidaprilat, its active metabolite. After oral doses, imidapril is rapidly but incompletely absorbed; absorption is about 70% and is reduced in the presence of food. Imidapril is metabolised in the liver to imidaprilat. The bioavailability of imidaprilat is about 42% after oral doses of imidapril, and peak plasma concentrations of imidaprilat occur in about 7 hours. Both imidapril and imidaprilat are moderately bound to plasma proteins. About 40% of an oral dose is excreted in the urine, the rest in the faeces. The terminal half-life of imidaprilat is more than 24 hours. Imidapril and imidaprilat are removed by haemodialysis.

References.

1. Hooglamer JFW, *et al.* Pharmacokinetics of imidapril and its active metabolite imidaprilat following single dose and during steady state in patients with impaired liver function. *Eur J Clin Pharmacol* 1997; 51: 489–91.
2. Hooglamer JFW, *et al.* Pharmacokinetics of imidapril and its active metabolite imidaprilat following single dose and during steady state in patients with chronic renal failure. *Eur J Clin Pharmacol* 1998; 54: 59–61.
3. Harder S, *et al.* Single dose and steady state pharmacokinetics and pharmacodynamics of the ACE-inhibitor imidapril in hypertensive patients. *Br J Clin Pharmacol* 1998; 45: 377–80.
4. Tsuruoka S, *et al.* Clearance of imidapril, an angiotensin-converting enzyme inhibitor, during hemodialysis in hypertensive renal failure patients: comparison with quinapril and enalapril. *J Clin Pharmacol* 2007; 47: 259–63.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Tanatril; *Austria*: Tanatril; *China*: Tanatril (达奥); *Cz.*: Tanatril; *Fr.*: Tanatril; *Ger.*: Tanatril†; *Gr.*: Tanatril; *Hong Kong*: Tanatril; *India*: Tanatril; *Indon.*: Tanapress; *Jpn*: Tanatril; *Malaysia*: Tanatril; *Philipp.*: Norten; Vascor; *Pol.*: Tanatril; *Port.*: Cardipril; *Singapore*: Tanatril; *Spain*: Hipertene; *Thai.*: Tanatril; *UK*: Tanatril.

Multi-ingredient Preparations. *Philipp.*: Norplus; Vascoride.

Indapamide *(BAN, USAN, rINN)* ⊗

Indapamid; Indapamida; Indapamidi; Indapamidum; SE-1520; Индапамид.

4-Chloro-*N*-(2-methylindolin-1-yl)-3-sulphamoylbenzamide.

$C_{16}H_{16}ClN_3O_3S$=365.8

CAS — 26807-65-8 (anhydrous indapamide).

ATC — C03BA11.

ATC Vet — QC03BA11.

UNII — F089I0511L.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Indapamide). A white or almost white powder. Practically insoluble in water; soluble in alcohol. Protect from light.

USP 36: (Indapamide). A white to off-white crystalline powder. Practically insoluble in water; soluble in alcohol, in glacial acetic acid, in acetonitrile, in ethyl acetate, and in methyl alcohol; very slighdly soluble in chloroform and in ether.

Uses and Administration

Indapamide is a diuretic with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1403.2) even though it does not contain a thiazide ring system. It is used for hypertension (p. 1251.1), and also for oedema, including that associated with heart failure (p. 1262.3).

In some countries indapamide is described as the hemihydrate. In the treatment of **hypertension** the usual oral dose is 1.25 to 2.5 mg once daily, either alone, or with other antihypertensives; a modified-release preparation may be given in a dose of 1.5 mg daily. At higher doses the diuretic effect may become apparent without appreciable additional antihypertensive effect although US licensed product information suggests that the dose may be increased to 5 mg after 4 weeks. In the treatment of **oedema** the usual dose is 2.5 mg once daily increasing to 5 mg daily after 1 week if necessary.

Reviews.

1. Chaffman M, *et al.* Indapamide: a review of its pharmacodynamic properties and therapeutic efficacy in hypertension. *Drugs* 1984; 28: 189–235.
2. Robinson DM, Wellington K. Indapamide sustained release: a review of its use in the treatment of hypertension. *Drugs* 2006; 66: 257–71.

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p. 1404.2.

Effects on the blood. A 58-year-old woman[1] had bleeding from the mucous membrane of the tongue 18 months after starting treatment with a modified-release form of indapamide; she was found to have mild thrombocytopenia, and petechiae were seen. After withdrawal of the drug, bleeding stopped immediately; the platelet count returned to normal within 10 days and the skin lesions faded quickly.

1. Hasanova EA, Agasiyeva NE. Bleeding associated with indapamide SR therapy. *Ann Pharmacother* 2005; 39: 199–200.

Effects on carbohydrate and lipid metabolism. Several studies have reported no changes in blood-glucose concentrations during indapamide treatment,[1-3] although elevated concentrations have been reported in individual patients.[4,5] There have been reports of increases in total cholesterol[2] and of no change.[3] No adverse biochemical changes were found in studies[4] of a modified-release preparation.

1. Velussi M, *et al.* Treatment of mild-to-moderate hypertension with indapamide in type II diabetics: midterm (six months) evaluation. *Curr Ther Res* 1988; 44: 1076–86.
2. Prisant LM, *et al.* Biochemical, endocrine, and mineral effects of indapamide in black women. *J Clin Pharmacol* 1990; 30: 121–6.
3. Leonetti G, *et al.* Long-term effects of indapamide: final results of a two-year Italian multicenter study in systemic hypertension. *Am J Cardiol* 1990; 65: 674–714.
4. Slotkoff L. Clinical efficacy and safety of indapamide in the treatment of edema. *Am Heart J* 1983; 106: 233–7.
5. Beling S, *et al.* Long term experience with indapamide. *Am Heart J* 1983; 106: 258–62.
6. Weidmann P. Metabolic profile of indapamide sustained-release in patients with hypertension: data from three randomised double-blind studies. *Drug Safety* 2001; 24: 1155–65.

Effects on electrolyte balance. By 2002, 164 cases of hyponatraemia with indapamide had been reported to the Australian Adverse Drug Reactions Advisory Committee (ADRAC),[1] of which 68 also described hypokalaemia. Most patients were elderly women. A review[2] of some of these cases suggested that hyponatraemia was more commonly reported with indapamide than with chlorothiazide, although it was pointed out[3] that the true incidence cannot be determined from spontaneous reports. ADRAC recommends that indapamide should be used cautiously. It may be that indapamide has no clinical advantage over low-dose thiazide diuretics.

1. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Indapamide and hyponatraemia. *Aust Adverse Drug React Bull* 2002; 21: 11. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0208.htm (accessed 06/07/04)
2. Chapman MD, *et al.* Hyponatraemia and hypokalaemia due to indapamide. *Med J Aust* 2002; 176: 219–21.
3. Howes LG. Hyponatraemia and hypokalaemia caused by indapamide. *Med J Aust* 2002; 177: 53–4.

Effects on the kidneys. Acute interstitial nephritis was associated with indapamide treatment in a 74-year-old patient.[1]

1. Newstead CG, *et al.* Interstitial nephritis associated with indapamide. *BMJ* 1990; 300: 1344.

Effects on the skin. Sixteen cases of rash attributed to indapamide had been reported to the Netherlands Centre for Monitoring of Adverse Reactions to Drugs.[1] All patients had taken indapamide 2.5 mg daily for hypertension. The rash was accompanied by fever in 5 cases. In all cases the rash subsided within 14 days of withdrawal, and 11 patients subsequently took thiazides, furosemide, or clopamide without recurrence. Among 188 cases of rash attributed to indapamide reported to the WHO Collaborating Centre for International Drug Monitoring were 4 cases of erythema multiforme and 2 of epidermal necrolysis. A further case of toxic epidermal necrolysis was reported by independent authors.[2]

1. Stricker BHC, Birkett C. Skin reactions and fever with indapamide. *BMJ* 1987; 295: 1313–14.
2. Black RJ, *et al.* Toxic epidermal necrolysis associated with indapamide. *BMJ* 1990; 301: 1280–1.

Interactions

As for Hydrochlorothiazide, p. 1406.1.

Pharmacokinetics

Indapamide is rapidly and completely absorbed from the gastrointestinal tract. Elimination is biphasic with a half-life in whole blood of about 14 hours. Indapamide is strongly bound to red blood cells. It is extensively metabolised. About 60 to 70% of the dose has been reported to be excreted in the urine; only about 5 to 7% is excreted unchanged. About 16 to 23% of dose is excreted in the faeces. Indapamide is not removed by haemodialysis but does not accumulate in patients with renal impairment.

References.

1. Beermann B, Grind M. Clinical pharmacokinetics of some newer diuretics. *Clin Pharmacokinet* 1987; 13: 254–66.
2. Schiavi P, *et al.* Pharmacokinetics of sustained and immediate release formulations of indapamide after single and repeated oral administration in healthy volunteers. *Fundam Clin Pharmacol* 2000; 14: 139–46.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bajaten; Duremid; Natrilix; Noranat; *Austral.*: Dapa-Tabs; Indahexal; Insig; Napamide; Natrilix; *Austria*: Fludex; *Belg.*: Docindapa†; Fludex; *Braz.*: Indapen; Natrilix; *Canad.*: Lozide; *Chile*: Indapress; Natrilix; *China*: An Tai Da (安泰达); Millibar (美利巴); Na Si Li Tuo (纳斯力妥); Natrilix (纳催离); Ping Zhi (平至); Sheng Chang (圣畅); Shoubishan (寿比山); Xi Er Da (希尔达); Ya Rong (雅荣); Yi Te An (伊特安); Yue Nan Shan (悦南珊); Cz.: Indap; Izepox; Rawel; Tertensif; *Denm.*: Indacar; Natrilix; Tertensif†; *Fin.*: Natrilix; Tertensif; *Fr.*: Fludex; *Ger.*: Inda-Puren†; Natrilix; *Gr.*: Dixamid; Fludex; Magniton-R; Transipen; *Hong Kong*: CP-Indap†; Dapa-Tabs; Diflerix†; Frumeron†; Indalix; Millibar†; Natrilix; Rinalix†; *Hung.*: Apadex; Indastad; Lapiden; Narva; Pretanix; Rawel; *India*: CGMide; Diurix; Divret; Fanton; In; Ind; Indacard; Indap; Indicontin†; Inditor; Inzu; Lorvas; Natrilix; *Indon.*: Natrilix; *Irl.*: Agelan†; Napamide; Natrilix; *Israel*: Pamid; *Ital.*: Damide†; Indaflex; Indamol; Ipamix; Millibar; Natrilix; Pressural; Veroxil; *Malaysia*: Dapa†; Diflerix†; Indalix; Napamide; Natrilix; Rinalix†; *Mex.*: Natrilix; *Neth.*: Flu-

dex; *NZ*: Dapa-Tabs; Napamide; Natrilix; ***Philipp.***: Natrilix; Vazamide; ***Pol.***: Apo-Indap; Diuresin; Indapen; Indapres; Indapsan†; Indix; Ipres; Opamid; Rawel; Symapamid; Tertensif; ***Port.***: Arifon†; Bulex; Fludex; Fluidema; Indir; Norpress; Pamir†; Rawel; Tandix; Vasodipin; ***Rus.***: Akripamide (Акрипамид); Arifon (Арифон); Arindap (Ариндап); Indap (Индап); Indipam (Индипам); Indiur (Индиур); Ionik (Ионик); Ipres (Ипрес); Lorvas (Лорвас); Rawel (Равел); Retapres (Ретапрес); ***S.Afr.***: Adco-Dapamax; Catexan; Daptril; Hydro-Less; Indalix†; Lixamide; Natrilix; ***Singapore***: Dapa-Tabs; Prumeron; Napamide; Natrilix; Rinalix; ***Spain***: Extur; Tertensif; ***Switz.***: Fludapamide; Fludex; ***Thai.***: Prumeron; Inpamide; Intril; Napamide; Natrilix; ***Turk.***: Flubest; Fludex; Fludin; Flupamid; Flutans; Indamid; Indapen; Indurin; ***UAE***: Indanorm; ***UK***: Ethibide; Indipam; Natrilix; Tensaid; ***Ukr.***: Arifon (Арифон); Hemopamid (Хемопамид); Indap (Индап); Indapen (Индапен); Indiure (Индиур)†; Indopres (Индопрес); Ipamid (Ипамид); Ravel (Равел); ***Venez.***: Natrilix.

Multi-ingredient Preparations. *Arg.*: Bipreterax†; Preterax; ***Austral.***: Coversyl Plus; Doprilamide; Perindo Combi; ***Austria***: Delapride†; Preterax; ***Belg.***: Bi Preterax†; Coperindo; Coversyl Plus; Preterax; ***Braz.***: Coversyl Plus; ***Canad.***: Coversyl Plus; Preterax†; ***China***: Biprel (百普乐); *Cz.*: Coverex Combi; Noliprel; Noliterax; Pamocombi; Parateraх; Perinpa; Prenewel; Prestarium Combi; Prestarium Neo Combi; ***Denm.***: Copreneesa; Coprindomid†; Coversyl Arginine Plus; Coversyl Comp Novum; Domanion Comp†; Paraterax; Tertensif kombi; ***Fin.***: Acertil Comp; Coprenessa; Coversyl Comp; Noliterax; Teraxans; *Fr.*: Bipreterax; Paraterax; Preterax; ***Ger.***: Bipreterax; Coversum Combi†; Preterax; *Gr.*: Dinapres; Pediur; Preterax; ***Hong Kong***: Acertil Plus; Predonium; ***Hung.***: Armix Komb; Armix Prekomb; Co-Perineva; Co-Prenessa; Coverex Komb; Coverex Prekomb†; Pretanix Komb; ***India***: Atelol-D; Aten-D; Coversyl Plus; Eviper-D; Inat; Indap-AT; Perigard-D; Perigard-DF; Tenolol-D; ***Indon.***: Bioprexum Plus; ***Irl.***: Bipreterax; Coversyl Plus; Pendrex Plus; Preterax; Prindavam; Teraxans; ***Ital.***: Delapride; Dinapres; Normopress; Prelectal; Preterax; ***Malaysia***: Coversyl Plus; ***Mex.***: Preterax; ***Neth.***: Comaranil; Coversyl Plus; Noliterax; Predonium†; Preterax; Preterian; *NZ*: Coversyl Plus; Predonium; ***Philipp.***: Bi-Preterax; *Coversyl Plus*; Preterax; ***Pol.***: *Co-Prenessa*; Noliprel; Prestarium Plus†; Tertensif Bi-Kombi; Tertensif Kombi; ***Port.***: Bi Predonium; Bi Preterax; Imprex; Predonium; Preterax; Prilpa; Tecazo; ***Rus.***: Enzix (Энзикс); Noliprel (Нолипрел); Noliprel A (Нолипрел А); Sonoprel (Сонопрел); ***S. Afr.***: Acesyl Co; Bipreterax†; Coversyl Plus; Pearinda Plus; Preterax; Prexum Plus; Vectoryl Plus; ***Singapore***: Coversyl Plus; Preterax†; ***Spain***: Bipreterax; Preterax; ***Switz.***: Coversum Combi; Preterax†; ***Thai.***: Coversyl Plus; ***Turk.***: Bipreterax; Coversyl Plus; Delapride; Perivel Plus; Preterax; Serperil Plus; ***UK***: Coversyl Plus; ***Ukr.***: Co-Prenesa (Ко-Пренеса); Enzix (Энзикс); Noliprel (Нолипрел); Prestarium Combi (Престариум Комби); ***Venez.***: Bipreterax; Preterax.

Pharmacopoeial Preparations
BP 2014: Indapamide Tablets; Prolonged-release Indapamide Tablets;
USP 36: Indapamide Tablets.

Indenolol Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de indenolol; Indénolol, Chlorhydrate d'; Indenolol, hidrocloruro de; Indenololi Hydrochloridum; Sch-28316Z (indenolol); YB-2; Инденолола гидрохлорид.

1-*H*-Inden-4(or 7)-yloxy-3-isopropylaminopropan-2-ol hydrochloride.

$C_{15}H_{21}NO_2$,HCl=283.8

CAS — 60607-68-3 (indenolol); 68906-88-7 (indenolol hydrochloride).

UNII — 2VLW0W0ZQ.

Pharmacopoeias. In *Jpn.*

Profile

Indenolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to possess potent membrane-stabilising properties and intrinsic sympathomimetic activity.

Indenolol has been used orally as the hydrochloride in the management of various cardiovascular disorders.

Indobufen *(rINN)*

Indobufén; Indobufène; Indobufenum; K-3920; Индобуфен.

(±)-2-[4-(1-Oxo-isoindolin-2-yl)phenyl]butyric acid.

$C_{18}H_{17}NO_3$=295.3

CAS — 63610-08-2.

ATC — B01AC10.

ATC Vet — QB01AC10.

UNII — 679949G4LZ.

Profile

Indobufen is an inhibitor of platelet aggregation used in various thromboembolic disorders (p. 1273.2) in oral doses of 200 to 400 mg daily given in 2 divided doses. For patients over the age of 65, the dose should be reduced to 100 to 200 mg daily. Doses should also be reduced in renal impairment (see below). Indobufen has also been given parenterally as the sodium salt.

References.

1. Wiseman LR, *et al.* Indobufen: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in cerebral, peripheral and coronary vascular disease. *Drugs* 1992; 44: 445–64.
2. Bhana N, McClellan KJ. Indobufen: an updated review of its use in the management of atherothrombosis. *Drugs Aging* 2001; 18: 369–88.

Administration in renal impairment. In patients with renal impairment the dose of indobufen should be reduced to 100 mg twice daily; it should not be used if the creatinine clearance is under 30 mL/minute.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: XinBei (辛贝); Yin Si Da (引思达); *Cz.*: Ibustrin; ***Ital.***: Ibustrin; ***Mex.***: Ibustrin; ***Pol.***: Ibustrin; ***Port.***: Ibustrin; ***Rus.***: Ibustrin (Ибустрин); ***Venez.***: Ibustrin.

Indoramin Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de indoramina; Indoramina, hidrocloruro de; Indoramine, Chlorhydrate d'; Indoramini Hydrochloridum; Wy-21901 (indoramin); Индорамина Гидрохлорид.

N-[1-(2-Indol-3-ylethyl)-4-piperidyl]benzamide hydrochloride.

$C_{22}H_{25}N_3O$,HCl=383.9

CAS — 26844-12-2 (indoramin); 33124-53-7 (indoramin hydrochloride); 38821-52-2 (indoramin hydrochloride).

ATC — C02CA02.

ATC Vet — QC02CA02.

UNII — DQ0Z3K8W92.

Pharmacopoeias. In *Br.*

BP 2014: (Indoramin Hydrochloride). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water; sparingly soluble in alcohol; very slightly soluble in ether; soluble in methyl alcohol. A 2% suspension in water has a pH of 4.0 to 5.5. Protect from light.

Uses and Administration

Indoramin is a selective and competitive alpha$_1$-adrenoceptor blocker (p. 1243.1) with actions similar to those of prazosin (p. 1474.1); it is also reported to have membrane-stabilising properties and to be a competitive antagonist at histamine H_1 and 5-hydroxytryptamine receptors. Indoramin is used in the management of hypertension (p. 1251.1), and in benign prostatic hyperplasia (p. 2347.1) to relieve symptoms of urinary obstruction. It has also been used in the prophylactic treatment of migraine.

Indoramin is given orally as the hydrochloride, but doses are usually expressed in terms of the base. Indoramin hydrochloride 11.0 mg is equivalent to about 10 mg of indoramin.

In **hypertension**, the initial dose is 25 mg twice daily, increased in steps of 25 or 50 mg at intervals of 2 weeks to a maximum of 200 mg daily in 2 or 3 divided doses.

In **benign prostatic hyperplasia**, the initial dose is 20 mg twice daily, increased if necessary by 20 mg at 2-week intervals, to a maximum of 100 mg daily in divided doses.

Lower doses may be required in the elderly.

Reviews.

1. Holmes B, Sorkin EM. Indoramin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in hypertension and related vascular, cardiovascular and airway diseases. *Drugs* 1986; 31: 467–99.

Migraine. Although propranolol is probably the most well-established drug for prophylaxis of migraine (p. 670.3) other drugs, including indoramin, have been used. In a double-blind study,[1] indoramin in a dose of 25 mg twice daily was reported to be as effective as dihydroergotamine mesilate in reducing the frequency of migraine attacks.

1. Pradalier A, *et al.* Etude comparative indoramine versus dihydroergotamine dans le traitement préventif de la migraine. *Therapie* 1988; 43: 293–7.

Adverse Effects, Treatment, and Precautions

The most common adverse effects in patients receiving indoramin are sedation and dizziness; dry mouth, nasal congestion, headache, fatigue, depression, weight gain (almost certainly due to fluid retention), and failure of ejaculation may also occur. Tachycardia does not seem to be a problem with therapeutic doses but orthostatic hypotension may occur and may produce syncope. Extrapyramidal disturbances have been reported.

After overdosage, coma, convulsions, and hypotension may occur; hypothermia has been reported in *animals*. In acute poisoning appropriate symptomatic and supportive care should be given; if the patient presents within 1 hour, activated charcoal may be considered.

Indoramin should be avoided in patients with heart failure; it has been recommended that incipient heart failure should be controlled before giving indoramin. Caution should be observed in patients with hepatic or renal impairment, a history of depression, epilepsy, or Parkinson's disease. Elderly patients may respond to lower doses.

Because indoramin can cause drowsiness care should be taken in patients who drive or operate machinery.

Cataract surgery. For a warning about intraoperative floppy iris syndrome during cataract surgery in patients taking alpha blockers, see Cataract Surgery, under Precautions for Tamsulosin Hydrochloride, p. 2369.3.

Effects on mental function. Sleep disturbances and vivid dreams were reported during a study in hypertensive patients when indoramin was added to therapy with a thiazide diuretic and a beta blocker.[1]

1. Marshall AJ, *et al.* Evaluation of indoramin added to oxprenolol and bendrofluazide as a third agent in severe hypertension. *Br J Clin Pharmacol* 1980; 10: 217–21.

Overdosage. A 43-year-old woman with a long history of heavy alcohol intake died after taking 100 tablets of indoramin 25 mg.[1] The main clinical features were deep sedation, respiratory depression, hypotension, and convulsions. Although the hypotension was satisfactorily controlled the CNS effects were resistant to treatment and proved fatal. Other clinical features included areflexia, metabolic acidosis, tachycardia, and later bradyarrhythmias. In another report,[2] self-poisoning with indoramin was associated with development of torsade de pointes.

1. Hunter R. Death due to overdose of indoramin. *BMJ* 1982; 285: 1011.
2. Nisse P, *et al.* Torsade de pointes: a severe and unknown adverse effect in indoramin self-poisoning. *Int J Cardiol* 2009; 133: e73–e75.

Interactions

The hypotensive effects of indoramin may be enhanced by diuretics and other antihypertensives. It has been reported that the ingestion of alcohol can increase the rate and extent of absorption and the sedative effects of indoramin (see below) and that indoramin should not be given to patients already receiving MAOIs.

Alcohol. In a study[1] in 9 healthy subjects alcohol 500 mg/kg significantly enhanced plasma-indoramin concentrations after an oral dose of 50 mg. The effect was most marked in the early period, corresponding to the absorptive phase. The mean peak plasma-indoramin concentration was increased from 15.0 to 23.7 nanograms/mL by alcohol; the area under the concentration/time curve was increased by 25%. Alcohol did not affect the pharmacokinetics of intravenous indoramin. The results suggest that alcohol increases indoramin bioavailability either by enhancing absorption or reducing first-pass metabolism. The combination was more sedative than either drug alone.

1. Abrams SML, *et al.* Pharmacokinetic interaction between indoramin and ethanol. *Hum Toxicol* 1989; 8: 237–41.

Pharmacokinetics

Indoramin is readily absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism. It is reported to be about 90% bound to plasma proteins. It has a half-life of about 5 hours which is reported to be prolonged in elderly patients. It is extensively metabolised and is excreted mainly as metabolites in the urine and faeces. There is evidence to suggest that some metabolites may have some alpha-adrenoceptor blocking activity.

The elderly. The plasma half-life of indoramin in 5 healthy elderly subjects after a single oral dose ranged from 6.6 to 32.8 hours with a mean of 14.7 hours.[1] The increased half-life may have been caused by reduced clearance in elderly patients.

1. Norbury HM, *et al.* Pharmacokinetics of oral indoramin in elderly and middle-aged female volunteers. *Eur J Clin Pharmacol* 1984; 27: 247–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Vidora; *Ger.*: Wydora†; *Gr.*: Wydora; ***Irl.***: Doralese†; ***S.Afr.***: Baratol†; ***UK***: Baratol†; Doralese.

Pharmacopoeial Preparations
BP 2014: Indoramin Tablets.

Inositol Nicotinate *(BAN, rINN)*

Inositol Niacinate (USAN); Inositol, Nicotinate d'; Inositoli Nicotinas; Inositolinikotinaatti; Inositolnikotinat; Nicotinato de inositol; NSC-49506; Win-9154; Инозитола Никотинат.

meso-Inositol hexanicotinate; *myo*-Inositol hexanicotinate.
$C_{42}H_{30}N_6O_{12}$=810.7
CAS — 6556-11-2
ATC — C04AC03.
ATC Vet — QC04AC03.
UNII — A99MK953KZ.

Pharmacopoeias. In *Br.*

BP 2014: (Inositol Nicotinate). A white or almost white, odourless or almost odourless powder. Practically insoluble in water, in alcohol, in acetone, and in ether; sparingly soluble in chloroform. It dissolves in dilute mineral acids.

Profile

Inositol nicotinate is a vasodilator and is believed to be slowly hydrolysed to nicotinic acid (p. 2083.1). It is given orally in the management of peripheral vascular disorders (p. 1272.3) although good evidence of efficacy is lacking. The usual dose is 3 g daily given in divided doses. The dose may be increased to 4 g daily if necessary.

Inositol nicotinate has been used in hyperlipidaemias.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Nianate; ***Gr.***: Hexaniton; ***India***: Nicovas; ***Irl.***: Hexopal; ***UK***: Hexopal.

Multi-ingredient Preparations. ***S.Afr.***: Geratar†.

Pharmacopoeial Preparations
BP 2014: Inositol Nicotinate Tablets.

Irbesartan *(BAN, USAN, rINN)*

BMS-186295; Irbesartaani; Irbesartán; Irbésartan; Irbesartanum; SR-47436; Ирбесартан.
2-Butyl-3-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one.
$C_{25}H_{28}N_6O$=428.5
CAS — 138402-11-6.
ATC — C09CA04.
ATC Vet — QC09CA04.
UNII — J0E2756Z7N.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Irbesartan). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; sparingly soluble in methyl alcohol; slightly soluble in dichloromethane.

USP 36: (Irbesartan). A white to off-white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane. Store in airtight containers at a temperature below 30 degrees.

Uses and Administration

Irbesartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p. 1422.2). It is used in the management of hypertension (p. 1251.1) including the treatment of renal disease in hypertensive diabetic patients (see Kidney Disorders, under Uses of Losartan, p. 1423.3). Irbesartan is also under investigation in heart failure.

Irbesartan is given orally. After a dose the hypotensive effect peaks within 3 to 6 hours and persists for at least 24 hours. The maximum hypotensive effect is achieved within 4 to 6 weeks after starting therapy.

In **hypertension**, irbesartan is given in a dose of 150 mg once daily increased, if necessary, to 300 mg once daily. A lower initial dose of 75 mg once daily may be considered in elderly patients over 75 years, for patients with intravascular volume depletion, and for those receiving haemodialysis.

For the treatment of **renal disease** in hypertensive type 2 diabetics, irbesartan should be given in an initial dose of 150 mg once daily, increased to 300 mg once daily for maintenance.

Irbesartan has been used similarly as the hydrochloride.

Reviews.

1. Ravera M, *et al.* Prevention and treatment of diabetic nephropathy: the program for irbesartan mortality and morbidity evaluation. *J Am Soc Nephrol* 2005; 16 (suppl 1): S48–S52.
2. Palmer AJ, *et al.* Irbesartan treatment of patients with type 2 diabetes, hypertension and renal disease: a UK health economics analysis. *Int J Clin Pract* 2007; 61: 1626–33.
3. Flack JM. Maximising antihypertensive effects of angiotensin II receptor blockers with thiazide diuretic combination therapy: focus on irbesartan/hydrochlorothiazide. *Int J Clin Pract* 2007; 61: 2093–1102.
4. Croom KF, Plosker GL. Irbesartan: a review of its use in hypertension and diabetic nephropathy. *Drugs* 2008; 68: 1543–69.
5. Negro R. Endothelial effects of antihypertensive treatment: focus on irbesartan. *Vasc Health Risk Manag* 2008; 4: 89–101.
6. Bramlage P, *et al.* The value of irbesartan in the management of hypertension. *Expert Opin Pharmacother* 2009; 10: 1817–31.
7. Bramlage P, Schindler C. Differences in pharmacology and their translation into differences in clinical efficacy—a comparison of the renin angiotensin blocking agents irbesartan and losartan. *Expert Opin Pharmacother* 2010; 11: 521–35.

Administration in children. Although irbesartan appears to be well-tolerated in children with hypertension and has been shown to reduce blood pressure in small studies,[1] US licensed product information notes that doses of up to 4.5 mg/kg once daily were ineffective in children aged 6 to 16 years and no longer recommends use in such patients.

In children with chronic kidney diseases, irbesartan has been reported to reduce blood pressure and proteinuria.[2,3] The initial dose was 37.5 mg once daily for children weighing 10 to 20 kg, 75 mg once daily for those weighing 21 to 40 kg, and 150 mg once daily for those weighing more than 40 kg; doses could be doubled if the blood pressure response was inadequate.

1. Sakarcan A, *et al.* The pharmacokinetics of irbesartan in hypertensive children and adolescents. *J Clin Pharmacol* 2001; 41: 742–9.
2. Franscini LMD, *et al.* Effectiveness and safety of the angiotensin II antagonist irbesartan in children with chronic kidney diseases. *Am J Hypertens* 2002; 15: 1057–63.
3. Gartenmann AC, *et al.* Better renoprotective effect of angiotensin II antagonist compared to dihydropyridine calcium channel blocker in childhood. *Kidney Int* 2003; 64: 1450–4.

Adverse Effects and Precautions

As for Losartan Potassium, p. 1424.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies irbesartan as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

As for Losartan Potassium, p. 1424.3.

Pharmacokinetics

Irbesartan is rapidly absorbed from the gastrointestinal tract with an oral bioavailability of 60 to 80%. Peak plasma concentrations of irbesartan occur 1.5 to 2 hours after an oral dose. Irbesartan is about 96% bound to plasma proteins. It undergoes some metabolism in the liver, primarily by the cytochrome P450 isoenzyme CYP2C9, to inactive metabolites. It is excreted as unchanged drug and metabolites in the bile and in urine; about 20% of an oral or intravenous dose is excreted in the urine, with less than 2% as unchanged drug. The terminal elimination half-life is about 11 to 15 hours.

References.

1. Sica DA, *et al.* The pharmacokinetics of irbesartan in renal failure and maintenance hemodialysis. *Clin Pharmacol Ther* 1997; 62: 610–18.
2. Marino MR, *et al.* Pharmacokinetics and pharmacodynamics of irbesartan in healthy subjects. *J Clin Pharmacol* 1998; 38: 246–55.
3. Marino MR, *et al.* Pharmacokinetics and pharmacodynamics of irbesartan in patients with hepatic cirrhosis. *J Clin Pharmacol* 1998; 38: 347–56.
4. Vachharajani NN, *et al.* Oral bioavailability and disposition characteristics of irbesartan, an angiotensin antagonist, in healthy volunteers. *J Clin Pharmacol* 1998; 38: 702–7.
5. Vachharajani NN, *et al.* The effects of age and gender on the pharmacokinetics of irbesartan. *Br J Clin Pharmacol* 1998; 46: 611–13.
6. Sakarcan A, *et al.* The pharmacokinetics of irbesartan in hypertensive children and adolescents. *J Clin Pharmacol* 2001; 41: 742–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Adana; Aprovel; Avapro; ***Austral.***: Avapro; Karvea; ***Belg.***: Aprovel; ***Braz.***: Aprovel; Avapro; ***Canad.***: Avapro; ***Chile***: Aprovel; ***China***: An Lai (安来); Aprovel (安博维); Gan Yue Xi (甘悦喜); Geping (格平); Ji Jia (吉加); KeSu (科苏); Pu Li Ning (普利宁); Ruo Peng (若朋); Su Shi (苏适); Xin Ping (欣平); Yi Da Li (伊达力); Yi Kang Ning (伊康宁); Yi Tai Qing; ***Cz.***: Aprovel; Ifirmasta; Irbec; Isame; Karvea; ***Denm.***: Aprovel; Ifirmasta; Irbenidda†; ***Fin.***: Aprovel†; ***Fr.***: Aprovel; ***Ger.***: Aprovel; Karvea; ***Gr.***: Alvein; Aprovel; Besartan; Irven; Karvea; ***Hong Kong***: Aprovel; ***Hung.***: Aprovel; Ebrit; Irabel; Irprestan; Pribercor; ***India***: Aprovel; Irbest; Irovel; Xarb; ***Indon.***: Aprovel; Elzar; Fritens; Iretensa; Irtan; Irvask; Irvell; ***Irl.***: Aprovel; Irbesan; Karvea; Licolin; ***Ital.***: Abesart; Aprovel; Karvea; Quartlintan; Rabesat; Sykratan; ***Malaysia***: Aprovel; ***Mex.***: Aprovel; Avapro; ***Neth.***: Abesart; Agepin; Aprovel; Ardinel; Artibesan; Bersin; Gemot; Ifirmasta; Irbec; Irbenahyp; Irbenidda†; Irberan; Irsalico; Junelic; Karvea; Licolin; Sabervel; Vilconir†; Ybersigax; ***Norw.***: Aprovel; ***NZ***: Karvea†; ***Philipp.***: Aprovel; Bezart; Izart; ***Pol.***: Aprovel; Ifirmasta; Karvea; ***Port.***: Abavil; Aprovel; Ifirmasta; Karvea; Trabiran†; ***Rus.***: Aprovel (Апровель); Firmasta (Фирмаста); ***S.Afr.***: Aprovel; Irbewin; ***Singapore***: Aprovel; ***Spain***: Aprovel; Ifirmasta; Karvea; ***Swed.***: Aprovel; ***Switz.***: Aprovel; ***Thai.***: Aprovel; Irbenox; Presolin; ***Turk.***: Irda; Karvea; ***UK***: Aprovel; Saberve!; ***Ukr.***: Aprovel (Апровель); Irebetan (Ирбетан); ***USA***: Avapro; ***Venez.***: Aprovel.

Multi-ingredient Preparations. ***Arg.***: Adana Plus; Avapro HCT; CoAprovel; ***Austral.***: Avapro HCT; Karvezide; ***Belg.***: CoAprovel; ***Braz.***: Aprozide; ***Canad.***: Avalide; ***Chile***: CoAprovel; ***China***: An Li Bo (安利博); CoAprovel (安博语); ***Cz.***: CoAprovel; Irbesartan HCT; Irbezyd Combi; Karvezide; Lartokaz; ***Denm.***: CoAprovel; ***Fr.***: CoAprovel; ***Ger.***: CoAprovel; Karvezide; ***Gr.***: CoAprovel; Karvezide; ***Hong Kong***: CoAprovel; ***Hung.***: CoAprovel; Ebrit HCT; Irprestan HCT; ***India***: CoAprovel; Irovel-H; Xarb-H; ***Indon.***: CoAprovel; Irtan Plus; ***Irl.***: CoAprovel; Ifirmacombi; Karvezide; ***Ital.***: CoAprovel; Karvezide; ***Jpn***: Aimix; Irtra; ***Malaysia***: CoAprovel; ***Mex.***: Avalide; CoAprovel; ***Neth.***: Arablocktans; Bloketangil; CoAprovel; Dazirok; Ebirintazide; Ifirmacombi; Karvezide; Lartokaz; Licarbetida; ***Norw.***: CoAprovel; ***NZ***: Karvezide†; ***Philipp.***: CoAprovel; ***Pol.***: CoAprovel; Karvezide; ***Port.***: CoAprovel; Karvezide; ***Rus.***: CoAprovel (Коапровель); ***S.Afr.***: Co-Irbewin; CoAprovel; ***Singapore***: CoAprovel; ***Spain***: CoAprovel; Ifirmacombi; Karvezide; ***Swed.***: CoAprovel; ***Switz.***: CoAprovel; ***Thai.***: CoAprovel; ***Turk.***: Co-Irda; Karvezide; ***UK***: CoAprovel; ***Ukr.***: Co-Irbesan (Ко-Ирбесан); ***USA***: Avalide; ***Venez.***: CoAprovel.

Pharmacopoeial Preparations
BP 2014: Irbesartan Tablets;
USP 36: Irbesartan and Hydrochlorothiazide Tablets; Irbesartan Tablets.

Isoprenaline *(BAN, rINN)* ⊗

Isoprenaliini; Isoprenalin; Isoprenalina; Isoprénaline; Isoprenalinum; Isopropilarterenol; Isopropilnoradrenalina; Isopropilnorepinefrina; Isopropylarterenol; Isopropylnoradrenaline; Isoproterenol; Изопреналин.
1-(3,4-Dihydroxyphenyl)-2-isopropylaminoethanol.
$C_{11}H_{17}NO_3$=211.3
CAS — 7683-59-2.
ATC — C01CA02; R03AB02; R03CB01.
ATC Vet — QC01CA02; QR03AB02; QR03CB01.
UNII — L628TT009W.

Isoprenaline Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de isoprenalina; Isoprenaliinihydrokloridi; Isoprenalina, hidrocloruro de; Isoprénaline, Chlorhydrate d'; Isoprenalinhydrochlorid; Isoprenalin-hydrochlorid; Isoprenalinhydroklorid; Isoprenalini Hydrochloridum; Isopropylarterenol Hydrochloride; Isopropylnoradrenaline Hydrochloride; Isoproterenol Hydrochloride; Izoprenalin Hidroklorür; Izoprenalin-hidroklorid; Izoprenalino hidrochloridas; Изопреналина Гидрохлорид.
$C_{11}H_{17}NO_3$,HCl=247.7
CAS — 51-30-9.
ATC — C01CA02; R03AB02; R03CB01.
ATC Vet — QC01CA02; QR03AB02; QR03CB01.
UNII — DIA2A74855.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Isoprenaline Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 4.3 to 5.5. Store in airtight containers. Protect from light.

USP 36: (Isoproterenol Hydrochloride). A white to practically white, odourless, crystalline powder. It gradually darkens on exposure to air and light. Soluble 1 in 3 of water and 1 in 50 of alcohol; less soluble in dehydrated alcohol; insoluble in chloroform and in ether. A 1% solution in water has a pH of about 5. Solutions become pink to brownish-pink on standing exposed to air and almost immediately so when made alkaline. Store in airtight containers. Protect from light.

Isoprenaline Sulfate *(BANM, rINNM)* ⊗

Isoprenaliinisulfaatti; Isoprenalin sulfát dihydrát; Isoprenalina, sulfato de; Isoprénaline, Sulfate d'; Isoprenaline Sulphate; Isoprenalini Sulfas; Isoprenalini Sulfas Dihydricus; Isoprenalinsulfat; Isopropylarterenol Sulphate; Isopropylnoradrenaline Sulphate; Isoproterenol Sulfate; Izoprenalino sulfatas; Izoprenalin-szulfát; Izoprenaliny siarczan; Sulfato de isoprenalina; Изопреналина Сульфат.
$(C_{11}H_{17}NO_3)_2,H_2SO_4,2H_2O$=556.6
CAS — 299-95-6 (anhydrous isoprenaline sulfate); 6700-39-6 (isoprenaline sulfate dihydrate).
ATC — C01CA02; R03AB02; R03CB01.
ATC Vet — QC01CA02; QR03AB02; QR03CB01.
UNII — 052RYE6JDD (anhydrous isoprenaline sulfate); 925FX3X776 (isoprenaline sulfate dihydrate).

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Isoprenaline Sulfate). A white or almost white crystalline powder. Freely soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 4.3 to 5.5. Store in airtight containers. Protect from light.

USP 36: (Isoproterenol Sulfate). A white to practically white, odourless, crystalline powder. It gradually darkens on exposure to light and air. Soluble 1 in 4 of water; very slightly soluble in alcohol, in chloroform, in ether, and in benzene. A 1% solution in water has a pH of about 5. Solutions become pink to brownish-pink on standing

exposed to air, and almost immediately so when made alkaline. Store in airtight containers. Protect from light.

Uses and Administration

Isoprenaline is a sympathomimetic (p. 1507.3) that acts almost exclusively on beta-adrenergic receptors. It has a powerful stimulating action on the heart and increases cardiac output, excitability, and rate; it also causes peripheral vasodilatation and produces a fall in diastolic blood pressure and usually maintains or slightly increases systolic blood pressure. In addition, isoprenaline has bronchodilating properties. It also stimulates the CNS.

Isoprenaline has been used in the temporary control of bradycardia that is unresponsive to atropine or dobutamine, in heart block, and in Stokes-Adams attacks, until a pacemaker is fitted; however, other drugs are often preferred. It has also been used as an adjunct in shock (p. 1279.3), congestive heart failure (p. 1262.3), and torsade de pointes (see Cardiac Arrhythmias, p. 1266.1). High doses may be of particular use in beta-blocker overdose. Isoprenaline has been used in the diagnosis of congenital heart defects and of coronary artery disease.

For **cardiac disorders** isoprenaline is given intravenously as the hydrochloride under ECG control; the dose is adjusted according to response and the patient's condition. In emergencies, a slow intravenous infusion is given in doses typically ranging from 0.5 to 5 micrograms/min, although higher doses may be necessary. Alternatively, a slow intravenous injection is given in initial doses ranging from 20 to 60 micrograms; repeat injections of 10 to 200 micrograms may be given if necessary. In extreme emergencies, an intracardiac injection of 20 micrograms may be given by those experienced in the technique. In less urgent situations, intramuscular or subcutaneous injections may be given in a typical initial dose of 200 micrograms, with subsequent doses adjusted according to response. Tablets of isoprenaline hydrochloride have been given orally or sublingually.

Isoprenaline has been used as a bronchodilator in the management of **reversible airways obstruction** but sympathomimetics with a selective action on beta$_2$ receptors, such as salbutamol, are now preferred (see Asthma, p. 1195.2). It has been given as the sulfate or hydrochloride, usually by inhalation; sublingual tablets have also been used. Low-dose injections of isoprenaline have been given to control bronchospasm during anaesthesia.

Adverse Effects, Treatment, and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3. Isoprenaline has almost exclusively beta-agonist properties but also stimulates the CNS; its main adverse effects include tachycardia and cardiac arrhythmias, palpitations, hypotension, tremor, headache, sweating, and facial flushing. Prolonged use of isoprenaline has been associated with swelling of the parotid glands.

Prolonged use of sublingual tablets may also cause severe damage to the teeth due to the acidic nature of the drug. Sublingual use or inhalation may colour the saliva or sputum red.

Increased mortality. For a discussion of the increased mortality and morbidity that has sometimes been seen in asthmatic patients using beta agonists and reference to an early epidemic associated with isoprenaline inhalers, see Fenoterol, p. 1208.3.

Interactions

As for Sympathomimetics, p. 1508.3. Due to the risk of arrhythmias, isoprenaline should not be used with other potent beta$_1$ agonists such as adrenaline.

Theophylline. For reports of increased theophylline clearance following use of isoprenaline, see Sympathomimetics, p. 1236.3.

Pharmacokinetics

As a result of sulfate conjugation in the gut, isoprenaline is considerably less active orally than after parenteral doses. It is absorbed through the oral mucosa and has accordingly been given sublingually, but absorption by this route remains very erratic. Isoprenaline in the body is resistant to metabolism by monoamine oxidase, but is metabolised by catechol-*O*-methyltransferase in the liver, lungs, and other tissues, the metabolite then being conjugated before excretion in the urine. Whereas the sulfate conjugate of isoprenaline is inactive the methylated metabolite has weak activity.

After intravenous injection isoprenaline has a plasma half-life of about one to several minutes according to whether the rate of injection is rapid or slow; it is almost entirely excreted in the urine as unchanged drug and metabolites within 24 hours. A much slower onset of action and a more extended initial half-life has been found after oral dosage. Isoprenaline is reported to have a duration of action of up to about 2 hours after inhalation; it has been shown that a large proportion of an inhaled dose is swallowed.

References.

1. Blackwell EW, *et al.* The fate of isoprenaline administered by pressurized aerosols. *Br J Pharmacol* 1970; 39: 194P–195P.
2. Conolly ME, *et al.* Metabolism of isoprenaline in dog and man. *Br J Pharmacol* 1972; 46: 458–72.
3. Blackwell EW, *et al.* Metabolism of isoprenaline after aerosol and direct intrabronchial administration in man and dog. *Br J Pharmacol* 1974; 50: 587–91.
4. Reyes G, *et al.* The pharmacokinetics of isoproterenol in critically ill pediatric patients. *J Clin Pharmacol* 1993; 33: 29–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Isuprel; *Belg.*: Isuprel; *Cz.*: Isuprel†; *Fr.*: Isuprel; *Gr.*: Isuprel; Neo-Elixir†; *India*: Autohaler; Isolin; Isosol; Neo-Epinine; *Indon.*: Isuprel†; *Israel*: Isuprel†; *NZ*: Isuprel; *S.Afr.*: Imuprel†; *Spain*: Aleudrina; *Thai.*: Isuprel; *USA*: Isuprel; Medihaler-Iso†.

Multi-ingredient Preparations. *Spain*: Aldo Asma†; Frenal Compositum†; *USA*: Norisodrine with Calcium Iodide.

Pharmacopoeial Preparations

BP 2014: Isoprenaline Injection;

USP 36: Acetylcysteine and Isoproterenol Hydrochloride Inhalation Solution; Isoproterenol Hydrochloride and Phenylephrine Bitartrate Inhalation Aerosol; Isoproterenol Hydrochloride Inhalation Aerosol; Isoproterenol Hydrochloride Injection; Isoproterenol Hydrochloride Tablets; Isoproterenol Inhalation Solution; Isoproterenol Sulfate Inhalation Aerosol; Isoproterenol Sulfate Inhalation Solution.

Isosorbide *(BAN, USAN, rINN)* ⊗

AT-101; Isosorbida; Isosorbidum; NSC-40725; Изосорбид.

1,4:3,6-Dianhydro-D-glucitol.

$C_6H_{10}O_4$=146.1

CAS — 652-67-5.

UNII — WXR179L51S.

Pharmacopoeias. In *Jpn.*

US includes Isosorbide Concentrate.

USP 36: (Isosorbide Concentrate). An aqueous solution containing 70.0 to 80.0% w/w of isosorbide. A colourless to slightly yellow liquid. Soluble in water and in alcohol. Store in airtight containers. Protect from light.

Profile

Isosorbide is an osmotic diuretic with properties similar to those of mannitol (p. 1427.3). It is reported to cause less nausea and vomiting than other oral osmotic diuretics.

Isosorbide is used for short-term reduction of intraocular pressure in acute glaucoma or before surgery (p. 1999.1). The usual oral dose is 1 to 3 g/kg 2 to 4 times daily. Its action usually begins within 30 minutes and lasts for up to 5 or 6 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Ismotic†.

Pharmacopoeial Preparations

USP 36: Isosorbide Concentrate; Isosorbide Oral Solution.

Isosorbide Dinitrate *(BAN, USAN, rINN)*

Dinitrato de isosorbida; ISDN; Isosorbid dinitrát; Isosorbida, dinitrato de; Isosorbiddinitraat; Isosorbide, Dinitrate d'; Isosorbidi dinitras; Isosorbididinitraatti; Izosorbid Dinitrat; Izosorbido dinitratas; Izosorbidu diazotan; Izoszorbid-dinitrát; Sorbide Nitrate; Изосорбида Динитрат.

1,4:3,6-Dianhydro-D-glucitol 2,5-dinitrate.

$C_6H_8N_2O_8$=236.1

CAS — 87-33-2.

ATC — C01DA08; C05AE02.

ATC Vet — QC01DA08; QC05AE02.

UNII — IA7306519N.

Pharmacopoeias. In *Chin.* and *Jpn.*

Eur. (see p. vii), *Int.*, and *US* include diluted isosorbide dinitrate.

Ph. Eur. 8: (Isosorbide Dinitrate, Diluted). A dry mixture of isosorbide dinitrate and lactose monohydrate or mannitol. The solubility of the diluted product depends on the diluent and its concentration. Protect from light.

Undiluted isosorbide dinitrate is a fine, white or almost white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; very soluble in acetone.

USP 36: (Diluted Isosorbide Dinitrate). A dry mixture of isosorbide dinitrate (usually about 25%) with lactose, mannitol, or other suitable inert excipients, the latter being added to minimise the risk of explosion. It may contain up to 1% of a suitable stabiliser such as ammonium phosphate. It is an ivory-white, odourless powder. Store in airtight containers.

Undiluted isosorbide dinitrate occurs as white crystalline rosettes. Very slightly soluble in water; sparingly soluble in alcohol; very soluble in acetone; freely soluble in chloroform.

Handling. Undiluted isosorbide dinitrate may explode if subjected to percussion or excessive heat.

Stability. The loss of isosorbide dinitrate from solution during infusion was found to be 30% with PVC plastic intravenous infusion sets but negligible when polyolefin or glass delivery systems were used.[1] Another study reported a 23% decrease in isosorbide dinitrate concentration after 24 hours of storage at 21 degrees in PVC containers; most of the loss occurred in the first 6 hours. Loss of potency was not noted when isosorbide dinitrate was stored under similar conditions in glass bottles or polyethylene, nylon, and polypropylene laminated bags.[2]

1. Kowaiuk EA, *et al.* Drug loss in polyolefin infusion systems. *Am J Hosp Pharm* 1983; 40: 118–19.
2. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; 47: 369–73.

Uses and Administration

Isosorbide dinitrate is a vasodilator with general properties similar to those of glyceryl trinitrate (p. 1391.3). It is used in the management of angina pectoris (p. 1254.3) and of heart failure (below). It has also been investigated in myocardial infarction (p. 1257.1).

Isosorbide dinitrate may be given by the sublingual, oral, transdermal, or intravenous route.

In **angina** isosorbide dinitrate may be given as sublingual tablets or spray for the relief of an acute attack, although glyceryl trinitrate may be preferred because it has a faster onset of action. Isosorbide dinitrate may also be used before an activity or stress which might provoke an attack. The usual dose in acute angina is 2.5 to 10 mg sublingually. As an alternative, one to three sprays (1.25 mg/spray) may be directed under the tongue.

Isosorbide dinitrate is also used in the long-term management of angina in oral doses of 20 to 120 mg daily in divided doses according to the patient's needs. Increases in dosage should be gradual to avoid adverse effects. Up to 240 mg daily in divided doses may be necessary. Modified-release formulations may be used in equivalent doses. Transdermal preparations such as topical sprays or ointments may also be used.

Isosorbide dinitrate is given by intravenous infusion for unstable angina. The dose is titrated according to patient response; doses in the range of 2 to 12 mg/hour are usually suitable but up to 20 mg/hour may be necessary in some patients. Some plastics used in the infusion equipment may adsorb isosorbide dinitrate (see Stability, above) and allowance may have to be made for this.

During percutaneous transluminal coronary angioplasty isosorbide dinitrate may be given by the intracoronary route to allow prolonged balloon inflation and to prevent or relieve coronary spasm. Only injections of isosorbide dinitrate which are approved for intracoronary use should be given by this route as preparations intended for normal intravenous use may contain additives that are harmful if injected into diseased coronary vessels. The usual dose is 1 mg as a bolus before balloon inflation. The maximum recommended dose is 5 mg within a 30-minute time period.

Isosorbide dinitrate is also used in the management of **heart failure**. It is given in doses of 5 to 10 mg sublingually every 2 hours as required, or in oral doses of 60 to 160 mg daily in divided doses. Oral doses of up to 240 mg daily may be required. It may also be given intravenously using the intravenous doses given above for angina. An oral combination preparation with hydralazine is also available for use in self-identified black patients. It is given in a dose of 20 mg of isosorbide dinitrate with 37.5 mg of hydralazine hydrochloride three times daily; the dose may be doubled if necessary.

Heart failure. Although direct-acting vasodilators do not have a major role in the management of chronic heart failure (p. 1262.3) there is some evidence that use of hydralazine with isosorbide dinitrate may be of benefit,[1] although the effect on mortality is less than that seen with ACE inhibitors.[2] Subgroup analysis suggested that the effect might be greater in black patients, and a later study[3] in black patients found that addition of isosorbide dinitrate

and hydralazine to standard therapy improved both morbidity and mortality.

1. Cohn JN, *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986; 314: 1547–52.
2. Cohn JN, *et al.* A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991; 325: 303–10.
3. Taylor AL, *et al.* African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004; 351: 2049–57. Correction. *ibid.* 2005; 352: 1276.

Non-cardiovascular disorders. Nitrates such as isosorbide dinitrate have been tried in conditions including anal fissure, erectile dysfunction, obstetric and gynaecological disorders, oesophageal motility disorders such as achalasia and spasm, and pain. Further details of these uses are given under Glyceryl Trinitrate (p. 1392.2).

Adverse Effects, Treatment, and Precautions

As for Glyceryl Trinitrate, p. 1393.3.

Effects on the blood. Haemolysis occurred in 2 patients with G6PD deficiency during treatment with isosorbide dinitrate.[1]

1. Aderka D, *et al.* Isosorbide dinitrate-induced hemolysis in G6PD-deficient subjects. *Acta Haematol (Basel)* 1983; 69: 63–4.

Headache. The most common adverse effect of nitrate therapy is headache which usually decreases after a few days. There has been a report[1] of a severe continuous unilateral headache with an oculosympathetic paresis on the same side associated with isosorbide dinitrate therapy.

1. Mueller RA, Meienberg O. Hemicrania with oculosympathetic paresis from isosorbide dinitrate. *N Engl J Med* 1983; 308: 458–9.

Hypersensitivity. Laryngeal oedema developed on two occasions in a woman after the use of isosorbide dinitrate spray;[1] nifedipine was also given sublingually which on the second occasion caused a noticeable increase in the laryngeal swelling induced by the nitrate.

1. Silfvast T, *et al.* Laryngeal oedema after isosorbide dinitrate spray and sublingual nifedipine. *BMJ* 1995; 311: 232.

Nitrate tolerance. Continuous use of organic nitrates is associated with tolerance to their haemodynamic effects; for an overview of nitrate tolerance, see under Precautions for Glyceryl Trinitrate, p. 1394.1.

A study in 12 patients with chronic stable angina[1] showed that after treatment for one week with isosorbide dinitrate 30 mg two or three times daily, treadmill-walking time was longer throughout a 5-hour testing period compared with placebo. In contrast, after treatment for one week with isosorbide dinitrate 30 mg four times daily, treadmill-walking time was prolonged at 1 hour but not at 3 or 5 hours. These results support the concept that clinical efficacy of isosorbide dinitrate is maintained if given in a dose schedule which provides a nitrate-free or a low-nitrate period.

The effect of sublingual isosorbide dinitrate in patients receiving chronic therapy with isosorbide dinitrate was evaluated in 24 patients with angina.[2] Sublingual use produced less reduction of aortic systolic pressure and left ventricular end-diastolic pressure and less dilatation of coronary artery diameter in patients who received chronic isosorbide dinitrate therapy compared with patients not receiving chronic therapy.

1. Parker JO, *et al.* Effect of intervals between doses on the development of tolerance to isosorbide dinitrate. *N Engl J Med* 1987; 316: 1440–4.
2. Naito H, *et al.* Effects of sublingual nitrate in patients receiving sustained therapy of isosorbide dinitrate for coronary artery disease. *Am J Cardiol* 1989; 64: 565–68.

Oedema. Reports of ankle oedema associated with isosorbide dinitrate therapy in 3 patients with heart failure.[1]

1. Rodger JC. Peripheral oedema in patients treated with isosorbide dinitrate. *BMJ* 1981; 283: 1365–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies isosorbide dinitrate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Glyceryl Trinitrate, p. 1394.2.

Disopyramide. The efficacy of sublingual isosorbide dinitrate was reduced in a patient taking disopyramide.[1] The interaction was considered to be due to diminished salivary secretions caused by the antimuscarinic action of disopyramide, which inhibited the dissolution of the sublingual isosorbide dinitrate tablet.

1. Barletta MA, Eisen H. Isosorbide dinitrate-disopyramide phosphate interaction. *Drug Intell Clin Pharm* 1985; 19: 764.

Pharmacokinetics

Like glyceryl trinitrate, isosorbide dinitrate is readily absorbed from the oral mucosa. Isosorbide dinitrate is also readily absorbed when given orally but owing to extensive first-pass metabolism in the liver and pre-systemic clearance its bioavailability is reduced. Isosorbide dinitrate is also absorbed through the skin from an ointment basis.

After sublingual doses, anti-anginal effect is apparent within 2 to 5 minutes and persists for about 1 to 2 hours. After oral dosage with conventional tablets, anti-anginal activity is present in less than 1 hour and lasts for 4 to 6 hours.

Isosorbide dinitrate is widely distributed with a large apparent volume of distribution. It is taken up by smooth muscle cells of blood vessels and the nitrate group is cleaved to inorganic nitrite and then to nitric oxide. It is also rapidly metabolised in the liver to the major active metabolites isosorbide 2-mononitrate and isosorbide 5-mononitrate (see Isosorbide Mononitrate, below).

After sublingual doses, isosorbide dinitrate has a plasma half-life of 45 to 60 minutes. Plasma half-lives of 20 minutes and 4 hours have been reported after intravenous and oral dosage, respectively. During prolonged use, the half-life is increased due to accumulation of the isosorbide 5-mononitrate metabolite which reduces hepatic isosorbide dinitrate extraction. Both primary metabolites have longer half-lives than the parent compound.

References.
1. Abshagen U, *et al.* Pharmacokinetics and metabolism of isosorbide-dinitrate after intravenous and oral administration. *Eur J Clin Pharmacol* 1985; 27: 637–44.
2. Straehl P, Galeazzi RL. Isosorbide dinitrate bioavailability, kinetics, and metabolism. *Clin Pharmacol Ther* 1985; 38: 140–9.
3. Thadani U, Whitsett T. Relationship of pharmacokinetic and pharmacodynamic properties of the organic nitrates. *Clin Pharmacokinet* 1988; 15: 32–43.
4. Schneider W, *et al.* Concentrations of isosorbide dinitrate, isosorbide-2-mononitrate and isosorbide-5-mononitrate in human vascular and muscle tissue under steady-state conditions. *Eur J Clin Pharmacol* 1990; 38: 145–7.
5. Vogt D, *et al.* Pharmacokinetics and haemodynamic effects of ISDN following different dosage forms and routes of administration. *Eur J Clin Pharmacol* 1994; 46: 319–24.
6. Bergami A, *et al.* Pharmacokinetics of isosorbide dinitrate in healthy volunteers after 24-hour intravenous infusion. *J Clin Pharmacol* 1997; 37: 828–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cortespasmo†; Isoket; Isordil; Medocor; *Austral.*: Isordil; Sorbidin; *Austria*: Cedocard†; Iso Mack†; Isoket; *Belg.*: Cedocard; *Braz.*: Angil; Isordil; *Canad.*: Apo-ISDN; Cedocard†; Novo-Sorbide†; *China*: Ai Bei (爱倍); An Nuo Xin Mei (安诺欣美); Angiolong (安其伦); Di Xin Ni (狄欣尼); Er Fu Xin (尔复新); Hao Xin (好欣); Iso Mack (易顺脉); Isoket (异舒吉); Kai Wei Xin (凯慰欣); Ling Xin (灵欣); Pei Xin (培欣); Pu Xin Qing (普辛清); Rui Li Xi (瑞立喜); Wei Xin Ping (卫昕平); Xin He Ping (欣荷平); Xin Shu (欣舒); Yan De (燕德); Yi Shu Da (易舒达); Zhong Sheng Rui Xing (众生瑞欣); *Cz.*: Cardiket; Dinisan†; Iso Mack†; Isoket; Isopelet; *Denm.*: Cardopax; *Fin.*: Dinit; Nitrosid; *Fr.*: Isocard; Langoran; Risordan; *Ger.*: Diconpin†; Iso-Puren†; Isoket; Jenacard; Nitrosorbon†; *Gr.*: Isotrate; Orbipront; Pensordil; Risordan; *Hong Kong*: Apo-ISDN; Isoket; Isorem; Sorbidin†; *India*: Anzidin; Cardicap; Isordil; Sorbitrate; *Indon.*: Cedocard; Farsorbid; Hapisor†; Isoket†; Isorbid; Isordil†; Sorbidin†; Vascardin; *Irl.*: Isoket; *Israel*: Cordil†; Isoket; Isolong†; *Ital.*: Carvasin; Diniket; Nitrosorbide; *Jpn*: Antup; Isobide; Nitoroi; *Malaysia*: Angsobide; Isoket; *Mex.*: Biderit†; Biordyn; Debisor; Insucar; Isoket; Isorbid; Zanisor; *Neth.*: Cedocard; Isordil; *Norw.*: Sorbangil; *Philipp.*: Bideren; Flasorbid; Isobar; Isobenil; Isoket; Isordil; Nitrosorbon; Novisor†; *Pol.*: Aerosonit; Cardonit†; Isoket†; Sorbonit; *Port.*: Flindix; Isoket; *Rus.*: Dinisorb (Динисорб); Isoket (Изокет); Isolong (Изолонг); Kardiket (Кардикет); *S.Afr.*: Angi-Spray†; Dinospray; Isoket; Isordil; *Singapore*: Angsobide; Apo-ISDN; Isoket†; *Spain*: Iso; *Swed.*: Sorbangil; *Switz.*: Iso Mack†; Isoket; Sorbidilat; *Thai.*: Angitrit†; Corodil; Hartsorb; Isobide; Isobinate; Isoket; Isordil†; Isorem; Isotrate; Sorbidin†; Sornil; *Turk.*: Cardioket; Isordil; Nitrofix; *UK*: Angitak; Cedocard†; Isoket; *Ukr.*: Cardiket (Кардикет); Dicor (Дикор); Isodinitrat (Изодинитрат)†; Isoket (Изокет); *USA*: Dilatrate; Isochron†; Isordil; *Venez.*: Isoket; Isomack.

Multi-ingredient Preparations. *USA*: BiDil.

Pharmacopoeial Preparations

BP 2014: Isosorbide Dinitrate Injection; Isosorbide Dinitrate Sublingual Tablets; Isosorbide Dinitrate Tablets;

USP 36: Isosorbide Dinitrate Chewable Tablets; Isosorbide Dinitrate Extended-release Capsules; Isosorbide Dinitrate Extended-release Tablets; Isosorbide Dinitrate Sublingual Tablets; Isosorbide Dinitrate Tablets.

Isosorbide Mononitrate

(BAN, USAN, rINN)

AHR-4698; BM-22145; IS-5-MN; Isosorbid mononitrát; Isosorbida, mononitrato de; Isosorbide, Mononitrate d'; Isosorbide-5-mononitrate; Isosorbidi Mononitras; Izosorbid Mononitrat; Izosorbide mononitratas; Izosorbid-mononitrát; Mononitrato de Isosorbida; Изосорбида Мононитрат.

1,4:3,6-Dianhydro-D-glucitol 5-nitrate.

$C_6H_9NO_6$=191.1.

CAS — 16051-77-7.

ATC — C01DA14.

ATC Vet — QC01DA14.

UNII — LX1OH63030.

Pharmacopoeias. *Eur.* (see p. vii) and *US* include diluted isosorbide mononitrate.

Ph. Eur. 8: (Isosorbide Mononitrate, Diluted). A dry mixture of isosorbide mononitrate and lactose monohydrate or mannitol. The solubility of the diluted product depends on the diluent and its concentration. Protect from light.

Undiluted isosorbide mononitrate is a white or almost white, crystalline powder. Freely soluble in water, in alcohol, in acetone, and in dichloromethane.

USP 36: (Diluted Isosorbide Mononitrate). A dry mixture of isosorbide mononitrate with lactose or other suitable excipients to permit safe handling. Store in airtight containers between 20 degrees and 30 degrees.

Uses and Administration

Isosorbide mononitrate is an active metabolite of the vasodilator isosorbide dinitrate and is used in the long-term management of angina pectoris (p. 1254.3) and heart failure (p. 1262.3). It has also been investigated in myocardial infarction (below).

The usual oral dose is 20 mg two or three times daily, although doses ranging from 20 to 120 mg daily have been given. Modified-release oral preparations have been developed for use in angina.

Myocardial infarction. Long-term management of myocardial infarction (p. 1257.1) can involve many drug therapies and some patients, for example those with myocardial ischaemia or poor left ventricular function, may require the long-term use of nitrates, although recent studies have thrown doubt on their routine use. In the GISSI-3 study[1] there was no significant benefit from the use of transdermal glyceryl trinitrate when assessed 6 weeks post-infarction and in the ISIS-4 study[2] oral isosorbide mononitrate apparently had no effect on 35-day mortality.

1. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994; 343: 1115–22.
2. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995; 345: 669–85.

Osteoporosis. Isosorbide mononitrate has been tried[1] in the management of osteoporosis (for more conventional management see p. 1168.1). Oral treatment with isosorbide mononitrate 20 mg daily was reported to produce comparable improvement in bone mineral density to alendronate 70 mg weekly in a study involving 60 postmenopausal women with osteoporosis but no history of fractures.

1. Nabhan AF, Rabie NH. Isosorbide mononitrate versus alendronate for postmenopausal osteoporosis. *Int J Gynaecol Obstet* 2008; 103: 213–16.

Termination of pregnancy. For mention of the use of isosorbide mononitrate to ripen the cervix before termination of pregnancy, see Obstetrics and Gynaecology, under Glyceryl Trinitrate, p. 1393.1.

Variceal haemorrhage. For reference to the use of isosorbide mononitrate in the management of variceal haemorrhage, see under Glyceryl Trinitrate, p. 1393.3.

Adverse Effects, Treatment, and Precautions

As for Glyceryl Trinitrate, p. 1393.3.

Myalgia has been reported very rarely.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies isosorbide mononitrate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Glyceryl Trinitrate, p. 1394.2.

Pharmacokinetics

Isosorbide mononitrate is readily absorbed from the gastrointestinal tract. After oral doses of conventional tablets, peak plasma concentrations occur in 30 minutes to 1 hour; onset of action occurs within 20 minutes and lasts for about 8 to 10 hours. Unlike isosorbide dinitrate, isosorbide mononitrate does not undergo first-pass hepatic metabolism and bioavailability is nearly 100%. Isosorbide mononitrate is widely distributed with a large apparent volume of distribution. It is taken up by smooth muscle cells of blood vessels and the nitrate group is cleaved to inorganic nitrite and then to nitric oxide. Isosorbide mononitrate is metabolised to inactive metabolites, including isosorbide and isosorbide glucuronide. Only about 2% of isosorbide mononitrate is excreted unchanged in the urine. An elimination half-life of about 4 to 5 hours has been reported.

References.

1. Taylor T, *et al.* Isosorbide 5-mononitrate pharmacokinetics in humans. *Biopharm Drug Dispos* 1981; 2: 255–63.
2. Thadani U, Whitsett T. Relationship of pharmacokinetic and pharmacodynamic properties of the organic nitrates. *Clin Pharmacokinet* 1988; 15: 32–43.
3. McClennen W, *et al.* The plasma concentrations of isosorbide 5-mononitrate (5-ISMN) administered in an extended-release form to patients with acute myocardial infarction. *Br J Clin Pharmacol* 1995; 39: 704–8.
4. Hutt V, *et al.* Evaluation of the pharmacokinetics and absolute bioavailability of three isosorbide-5-mononitrate preparations in healthy volunteers. *Arzneimittelforschung* 1995; 45: 142–5.
5. Baxter T, Eadie CJ. Twenty-four hour plasma profile of sustained-release isosorbide mononitrate in healthy volunteers and in patients with chronic stable angina: two open label trials. *Br J Clin Pharmacol* 1997; 43: 333–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cilatron; Medocor; Monoket; Monotrin; *Austral.*: Arsorb†; Duride; Imdur; Imtrate; Isomonit; Monodur; *Austria*: Elantan†; Isomonat; Mono Mack; Monoket; Myocardon mono†; Olicardin; *Braz.*: Cincordil; Coronar; Monocordil; Vexell; *Canad.*: Apo-ISMN; Imdur; PMS-ISMN; *Chile*: Ismo; Monopack; *China*: Ai Mai Shu (艾麦舒); Ai Si Mo (艾司莫); Ai Tong (艾同); Ai Xin (艾欣); Ai Xin Mo Er (爱欣莫尔); An Lan Shu (安兰舒); Ao Di Ya (奥帝亚); Da Fen Shu Ji (达芬舒吉); Danlixin (丹力欣); Danzuo (丹佐); De Rui Ning (德瑞宁); Di Su Ni (狄苏尼); Efforeen (艾复吟); Elantan (异乐定); Etimonis (艾狄莫尼); Fei Ke Xin Kang (菲克芯康); Feng Nuo (丰诺); Pu Shun (孚顺); Pu Xin Tian (富欣恬); Gefenda (格芬达); Huaren XinShu (华仁欣舒); Imdur (依姆多); Isomonit (索尼特); Jin Xin Tai (晋新泰); Kaiweifu (开韦夫); Ke Er Le (科尔乐); Li Wei (力唯); Li Xin Tong (理新彤); Mono Mack (安辛迈); Monotrate (莫诺确特); Nuo Ke Da (诺可达); Pentacard (盘得高); Ping Fu (平福); Qi Hao (奇豪); Qian Xin (千新); Ruideming (瑞德明); Sai Da Lin (赛达林); Shan Su (山苏); Shu Bi Lai Te (舒必莱特); Shu Tan (舒坦); Shu Ya (舒亚); Xin Ao Le (欣奥乐); Xin Kang (欣康); Xin Tai (欣泰); Xinle (欣乐); Ya Xu (亚旭); Yan Nuo Xin (延诺信); Yi Mai Qing (伊迈清); Yi Xin Jian (易欣建); Yisuoman (伊索曼); Zai Sheng (再晟); Zaijia (再佳); *Cz.*: Conpin†; Ismin†; Mono Mack; Monosan; Monosor; Monotab; Olicard; Sorbimon; *Denm.*: Fem-Mono; Imdur; Isodur; *Fin.*: Imdur; Isangina; Ismexin; Ismox; Isosor†; Ormox; *Fr.*: Monicor; *Ger.*: Coleb†; Conpin†; Corangin†; Elantan†; IS 5 Mono; Ismanton†; Ismo; Isomonit†; Moni-Sanorania†; Monit-Puren†; mono corax†; Mono Mack; Monobeta†; Monoclair; Monolong†; Mononitrat†; Monopur†; Nitrolingual protect†; Olicard†; Turimonit†; *Gr.*: Angioval; Dilavenil; G-Dil; Imdur; Isomon; Monoginal; Monoket; Monorythm; Monosordil; Nitramin; Nitrilan; Procardol; *Hong Kong*: Apo-ISMN; Duride†; Elantan; Imdex; Imdur; Monocinque; *Hung.*: Cardisorb†; Isospan; Mono Mack; Olicard; Rangin; *India*: 5-Mono; Angicor; Anginex; Angitab; Diltrate; IHD; Imdur; Imnit; Ismo; Isocor; Isomin; Isonorm; Isotop; Monet; Monicor; Monit; Monn; Monocontin; Monomen; Monopark; Monosorbitrate; Monotrace; Monotrate; Nican; Nitrofix; Nitrovas; *Indon.*: Cardismo; Imdur; Isomonit; Monecto; Pentacard†; *Iri.*: Cardox; Elantan; Imdur; Isomel; Isomonit; Sormon; *Israel*: Monocord; Monolong; Mononit; *Ital.*: Duronitrin; Elan; Ismo; Leicester; Monocinque; Monoket; Vasdilat; *Malaysia*: Duride†; Elantan; Imdex; Imdur; Ismo; *Mex.*: Elantan; Imdur; Kenbrid; Monocorat; *Neth.*: Mono-Cedocard; Promocard; *Norw.*: Imdur; Ismo; Monoket; *NZ*: Corangin; Duride; Imtrate; Ismo; *Philipp.*: Angistad; Elantan; Imdur; Isomonit; Isonate; Monosorb; Vasotrate; *Pol.*: Effox; Isomonit†; Isosor; Izonit†; Mono Mack; Mono Tad; Monocard†; Mononit; Monosan; Olicard; *Port.*: Imdur; Ismo; Monoket; Monopront; Orasorbil; *Rus.*: Effox (Эфокс); Monisol (Монизол); Mono Mack (Моно Мак); Mono Rom (Моно Ром); Monocinque (Моночинкве); Monolong (Монолонг); Monosan (Моносан); Olicard (Оликард); Pektrol (Пектрол); *S.Afr.*: Angitrate†; Elantan; Imdur; Ismo; Monicor; *Singapore*: Elantan†; Imdex; Imdur; Ismo; Vasotrate; *Spain*: Cardionil; Coronur; Dolak; Pertil†; Uniket; *Swed.*: Imdur; Ismo; Isodur†; Monoket; *Switz.*: Corangine; *Thai.*: Elantan†; Imdex; Imdur; Ismo; Isopen; Monolin; Monosorb; Monotrate; Solotrate; Sorbinate; *Turk.*: Isorat; Monodur; Monoket; Monolong; *UK*: Angeze; Chemydur; Cibral; Dynamin; Elantan; Imdur; Isib; Ismo; Isodur; Isotard; Modisal; Monigen; Monomax; Monomil; Monosorb; Trangina; Xismox; Zemon; *Ukr.*: Efox Long (Эфокс Лонг); Mononitrosid (Мононитросид); Monosan (Моносан); Olicard (Оликард); *USA*: Imdur; Ismo; Monoket; *Venez.*: Elantan; Ismo; Mono Mack.

Multi-ingredient Preparations. *Braz.*: Vasclin; *China*: Jia Yi Ke (佳伊可); Li Li Kai (利力凯); Mei Lan Te (美兰特); Si Yue (司悦); Zi Lin (滋霖); *India*: Aspitrate; Ecosmin; Ismorin; Isoact; Monit-AS; Mono-A; Monosprin; Nitren; Nitrofix-AS; Nitroprin; Solosprin.

Pharmacopoeial Preparations

BP 2014: Isosorbide Mononitrate Tablets; Prolonged-release Isosorbide Mononitrate Capsules; Prolonged-release Isosorbide Mononitrate Tablets;

USP 36: Isosorbide Mononitrate Extended-Release Tablets; Isosorbide Mononitrate Tablets.

Isradipine *(BAN, USAN, rINN)*

Isradipilini; Isradipin; Isradipinas; Isradipino; Isradipinum; Izradypina; PN-200-110; Isradipin; Израдипин.

Isopropyl methyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate.

$C_{19}H_{21}N_3O_5$=371.4

CAS — 75695-93-1.

ATC — C08CA03.

ATC Vet — QC08CA03.

UNII — YO1UK1S598.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Isradipine). A yellow crystalline powder. Practically insoluble in water; freely soluble in acetone; soluble in methyl alcohol. Protect from light.

USP 36: (Isradipine). A yellow fine crystalline powder. Protect from light.

Stability. An oral preparation of isradipine 1 mg/mL, prepared using the powder from capsules of isradipine suspended in syrup,[1] was stable when stored at 4 degrees for up to 35 days after preparation.

1. MacDonald JL, *et al.* Stability of isradipine in an extemporaneously compounded oral liquid. *Am J Hosp Pharm* 1994; 51: 2409–11.

Uses and Administration

Isradipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p. 1447.2). It is used in the treatment of hypertension (p. 1251.1).

The usual initial oral dose of isradipine is 2.5 mg twice daily increased if necessary after 3 to 4 weeks to 5 mg twice daily. Some patients may require 10 mg twice daily. In elderly patients an initial dose of 1.25 mg twice daily may be preferable; a maintenance dose of 2.5 or 5 mg once daily may sometimes be sufficient. A reduced dose should also be used in patients with hepatic or renal impairment (see below).

The dose of isradipine should be reduced in patients who are also taking cimetidine (see Interactions, below).

For doses in children, see below.

A modified-release preparation allowing once-daily dosing is available in some countries.

Reviews.

1. Fitton A, Benfield P. Isradipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cardiovascular disease. *Drugs* 1990; 40: 31–74.
2. Walton T, Symes LR. Felodipine and isradipine: new calcium-channel blocking agents for the treatment of hypertension. *Clin Pharm* 1993; 12: 261–75.
3. Brogden RN, Sorkin EM. Isradipine: an update of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the treatment of mild to moderate hypertension. *Drugs* 1995; 49: 618–49.

Administration in children. Retrospective studies in limited numbers of patients have reported on the use of isradipine alone or as an adjunct in the treatment of hypertension in children. In 12 patients aged from 10 days to 11 years an initial oral dose of 100 micrograms/kg was increased as necessary by 50 to 100 micrograms/kg every 3 to 6 doses, doses being given at an interval of 6 or 8 hours.[1] The dose range needed to control blood pressure was from 300 to 1200 micrograms/kg per day. Similarly, a study[2] in 72 children aged from 1 week to 16 years reported initial oral doses of 50 to 100 micrograms/kg given every 8 hours, or every 6 hours if necessary. The dose range needed to control blood pressure was from 70 to 900 micrograms/kg per day, which appeared significantly higher than doses usually given to adults.

To prevent steep drops in blood pressure, some[3] have suggested that children aged under 2 years should be given initial doses of no more than 50 micrograms/kg.

1. Strauser LM, *et al.* Initial experience with isradipine for the treatment of hypertension in children. *South Med J* 2000; 93: 287–93.
2. Flynn JT, Warnick SJ. Isradipine treatment of hypertension in children: a single-center experience. *Pediatr Nephrol* 2002; 17: 748–53.
3. Miyashita Y, *et al.* Isradipine for treatment of acute hypertension in hospitalized children and adolescents. *J Clin Hypertens (Greenwich)* 2010; 12: 850–5.

Administration in hepatic or renal impairment. In patients with hepatic or renal impairment UK licensed product information recommends an initial dose of isradipine of 1.25 mg twice daily. The dose may be increased as required, but a maintenance dose of 2.5 or 5 mg once daily may be sufficient in some patients.

Neurological disorders. Although preclinical data had suggested that isradipine might be of benefit in **cocaine dependence** by antagonising the abuse potential of the drug, a small double-blind crossover study in 12 cocaine-dependent subjects indicated that it enhanced, rather than antagonised, the subjective effects of cocaine.[1]

As with related dihydropyridines (see under Nifedipine, p. 1449.2) there has been some interest in the potential neuroprotective effect of isradipine in patients with **parkinsonism**, and the tolerability of the drug has been investigated in patients with early Parkinson's disease.[2] Studies in *animals* have also suggested potential benefit in the management of **Alzheimer's disease.**[3]

1. Roache JD, *et al.* Effects of repeated-dose isradipine on the abuse liability of cocaine. *Exp Clin Psychopharmacol* 2005; 13: 319–26.
2. Simuni T, *et al.* Tolerability of isradipine in early Parkinson's disease: a pilot dose escalation study. *Mov Disord* 2010; 25: 2863–6.
3. Anekonda TS, *et al.* L-type voltage-gated calcium channel blockade with isradipine as a therapeutic strategy for Alzheimer's disease. *Neurobiol Dis* 2011; 41: 62–70.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2).

Incidence of adverse effects. Multicentre studies[1,2] have reported adverse effects in about half of all patients taking isradipine, the commonest being flushing, palpitations, dizziness, oedema, fatigue, headache, and pruritus. The incidence of adverse effects has been reported to be higher than with a thiazide[1] and similar to that with an ACE inhibitor.[2] However, in another study,[3] spontaneously reported adverse effects occurred less frequently in patients taking isradipine (18.4% of 103 patients) than in those taking amlodipine (33.3% of 102 patients). In particular, ankle oedema was less frequent, severe, and prolonged with isradipine than with amlodipine.

1. Carlsen JE, Kober L. Blood pressure lowering effect and adverse events during treatment of arterial hypertension with isradipine and hydrochlorothiazide. *Drug Invest* 1990; 2: 10–16.
2. Johnson BF, *et al.* A multicenter comparison of adverse reaction profiles of isradipine and enalapril at equipotent doses in patients with essential hypertension. *J Clin Pharmacol* 1995; 35: 484–92.
3. Hermans L, *et al.* At equipotent doses, isradipine is better tolerated than amlodipine in patients with mild-to-moderate hypertension: a double-blind, randomized, parallel-group study. *Br J Clin Pharmacol* 1994; 38: 335–40.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies isradipine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Cimetidine increases the bioavailability of isradipine and the dose of isradipine should be reduced by 50% in patients receiving both drugs.

Pharmacokinetics

Isradipine is almost completely absorbed from the gastrointestinal tract after oral doses but undergoes extensive first-pass metabolism; the bioavailability is reported to be 15 to 24%. Peak plasma concentrations occur about 2 hours after oral dosage. It is about 95% bound to plasma proteins. Isradipine is extensively metabolised in the liver, at least partly by the cytochrome P450 isoenzyme CYP3A4. About 70% of an oral dose is reported to be excreted as metabolites in urine, the remainder in faeces. The terminal elimination half-life is often stated to be about 8 hours although a value of less than 4 hours has also been reported.

In single-dose and steady-state pharmacokinetic studies of isradipine in 9 hypertensive subjects using a specific HPLC assay, isradipine was rapidly absorbed with peak concentrations occurring 1.2 (steady state) to 1.5 (single dose) hours after dosing.[1] The mean terminal elimination half-life at steady state was 3.8 hours, suggesting that duration of action is likely to be short and that isradipine would need to be given at least twice daily. There was considerable interindividual variation in the pharmacokinetics. In an earlier study[2] in healthy subjects the effective half-life of isradipine was calculated to be 8.8 hours, but

radiolabelled isradipine was used and the assay method might have been less specific for unchanged drug.

1. Shenfield GM, *et al.* The pharmacokinetics of isradipine in hypertensive subjects. *Eur J Clin Pharmacol* 1990; 38: 209–11.
2. Tse FLS, Jaffe JM. Pharmacokinetics of PN 200-110 (isradipine), a new calcium antagonist, after oral administration in man. *Eur J Clin Pharmacol* 1987; 32: 361–5.

Hepatic impairment. Systemic availability after a radiolabelled oral dose of isradipine 5 mg was no different at 15.6% in 7 patients with non-cirrhotic chronic liver disease from the value of 16.5% in 8 healthy subjects.[1] However, in 8 patients with cirrhosis of the liver availability was markedly increased to a mean of 36.9%; this was associated with decreased clearance (1.6 litres/minute, compared with 9.9 in controls). Terminal half-life, as measured after intravenous dosage, was greater at 11.9 hours in cirrhotic patients than the 5.1 hours seen in controls.

Reduced doses in patients with hepatic impairment have been recommended—see Administration in Hepatic or Renal Impairment under Uses and Administration, p. 1414.3.

1. Cotting J, *et al.* Pharmacokinetics of isradipine in patients with chronic liver disease. *Eur J Clin Pharmacol* 1990; 38: 599–603.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Lomir; ***Belg.***: Lomir; ***Braz.***: Lomir; ***Cz.***: Lomir; ***Denm.***: Lomir; ***Fin.***: Lomir; ***Fr.***: Icaz; ***Ger.***: Lomir†; Vascal; ***Gr.***: Lomir; ***Hong Kong***: Dynacirc; ***Hung.***: Lomir; ***Ital.***: Clivoten; Esradin; Lomir; ***Malaysia***: Dynacirc; ***Mex.***: Dynacirc; ***Neth.***: Lomir; ***Norw.***: Lomir; ***NZ***: Dynacirc; ***Philipp.***: Icaz; ***Pol.***: Lomir; ***Port.***: Dilatol; Lomir; ***Rus.***: Lomir (Ломир); ***S.Afr.***: Dynacirc; ***Singapore***: Dynacirc; ***Spain***: Lomir†; ***Swed.***: Lomir; ***Switz.***: Lomir; ***Thai.***: Dynacirc†; ***Turk.***: Dynacirc; ***UK***: Prescal†; ***USA***: Dynacirc.

Pharmacopoeial Preparations
BP 2014: Isradipine Tablets;
USP 36: Isradipine Capsules; Isradipine Oral Suspension.

Ivabradine *(BAN, rINN)*

Ivabradina; Ivabradinum; S-16257; Ивабрадин.
3-[3-({[(7*S*)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}methylamino)propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-2*H*-3-benzazepin-2-one.
$C_{27}H_{36}N_2O_5$=468.6
CAS — 155974-00-8.
ATC — C01EB17.
ATC Vet — QC01EB17.
UNII — 3H48L0LPZQ.

Ivabradine Hydrochloride *(BANM, rINNM)*

Ivabradina, hidrocloruro de; Ivabradine, Chlorhydrate de; Ivabradinum Hydrochloridum; S-16257-2; Ивабрадина Гидрохлорид.
$C_{27}H_{36}N_2O_5$,HCl=505.1
CAS — 148849-67-6.
ATC — C01EB17.
ATC Vet — QC01EB17.
UNII — TP19837BZK.

Uses and Administration

Ivabradine is a selective sinus node I_f inhibitor that lowers the heart rate. It is used in the treatment of stable angina pectoris (p. 1254.3) in patients unable to take beta blockers, or it is added to beta blockers when angina is not adequately controlled and the patient has a heart rate of more than 60 beats/minute. Ivabradine is also used in chronic heart failure (p. 1262.3) in patients whose heart rate is 75 beats/minute or more; it may be added to standard therapy including beta blockers, or given when beta blockers cannot be used. It is given as the hydrochloride, but doses are expressed in terms of the base; 5.4 mg of ivabradine hydrochloride is equivalent to about 5 mg of ivabradine. It is given orally with food in a usual initial dose of 5 mg twice daily. In stable angina pectoris the dose may be increased after 3 to 4 weeks if necessary to 7.5 mg twice daily. In patients with heart failure the dose may be adjusted after 2 weeks, and increased to 7.5 mg twice daily if the heart rate is persistently above 60 beats/minute. If the heart rate falls persistently below 50 beats/minute in patients with either indication, or there are symptoms of bradycardia, the dose should be titrated downwards to as low as 2.5 mg twice daily if necessary. Treatment should be stopped if this low heart rate or symptoms of bradycardia persist.

In the elderly (75 years or above), a lower initial dose of 2.5 mg twice daily should be considered, before increasing if necessary.

References.
1. DiFrancesco D, Camm JA. Heart rate lowering by specific and selective I_f current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease. *Drugs* 2004; 64: 1757–65.
2. Sulfi S, Timmis AD. Ivabradine—the first selective sinus node I_f channel inhibitor in the treatment of stable angina. *Int J Clin Pract* 2006; 60: 222–8.
3. Menown IBA. Ivabradine: a new strategy for management of stable angina. *Br J Hosp Med* 2007; 68: 321–5.
4. Böhm M, Reil J-C. Perspectives of I_f inhibition by ivabradine in cardiology. *Drugs* 2007; 67 (suppl 2): 43–9.
5. Fox K, *et al.* BEAUTIFUL Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; 372: 807–16.
6. Tardif JC, *et al.* ASSOCIATE Study Investigators. Efficacy of the I_f current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. *Eur Heart J* 2009; 30: 540–8.
7. Rakovec P. Treatment of inappropriate sinus tachycardia with ivabradine. *Wien Klin Wochenschr* 2009; 121: 715–8.
8. Köster R, *et al.* REDUCTION Study Group. Treatment of stable angina pectoris by ivabradine in every day practice: the REDUCTION study. *Am Heart J* 2009; 158: e51–e57.
9. Borer JS, Tardif JC. Efficacy of ivabradine, a selective I(f) inhibitor, in patients with chronic stable angina pectoris and diabetes mellitus. *Am J Cardiol* 2010; 105: 29–35.
10. Swedberg K, *et al.* SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010; 376: 875–85. Correction. *Ibid.*; 1988.

Adverse Effects

The most common adverse effects seen with ivabradine are luminous phenomena in the visual field (phosphenes). They generally begin within the first 2 months of treatment and may occur repeatedly, although they will resolve during therapy in most patients. Bradycardia is another common effect of ivabradine, and signs and symptoms such as dizziness, syncope, hypotension, asthenia, and fatigue may be related. Other adverse effects include blurred vision, other cardiac arrhythmias, nausea, constipation, diarrhoea, headache, dyspnoea, muscle cramps, skin reactions, and cases of angioedema. Hyperuricaemia, eosinophilia, and elevated blood-creatinine concentrations have been reported.

Reviews.
1. Savelieva I, Camm AJ. I_f inhibition with ivabradine: electrophysiological effects and safety. *Drug Safety* 2008; 31: 95–107.

Precautions

Ivabradine should not be started in patients with resting heart rate below 60 beats/minute, or in patients with cardiogenic shock, severe conduction defects, acute myocardial infarction, or unstable angina. Heart failure should be stable before ivabradine is started; it should be used with caution in severe heart failure. Ivabradine should not be used in patients with congenital QT prolongation. Ivabradine is not recommended in atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function, and regular monitoring for such arrhythmias should be performed. If resting heart rate falls below 50 beats/minute the dose should be reduced; treatment should be stopped if this rate persists.

Ivabradine is contra-indicated in severe hypotension and severe hepatic impairment, and should be used with caution in severe renal impairment (creatinine clearance of less than 15 mL/minute).

If unexpected deterioration in visual function occurs, stopping treatment may be considered. Caution is advisable in patients with retinitis pigmentosa.

Studies in *animals* have shown that ivabradine is embryotoxic and teratogenic, and is distributed into breast milk.

Interactions

Ivabradine should not generally be used with drugs that prolong the QT interval.

Ivabradine is metabolised by the cytochrome P450 isoenzyme CYP3A4, and should not be used with potent inhibitors of this enzyme, including azole antifungals such as ketoconazole and itraconazole, macrolide antibacterials such as clarithromycin, HIV-protease inhibitors such as nelfinavir and ritonavir, and nefazodone. Use with the moderate CYP3A4 inhibitors diltiazem and verapamil is also not recommended as the increase in exposure to ivabradine may cause an additional reduction in heart rate. Ivabradine may be used cautiously with other moderate inhibitors, such as fluconazole, at a lower starting dose of 2.5 mg orally twice daily, with monitoring of the heart rate. Consumption of grapefruit juice should be restricted.

Use with CYP3A4 inducers, such as rifampicin and phenytoin, may require an increase in the dose of ivabradine. St John's wort reduces the exposure to ivabradine by half and its use should be restricted.

Pharmacokinetics

Ivabradine is almost completely absorbed after oral doses but bioavailability is about 40% because of first-pass metabolism. Peak plasma concentrations occur after about 1 hour in the fasting state but this is delayed by 1 hour by food and the extent of absorption increased by 20 to 30%. Ivabradine is about 70% bound to plasma proteins.

Ivabradine undergoes extensive metabolism in the liver and gut via the cytochrome P450 isoenzyme CYP3A4 to its main active metabolite *N*-desmethyl-ivabradine (S-18982). This is further metabolised to some degree by CYP3A4. Ivabradine has a plasma elimination half-life of 2 hours and an effective half-life of 11 hours. Its metabolites are excreted to a similar extent in the urine and faeces. About 4% of a dose appears in the urine as the parent drug. *Animal* studies indicate that ivabradine is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Procoralan; ***Austral.***: Coralan; ***Austria***: Procoralan; ***Belg.***: Procoralan; ***Braz.***: Procoralan; ***Cz.***: Corlentor; Procoralan; ***Denm.***: Procoralan; ***Fr.***: Procoralan; ***Ger.***: Procoralan; ***Gr.***: Procoralan; ***Hong Kong***: Coralan; ***Hung.***: Procoralan; ***India***: Bradia; Ivabid; Ivabrad; Ivazine; ***Indon.***: Coralan; ***Irl.***: Corlentor; Procoralan; ***Israel***: Coralan; ***Ital.***: Corlentor; Procoralan; ***Malaysia***: Coralan; ***Neth.***: Corlentor; Procoralan; ***Philipp.***: Coralan; ***Pol.***: Corlentor; Procoralan; ***Port.***: Corlentor; Procoralan; ***Rus.***: Coraxan (Кораксан); ***S.Afr.***: Coralan; ***Singapore***: Coralan; ***Spain***: Corlentor; Procoralan; ***Swed.***: Procoralan; ***Switz.***: Procoralan; ***Thai.***: Coralan; ***Turk.***: Coralan; ***UK***: Procoralan; ***Ukr.***: Coraxan (Кораксан).

Ketanserin *(BAN, USAN, rINN)*

Ketanserilini; Ketanserina; Kétansérine; Ketanserinum; R-41468; Кетансерин.
3-[2-[4-(4-Fluorobenzoyl)piperidino]ethyl]quinazoline-2,4(1*H*,3*H*)-dione.
$C_{22}H_{22}FN_3O_3$=395.4
CAS — 74050-98-9.
ATC — C02KD01.
ATC Vet — QC02KD01; QD03AX90.
UNII — 97F9DE4CT4.

Ketanserin Tartrate *(BANM, rINNM)*

Ketanserina, tartrato de; Kétansérine, Tartrate de; Ketanserini Tartras; R-49945; Tartrato de ketanserina; Кетансерина Тартрат.
$C_{22}H_{22}FN_3O_3C_4H_6O_6$=545.5
CAS — 83846-83-7.
ATC — C02KD01.
ATC Vet — QC02KD01.
UNII — 645498QK7H.

Uses and Administration

Ketanserin is a serotonin antagonist with a high affinity for peripheral 5-HT^{2A} receptors and thus inhibits serotonin-induced vasoconstriction, bronchoconstriction, and platelet aggregation. It is also a less potent antagonist at 5-HT_{2C}, alpha$_1$, and histamine H_1 receptors, but the clinical significance of this is unclear. Ketanserin has no significant effect on 5-HT_1, 5-HT_3, or 5-HT_4 receptors.

Ketanserin is mainly used in the management of hypertension (p. 1251.1).

Ketanserin is given as the tartrate, but doses are usually expressed in terms of the base. Ketanserin tartrate 27.6 mg is equivalent to about 20 mg of ketanserin.

Ketanserin produces a gradual hypotensive effect when given orally, and 2 or 3 months of therapy may be required to produce the maximum reduction in blood pressure. After intravenous injection a fall in blood pressure is generally produced in 1 or 2 minutes and lasts for 30 to 60 minutes.

In **hypertension** the usual initial oral dose is 20 mg twice daily, increasing, if necessary, after 4 weeks, to 40 mg twice daily. It has also been given by intravenous or intramuscular injection. The dose of ketanserin may need to be reduced, or the dosage intervals increased, in patients with hepatic impairment (see below).

Reviews.
1. Brogden RN, Sorkin EM. Ketanserin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in hypertension and peripheral vascular disease. *Drugs* 1990; 40: 903–49.

Administration in hepatic impairment. A study[1] in patients with cirrhosis found that the half-life and volume of distribution of ketanserin were decreased but the area under the concentration-time curve was markedly increased; the rate of metabolism was reduced. The results suggested that the dosage should be reduced or the dosage interval increased when ketanserin is given to patients with cirrhosis.

Licensed product information recommends a maximum oral dose of 20 mg twice daily for patients with severe hepatic impairment.

1. Lebrec D, *et al.* Pharmacokinetics of ketanserin in patients with cirrhosis. *Clin Pharmacokinet* 1990; 19: 160–6.

Administration in renal impairment. Results from a study in 12 patients with chronic renal impairment, of whom 6 required haemodialysis, suggested that no adjustment of a dose of ketanserin 20 mg twice daily was required in patients with renal impairment.[1]

1. Barendregt JNM, *et al.* Ketanserin pharmacokinetics in patients with renal failure. *Br J Clin Pharmacol* 1990; 29: 715–23.

Peripheral vascular disease. Ketanserin is one of many drugs that have been tried in the management of peripheral vascular disorders (p. 1272.3) but results have been contradictory. Subgroup analysis of the multicentre Prevention of Atherosclerotic Complications with Ketanserin Trial (PACK),[1] involving 3899 patients with intermittent claudication, suggested that ketanserin might be of benefit in preventing limb amputation in some patients. Conflicting results have also been reported in patients with Raynaud's syndrome. A systematic review[2] found that ketanserin led to a small improvement in Raynaud's syndrome in patients with systemic sclerosis but that adverse effects increased; the authors concluded that ketanserin was not clinically beneficial in such patients. For the general management of Raynaud's syndrome see Vasospastic Arterial Disorders, p. 1275.3.

Ketanserin has also been tried in other conditions associated with impaired peripheral blood flow: see Wounds and Ulcers, below.

1. Prevention of Atherosclerotic Complications with Ketanserin Trial Group. Prevention of atherosclerotic complications: controlled trial of ketanserin. *BMJ* 1989; 298: 424–30. Correction. *ibid.*: 644.
2. Pope JE, *et al.* Ketanserin for Raynaud's phenomenon in progressive systemic sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 26/09/05).

Shivering. Many drugs, including ketanserin, have been tried for the treatment of postoperative shivering (p. 1900.2). Ketanserin 10 mg given intravenously has stopped shivering after general anaesthesia.[1,2]

1. Joris J, *et al.* Clonidine and ketanserin both are effective treatment for postanesthetic shivering. *Anesthesiology* 1993; 79: 532–9.
2. Crisinel D, *et al.* Efficacité de la kétansérine sur le frisson postanesthésique. *Ann Fr Anesth Reanim* 1997; 16: 120–5.

Wounds and ulcers. Several controlled studies[1-6] have noted improved healing of decubitus, venous, and ischaemic ulcers (see Wounds and Ulcers, p. 1690.1) after topical use of ketanserin 2%. However, when applied topically to surgical wounds no improvement was found and it was suggested that ketanserin is only of benefit where blood supply is compromised.[7]

1. Tytgat H, van Asch H. Topical ketanserin in the treatment of decubitus ulcers: a double-blind study with 2% ketanserin ointment against placebo. *Adv Therapy* 1988; 5: 143–52.
2. Roelens P. Double-blind placebo-controlled study with topical 2% ketanserin ointment in the treatment of venous ulcers. *Dermatologica* 1989; 178: 98–102.
3. Janssen PAJ, *et al.* Use of topical ketanserin in the treatment of skin ulcers: a double-blind study. *J Am Acad Dermatol* 1989; 21: 85–90.
4. Martinez-de Jesus FR, *et al.* Randomized single-blind trial of topical ketanserin for healing acceleration of diabetic foot ulcers. *Arch Med Res* 1997; 28: 95–9.
5. Salazar JJ, *et al.* Use of topical ketanserin for the treatment of ulcers in leprosy patients. *Indian J Lepr* 2001; 73: 103–10.
6. Quatresooz P, *et al.* Healing effect of ketanserin on chronic leg ulcers in patients with diabetes. *J Eur Acad Dermatol Venereol* 2006; 20: 277–81.
7. Lawrence CM, *et al.* The effect of ketanserin on healing of fresh surgical wounds. *Br J Dermatol* 1995; 132: 580–6.

Adverse Effects and Precautions

Ketanserin has been reported to cause sedation, fatigue, light-headedness, dizziness, headache, dry mouth, and gastrointestinal disturbances. Oedema has been reported rarely. In patients with predisposing factors such as QT prolongation, chronic use of ketanserin has been associated with ventricular arrhythmias including torsade de pointes; ketanserin should be used with caution in patients taking antiarrhythmics and should not be used in second- or third-degree AV block. Care should be taken to avoid the development of hypokalaemia in patients taking ketanserin, for example if diuretics are also given.

Because ketanserin may cause drowsiness care should be taken in patients who drive or operate machinery.

Ketanserin is reported to be better tolerated in elderly than in younger patients.

Interactions

The hypotensive effects of ketanserin may be enhanced by diuretics and other antihypertensives. Ketanserin should be used with caution in patients taking antiarrhythmics or drugs that cause hypokalaemia since the risk of arrhythmias is increased.

Beta blockers. Profound hypotension occurred in 2 patients one hour after taking ketanserin 40 mg orally.[1] Both patients were also taking a beta blocker which may have exacerbated the reaction.

1. Waller PC, *et al.* Profound hypotension after the first dose of ketanserin. *Postgrad Med J* 1987; 63: 305–7.

Pharmacokinetics

Ketanserin is rapidly absorbed from the gastrointestinal tract but has a bioavailability of about 50% due to first-pass hepatic metabolism. Peak plasma concentrations occur between 30 and 120 minutes after an oral dose. Ketanserin is about 95% bound to plasma proteins. The terminal half-life is stated to be between 13 and 18 hours but some studies report that after multiple doses the half-life is 19 to 29 hours. The metabolite ketanserinol has a terminal half-life of 31 to 35 hours after multiple doses, and it has been suggested that reconversion of ketanserinol to ketanserin may be responsible for the prolonged half-life of the parent compound during chronic use.

About 68% of an oral dose is excreted in urine, and 24% in faeces, mainly as metabolites. Ketanserin readily crosses the placenta (see also below). Studies in *animals* suggest that it is also present, with metabolites, in breast milk.

References.

1. Persson B, *et al.* Clinical pharmacokinetics of ketanserin. *Clin Pharmacokinet* 1991; 20: 263–79.

Pregnancy. A study[1] in 22 mothers (23 neonates) showed that ketanserin readily crossed the placenta, resulting in high levels of the drug and its metabolite, ketanserinol, in both umbilical cord and neonate. Despite pharmacologically significant plasma concentrations in the neonates, and slower clearance than in adults, no neonatal adverse effects were noted.

1. Hanff LM, *et al.* Ketanserin in pre-eclamptic patients: transplacental transmission and disposition in neonates. *BJOG* 2004; 111: 863–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Aseranox; *Mex.*: Sufrexal; *Neth.*: Ketensin.

Multi-ingredient Preparations. *Mex.*: Sufrexal P.

Labetalol Hydrochloride

(BANM, USAN, rINNM) ⊗

AH-5158A; Hidrocloruro de labetalol; Ibidomide Hydrochloride; Labétalol, chlorhydrate de; Labetalol, hidrocloruro de; Labetalol hydrochlorid; Labetalol-hidroklorid; Labetalolhydrochlorid; Labetalolhydroklorid; Labetaloli Hydrochloridum; Labetalolihydrokloridi; Labetalolio hidrochloridas; Sch-15719W; Лабеталола Гидрохлорид.

5-[1-Hydroxy-2-(1-methyl-3-phenylpropylamino)ethyl]salicylamide hydrochloride.

$C_{19}H_{24}N_2O_3HCl$=364.9

CAS — 36894-69-6 (labetalol); 32780-64-6 (labetalol hydrochloride).

ATC — C07AG01.

ATC Vet — QC07AG01.

UNII — 1GEV3BAW9J.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Labetalol Hydrochloride). A white or almost white powder. Sparingly soluble in water and in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 4.0 to 5.0.

USP 36: (Labetalol Hydrochloride). A white to off-white powder. Soluble in water and in alcohol; insoluble in chloroform and in ether. A 1% solution in water has a pH of 4.0 to 5.0. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Labetalol hydrochloride is compatible with standard intravenous solutions such as glucose 5% and sodium chloride 0.9%. However, precipitation has been reported when labetalol hydrochloride is added to sodium bicarbonate injection 5%.[1] The precipitate is probably labetalol base.[2]

Immediate formation of a precipitate has also been reported when labetalol (generally 5 mg/mL in glucose 5%) was mixed with other drugs including ceftriaxone,[3] furosemide,[4] heparin,[5] insulin,[5] proton pump inhibitors such as pantoprazole,[6] and thiopental.[4] There has also been a report of immediate haze after admixture of labetalol hydrochloride (800 micrograms/mL) with warfarin sodium.[7]

1. Yuen P-HC, *et al.* Compatibility and stability of labetalol hydrochloride in commonly used intravenous solutions. *Am J Hosp Pharm* 1983; 40: 1007–9.
2. Alam AS. Identification of labetalol precipitate. *Am J Hosp Pharm* 1984; 41: 74.
3. Leader WG, Jones JM. Incompatibility between ceftriaxone sodium and labetalol hydrochloride. *Am J Health-Syst Pharm* 1996; 53: 2639.
4. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; 54: 64–5.
5. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; 53: 1048–51.
6. Péré H, *et al.* Compatibilité du pantoprazole injectable lors d'administration en Y. *Pharmactuel* 2004; 37: 193–6.
7. Bahal SM, *et al.* Visual compatibility of warfarin sodium injection with selected medications and solutions. *Am J Health-Syst Pharm* 1997; 54: 2599–2600.

Uses and Administration

Labetalol is a non-cardioselective beta blocker (p. 1316.3). It is reported to possess some intrinsic sympathomimetic and membrane-stabilising activity. In addition, it has selective alpha$_1$-blocking properties which decrease peripheral vascular resistance. The ratio of alpha- to beta-blocking activity has been estimated to be about 1:3 after oral doses and 1:7 after intravenous doses.

Labetalol is used as the hydrochloride in the management of hypertension (p. 1251.1). It is also used to induce hypotension during surgery. Labetalol decreases blood pressure more rapidly than other beta blockers; the full antihypertensive effect may be seen within 1 to 3 hours of an oral dose.

In **hypertension** labetalol hydrochloride is usually given in an initial oral dose of 100 mg twice daily with food, gradually increased if necessary according to response and standing blood pressure, to 200 to 400 mg twice daily; total daily doses of 2.4 g, in two to four divided doses, have occasionally been required. Lower doses may be adequate in elderly patients; an initial dose of 50 to 100 mg twice daily has been recommended, and the usual maintenance dose is 100 to 200 mg twice daily.

For the emergency treatment of hypertension labetalol hydrochloride may be given by slow intravenous injection. In the UK a dose of 50 mg is recommended, given over a period of at least 1 minute; if necessary this dose may be repeated at intervals of 5 minutes until a total of 200 mg has been given. In the USA an initial dose of 20 mg is recommended, given over 2 minutes; subsequent doses of 40 to 80 mg may be given every 10 minutes, if necessary, up to a maximum of 300 mg. Blood pressure should be monitored, and the patient should remain supine during the injection and for 3 hours afterwards, to avoid excessive orthostatic hypotension. After bolus intravenous injection a maximum effect is usually obtained within 5 minutes and usually lasts up to 6 hours, although it may extend as long as 18 hours.

Labetalol hydrochloride has also been given by intravenous infusion in usual doses of 2 mg/minute. Suggested concentrations for intravenous infusions are 1 mg/mL or 2 mg/3 mL of suitable diluent. In hypertension in pregnancy, labetalol infusion may be started at the rate of 20 mg/hour, then doubled every 30 minutes until a satisfactory response is obtained or a dose of 160 mg/hour is reached. In hypertension after myocardial infarction, labetalol infusion may be started at the rate of 15 mg/hour and gradually increased until a satisfactory response is obtained or a dose of 120 mg/hour is reached.

The initial dose in **hypotensive anaesthesia** is 10 to 20 mg intravenously, with increments of 5 to 10 mg if satisfactory hypotension is not achieved after 5 minutes. A higher initial dose may be required in patients who do not receive halothane anaesthesia.

For the use of labetalol in children, see below.

Action. Labetalol has 2 optical centres; it is used as the racemic mixture of the 4 stereoisomers. The *R,R*-isomer is responsible for the beta-blocking activity and has limited alpha-blocking activity; it also has beta-adrenergic mediated peripheral vasodilating activity. The *S,R*-isomer has the most potent alpha-blocking activity. The *S,S*-isomer has some alpha-blocking activity and the *R,S*-isomer does not appear to have either alpha- or beta-adrenergic blocking effect.[1] The pure *R,R*-isomer, dilevalol, was withdrawn from the market because of hepatotoxicity.

1. Gold EH, *et al.* Synthesis and comparison of some cardiovascular properties of the stereoisomers of labetalol. *J Med Chem* 1982; 25: 1363–70.

Administration in children. Labetalol has been used in the management of hypertension in children,[1] although experience is limited. The *BNFC* suggests the following doses:

for **hypertensive emergencies**, labetalol hydrochloride may be given by intravenous infusion as follows:

- neonates: 500 micrograms/kg per hour adjusted at intervals of at least 15 minutes according to response to a maximum of 4 mg/kg per hour

- 1 month to 12 years: 0.5 to 1 mg/kg per hour adjusted at intervals of at least 15 minutes according to response, to a maximum of 3 mg/kg per hour
- 12 to 18 years: 30 to 120 mg/hour adjusted at intervals of at least 15 minutes according to response

for **hypertension**, labetalol hydrochloride may be given as follows:

- 1 month to 12 years: 1 to 2 mg/kg three or four times daily by mouth or a single intravenous injection in a dose of 250 to 500 micrograms/kg to a maximum of 20 mg
- 12 to 18 years: similar doses to adults (see p. 1416.3) although a lower initial oral dose of 50 to 100 mg twice daily is recommended

1. Bunchman TE, *et al.* Intravenously administered labetalol for treatment of hypertension in children. *J Pediatr* 1992; **120**: 140–4.

Adverse Effects

The adverse effects associated with beta blockers are described on p. 1319.1. Labetalol also has alpha-blocking activity, which contributes to its adverse effects and these effects may predominate. Orthostatic hypotension may be a problem with high doses or at the start of treatment. Other effects associated with alpha blockade include dizziness, scalp tingling, and nasal congestion. Male sexual function may be impaired to a greater extent than with beta blockade alone. Muscle weakness, tremor, urinary retention, hepatitis, and jaundice have also been reported.

Effects on the liver. By 1990, the FDA had received 11 reports of hepatocellular damage associated with labetalol therapy.[1] Three patients died. Liver function should be monitored and labetalol stopped in patients who develop liver function abnormalities. The *R,R*-isomer of labetalol, dilevalol, was withdrawn from the market because of hepatotoxicity.[2]

1. Clark JA, *et al.* Labetalol hepatotoxicity. *Ann Intern Med* 1990; **113**: 210–13.
2. Harvengt C. Labetalol hepatotoxicity. *Ann Intern Med* 1991; **114**: 341.

Hypersensitivity. Hypersensitivity reactions associated with labetalol may manifest as fever.[1-3] Anaphylactoid reaction to labetalol has also been reported.[4]

1. D'Arcy PF. Drug reactions and interactions: drug fever with labetalol. *Int Pharm J* 1987; **1**: 43–4.
2. Stricker BH, *et al.* Fever induced by labetalol. *JAMA* 1986; **256**: 619–20.
3. Kamel J, *et al.* Drug fever due to labetalol. *Intern Med J* 2008; **38**: 871–2.
4. Ferree CE. Apparent anaphylaxis from labetalol. *Ann Intern Med* 1986; **104**: 729–30.

Overdosage. Acute oliguric renal failure developed after a short period of moderate hypotension in a patient who ingested labetalol 16 g. Renal function subsequently recovered.[1] Renal failure has also been reported[2] after ingestion of labetalol 6 g. The patient recovered after treatment with glucagon, isoprenaline, and dialysis. Another patient[3] developed circulatory collapse and impaired consciousness after being given labetalol 800 mg orally for hypertensive crisis; glucagon and sympathomimetics were given to restore blood pressure, but amrinone infusion was also needed to improve cardiac output and mental state. In contrast to this, a large intravenous overdose of labetalol 17.2 mg/kg was reported[4] to produce only mild and transient symptoms of drowsiness and hypotension in an 8-month-old infant after cardiac surgery.

1. Smit AJ, *et al.* Acute renal failure after overdose of labetalol. *BMJ* 1986; **293**: 1142–3.
2. Korzets A, *et al.* Acute renal failure associated with a labetalol overdose. *Postgrad Med J* 1990; **66**: 66–7.
3. Kollef MH. Labetalol overdose successfully treated with amrinone and alpha-adrenergic receptor agonists. *Chest* 1994; **105**: 626–7.
4. Thorsteinsson A, *et al.* Severe labetalol overdose in an 8-month-old infant. *Paediatr Anaesth* 2008; **18**: 435–8.

Precautions

As for Beta Blockers, p. 1320.3.

Because labetalol causes orthostatic hypotension it is recommended that injections are given to patients when they are lying down and that patients should remain lying down for the next 3 hours.

Labetalol should be withdrawn from patients who develop signs of hepatic impairment.

Breast feeding. Labetalol is distributed into breast milk, although it has been suggested[1] that the proportion of a maternal dose likely to be ingested by the infant is very low. In a study[2] in 25 patients, the mean concentration of labetalol in breast milk was less than in maternal plasma in patients given doses between 330 and 800 mg daily, although in 1 patient given 1200 mg daily a higher concentration was found in breast milk. In another study,[3] the concentration of drug in milk exceeded maternal plasma concentration in 2 of 3 mothers, and in 1 infant the plasma-labetalol concentration was similar to that of the mother. However, no adverse effects have been seen in breast-feeding infants whose mothers were given labetalol, and the American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding.

1. Atkinson H, Begg EJ. Concentrations of beta-blocking drugs in human milk. *J Pediatr* 1990; **116**: 156.
2. Michael CA. Use of labetalol in the treatment of severe hypertension during pregnancy. *Br J Clin Pharmacol* 1979; **8** (suppl 2): 211S–215S.
3. Lunell NO, *et al.* Transfer of labetalol into amniotic fluid and breast milk in lactating women. *Eur J Clin Pharmacol* 1985; **28**: 597–9.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies labetalol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Labetalol is readily absorbed from the gastrointestinal tract, but is subject to considerable first-pass metabolism. Bioavailability varies widely between patients and may be increased in the presence of food. Peak plasma concentrations occur about 1 to 2 hours after an oral dose. Labetalol has low lipid solubility and only very small amounts appear to cross the blood-brain barrier in *animals*. It is about 50% protein bound. Labetalol crosses the placenta and is distributed into breast milk (see above). Labetalol is metabolised mainly in the liver, the metabolites being excreted in the urine with only small amounts of unchanged labetalol; its major metabolite has not been found to have significant alpha- or beta-blocking effects. Excretion also occurs in the faeces via the bile. The elimination half-life at steady state is reported to be about 6 to 8 hours. On intravenous infusion, the elimination half-life is about 5.5 hours. Labetalol is not removed by dialysis.

The elderly. Analysis[1] of data from 4 single-dose studies and 3 multidose studies indicated that age did not appear to be a significant factor in oral clearance in elderly patients receiving labetalol for long-term management of hypertension.

1. Rocci ML, *et al.* Effects of age on the elimination of labetalol. *Clin Pharmacokinet* 1989; **17**: 452–7.

Pregnancy. The concentration of labetalol has been found to be lower in amniotic fluid[1] and fetal plasma[2] than in maternal plasma. A ratio of infant to maternal drug concentration of 0.2 to 0.8 has been reported[2] based on concentration in infant cord blood at delivery [time since last maternal dose not stated]. In another study,[3] however, higher concentrations were found in cord plasma than in maternal plasma at delivery when infants were delivered 12 to 24 hours after the last maternal dose.

The half-life of labetalol was reported as 24 hours in a neonate of 37 weeks' gestation whose mother had received labetalol 600 mg daily for 11 weeks before delivery.[4]

1. Lunell NO, *et al.* Transfer of labetalol into amniotic fluid and breast milk in lactating women. *Eur J Clin Pharmacol* 1985; **28**: 597–9.
2. Michael CA. Use of labetalol in the treatment of severe hypertension during pregnancy. *Br J Clin Pharmacol* 1979; **8** (suppl 2): 211S–215S.
3. Boulton DW, *et al.* Transplacental distribution of labetalol stereoisomers at delivery. *Br J Clin Pharmacol* 1999; **47**: 573–4.
4. Haraldsson A, Geven W. Half-life of maternal labetalol in a premature infant. *Pharm Weekbl (Sci)* 1989; **11**: 229–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Biascor; Blocamine; *Austral.*: Presolol; Trandate; *Austria*: Trandate; *Belg.*: Trandate; *Canad.*: Trandate; *Chile*: Trandate; *China*: Xin Yu Sen (欣宇森); *Cz.*: Trandate; *Denm.*: Trandate; *Fin.*: Albetol; *Fr.*: Trandate; *Gr.*: Ftalined; Lircapil; Salmagne; Trandate; *Hong Kong*: Presolol†; Trandate†; *India*: Labesol; Labeta; Labil; Lobet; *Irl.*: Trandate; *Israel*: Trandate; *Ital.*: Ipolab; Trandate; *Malaysia*: Trandate; Trantalol; *Neth.*: Trandate; *Norw.*: Trandate; *NZ*: Hybloc; Trandate; *S.Afr.*: Trandate; *Singapore*: Trandate; Trantalol; *Spain*: Trandate; *Swed.*: Trandate; *Switz.*: Trandate; *Thai.*: Avexa; Trandate; *UK*: Trandate; *USA*: Trandate.

Multi-ingredient Preparations. *Ital.*: Trandiur.

Pharmacopoeial Preparations

BP 2014: Labetalol Injection; Labetalol Tablets;
USP 36: Labetalol Hydrochloride Injection; Labetalol Hydrochloride Oral Suspension; Labetalol Hydrochloride Tablets.

Lacidipine *(BAN, USAN, rINN)*

GR-43659X; GX-1048; Lacidipin; Lacidipino; Lacidipinum; Lasidipilni; Lasidipin; Лацидипин.

Diethyl 4-[2-[(*tert*-butoxycarbonyl)vinyl]phenyl]-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate.

$C_{26}H_{33}NO_6$=455.6

CAS — 103890-78-4.

ATC — C08CA09.

ATC Vet — QC08CA09.

UNII — 260080034N.

Pharmacopoeias. In *Br.*

BP 2014: (Lacidipine). A white to pale yellow crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone and in dichloromethane.

Uses and Administration

Lacidipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p. 1447.2). It is used in the treatment of hypertension (p. 1251.1).

The usual initial oral dose of lacidipine is 2 mg once daily, increased if necessary after 3 to 4 weeks or more to 4 mg daily; a further increase in dose to 6 mg daily may be necessary in some patients. Reduced doses may be required in patients with severe hepatic impairment.

Lacidipine has been investigated for its apparent antimicrobial properties.

Reviews.

1. Lee CR, Bryson HM. Lacidipine: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of hypertension. *Drugs* 1994; **48**: 274–96.
2. Zanchetti A, ed. Cardiovascular advantages of a third generation calcium antagonist: symposium on lacidipine. *Drugs* 1999; **57** (suppl 1): 1–29.
3. McCormack PL, Wagstaff AJ. Lacidipine: a review of its use in the management of hypertension. *Drugs* 2003; **63**: 2327–56.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Pharmacokinetics

Lacidipine is rapidly but poorly absorbed from the gastrointestinal tract after oral doses and undergoes extensive first-pass metabolism; the bioavailability has been reported to be 2 to 9%, or 18.5% (range 4 to 52%) using a more sensitive assay method. Peak plasma concentrations occur within 30 to 150 minutes. It is more than 95% bound to plasma proteins. Lacidipine is eliminated by metabolism in the liver and metabolites are excreted mainly by the biliary route. About 70% of an oral dose is eliminated in the faeces, the remainder in the urine. The average steady-state terminal elimination half-life of lacidipine is 13 to 19 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Motens; *Braz.*: Lacipil; Midotens; *China*: Lacipil (乐息平); Sileping (司乐平); *Cz.*: Lacipil; *Denm.*: Lacipil; Midotens; Motens; *Fr.*: Caldine; *Gr.*: Balnox: Lacipil; Lacitens; Motens; *Hong Kong*: Lacipil†; *Hung.*: Lacipil; *India*: Lacivas; Sinopil; *Indon.*: Lacipil†; *Ital.*: Aponil; Lacipil; Lacirex; Ladip; Viapres; *Malaysia*: Lacipil; *Mex.*: Lacipil; Midotens; *Neth.*: Motens; *Philipp.*: Lacipil; *Pol.*: Lacipil; *Port.*: Lacipil: Tens; *Rus.*: Lacipil (Лацилил); Sakure (Сакур); *Singapore*: Lacipil; *Spain*: Lacimen; Lacipil; Motens; *Switz.*: Motens; *Thai.*: Motens†; *Turk.*: Lacipil; *UK*: Motens; *Venez.*: Lacipil.

Pharmacopoeial Preparations

BP 2014: Lacidipine Tablets.

Lanatoside C *(BAN, rINN)*

Celanide; Celanidum; Lanatosid C; Lanatosidi C; Lanatósido C; Lanatosidum C; Lanatozyd C; Ланатозид С.

3-[(*O*-β-D-Glucopyranosyl-(1→4)-*O*-3-acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12,14-dihydroxy-3β,5β,12β-card-20(22)-enolide.

$C_{49}H_{76}O_{20}$=985.1

CAS — 17575-22-3.

ATC — C01AA06.

ATC Vet — QC01AA06.

UNII — SRR3JFZ771.

Pharmacopoeias. In *Jpn* and *Pol.*

Profile

Lanatoside C is a cardiac glycoside with positive inotropic activity. It is obtained from digitalis lanata leaf (p. 1352.3). It has general properties similar to those of digoxin (p. 1353.3) and has been used in the treatment of some cardiac arrhythmias and in heart failure.

Mixtures of lanatosides A, B, and C have also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mex.*: Cedilanid; *Rus.*: Celanid (Целанид); *Ukr.*: Celanid-KMP (Целанид-КМП)†.

Landiolol Hydrochloride *(rINN)* ⊗

Hidrocloruro de landiolol; Landiolol, Chlorhydrate de; Landiolol, hidrocloruro de; Landiololi Hydrochloridum; ONO-1101; Ландиолола Гидрохлорид.

(-)-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl *p*-((*S*)-2-hydroxy-3-[[2-(4-morpholinecarboxamido)ethyl]amino]propoxy) hydrocinnamate hydrochloride.

$C_{25}H_{39}N_3O_8$,HCl=546.1

CAS — 133242-30-5 (landiolol); 144481-98-1 (landiolol hydrochloride).

UNII — G8HQ634Y17.

Profile

Landiolol is a short-acting, cardioselective beta blocker given intravenously as the hydrochloride in the management of intra- and postoperative cardiac arrhythmias.

References.

1. Kitamura A, *et al.* Efficacy of an ultrashort-acting beta-adrenoceptor blocker (ONO-1101) in attenuating cardiovascular responses to endotracheal intubation. *Eur J Clin Pharmacol* 1997; 51: 467–71.
2. Atarashi H, *et al.* Pharmacokinetics of landiolol hydrochloride, a new ultra-short-acting beta-blocker, in patients with cardiac arrhythmias. *Clin Pharmacol Ther* 2000; 68: 143–50.
3. Mizuno J, *et al.* Age and sex-related differences in dose-dependent hemodynamic response to landiolol hydrochloride during general anesthesia. *Eur J Clin Pharmacol* 2007; 63: 243–52.
4. Inoue S, *et al.* The efficacy of landiolol for suppressing the hyperdynamic response following laryngoscopy and tracheal intubation: a systematic review. *Anaesth Intensive Care* 2009; 37: 893–902.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Corebeta; Onoact.

Lappaconitine Hydrobromide

Лаппаконитина Гидробромид.

(1α,14α,16β)-20-Ethyl-1,14,16-trimethoxyaconitane-4,8,9-triol 4-[2-(acetylamino)benzoate] hydrobromide.

$C_{32}H_{44}N_2O_8$,HBr=665.6

CAS — 32854-75-4 (lappaconitine); 97792-45-5 (lappaconitine hydrobromide).

Profile

Lappaconitine hydrobromide is an antiarrhythmic drug given orally in a usual dose of 25 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Bo Si Te (博斯特); Hai Feng Quan (海丰泉); Jie Qing (捷清); Jin Da Xin (金达欣); Li Kang Ping (黎康平); Lin Yuan Li Shu (林源立舒); Ning Sheng Xin (宁圣欣); Pu Le (朴乐); Qing Tong (清通); Wu Hen (无痕); Xi Song (西松); You Yi Xin (优一欣); Zhi Teng (知腾); Zhuo Ning (卓宁); *Rus.*: Allapinin (Аллапинин).

Leech

Biodigel; Bloedzuiger; Blutegel; Dêle; Dele; Egel; Hirudo; Iilimato; Juotikas; Kaan; Pijavka; Pijawka; Pióca; Sangonera; Sangsue; Sanguessugas; Sanguijuela; Sanguisuga; Sülük; Пиявка; Пиявици.

Description. *Hirudo medicinalis* is the leech commonly used in medicine and is a fresh-water annelid.

NOTE. The substance described in the *Chin. P.* as Hirudo (Leech) is the dried body of *Whitmania pigra*, *Hirudo nipponica*, or *Whitmania acranulata*.

Profile

Leeches are used for withdrawing blood from congested areas and have been found to be of value in plastic surgery. The buccal secretion of the leech contains the anticoagulant hirudin (p. 1401.2). Once used a leech should not be applied to another patient.

There have been reports of wound infection from *Aeromonas hydrophila* transmitted by leeches. Prolonged bleeding for up to 10 hours may occur from the site of attachment after removal of the leech.

Leeches are commonly used in plastic surgery and this has been reviewed.[1,2]

Wound infection by *Aeromonas hydrophila*, an organism normally found in the gut of the leech, is a recognised complication of the use of leeches for decongestion after plastic surgery. Other infecting organisms include *Aeromonas sobria* and *Serratia marcescens*. Infections have caused minor wound drainage, cellulitis, abscess, tissue loss, and sepsis, and a case of meningitis secondary to *Aeromonas* infection has been reported.[3] The following protocol has been suggested:[1] the site of application should first be cleaned with heparinised saline, and antibacterial prophylaxis with a quinolone and an aminoglycoside given for the duration of application. Patients discharged with open wounds should continue with oral antibacterials until wound closure.

In addition to its anticoagulant properties the buccal secretion of the leech contains anti-inflammatory substances, and leeches have been reported to provide subjective relief of osteoarthritis[4,5] and cancer pain.[6]

1. Whitaker IS, *et al.* Hirudo medicinalis and the plastic surgeon. *Br J Plast Surg* 2004; 57: 348–53.
2. Porshinsky BS, *et al.* Clinical uses of the medicinal leech: a practical review. *J Postgrad Med* 2011; 57: 65–71.
3. Ouderkirk JP, *et al. Aeromonas* meningitis complicating medicinal leech therapy. Abstract: *Clin Infect Dis* 2004; 38: 603. Full version: http://www.journals.uchicago.edu/doi/full/10.1086/381438 (accessed 19/08/08)
4. Michalsen A, *et al.* Effect of leeches therapy (Hirudo medicinalis) in painful osteoarthritis of the knee: a pilot study. *Ann Rheum Dis* 2001; 60: 986.
5. Michalsen A, *et al.* Effectiveness of leech therapy in osteoarthritis of the knee: a randomized, controlled trial. *Ann Intern Med* 2003; 139: 724–30.
6. Kalender ME, *et al.* Leech therapy for symptomatic relief of cancer pain. *Pain Med* 2010; 11: 443–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Piyavit (Пиявит).

Multi-ingredient Preparations. *Hung.*: Antikeloid; Forte Hirudo; Medhirud; Plerudin; *Malaysia*: NeuroAid; *Singapore*: NeuroAid.

Lepirudin *(BAN, rINN)*

HBW-023; Lepirudiini; Lepirudina; Lépirudine; Lepirudinum; Лепирудин.

1-L-Leucine-2-L-threonine-63-desulfohirudin (*Hirudo medicinalis* isoform HV1).

$C_{287}H_{440}N_{80}O_{111}S_6$=6979.5

CAS — 138068-37-8.

ATC — B01AE02.

ATC Vet — QB01AE02.

UNII — Y43GF64R34.

Uses and Administration

Lepirudin is a recombinant hirudin (p. 1401.2) that is a direct inhibitor of thrombin. It is used as an anticoagulant in the management of thromboembolic disorders (p. 1273.2) in patients with heparin-induced thrombocytopenia. It has been investigated in arterial thromboembolic disorders such as myocardial infarction and unstable angina.

In the management of thromboembolism in patients with heparin-induced thrombocytopenia, lepirudin is given in an initial dose of 400 micrograms/kg by slow intravenous injection. This may be followed by a maintenance dose of 150 micrograms/kg per hour by continuous intravenous infusion, adjusted according to response, usually for 2 to 10 days. Response should be monitored according to the activated partial thromboplastin time (APTT) ratio to achieve a target of 1.5 to 2.5. Doses must not exceed those based on a patient weight of 110 kg and in general an infusion rate of 210 micrograms/kg per hour should not be exceeded.

Doses of lepirudin should be reduced in patients with renal impairment, and it should generally be avoided in those on haemodialysis. Some have found licensed doses to be excessive, and lower doses have been suggested for both patients with normal renal function and those with renal impairment. For a discussion of these doses, see Heparin-induced Thrombocytopenia, below.

Administration in renal impairment. For both licensed and alternative doses of lepirudin in patients with renal impairment, see Heparin-induced Thrombocytopenia, below.

Extracorporeal circulation. Heparin is the anticoagulant most frequently used to prevent occlusion of extracorporeal circuits during haemodialysis and haemofiltration. The direct thrombin inhibitors have been tried as alternatives, and may be especially useful when heparin is contra-indicated because of heparin-induced thrombocytopenia (HIT). *Lepirudin* has been used with moderate efficacy,[1,2] although it is renally cleared and bleeding may be a problem. *Bivalirudin* was tried successfully in a patient who developed HIT during continual venovenous haemofiltration (CVVH).[3] A subsequent randomised study[4] in 10 adults undergoing CVVH found that bivalirudin was effective, with a similar tolerability and improved haemofilter survival compared with heparin. *Argatroban* was also effective in 5 patients with HIT requiring haemodialysis or CVVH.[5] The drug was not significantly removed by dialysis or CVVH, and no dosage adjustment was required.

1. Vargas Hein O, *et al.* Hirudin versus heparin for anticoagulation in continuous renal replacement therapy. *Intensive Care Med* 2001; 27: 673–9.
2. Hein OV, *et al.* Intermittent hirudin versus continuous heparin for anticoagulation in continuous renal replacement therapy. *Ren Fail* 2004; 26: 297–303.
3. Mueller SW, *et al.* Prefilter bivalirudin for preventing hemofilter occlusion in continuous renal replacement therapy. *Ann Pharmacother* 2009; 43: 1360–5.
4. Kiser TH, *et al.* Bivalirudin versus unfractionated heparin for prevention of hemofilter occlusion during continuous renal replacement therapy. *Pharmacotherapy* 2010; 30: 1117–26.
5. Tang IY, *et al.* Argatroban and renal replacement therapy in patients with heparin-induced thrombocytopenia. *Ann Pharmacother* 2005; 39: 231–6.

Heparin-induced thrombocytopenia. Lepirudin is effective for the management of thromboembolism in patients with heparin-induced thrombocytopenia[1] (see Effects on the Blood under Adverse Effects of Heparin, p. 1399.1). Bleeding is the main complication during treatment and use of lower doses[1-4] than those licensed has been suggested for both patients with normal renal function and those with renal impairment.

Licensed doses of lepirudin in patients with renal impairment are as follows: the initial dose should be reduced to 200 micrograms/kg, and the maintenance infusion rate reduced according to creatinine clearance (CC):

- CC 45 to 60 mL/minute: 75 micrograms/kg per hour
- CC 30 to 44 mL/minute: 45 micrograms/kg per hour
- CC 15 to 29 mL/minute: 22.5 micrograms/kg per hour
- CC below 15 mL/minute: infusion of lepirudin should be avoided, although in haemodialysis patients or cases of acute renal failure further intravenous bolus doses of 100 micrograms/kg may be used on alternate days, according to response

However, in one centre experience[3] in 68 patients led to the suggestion that lower doses may be more appropriate, with the initial intravenous injection omitted altogether and the infusion rates as follows:

- normal renal function: 80 micrograms/kg per hour
- CC 30 to 60 mL/minute: 40 micrograms/kg per hour
- CC less than 30 mL/minute: 10 to 20 micrograms/kg per hour

American College of Chest Physicians (ACCP) guidelines[4] also suggest that the initial injection may be omitted, or an initial dose of 200 micrograms/kg may be given to those with life- or limb-threatening thrombosis. Suggested infusion rates, based on serum-creatinine concentrations, are:

- creatinine less than 90 micromoles/litre: 100 micrograms/kg per hour
- creatinine 90 to 140 micromoles/litre: 50 micrograms/kg per hour
- creatinine 140 to 400 micromoles/litre: 10 micrograms/kg per hour
- creatinine more than 400 micromoles/litre: 5 micrograms/kg per hour

The ACCP also recommends that APTT is monitored at 4-hourly intervals with a target ratio of 1.5 to 2.0.

1. Lubenow N, *et al.* HIT Investigators Group. Lepirudin in patients with heparin-induced thrombocytopenia—results of the third prospective study (HAT-3) and a combined analysis of HAT-1, HAT-2, and HAT-3. *J Thromb Haemost* 2005; 3: 2428–36.
2. Tardy B, *et al.* GEHT-HIT Study Group. Predictive factors for thrombosis and major bleeding in an observational study in 181 patients with heparin-induced thrombocytopenia treated with lepirudin. *Blood* 2006; 108: 1492–6.
3. Tschudi M, *et al.* Dosing lepirudin in patients with heparin-induced thrombocytopenia and normal or impaired renal function: a single-center experience with 68 patients. *Blood* 2009; 113: 2402–9.
4. Warkentin TE, *et al.* American College of Chest Physicians. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest* 2008; 133 (suppl): 340S–380S. Also available at: http://chestjournal.chestpubs.org/content/139/5/1261.full.pdf (accessed 25/10/11) Correction. *ibid.* 2011; 139: 1261. [dose]

Ischaemic heart disease. Recombinant hirudins have been investigated as alternatives to heparin in the management of acute ST-elevation myocardial infarction (p. 1257.1) and in non-ST elevation myocardial infarction and unstable angina (see Angina Pectoris, p. 1254.3), and have been used as adjuncts to medical or interventional treatment. Overall they appear to have some benefit over heparin,[1] but their precise role in each situation remains to be confirmed.

Initial studies comparing heparin with the recombinant hirudins desirudin[2,3] (p. 1351.1) or lepirudin[4] in patients with acute ST-elevation **myocardial infarction** treated with thrombolytics had to be stopped because of higher than expected haemorrhagic stroke rates,[5,6] and subsequent studies using lower doses of desirudin[7,8] or lepirudin[9] failed to show a clear benefit over heparin. A study[10] with bivalirudin, a synthetic analogue of hirudin, in similar patients also found no mortality benefit; there were fewer re-infarctions in the bivalirudin group, but the risk of bleeding was increased. The role of hirudins is therefore not established in patients treated with thrombolytics, although they may be useful in patients with heparin-induced thrombocytopenia. They may also have a role in PCI (see below).

Studies in patients with **acute coronary syndromes** (non-ST elevation myocardial infarction and unstable angina) suggest that lepirudin is superior to heparin in preventing cardiovascular death, myocardial infarction, and refractory angina.[11,12] A study[13] comparing desirudin with heparin in unstable angina found that angiographic outcomes were better with desirudin, but another study[7] found little benefit in terms of mortality or recurrent ischaemia. Bivalirudin appears to be as effective as heparin in patients with acute coronary syndromes, but unlike the other hirudins the risk of major bleeding may be reduced.[14,15]

Hirudins have also been studied in patients undergoing **percutaneous coronary interventions** (see Reperfusion and Revascularisation Procedures, p. 1259.2). Desirudin has been used in patients undergoing angioplasty[16,17] and appears to be safe, although no benefit has been shown over heparin. Lepirudin has been used as an alternative to heparin in patients with heparin-induced thrombocytopenia.[18-20] Bivalirudin is an effective alternative to heparins during percutaneous coronary interventions in patients with stable coronary artery disease,[21,22] or acute coronary syndromes,[21-24] or acute myocardial infarction,[25] and may reduce the need for adjunctive glycoprotein IIb/IIIa inhibitors.[21-23] Again there is evidence[26,27] that it is associated with less bleeding than heparin.

In patients undergoing **coronary artery bypass grafting**, hirudins may be an alternative to unfractionated heparin, and positive results have been reported with bivalirudin[28] and with lepirudin;[29] however, postoperative bleeding is increased and it was suggested[29] that hirudins should be reserved for patients with contra-indications to heparin, such as those with heparin-induced thrombocytopenia.

1. Direct Thrombin Inhibitor Trialists' Collaborative Group. Direct thrombin inhibitors in acute coronary syndromes: principal results of a meta-analysis based on individual patients' data. *Lancet* 2002; 359: 294–302.
2. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators. Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. *Circulation* 1994; 90: 1631–7.
3. Antman EM, *et al.* Hirudin in acute myocardial infarction: safety report from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9A trial. *Circulation* 1994; 90: 1624–30.
4. Neuhaus K-L, *et al.* Safety observations from the pilot phase of the randomized r-Hirudin for Improvement of Thrombolysis (HIT-III) study: a study of the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausärzte (ALKK). *Circulation* 1994; 90: 1638–42.
5. Zeymer U, Neuhaus K-L. Hirudin and excess bleeding: implications for future use. *Drug Safety* 1995; 12: 234–9.
6. Conrad KA. Clinical pharmacology and drug safety: lessons from hirudin. *Clin Pharmacol Ther* 1995; 58: 123–6.
7. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996; 335: 775–82.
8. Antman EM. Hirudin in acute myocardial infarction: thrombolysis and thrombin inhibition in myocardial infarction (TIMI) 9B trial. *Circulation* 1996; 94: 911–21.
9. Neuhaus K-L, *et al.* Recombinant hirudin (lepirudin) for the improvement of thrombolysis with streptokinase in patients with acute myocardial infarction: results of the HIT-4 trial. *J Am Coll Cardiol* 1999; 34: 966–73.
10. The Hirulog and Early Reperfusion or Occlusion (HERO)-2 Trial Investigators. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. *Lancet* 2001; 358: 1855–63.
11. Organization to Assess Strategies for Ischemic Syndromes (OASIS) Investigators. Comparison of the effects of two doses of recombinant hirudin compared with heparin in patients with acute myocardial ischemia without ST elevation: a pilot study. *Circulation* 1997; 96: 769–77.
12. Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) Investigators. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularisation procedures in patients with acute myocardial ischaemia without ST elevation: a randomised trial. *Lancet* 1999; 353: 429–38.
13. Topol EJ, *et al.* Recombinant hirudin for unstable angina pectoris: a multicenter, randomized angiographic trial. *Circulation* 1994; 89: 1557–66.
14. Kong DF, *et al.* Clinical outcomes of bivalirudin for ischemic heart disease. *Circulation* 1999; 100: 2049–53.
15. Stone GW, *et al.* The ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; 355: 2203–16.
16. van den Bos AA, *et al.* Safety and efficacy of recombinant hirudin (CGP 39 393) versus heparin in patients with stable angina undergoing coronary angioplasty. *Circulation* 1993; 88: 2058–66.
17. Serruys PW, *et al.* A comparison of hirudin with heparin in the prevention of restenosis after coronary angioplasty. *N Engl J Med* 1995; 333: 757–63.
18. Manfredi JA, *et al.* Lepirudin as a safe alternative for effective anticoagulation in patients with known heparin-induced thrombocytopenia undergoing percutaneous coronary intervention: case reports. *Catheter Cardiovasc Interv* 2001; 52: 468–72.
19. Pinto DS, *et al.* Combination platelet glycoprotein IIb/IIIa receptor and lepirudin administration during percutaneous coronary intervention in patients with heparin-induced thrombocytopenia. *Catheter Cardiovasc Interv* 2003; 58: 65–8.
20. Cochran K, *et al.* Use of lepirudin during percutaneous vascular interventions in patients with heparin-induced thrombocytopenia. *J Invasive Cardiol* 2003; 15: 617–21.
21. Lincoff AM, *et al.* Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003; 289: 853–63. Correction. *ibid.*; 1638.
22. Lincoff AM, *et al.* Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. *JAMA* 2004; 292: 696–703. Correction. *ibid.* 2006; 296: 46.
23. Stone GW, *et al.* Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial. *Lancet* 2007; 369: 907–19.
24. White HD, *et al.* Safety and efficacy of bivalirudin with and without glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes undergoing percutaneous coronary intervention 1-year results from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. *J Am Coll Cardiol* 2008; 52: 807–14.
25. Mehran R, *et al.* HORIZONS-AMI Trial Investigators. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. *Lancet* 2009; 374: 1149–59.
26. Stone GW, *et al.* HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008; 358: 2218–30.
27. Kastrati A, *et al.* ISAR-REACT 3 Trial Investigators. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *N Engl J Med* 2008; 359: 688–96.
28. Dyke CM, *et al.* A comparison of bivalirudin to heparin with protamine reversal in patients undergoing cardiac surgery with cardiopulmonary bypass: the EVOLUTION-ON study. *J Thorac Cardiovasc Surg* 2006; 131: 533–9.
29. Riess F-C, *et al.* Recombinant hirudin for cardiopulmonary bypass anticoagulation: a randomized, prospective, and heparin-controlled pilot study. *Thorac Cardiovasc Surg* 2007; 55: 233–8.

Adverse Effects and Precautions

The most frequent adverse effect of the direct thrombin inhibitors is bleeding. Hypersensitivity reactions have been reported. There have been reports of severe anaphylactic reactions, including death, with many occurring on re-exposure. There may be cross-reactivity with other hirudins or hirudin analogues.

Intramuscular injection should be avoided as it may cause local haematoma.

Direct thrombin inhibitors should be used with caution or avoided in patients with hepatic or renal impairment, and in those who are bleeding or at serious risk of bleeding, including those with haemorrhagic blood disorders, recent major bleeding, cerebrovascular disorders, bacterial endocarditis, severe hypertension, or patients who have recently undergone major surgery or puncture of large vessels or organ biopsy.

Effects on the blood. Lepirudin is reported[1] to have twice induced thrombocytopenia in a patient with recurrent venous thrombosis and a recent history of heparin-induced thrombocytopenia. Both drops in platelet count occurred when administration was changed from the intravenous to the subcutaneous route.

1. Schroeder WS, *et al.* Lepirudin-induced thrombocytopenia following subcutaneous administration. *Am J Health-Syst Pharm* 2009; 66: 834–7.

Hypersensitivity. The EMEA reported[1] in October 2002 that it was aware of 7 cases of severe anaphylactic reactions in patients given lepirudin; in 6 cases this followed re-exposure to the drug, and in 5 cases the patient died. A review[2] of the manufacturer's safety database identified 9 patients with severe anaphylactic reactions associated with lepirudin; 4 patients died, all of whom had received lepirudin within the previous 1 to 12 weeks. Although the risk of severe anaphylaxis was estimated to be low (0.015% on first exposure and 0.16% on re-exposure),[2] alternative treatment should be considered before re-exposure to lepirudin and it should only be used where treatment for an anaphylactic reaction is available.[1,2]

1. EMEA. EMEA public statement on Refludan (lepirudin)—fatal anaphylactic reactions (issued October 2002). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2010/08/WC500095474.pdf (accessed 10/08/10)
2. Greinacher A, *et al.* Anaphylactic and anaphylactoid reactions associated with lepirudin in patients with heparin-induced thrombocytopenia. *Circulation* 2003; 108: 2062–5.

Treatment of Adverse Effects

If bleeding occurs lepirudin should be stopped and appropriate therapy given. Unlike heparin, there is no specific antidote for lepirudin (but see below).

Overdosage. A review[1] concluded that the use of activated eptacog alfa (recombinant factor VIIa) was of benefit in the management of bleeding associated with certain anticoagulants, including direct thrombin inhibitors. Although the lowest effective dose was uncertain, 30 to 90 micrograms/kg had been reported to be effective for direct thrombin inhibitor reversal. Use of repeat doses of eptacog alfa was not recommended.

1. Vavra KA, *et al.* Recombinant factor VIIa to manage major bleeding from newer parenteral anticoagulants. *Ann Pharmacother* 2010; 44: 718–26.

Interactions

Use of direct thrombin inhibitors with thrombolytics, oral anticoagulants, or drugs that affect platelet function may increase the risk of bleeding.

Pharmacokinetics

Lepirudin is metabolised and excreted by the kidney. About 45% of an intravenous dose is detected in the urine and about 35% is excreted unchanged. The terminal elimination half-life of lepirudin is about 1.3 hours. In patients with severe renal impairment the half-life may be prolonged to about 2 days.

Breast feeding. Three hours after injection, plasma concentrations of hirudin in a woman receiving lepirudin 50 mg subcutaneously twice daily were 0.5 to 1 microgram/mL, but no hirudin was detected in the breast milk.

1. Lindhoff-Last E, *et al.* Hirudin treatment in a breastfeeding woman. *Lancet* 2000; 355: 467–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Refludan; *Austria*: Refludan†; *Belg.*: Refludan†; *Canad.*: Refludan; *Cz.*: Refludan†; *Fr.*: Refludan†; *Ger.*: Refludan†; *Gr.*: Refludan†; *Hung.*: Refludan†; *Irl.*: Refludan†; *Ital.*: Refludan†; *Neth.*: Refludan†; *Norw.*: Refludan†; *NZ*: Refludan†; *Pol.*: Refludan†; *Port.*: Refludan†; *S.Afr.*: Refludin; *Spain*: Refludin†; *Swed.*: Refludan†; *Switz.*: Refludan†; *UK*: Refludan†; *USA*: Refludan†.

Lercanidipine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de lercanidipino; Lercandipinhydrochlorid; Lercanidipine, Chlorhydrate de; Lercanidipini Hydrochloridum; Lercanidipino, hidrocloruro de; Lerkanidipin Hidroklorür; Masnidipine Hydrochloride; R-75; Rec-15-2375; Лерканидипина Гидрохлорид.

(±)-2-[(3,3-Diphenylpropyl)methylamino]-1,1-dimethylethyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate hydrochloride.

$C_{36}H_{41}N_3O_6HCl$=648.2

CAS — 100427-26-7 (lercanidipine); 132866-11-6 (lercanidipine hydrochloride).

ATC — C08CA13.

ATC Vet — QC08CA13.

UNII — OA8TEX68PE.

Uses and Administration

Lercanidipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p. 1447.2). It is used in the treatment of hypertension (p. 1251.1).

Lercanidipine is given orally as the hydrochloride in a usual initial dose of 10 mg once daily before food, increased if necessary, after at least 2 weeks, to 20 mg daily.

Reviews.

1. McClellan KJ, Jarvis B. Lercanidipine: a review of its use in hypertension. *Drugs* 2000; 60: 1123–40.
2. Bang LM, *et al.* Lercanidipine: a review of its efficacy in the management of hypertension. *Drugs* 2003; 63: 2449–72.
3. Beckey C, *et al.* Lercanidipine in the treatment of hypertension. *Ann Pharmacother* 2007; 41: 465–74.
4. Burnier M, *et al.* Treatment of essential hypertension with calcium channel blockers: what is the place of lercanidipine? *Expert Opin Drug Metab Toxicol* 2009; 5: 981–7.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2). Lercanidipine should not be used in those with severe hepatic impairment or renal impairment (creatinine clearance less than 30 mL/minute).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lercanidipine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Tolerability. A meta-analysis[1] of 8 comparative studies suggested that oedema was less likely with lercanidipine than

with first-generation dihydropyridine calcium-channel blockers such as amlodipine, felodipine, or nifedipine, and lercanidipine-treated patients were less likely to withdraw from treatment due to adverse effects; however, no difference could be shown versus the lipophilic second-generation drugs lacidipine or manidipine. There were no differences in the incidence of flushing or headache versus either generation of drugs.

1. Makaroumas-Kirchmann K, *et al.* Results of a meta-analysis comparing the tolerability of lercanidipine and other dihydropyridine calcium channel blockers. *Clin Ther* 2009; 31: 1652–63.

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Pharmacokinetics

Lercanidipine is completely absorbed from the gastrointestinal tract after oral doses but undergoes extensive saturable first-pass metabolism. Bioavailability is low but is increased in the presence of food. Peak plasma concentrations occur about 1.5 to 3 hours after oral dosage. Lercanidipine is rapidly and widely distributed. It is more than 98% bound to plasma proteins. Lercanidipine is extensively metabolised, mainly by the cytochrome P450 isoenzyme CYP3A4, mainly to inactive metabolites; about 50% of an oral dose is excreted in the urine. A terminal elimination half-life of about 2 to 5 hours has been reported, but studies using a more sensitive assay have suggested a value of 8 to 10 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lercadip; ***Austral.***: Lercadip; Lercan; Zanidip; Zircol; ***Austria***: Zanidip; ***Belg.***: Zanidip; ***Braz.***: Zanidip; ***Chile***: Zanidip†; ***China***: Zanidip (再宁平); ***Cz.***: Kapidin; Lerpin; ***Denm.***: Lercastad; Lercatio; Lercinigen; Nircadel†; Zanedip†; Zanidip; ***Fin.***: Nircadel†; Oridip; Zanidip; ***Fr.***: Lercan; Zanidip; ***Ger.***: Carmen; Corifeo; ***Gr.***: Lercadip; Zanidip; ***Hong Kong***: Zanidip; ***Hung.***: Lercaton; Zanidip; ***India***: Landip; Lerez; Lerka; Lervasc; Lotensyl; ***Indon.***: Zanidip; ***Irl.***: Lecalpin: Zanidip; ***Israel***: Lercapress; Vasodip; ***Ital.***: Cardiovasc; Lercadip; Zanedip; ***Malaysia***: Zanidip; ***Mex.***: Evipress; Zanidip; ***Neth.***: Lerdip; ***Norw.***: Zanidip; ***NZ***: Zanidip; ***Philipp.***: Zanidip; ***Port.***: Calcan; Zanicor; Zanidip; ***Rus.***: Lercamen (Леркамен); ***S.Afr.***: Zanidip; ***Spain***: Lercadip; Lerzam; Zanidip; ***Swed.***: Zanidip; ***Switz.***: Zanidip; ***Thai.***: Zanidip; ***Turk.***: Lercadip; ***UK***: Zanidip; ***Ukr.***: Lercamen (Леркамен); Zanidip (Занидип); ***Venez.***: Lercadip; Zanidip.

Multi-ingredient Preparations. ***Austral.***: Zan-Extra; ***Austria***: Lercaprel; Zanipril; ***Belg.***: Zanicombo; ***Cz.***: Lercaprel; Zanicombo; ***Denm.***: Zanipress; ***Fin.***: Zanipress; ***Fr.***: Lercapress; Zanextra; ***Ger.***: Carmen ACE; Zaneril; Zanipress; ***Gr.***: Lercaprel; Zaneril; ***India***: Lotensyl-AT; ***Irl.***: Lercaril; ***Israel***: Vasodip Combo; ***Neth.***: Lercaprel†; Lertec; ***Norw.***: Zanipress; ***Port.***: Zanipress; Zanitek; ***S.Afr.***: Zaneril; ***Spain***: Coripren; Lercapress; Zanipress; ***Switz.***: Zanipress; ***Ukr.***: Coripren (Коприен).

Levosimendan *(USAN, rINN)*

Levosimendán; Levosimendan; Levosimendanum; (-)-OR-1259; Левосимендан.

Mesoxalonitrile (-)-(*p*-[(*R*)-1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl]phenyl)hydrazone.

$C_{14}H_{12}N_6O$=280.3.

CAS — 141505-33-1.

ATC — C01CX08.

ATC Vet — QC01CX08.

UNII — C6T4514L4E.

Uses and Administration

Levosimendan is a cardiac inotrope and vasodilator with calcium-sensitising properties, used in the management of acute heart failure (p. 1262.3), although its place in therapy is unclear. It is given intravenously in a loading dose of 6 to 12 micrograms/kg over 10 minutes followed by a continuous infusion of 50 to 200 nanograms/kg per minute, adjusted according to response. The recommended duration of infusion is 24 hours.

Levosimendan has been tried in several other indications including cardiogenic and septic shock, and calcium-channel blocker toxicity.

References.

1. Figgin DP, *et al.* Levosimendan. *Drugs* 2001; 61: 613–27.
2. Follath F, *et al.* Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet* 2002; 360: 196–202.
3. McBride BF, White CM. Levosimendan: implications for clinicians. *J Clin Pharmacol* 2003; 43: 1071–81.
4. Innes CA, Wagstaff AJ. Levosimendan: a review of its use in the management of acute decompensated heart failure. *Drugs* 2003; 63: 2651–71.
5. Earl GL, Fitzpatrick JT. Levosimendan: a novel inotropic agent for treatment of acute, decompensated heart failure. *Ann Pharmacother* 2005; 39: 1888–96.
6. De Luca L, *et al.* Evidence-based use of levosimendan in different clinical settings. *Eur Heart J* 2006; 27: 1908–20.
7. Antila S, *et al.* Clinical pharmacology of levosimendan. *Clin Pharmacokinet* 2007; 46: 535–52.
8. Mebazaa A, *et al.* Levosimendan vs dobutamine: outcomes for acute heart failure patients on β-blockers in SURVIVE. *Eur J Heart Fail* 2009; 11: 304–11.
9. Follath F. Newer treatments for decompensated heart failure: focus on levosimendan. *Drug Des Devel Ther* 2009; 3: 73–8.
10. Antoniades C, *et al.* Relationship between the pharmacokinetics of levosimendan and its effects on cardiovascular system. *Curr Drug Metab* 2009; 10: 95–103.
11. Delaney A, *et al.* Levosimendan for the treatment of acute severe heart failure: a meta-analysis of randomised controlled trials. *Int J Cardiol* 2010; 138: 281–9.
12. Landoni G, *et al.* Levosimendan reduces mortality in critically ill patients: a meta-analysis of randomized controlled studies. *Minerva Anestesiol* 2010; 76: 276–86.

Adverse Effects and Precautions

Hypotension, headache, and ventricular tachycardia are reported to be the most frequent adverse effects with levosimendan; extrasystoles, atrial fibrillation, hypokalaemia, insomnia, dizziness, gastrointestinal disturbances, and anaemia are also reported to be common.

It should not be used in patients with severe hypotension and tachycardia, or with mechanical obstruction affecting ventricular filling or outflow. It should be given with care and under close ECG monitoring to patients with ongoing coronary ischaemia or long QTc interval regardless of aetiology; care is also required in those with potentially life-threatening arrhythmias, tachycardia, or atrial fibrillation with rapid ventricular response; it is contra-indicated where there is a history of torsade de pointes. Serum-potassium concentrations should be measured during treatment. Haemodynamic effects should continue to be monitored for several days after the end of infusion, as they may be prolonged. Levosimendan should be used with caution in patients with renal or hepatic impairment and should be avoided if these are severe.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies levosimendan as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pharmacokinetics

On infusion of levosimendan it is extensively metabolised, with a half-life of about 1 hour. Its active metabolites OR-1855 and OR-1896 are interconverted by acetylation and de-acetylation and have half-lives of about 75 to 80 hours, producing a prolonged duration of action. Metabolites and a small amount of unchanged drug are excreted in urine and faeces. More than 95% of a dose is excreted within one week. Levosimendan is about 98% bound to plasma proteins, mainly albumin, but the active metabolites have much lower protein binding of about 40%.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Simdax; ***Austria***: Simdax; ***Braz.***: Simdax; ***Chile***: Daxim; ***Cz.***: Simdax; ***Fin.***: Simdax; ***Gr.***: Simdax; ***Hong Kong***: Simdax†; ***Hung.***: Simdax; ***Israel***: Simdax; ***Ital.***: Simdax; ***Mex.***: Simdax; ***Norw.***: Simdax; ***NZ***: Simdax; ***Port.***: Simdax; ***Rus.***: Simdax (Симдакс); ***Singapore***: Simdax†; ***Spain***: Simdax; ***Swed.***: Simdax; ***Turk.***: Simdax; ***Ukr.***: Simdax (Симдакс); ***Venez.***: Daxim.

Lidoflazine *(BAN, USAN, rINN)*

Lidoflazin; Lidoflazina; Lidoflazinum; McN-JR-7904; Ordiflazine; R-7904; Лидофлазин.

4-[3-(4,4'-Difluorobenzhydryl)propyl]piperazin-1-ylaceto-2',6'-xylidide.

$C_{30}H_{35}F_2N_3O$=491.6.

CAS — 3416-26-0.

ATC — C08EX01.

ATC Vet — QC08EX01.

UNII — J4ZHN3HBTE.

Profile

Lidoflazine is a calcium-channel blocker (p. 1244.2) that reduces AV conduction. It has been used in angina pectoris.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Clinium†; ***S.Afr.***: Clinium†.

Limaprost *(rINN)*

Limaprostum; ONO-1206; OP-1206; Лимапрост.

(*E*)-7-[(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*S*,5*S*)-3-hydroxy-5-methyl-1-nonenyl]-5-oxocyclopentyl]-2-heptenoic acid.

$C_{22}H_{36}O_5$=380.5.

CAS — 74397-12-9 (limaprost); 88852-12-4 (limaprost alfadex).

UNII — L02U804092.

Pharmacopoeias. *Jpn* includes limaprost alfadex.

Profile

Limaprost is a synthetic analogue of alprostadil (prostaglandin E_1) used in the management of peripheral vascular disorders (p. 1272.3). It is given orally as limaprost alfadex in a dose equivalent to limaprost 15 to 30 micrograms daily in three divided doses.

References.

1. Shono T, Ikeda K. Rapid effect of oral limaprost in Raynaud's disease in childhood. *Lancet* 1989; i: 908.
2. Murai C, *et al.* Oral limaprost for Raynaud's phenomenon. *Lancet* 1989; ii: 1218.
3. Aoki Y, *et al.* Possible participation of a prostaglandin E1 analogue in the aggravation of diabetic nephropathy. *Diabetes Res Clin Pract* 1992; 16: 233–8.
4. Sato Y, *et al.* Effect of oral administration of prostaglandin E1 on erectile dysfunction. *Br J Urol* 1997; 80: 772–5.
5. Swainston Harrison T, Plosker GL. Limaprost. *Drugs* 2007; 67: 109–18.

Interactions. A woman who had been taking limaprost for peripheral vascular symptoms had 2 episodes of massive epistaxis about a month after starting *paroxetine*,[1] the second after a reduction in paroxetine dose. No further episodes of epistaxis occurred once the dose of limaprost was reduced from 15 to 10 micrograms daily. Limaprost dosage was subsequently returned to 15 micrograms daily without a recurrence in epistaxis, but evidence of subconjunctival bleeding developed.

1. Sugiyama N, *et al.* Massive epistaxis and subconjunctival hemorrhage due to combination of paroxetine and limaprost alfadex: a case report. *Prim Care Companion J Clin Psychiatry* 2007; 9: 240–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Opalmon.

Linsidomine Hydrochloride *(rINNM)*

Hidrocloruro de linsidomina; Linsidomina, hidrocloruro de; Linsidomine, Chlorhydrate de; Linsidomini Hydrochloridum; Линсидомина Гидрохлорид.

3-Morpholinosydnonimine hydrochloride.

$C_6H_{10}N_4O_3$,HCl=206.6.

CAS — 33876-97-0 (linsidomine); 16142-27-1 (linsidomine hydrochloride).

ATC — C01DX18.

ATC Vet — QC01DX18.

UNII — Y0054U597M.

Profile

Linsidomine is a nitrovasodilator and a metabolite of molsidomine (p. 1441.1) and has been given intravenously or via the intracoronary route for coronary vasodilatation.

References.

1. Delonca J, *et al.* Comparative efficacy of the intravenous administration of linsidomine, a direct nitric oxide donor, and isosorbide dinitrate in severe unstable angina: a French multicentre study. *Eur Heart J* 1997; 18: 1300–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Corvasal†.

Lisinopril *(BAN, USAN, rINN)*

L-154826; Lisinopriili; Lisinoprilum; Lizinopril; Lizinoprilis; MK-521; Лизиноприл.

N-[*N*-[(*S*)-1-Carboxy-3-phenylpropyl]-L-lysyl]-L-proline dihydrate.

$C_{21}H_{31}N_3O_5.2H_2O$=441.5.

CAS — 76547-98-3 (anhydrous lisinopril); 83915-83-7 (lisinopril dihydrate).

ATC — C09AA03.

ATC Vet — QC09AA03.
UNII — E7199S1YWR (lisinopril); 7Q3P4BS2FD (anhydrous lisinopril).

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Lisinopril Dihydrate). A white or almost white crystalline powder. Soluble in water; practically insoluble in dehydrated alcohol and in acetone; sparingly soluble in methyl alcohol.

USP 36: (Lisinopril). A white crystalline powder. Soluble 1 in 10 of water and 1 in 70 of methyl alcohol; practically insoluble in alcohol, in acetone, in acetonitrile, in chloroform, and in ether.

Suspension. The US licensed prescribing information provides the following method for making 200 mL of a suspension containing lisinopril 1 mg/mL. Add 10 mL of purified water to a polyethylene terephthalate bottle containing ten 20-mg tablets (*Prinivil, Merck* or *Zestril, AstraZeneca*) and shake for at least 1 minute. Add 30 mL of *Bicitra* (*Alza, USA*) and 160 mL of *Ora-Sweet SF* (*Paddock, USA*) to the bottle and gently shake for several seconds. The suspension should be stored at or below 25 degrees and can be stored for up to 4 weeks. Studies of the characteristics of this and other liquid dosage forms of lisinopril have been published.[1,2]

1. Thompson KC, *et al.* Characterization of an extemporaneous liquid formulation of lisinopril. *Am J Health-Syst Pharm* 2003; 60: 69–74.
2. Nahata MC, Morosco RS. Stability of lisinopril in two liquid dosage forms. *Ann Pharmacother* 2004; 38: 396–9.

Uses and Administration

Lisinopril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1) and heart failure (p. 1262.3), prophylactically after myocardial infarction (p. 1257.1), and in diabetic nephropathy (see Kidney Disorders, p. 1284.1).

The haemodynamic effects of lisinopril are seen within 1 to 2 hours of a single oral dose and the maximum effect occurs after about 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic action lasts for about 24 hours after once-daily dosing. Lisinopril is given orally as the dihydrate, but doses are expressed in terms of the anhydrous substance. Lisinopril 2.72 mg as the dihydrate is equivalent to about 2.5 mg of anhydrous lisinopril. The dose of lisinopril should be reduced in patients with renal impairment (see below).

In the treatment of **hypertension**, the usual initial dose is 10 mg daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Hypotension is particularly likely in patients with renovascular hypertension, volume depletion, heart failure, or severe hypertension and such patients should be given a lower initial dose of 2.5 to 5 mg once daily. Patients taking diuretics should have the diuretic withdrawn 2 or 3 days before lisinopril is started and resumed later if required; if this is not possible, an initial dose of 5 mg once daily should be given. The usual maintenance dose is 20 mg given once daily, though up to 80 mg daily may be given if necessary.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should be started with a low dose under close medical supervision. Lisinopril is given in an initial dose of 2.5 mg (or 5 mg in the USA) daily, increased as necessary in steps of no more than 10 mg at intervals of at least 2 weeks, to a maximum maintenance dose of 35 mg (or 40 mg in the USA) daily.

After **myocardial infarction**, lisinopril is licensed for use starting within 24 hours of the onset of symptoms in an initial dose of 5 mg once daily for two days, then increased to 10 mg once daily. An initial dose of 2.5 mg once daily is recommended for patients with a low systolic blood pressure.

In the management of **diabetic nephropathy**, hypertensive type 2 diabetics with microalbuminuria may be given a dose of 10 mg once daily, increased if necessary to 20 mg once daily to achieve a sitting diastolic blood pressure below 90 mmHg.

For doses in children, see below.

Reviews.

1. Lancaster SG, Todd PA. Lisinopril: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and congestive heart failure. *Drugs* 1988; 35: 646–69.
2. Goa KL, *et al.* Lisinopril: a review of its pharmacology and clinical efficacy in the early management of acute myocardial infarction. *Drugs* 1996; 52: 564–88.
3. Goa KL, *et al.* Lisinopril: a review of its pharmacology and use in the management of the complications of diabetes mellitus. *Drugs* 1997; 53: 1081–1105.
4. Simpson K, Jarvis B. Lisinopril: a review of its use in congestive heart failure. *Drugs* 2000; 59: 1149–67.

Administration in children. Lisinopril has been reported to be an effective and well-tolerated antihypertensive in children 6 years of age and older;[1] it has also been used successfully in younger children.[2] US licensed product information recommends for hypertension an oral starting dose for lisinopril of 70 micrograms/kg (up to 5 mg) once daily for children 6 years of age and older (but see also Administration in Renal Impairment, below). The *BNFC* recommends similar doses for children aged 6 to 12 years with hypertension or proteinuria in nephritis and states that this dose may be increased at intervals of 1 to 2 weeks to a maximum of 600 micrograms/kg or 40 mg once daily. For children between 12 and 18 years of age with hypertension, proteinuria in nephritis, or diabetic nephropathy, the *BNFC* recommends an initial dose of 5 mg once daily increased as necessary; the usual maintenance dose is 10 to 20 mg once daily (maximum 80 mg once daily).

In the treatment of heart failure in children between 12 and 18 years of age the *BNFC* recommends an initial dose of 2.5 mg once daily increased as necessary in steps of no more than 10 mg at intervals of at least 2 weeks to a maximum of 35 mg once daily.

1. Soffer B, *et al.* A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of lisinopril for children with hypertension. *Am J Hypertens* 2003; 16: 795–800.
2. Raes A, *et al.* Lisinopril in paediatric medicine: a retrospective chart review of long-term treatment in children. *J Renin Angiotensin Aldosterone Syst* 2007; 8: 3–12.

Administration in renal impairment. In *adult* patients with renal impairment, the initial dose of lisinopril should be reduced depending on the creatinine clearance (CC) as follows:

- CC 31 to 80 mL/minute: 5 to 10 mg once daily
- CC 10 to 30 mL/minute: 2.5 to 5 mg once daily
- CC less than 10 mL/minute or on dialysis: 2.5 mg once daily

The dose should be adjusted according to response, to a maximum of 40 mg once daily.

US licensed prescribing information states that lisinopril should not be given to *children* with a glomerular filtration rate of less than 30 mL/minute per 1.73 m^2 but gives no guidance on dosage in other children with renal impairment.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lisinopril as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Lisinopril is slowly and incompletely absorbed after oral doses. About 25% of a dose is absorbed on average, but the amount varies considerably between individuals, ranging from about 6 to 60%. It is already an active diacid and does not need to be metabolised *in vivo*. Peak concentrations in plasma are reported to occur after about 7 hours. Lisinopril is reported not to be significantly bound to plasma proteins. It is excreted unchanged in the urine. The effective half-life for accumulation after multiple doses is 12 hours in patients with normal renal function. Lisinopril is removed by haemodialysis.

References.

1. Till AE, *et al.* The pharmacokinetics of lisinopril in hospitalized patients with congestive heart failure. *Br J Clin Pharmacol* 1989; 27: 199–204.
2. Neubeck M, *et al.* Pharmacokinetics and pharmacodynamics of lisinopril in advanced renal failure: consequence of dose adjustment. *Eur J Clin Pharmacol* 1994; 46: 537–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Doxapril; Lisinal; Sedotensil; Tensopril; Tersif; Zestril; ***Austral.***: Fibsol; Liprace; Lisinobell†; Lisodur; Prinivil; Zestril; ***Austria***: Acemin; Acetan; Lisihexal; Lisinostad; ***Belg.***: Zestril; ***Braz.***: Lisinovil; Lisopril; Listril; Lonipril; Prilcor; Prinivil; Prinopril; Vasojet; Zestril; Zinopril; ***Canad.***: Prinivil; Zestril; ***Chile***: Acerdil; Liprerent†; Presokin†; Tonotensil; ***China***: Diyiluo (帝益洛); Yi Mai Ou (益迈欧); Yijikang (易集康); Zestril (捷赐瑞); ***Cz.***: Dapril; Diroton; Lipribela†; Lisigamma†; Lisipril; Prinivil†; ***Denm.***: Cardiostad; Lisinomed†; Lisinomer; Lisinotens; ***Fin.***: Cardiostad; Lisipril; ***Fr.***: Prinivil; Zestril; ***Ger.***: Acerbon†; Coric†; Lisi Lich; Lisi-Puren†; Lisi; Lisibeta; Lisidigal; Lisidoc†; Lisigamma; Lisihexal†; ***Gr.***: Adicanil; Axelvin; Gnostoval; Hyperliz; Icoran; Landolaxin; Leruze; Lisinospes; Lisodinol; Mealis; Nafordyl; Perenal; Press-12; Pressamea; Pressuril; Prinivil; Terolinal; Thriusedon; Tivirlon; Vercol; Veroxil; Z-Bec; Zestril; ***Hong Kong***: Cipril; Prinivil; Zestril; ***Hung.***: Conpres†; Linipril; Lisopress; Press-12; ***India***: Acebitor; Biopril; Cipril; Dilace; Dilis; ES; Hipril; L-Pril; Lesopril; Linopril; Linoril; Linvas; Lipril; Liscard; Lisicard; Lisinace; Lisir; Lisiriv; Lisitec; Lislo; Lisnop; Lisoril; Lisotec; Listril; Nivant; Normopril; Odace; ***Indon.***: Inhitril; Interpril; Linoxal; Noperten; Nopril; Odace; Tensinop; Tensiphar; Zestril; ***Irl.***: Bellisin; ByZestra; Caracе†; Lestace; Lisopress; Lispril; Zesger; Zestan; Zestril; ***Israel***: Tensopril; ***Ital.***: Alapril; Prinivil; Zestril; ***Jpn***: Longes; ***Malaysia***: Acepril; Dapril; Lisdene; Ranopril; Zestril; ***Mex.***: Alfaken; Dosteril; Fersivag; Linospril†; Noril†; Priniser; Prinivil; Zestril; ***Neth.***: Zestril; ***Norw.***: Vivatec†; Zestril; ***NZ***: Prinivil; ***Philipp.***: Listril; Sinolip†; Zestril; ***Pol.***: Diroton; Ikapril; Lisdene†; Lisihexal; Lisinoratio; Lisiprol; Prinivil; Ranopril; ***Port.***: Benzin†; Ecapril; Lipril; Lisinol†; Lisopress†; Prinivil; Zestril; ***Rus.***: Dapril (Даприл); Diropress (Дироппресс); Diroton (Диротон); Irumed (Ирумед); Lisacard (Лизакард); Lisigamma (Лизигамма); Lisinoton (Лизинотон); Lisoril (Лизорил); Listril (Листрил); Liten (Литэн); Lysonorm (Лизонорм); Rilace (Рилейс); Sinopril (Синоприл); ***S.Afr.***: Adco-Zetomax; Lizro; Lysin; Prinivil†; Sinopren; Zemax; Zeprosil†; Zestril; ***Singapore***: Dapril; Hipril; Lisdene; Lisoril; Noperten; Prinivil; Zestril; ***Spain***: Belprel†; Doneka; Iricil†; Likenil; Prinivil; Tensikey†; Zestril; ***Swed.***: Zestril; ***Switz.***: Listril; Lisopril; Prinil; Zestril; ***Thai.***: Lisdene; Lisir; Lispril; Zestril; ***Turk.***: Acerilin; Inhibril; Rilace; Sinopryl; Zestril; ***UAE***: Lisotec; ***UK***: Caracе†; Zestril; ***Ukr.***: Diroton (Диротон); Linotor (Линотор); Lipril (Липрил); Lisigamma (Лизигамма)†; Lisihexal (ЛизиГЕКСАЛ)†; Lopril (Лоприл); Vitopril (Витоприл); ***USA***: Prinivil; Zestril; ***Venez.***: Cotensil; Lisilet; Prinivil; Rantex; Tonoten.

Multi-ingredient Preparations. *Arg.*: Tensopril D; Zestoretic; ***Austria***: Acecomb; Acelisino comp; Co-Acetan; Co-Lisinostad; Lisihexal comb; Lisinocomp; Lisinopril comp; ***Belg.***: Co-Lisinopril; Zestoretic; ***Braz.***: Lisodor; Lonipril-H; Prinzide; Zestoretic; ***Canad.***: Prinzide; Zestoretic; ***Chile***: Acerdil-D; Tonotensil D; ***Cz.***: Amesos; Lipribela plus H†; Skopryl Plus H; ***Denm.***: Evapril comp†; Krinolis; Lisinoplus; ***Fin.***: Lisipril Comp; ***Fr.***: Prinzide; Zestoretic; ***Ger.***: Acercomp; Coric Plus†; Lisi HCT; Lisi-Puren comp†; Lisibeta comp; Lisidigal HCT; Lisigamma HCT; Lisihexal comp†; LisiLich comp†; Lisinopril comp; Lisinopril HCT†; Lisiplus†; ***Gr.***: Prinzide; Z-Bec Plus; Zestoretic; ***Hong Kong***: Zestoretic; ***Hung.***: Lisonorm; Lisopress HCT; ***India***: Aamin-L; Acedip; Acinopril; Alis-Plus; Alis; Amchek L; Amdepin-L; Amlace; Amlo-L; Amlodac-L; Amlokath-L; Amlopres L; Amlosafe-LS; Amlot-L; Amlovas-L; Amtas-LP; Biopril AM; Calchek L; Carvasc-L; Cipril-H; Dip-A; Hipril-A; Inace; Lipril-AM; Lipril-H; Lismol; Lisoril-5HT; Listril AM; Listril Plus; Listril-SM; Neocard-Lis; Numlo-L; ***Indon.***: Zestoretic; ***Irl.***: Carace Plus†; Lisprilhydrochlorothiazide; Zesger Plus; Zestoretic; ***Ital.***: Nalapres; Prinzide; Zestoretic; ***Mex.***: Prinzide; Zestoretic; ***Neth.***: Lisidigal HCT; Lizam; Zestoretic; ***Norw.***: Vivatec Comp†; Zestoretic; ***Philipp.***: Zestoretic; ***Pol.***: Dironorm; ***Port.***: Ecamais; Lisoplus†; Prinzide; Tiazinol†; Zestoretic; ***Rus.***: Co-Diroton (Ко-Диротон); Ekvator (Экватор); Iruzid (Ирузид); Lisinoton H (Лизинотон H); Lisoretic (Лизоретик); Listril Plus (Листрил Плюс); Liten H (Литэн H); Rilace Plus (Рилейс Плюс); Sinorezid (Синорезид); ***S. Afr.***: Adco-Zetomax Co†; Diace Co; Hexal-Lisinopril Co; Lisinozide; Lisoretic; Lisozide; Zestoretic; Zestozide; ***Spain***: Doneka Plus; Iricil Plus†; Prinivil Plus; Secubar Diu†; Tensikey Complex; Zestoretic; ***Swed.***: Zestoretic†; ***Switz.***: Co-Lisinopril; Lisitril comp; Lisopril plus; Prinzide; Zestoretic; ***Turk.***: Rilace Plus; Sinoretik; Zestoretic; ***UK***: Carace Plus; Caralpha; Lisicostad; Zestoretic; ***Ukr.***: Co-Diroton (Ко-Диротон); Combipril (Комбиприл); Ekvator (Экватор); Hypril-A (Гиприл-А); Liprazid (Липразид); Lisopres (Лизопрес); Lisoretic (Лизоретик); Lisotiasid (Лизотиазид); Lopril H (Лоприл H); Neocard-Lis (НеокардЛиз)†; ***USA***: Prinzide; Zestoretic; ***Venez.***: Lisiletic.

Pharmacopoeial Preparations

BP 2014: Lisinopril Oral Solution; Lisinopril Tablets;
USP 36: Lisinopril and Hydrochlorothiazide Tablets; Lisinopril Oral Suspension; Lisinopril Tablets.

Lomitapide (USAN, rINN)

AEGR-733; BMS-201038-01; Lomitapida; Lomitapidum; Ломитапид.

N-(2,2,2-Trifluoroethyl)-9-(4-{4-[4'-(trifluoromethyl)(1,1'-biphenyl)-2-carboxamido]piperidin-1-yl}butyl)-9*H*-fluorene-9-carboxamide.

$C_{39}H_{37}F_6N_3O_2$=693.7

CAS — 182431-12-5.
ATC — C10AX12.
ATC Vet — QC10AX12.
UNII — 82KUB0583F.

Lomitapide Mesilate (rINNM)

AEGR-733; BMS-201038-04; BMS-201038; Lomitapide Mesilate de; Lomitapide Mesylate (USAN); Lomitapidi Mesilas; Mesilato de Lomitapida; Ломитапида Мезилат.

$C_{39}H_{37}F_6N_3O_2.CH_4O_3S$=789.8

CAS — 202914-84-9.
ATC — C10AX12.
ATC Vet — QC10AX12.
UNII — X4S83CP54E.

Uses and Administration

Lomitapide directly binds to and inhibits microsomal triglyceride transfer protein, thereby inhibiting the synthesis of chylomicrons and very-low-density lipoprotein. It is used in the treatment of homozygous familial hypercholesterolaemia as an adjunct to dietary measures and other lipid-lowering treatments to reduce low-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and non-high-density lipoprotein cholesterol.

Lomitapide is given as the mesilate but doses are expressed as the base; lomitapide mesilate 11.4 mg is equivalent to about 10 mg of lomitapide. It is taken orally on an empty stomach once daily; during treatment, patients should take daily vitamin E and fatty acids supplementation to reduce the risk of a fat-soluble nutrient deficiency. An initial dose of 5 mg daily is given for at least 2 weeks and then is increased incrementally according to response and tolerance:

- 10 mg daily for at least 4 weeks
- 20 mg daily for at least 4 weeks
- 40 mg daily for at least 4 weeks
- 60 mg daily (maximum dose)

When lomitapide is given with weak cytochrome P450 isoenzyme CYP3A4 inhibitors, the maximum dose should be 30 mg daily; moderate and strong CYP3A4 inhibitors should not be used with lomitapide, see Interactions, below. Treatment may need to be modified for hepatic or renal impairment, see below.

References.
1. Anonymous. Lomitapide. *Am J Cardiovasc Drugs* 2011; 11: 347–52.
2. Cuchel M, *et al.* Phase 3 HoFH Lomitapide Study investigators. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. *Lancet* 2013; 381: 40–6.

Administration in hepatic impairment. Patients with active liver disease, including unexplained persistent increases in serum transaminases, and those with pre-existing moderate or severe hepatic impairment (defined as Child-Pugh class B or C) should not be treated with lomitapide. Exposure to lomitapide was increased by about 50% in patients with mild hepatic impairment (Child-Pugh class A) and the oral dose of lomitapide should not exceed 40 mg daily in these patients.

Treatment should also be modified for increases in serum transaminases occurring during lomitapide therapy.

- for increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) concentrations between 3 times the upper limit of normal (ULN) and 5 times the ULN: reduce the dose of lomitapide and repeat liver function tests weekly; withhold dosing if there are other associated signs of abnormal hepatic function such as increased bilirubin or INR, or if transaminases do not recover to below 3 times the ULN within about 4 weeks. If resuming lomitapide treatment once transaminases have recovered to below 3 times the ULN, consider reducing the dose and measure liver function tests more frequently
- for ALT or AST concentrations 5 times the ULN or above: withhold lomitapide. If resuming lomitapide treatment once transaminases have recovered to below 3 times the ULN, reduce the dose and measure liver function tests more frequently
- if increased transaminase concentrations are accompanied by signs of liver injury (such as nausea, vomiting, abdominal pain, fever, jaundice, lethargy, and flu-like symptoms), active liver disease, or increases in bilirubin 2 or more times the ULN, lomitapide should be stopped

Administration in renal impairment. Exposure to lomitapide was increased by about 50% in patients with end-stage renal disease on dialysis and the oral dose of lomitapide should not exceed 40 mg daily in these patients; licensed product information states that there is no data to guide dosing in other patients with renal impairment.

Adverse Effects and Precautions

Gastrointestinal adverse effects, particularly diarrhoea, and also nausea, vomiting, dyspepsia, constipation, and abdominal pain are commonly reported with lomitapide. There may be reduced absorption of fat-soluble vitamins and serum fatty acids, and supplements are required.

Increases in liver enzyme values have been seen and lomitapide should not be used in patients with moderate or severe hepatic impairment or those with active liver disease. It may also cause hepatic steatosis, which is thought to be reversible upon stopping treatment. Liver function tests should be measured before starting treatment and then for the first year repeated at least every month and before any increase in dose. Thereafter, tests should be repeated at least every 3 months and before any increase in dose. Treatment may need to be modified if hepatotoxicity occurs, see Administration in Hepatic Impairment, above.

Lomitapide is teratogenic in some *animals* and should not be used in pregnant women.

Interactions

Lomitapide is metabolised by the cytochrome P450 isoenzyme CYP3A4. The potent CYP3A4 inhibitor ketoconazole increased exposure to lomitapide 27-fold, and both moderate and potent CYP3A4 inhibitors should not be given with lomitapide; dose modification may be necessary if weak CYP3A4 inhibitors are used, see Uses and Administration, above.

Lomitapide also inhibits CYP3A4 and can increase exposure to CYP3A4 substrates, such as simvastatin; dose adjustments may be required, see Uses and Administration of Simvastatin, p. 1489.3.

Lomitapide is also an inhibitor of P-glycoprotein and may increase the absorption of P-glycoprotein substrates; dose reduction of the P-glycoprotein substrate should be considered.

Lomitapide increases warfarin concentrations and may affect INR.

Pharmacokinetics

Peak plasma concentrations of lomitapide occur about 6 hours after an oral dose. The absolute bioavailability is about 7% and plasma-protein binding is 99.8%. It is extensively metabolised in the liver, with cytochrome P450 isoenzyme CYP3A4 an important pathway; CYP1A2, CYP2B6, CYP2C8, and CYP2C19 may play a minor role. Just over half of a dose is excreted in the urine and about a third in the faeces. The mean terminal half-life is 39.7 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Lojuxta; *USA*: Juxtapid.

Losartan Potassium *(BANM, USAN, rINNM)*

DuP-753; E-3340; Kalii Losartanum; Losartaanikalium; Losartan-Kalium;. Losartán potásico; Losartan Potassique; Losartan Potasyum; Losartankalium; Losartanum Kalicum; MK-0954; Калия Лозартан.

2-Butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol potassium.

$C_{22}H_{22}ClKN_6O$=461.0

CAS — 114798-26-4 (losartan); 124750-99-8 (losartan potassium).

ATC — C09CA01.

ATC Vet — QC09CA01.

UNII — 3ST302B24A.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Losartan Potassium). A white or almost white, hygroscopic crystalline powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; slightly soluble in acetonitrile. Store in airtight containers.

USP 36: (Losartan Potassium). A white to off-white powder. Freely soluble in water; slightly soluble in acetonitrile; soluble in isopropyl alcohol.

Uses and Administration

Losartan is an angiotensin II receptor antagonist with antihypertensive activity due mainly to selective blockade of AT_1 receptors and the consequent reduced pressor effect of angiotensin II. It is used in the management of hypertension (p. 1251.1) and heart failure (p. 1262.3), particularly in patients who develop cough with ACE inhibitors. It is also used to reduce the risk of stroke in patients with left ventricular hypertrophy, and in the treatment of diabetic nephropathy (see Kidney Disorders, p. 1423.3), and has been tried in myocardial infarction (p. 1257.1).

Losartan is given orally as the potassium salt. The maximum hypotensive effect is achieved in about 3 to 6 weeks after starting treatment.

In **hypertension** the usual dose of losartan potassium is 50 mg once daily. The dose may be increased, if necessary, to 100 mg daily as a single dose or in two divided doses. An initial dose of 25 mg once daily should be given to patients with intravascular fluid depletion, and to those with hepatic impairment.

Losartan potassium is used for **heart failure** in those aged 60 years and over. An initial dose of 12.5 mg is given once daily, and may be doubled at weekly intervals to a usual maintenance dose of 50 mg once daily.

In **diabetic nephropathy** losartan potassium is given in an initial dose of 50 mg once daily, increased to 100 mg once daily depending on the blood pressure.

For the use of losartan in children, see below.

Reviews.
1. Carr AA, Prisant LM. Losartan: first of a new class of angiotensin antagonists for the management of hypertension. *J Clin Pharmacol* 1996; 36: 3–12.
2. Goa KL, Wagstaff AJ. Losartan potassium: a review of its pharmacology, clinical efficacy and tolerability in the management of hypertension. *Drugs* 1996; 51: 820–45.
3. Schaefer KL, Porter JA. Angiotensin II receptor antagonists: the prototype losartan. *Ann Pharmacother* 1996; 30: 625–36.
4. Burrell LM. A risk-benefit assessment of losartan potassium in the treatment of hypertension. *Drug Safety* 1997; 16: 56–65.
5. McConnaughey MM, *et al.* Practical considerations of the pharmacology of angiotensin receptor blockers. *J Clin Pharmacol* 1999; 39: 547–59.
6. Burnier M, Brunner HR. Angiotensin II receptor antagonists. *Lancet* 2000; 355: 637–45.
7. Dina R, Jafari M. Angiotensin II-receptor antagonists: an overview. *Am J Health-Syst Pharm* 2000; 57: 1231–41.
8. Rodgers JE, Patterson JH. Angiotensin II-receptor blockers: clinical relevance and therapeutic role. *Am J Health-Syst Pharm* 2001; 58: 671–81. Correction. *ibid.*: 1658.
9. Moen MD, Wagstaff AJ. Losartan: a review of its use in stroke risk reduction in patients with hypertension and left ventricular hypertrophy. *Drugs* 2005; 65: 2657–74.

Administration. Although the conventional dose of losartan in adults with heart failure is 50 mg daily (see above) it has been suggested that higher doses might produce greater benefit. A large multicentre study[1] in patients with moderate to severe heart failure who were intolerant of ACE inhibitors compared treatment with losartan 50 mg daily (in 1913 patients) and 150 mg daily (in 1921). Over a median follow-up of 4.7 years, patients in the higher dose group had a reduced rate of death or hospital admission for heart failure. Renal impairment, hypotension, and hyperkalaemia were more common in patients taking the higher dose than in those on the lower, but these adverse events did not result in a significantly increased rate of stopping the drug. Angioedema occurred in 6 patients in the high-dose group, 4 of whom stopped the drug, and in none of those taking the lower dose. It was suggested that increased doses of an angiotensin II receptor antagonist are needed to produce optimum benefit in this population.

1. Konstam MA, *et al.* HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* 2009; 374: 1840–8. Correction. *ibid.*: 1888.

Administration in children. Losartan has been studied in a limited number of children with **hypertension.** A study[1] in children aged 6 to 16 years, about half of whom also had renal disorders, found that losartan effectively lowered blood pressure and was well tolerated. Another study,[2] in which all of the children had hypertension associated with chronic renal disorders, also found that losartan was effective.

Children aged from 6 years and weighing from 20 to 50 kg may be given losartan potassium in a usual initial oral dose of 700 micrograms/kg (maximum 25 mg) daily, adjusted if necessary to a maximum of 50 mg daily. Those weighing over 50 kg may be given an initial oral dose of 1.4 mg/kg (maximum 50 mg) daily, adjusted if necessary to a maximum of 100 mg daily.

There are no data to recommend doses for children with a glomerular filtration rate below 30 mL/min per 1.73 m^2. In the UK, use of losartan in children with hepatic impairment is also not recommended.

Losartan has also been used in children with **proteinuria associated with renal disorders** and appears to have an antiproteinuric and renoprotective effect.[2-4]

A retrospective cohort study[5] in 18 children with **Marfan's syndrome,** suggested that angiotensin II receptor antagonists (losartan in 17; irbesartan in 1) may reduce the progression of aortic root dilatation, but these results require confirmation.

1. Shahinfar S, *et al.* A double-blind, dose-response study of losartan in hypertensive children. *Am J Hypertens* 2005; 18: 183–90.
2. Ellis D, *et al.* Antihypertensive and renoprotective efficacy and safety of losartan: a long-term study in children with renal disorders. *Am J Hypertens* 2004; 17: 928–35.
3. Ellis D, *et al.* Long-term antiproteinuric and renoprotective efficacy and safety of losartan in children with proteinuria. *J Pediatr* 2003; 143: 89–97.
4. Lubrano R, *et al.* Renal and cardiovascular effects of angiotensin-converting enzyme inhibitor plus angiotensin II receptor antagonist therapy in children with proteinuria. Abstract: *Pediatrics* 2006; 118: e833. Full text: http://pediatrics.aappublications.org/cgi/reprint/118/3/e833 (accessed 13/03/08)
5. Brooke BS, *et al.* Angiotensin II blockade and aortic-root dilation in Marfan's syndrome. *N Engl J Med* 2008; 358: 2787–95.

Administration in hepatic impairment. Lower initial doses are recommended in mild or moderate hepatic impairment—see above. Losartan is contra-indicated in severe hepatic impairment.

Cardiac arrhythmias. Long-term studies of angiotensin II receptor antagonists for heart failure or hypertension have suggested that they may reduce the incidence of new-onset atrial fibrillation.[1,2] There is also some evidence[3,4] that they may increase the efficacy of amiodarone for preventing recurrence of atrial fibrillation after cardioversion. However, addition of valsartan to established therapies in

patients with a history of atrial fibrillation had no effect on the risk of the arrhythmia recurring,[3] and the role of angiotensin II receptor blockers in the management of cardiac arrhythmias (p. 1266.1) remains to be established.

1. Healey JS, *et al.* Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol* 2005; **45**: 1832–9.
2. Schmieder RE, *et al.* Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. *J Hypertens* 2008; **26**: 403–11.
3. Madrid AH, *et al.* Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation: a prospective and randomized study. *Circulation* 2002; **106**: 331–6.
4. Pogari R, *et al.* Losartan and prevention of atrial fibrillation recurrence in hypertensive patients. *J Cardiovasc Pharmacol* 2006; **47**: 46–50.
5. Disertori M, *et al.* GISSI-AF Investigators. Valsartan for prevention of recurrent atrial fibrillation. *N Engl J Med* 2009; **360**: 1606–17. Correction. *ibid.*: 2379.

Cardiovascular risk reduction. Antihypertensive drugs have an established role in patients with high cardiovascular risk (see Cardiovascular Risk Reduction, p. 1246.1) and it has been suggested that those targeting the renin-angiotensin system have particular benefits. Angiotensin II receptor antagonists have been shown to reduce the incidence of cardiovascular events, but whether they are superior to other antihypertensives remains unclear. In the LIFE study,[1] losartan reduced cardiovascular events more than a beta blocker (atenolol), despite a similar effect on blood pressure. In VALUE,[2] there was no difference in the incidence of cardiovascular events between valsartan and a calcium-channel blocker (amlodipine), although the calcium-channel blocker reduced blood pressure to a greater extent. However, in hypertensive stroke patients,[3] eprosartan reduced the risk of cardiovascular and cerebrovascular events more than another calcium-channel blocker (nitrendipine); blood pressure reduction was similar with both drugs. A study[4] comparing telmisartan with the ACE inhibitor ramipril, found that both reduced cardiovascular events to a similar extent; there was no additional benefit in patients given both drugs. Use of telmisartan in patients unable to tolerate ACE inhibitors was associated with a modest benefit in terms of cardiovascular death, myocardial infarction, and stroke, but there was no effect on hospitalisations for heart failure.[5]

Some studies have suggested that angiotensin II receptor antagonists may be particularly effective at reducing the incidence of stroke.[3,6] However, use of candesartan to treat hypertension in patients with acute stroke[7] had no effect on cerebrovascular events, although cardiovascular mortality was reduced, while a study[8] in patients with recent ischaemic stroke found that telmisartan had no significant effect on recurrent stroke or major cardiovascular events.

Based on the results of VALUE, there has been concern that angiotensin II receptor antagonists may increase the risk of myocardial infarction, but a systematic review and meta-analysis[9] of 37 randomised controlled studies (including 147 020 patients) found no evidence of excess risk.

1. Dahlöf B, *et al.* Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**: 995–1003.
2. Julius S, *et al.* Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004; **363**: 2022–31.
3. Schrader J, *et al.* Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomized controlled study (MOSES). *Stroke* 2005; **36**: 1218–24.
4. Yusuf S, *et al.* ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; **358**: 1547–59.
5. Yusuf S, *et al.* Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* 2008; **372**: 1174–83. Correction. *ibid.*: 1384.
6. Moen MD, Wagstaff AJ. Losartan: a review of its use in stroke risk reduction in patients with hypertension and left ventricular hypertrophy. *Drugs* 2005; **65**: 2657–74.
7. Schrader J, *et al.* The ACCESS Study: evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. *Stroke* 2003; **34**: 1699–1703.
8. Yusuf S, *et al.* PRoPESS Study Group. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med* 2008; **359**: 1225–37.
9. Bangalore S, *et al.* Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147 020 patients from randomised trials. *BMJ* 2011; **342**: d2234.

Diabetic complications. Although angiotensin II receptor antagonists have been associated with a reduced awareness of hypoglycaemia (see Diabetes Mellitus under Precautions, p. 1424.3) they have an established role as an alternative to ACE inhibitors in the management of diabetic nephropathy (see Kidney Disorders, below). ACE inhibitors may also reduce the progression of retinopathy in type 1 diabetics (see Diabetic Complications under Uses of ACE Inhibitors, p. 1282.3) and angiotensin II antagonists have therefore been investigated for similar effects. Studies with candesartan in type 1 and type 2 diabetics have suggested little effect on the progression of retinopathy,[1,2] but the incidence of retinopathy in type 1 diabetics was reduced.[1]

There is also some evidence[3-7] that angiotensin II receptor antagonists may prevent the development of diabetes in non-diabetic patients.

1. Chaturvedi N, *et al.* Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials. *Lancet* 2008; **372**: 1394–1402.
2. Sjølie AK, *et al.* Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial. *Lancet* 2008; **372**: 1384–93.
3. Padwal R, Laupacis A. Antihypertensive therapy and incidence of type 2 diabetes: a systematic review. *Diabetes Care* 2004; **27**: 247–55.
4. Gillespie EL, *et al.* The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. *Diabetes Care* 2005; **28**: 2261–6.
5. Abuissa H, *et al.* Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 2005; **46**: 821–6.
6. Yusuf S, *et al.* Effects of candesartan on the development of a new diagnosis of diabetes mellitus in patients with heart failure. *Circulation* 2005; **112**: 48–53. Correction. *ibid.*: e292.
7. Aguilar D, Solomon SD. ACE inhibitors and angiotensin receptor antagonists and the incidence of new-onset diabetes mellitus: an emerging theme. *Drugs* 2006; **66**: 1169–77.

Erythrocytosis. For reference to the use of losartan in the management of secondary erythrocytosis, see under ACE inhibitors, p. 1283.1

Heart failure. Angiotensin II receptor antagonists have been studied as an alternative to ACE inhibitors in the management of heart failure (p. 1262.3). In the ELITE study,[1] which compared losartan with captopril, both drugs had similar effects on renal function but other adverse effects were fewer with losartan and there was also a reduction in mortality in patients taking losartan. However, the larger ELITE II study[2] failed to confirm any survival benefit with losartan, and studies with losartan[3] and valsartan[4] in patients with heart failure after myocardial infarction have also failed to show superiority over ACE inhibitors. ACE inhibitors therefore remain first-line therapy, although angiotensin II receptor antagonists may be used as an alternative, particularly in patients unable to tolerate ACE inhibitors.[5,6] The combination of angiotensin II receptor antagonists with ACE inhibitors has also shown some benefit.[6] In the ValHeFT study,[7] valsartan was added to standard therapy (including ACE inhibitors in most patients) and reduced the combined end-point of death or hospitalisation for heart failure, although the effect on mortality alone was not significant. In the CHARM-Added study,[8] addition of candesartan to therapy including an ACE inhibitor also led to a reduction in cardiovascular events. However, in the VALIANT study,[4] no additional benefit was found from using valsartan with captopril. There has been some concern that use of triple therapy with angiotensin II receptor antagonists, ACE inhibitors, and beta blockers might be detrimental, but this has not been confirmed. In ValHeFT,[7] mortality appeared to be increased in patients taking all three drug classes, but in both CHARM-Added[8] and VALIANT[4] use of beta blockers had no effect on the results. Use of ACE inhibitors and angiotensin II receptor antagonists together may therefore be considered in patients who remain symptomatic despite standard therapy, including patients taking beta blockers.[9,10]

For a study reporting greater benefit in heart failure with increased doses of an angiotensin II receptor antagonist see Administration, p. 1422.3.

1. Pitt B, *et al.* Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997; **349**: 747–52.
2. Pitt B, *et al.* Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000; **355**: 1582–7.
3. Dickstein K, *et al.* Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *Lancet* 2002; **360**: 752–60.
4. Pfeffer MA, *et al.* Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; **349**: 1893–1906. Correction. *ibid.* 2004; **350**: 203.
5. Granger CB, *et al.* Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003; **362**: 772–6.
6. Jong P, *et al.* Angiotensin receptor blockers in heart failure: meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2002; **39**: 463–70.
7. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; **345**: 1667–75.
8. McMurray JJV, *et al.* Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; **362**: 767–71.
9. NICE. Chronic heart failure: management of chronic heart failure in adults in primary and secondary care (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13099/50517/50517.pdf (accessed 13/10/10)
10. Dickstein K, *et al.* Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. *Eur Heart J* 2008; **29**: 2388–2442. Correction. *ibid.* 3069. [dose] Also available at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-HF-FT.pdf (accessed 14/10/08)

Kidney disorders. ACE inhibitors have an established role in the management of type 1 and type 2 diabetics with nephropathy, whether or not they are hypertensive, and may also slow the progression of nephropathy in diabetics with microalbuminuria (but see p. 1284.1). A number of studies have investigated the effects of angiotensin II receptor antagonists in type 2 diabetics with varying degrees of nephropathy (see p. 465.1). Irbesartan,[1,2] losartan,[3,4] olmesartan,[5] and valsartan[6] have all been reported to reduce the progression of nephropathy independently of their effect on blood pressure. The magnitude of the benefit in retarding progression of nephropathy seems to be similar with angiotensin II receptor antagonists and ACE inhibitors,[7-9] and the American Diabetes Association considers them equal first choices in the management of the condition.[10] However, the value of these drugs in very early disease has been questioned by a 5-year study of losartan or enalapril in patients with type 1 diabetes who were normotensive and had no albuminuria at the start;[11] this study, which directly measured structural changes in the kidney, found that neither drug slowed the progression of nephropathy.[11]

Angiotensin II receptor antagonists have also reduced urinary albumin excretion in non-diabetic patients, including those with hypertension,[12] and those with IgA nephropathy.[13]

A study[14] in diabetics using a combination of candesartan with lisinopril found that blood pressure and microalbuminuria were reduced more with combination therapy than with either drug alone. However, in another study[15] in patients at high vascular risk but mostly without evidence of advanced renal disease, telmisartan had similar effects on renal outcomes to the ACE inhibitor ramipril, but combination therapy had detrimental effects.

1. Lewis EJ, *et al.* Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; **345**: 851–60.
2. Parving H-H, *et al.* The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001; **345**: 870–8.
3. Brenner BM, *et al.* Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; **345**: 861–9.
4. Zandbergen AAM, *et al.* Effect of losartan on microalbuminuria in normotensive patients with type 2 diabetes mellitus: a randomized clinical trial. *Ann Intern Med* 2003; **139**: 90–6.
5. Haller H, *et al.* Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med* 2011; **364**: 907–17.
6. Viberti G, Wheeldon NM. MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. *Circulation* 2002; **106**: 672–8.
7. Barnett AH, *et al.* Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004; **351**: 1952–61. Correction. *ibid.* 2005; **352**: 1731.
8. Strippoli GFM, *et al.* Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 15/06/09).
9. Kunz R, *et al.* Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin-angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008; **148**: 30–48.
10. American Diabetes Association. Nephropathy in diabetes. *Diabetes Care* 2004; **27** (suppl 1): S79–S83. Also available at: http://care.diabetesjournals.org/content/27/suppl_1/s79.full.pdf (accessed 15/06/09)
11. Mauer M, *et al.* Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med* 2009; **361**: 40–51.
12. Vogt L, *et al.* Angiotensin II Receptor Antagonist Telmisartan Micardis in Isolated Systolic Hypertension (ARAMIS) Study Group. The angiotensin II receptor antagonist telmisartan reduces urinary albumin excretion in patients with isolated systolic hypertension: results of a randomized, double-blind, placebo-controlled trial. *J Hypertens* 2005; **23**: 2055–61.
13. Li PK-T, *et al.* Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. *Am J Kidney Dis* 2006; **47**: 751–60.
14. Mogensen CE, *et al.* Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ* 2000; **321**: 1440–4.
15. Mann JFE, *et al.* Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 2008; **372**: 547–53.

Marfan's syndrome. See Administration in Children, p. 1422.3.

Migraine. Angiotensin II receptor antagonists may reduce the incidence of headache. A randomised study[1] in 60 patients with migraine suggested that candesartan might be effective for prophylaxis, and beneficial results have also been reported[2] with olmesartan. However, there has been a report of migraine caused by losartan (see under Adverse Effects, p. 1424.2).

1. Tronvik E, *et al.* Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. *JAMA* 2003; **289**: 65–9.
2. Charles JA, *et al.* Prevention of migraine with olmesartan in patients with hypertension/prehypertension. *Headache* 2006; **46**: 503–7.

Stroke. See Cardiovascular Risk Reduction, above.

Uricosuric action. Losartan has been found to increase urinary uric acid excretion and reduce serum uric acid concentrations in healthy subjects[1] and in hypertensive

patients.[2,3] However, the effect is generally small and the clinical significance is not clear. Other angiotensin II receptor antagonists do not appear to have such an effect.[2,3]

1. Nakashima M, *et al.* Pilot study of the uricosuric effect of DuP-753, a new angiotensin II receptor antagonist, in healthy subjects. *Eur J Clin Pharmacol* 1992; 42: 333–5.
2. Puig JG, *et al.* Effect of eprosartan and losartan on uric acid metabolism in patients with essential hypertension. *J Hypertens* 1999; 17: 1033–9.
3. Würzner G, *et al.* Comparative effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricaemia and gout. *J Hypertens* 2001; 19: 1855–60.

Adverse Effects

Adverse effects of losartan have been reported to be usually mild and transient, and include dizziness, headache, and dose-related orthostatic hypotension. Hypotension may occur particularly in patients with volume depletion (for example those who have received high-dose diuretics). Impaired renal function and, rarely, rash, urticaria, pruritus, angioedema, and raised liver enzyme values may occur. Hyperkalaemia, myalgia, and arthralgia have been reported. Losartan appears less likely than ACE inhibitors to cause cough. Other adverse effects that have been reported with angiotensin II receptor antagonists include respiratory-tract disorders, back pain, gastrointestinal disturbances, fatigue, and neutropenia. Rhabdomyolysis has been reported rarely.

Reviews.

1. Mazzolai L, Burnier M. Comparative safety and tolerability of angiotensin II receptor antagonists. *Drug Safety* 1999; 21: 23–33.

Angioedema. Angioedema is a recognised adverse effect of ACE inhibitors and is thought to be due to accumulation of bradykinins. Although angiotensin II receptor antagonists were thought to lack effects on bradykinin, several have been associated with reports[1-7] of angioedema, and increased levels of bradykinin have been shown[8] with losartan. In some cases patients had previously experienced angioedema with ACE inhibitors and caution is advised when using angiotensin II receptor antagonists in such patients.[4,9]

1. Acker CG, Greenberg A. Angioedema induced by the angiotensin II blocker losartan. *N Engl J Med* 1995; 333: 1572.
2. van Rijnsoever EW, *et al.* Angioneurotic edema attributed to the use of losartan. *Arch Intern Med* 1998; 158: 2063–5.
3. Adverse Drug Reactions Advisory Committee. Angiotensin II receptor antagonists. *Aust Adverse Drug React Bull* 1999; 18: 2. Available at: http://www.tga.gov.au/adr/aadrb/aadr9902.pdf (accessed 13/03/08)
4. Howes LG, Tran D. Can angiotensin receptor antagonists be used safely in patients with previous ACE inhibitor-induced angioedema? *Drug Safety* 2002; 25: 73–6.
5. Irons BK, Kumar A. Valsartan-induced angioedema. *Ann Pharmacother* 2003; 37: 1024–7.
6. Nykamp D, Winter EE. Olmesartan medoxomil-induced angioedema. *Ann Pharmacother* 2007; 41: 518–20.
7. McCabe J, *et al.* Penile angioedema associated with the use of angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers. *Am J Health-Syst Pharm* 2008; 65: 420–1.
8. Campbell DJ, *et al.* Losartan increases bradykinin levels in hypertensive humans. *Circulation* 2005; 111: 315–20.
9. Warner KK, *et al.* Angiotensin II receptor blockers in patients with ACE inhibitor-induced angioedema. *Ann Pharmacother* 2000; 34: 526–8.

Carcinogenicity. A meta-analysis[1] that combined cancer-related findings from randomised controlled studies of angiotensin receptor blockers (ARBs) found that they were associated with a modest increase in occurrence of new cancers, with an absolute excess risk of cancer over four years of 1.2%. Later meta-analyses[2,3] did not support an association between use of ARBs and increased cancer risk, although an increased risk associated with the combined use of ARBs and ACE inhibitors could not be discounted.[2] In 2011, both the FDA[4] and EMEA[5] completed safety reviews examining the risk of cancer associated with ARB use; both agencies concluded that available evidence did not support a link between ARB use and increased cancer risk.

The possibility of a class variation in the risk of cancer with individual ARBs has also been suggested. A case-control study[6] in diabetic patients found that although ARBs as a class had no effect on cancer risk, an increased risk was noted for candesartan and telmisartan, individually, while losartan had a decreased risk.

1. Sipahi I, *et al.* Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. *Lancet Oncol* 2010; 11: 627–36.
2. Bangalore S, *et al.* Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324 168 participants from randomised trials. *Lancet Oncol* 2011; 12: 65–82.
3. Yoon C, *et al.* Use of angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers and cancer risk: a meta-analysis of observational studies. *CMAJ* 2011; 183: E1073–E1084.
4. FDA. Drug Safety Communication: no increase in risk of cancer with certain blood pressure drugs—angiotensin receptor blockers (ARBs) (issued 2nd June, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm257516.htm (accessed 07/02/12)
5. EMEA. European Medicines Agency concludes that benefit-risk balance of angiotensin II receptor antagonists remains positive (issued 20th October, 2011). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/10/WC500116865.pdf (accessed 07/02/11)
6. Chang CH, *et al.* Angiotensin receptor blockade and risk of cancer in type 2 diabetes mellitus: a nationwide case-control study. *J Clin Oncol* 2011; 29: 3001–7.

Effects on the blood. Symptomatic anaemia occurred[1] in a patient with a renal transplant 6 weeks after starting therapy with losartan. Decreased haemoglobin concentrations have also been reported[2] in patients with severe renal impairment undergoing haemodialysis.

Immune thrombocytopenia has been reported[3] in a patient shortly after starting losartan.

1. Horn S, *et al.* Losartan and renal transplantation. *Lancet* 1998; 351: 111.
2. Schwarzbeck A, *et al.* Anaemia in dialysis patients as a side-effect of sartanes. *Lancet* 1998; 352: 286.
3. Ada S, *et al.* Immune thrombocytopenia after losartan therapy. *Ann Intern Med* 2002; 137: 704.

Effects on the liver. Raised liver enzyme values have occurred rarely in patients receiving losartan. Severe, acute hepatotoxicity developed in a patient 1 month after losartan was substituted for enalapril because of ACE inhibitor-induced cough.[1] The patient recovered when losartan was withdrawn but symptoms and raised liver enzyme concentrations recurred following rechallenge. Acute, reversible hepatotoxicity also occurred in a patient who had been taking losartan 150 mg daily for 6 weeks.[2] A case of cholestatic jaundice associated with irbesartan therapy has also been reported;[3] the jaundice resolved slowly once irbesartan was withdrawn.

1. Bosch X. Losartan-induced hepatotoxicity. *JAMA* 1997; 278: 1572.
2. Andrade RJ, *et al.* Hepatic injury associated with losartan. *Ann Pharmacother* 1998; 32: 1371.
3. Hariraj R, *et al.* Prolonged cholestasis associated with irbesartan. *BMJ* 2000; 321: 547.

Effects on the skin. Atypical cutaneous lymphoid infiltrates developed in 2 patients receiving losartan for hypertension.[1] In both cases the lesions disappeared within a few weeks of stopping the drug.

Henoch-Schönlein purpura has been reported[2,3] in patients taking losartan; in 1 case[2] the reaction recurred on rechallenge. A purpuric rash with evidence of vasculitis has been reported with candesartan;[4] the patient also developed acute nephritis.

A polycyclic rash associated with systemic illness developed in a patient who had been taking irbesartan for 2 years;[5] improvement occurred within 2 days of stopping the drug.

Patients have been reported[6] in whom psoriasis either developed or was exacerbated after treatment with an angiotensin II receptor antagonist; the drugs involved included candesartan, irbesartan, losartan, and valsartan. In most cases the lesions regressed after the drug was withdrawn.

1. Viraben R, *et al.* Losartan-associated atypical cutaneous lymphoid hyperplasia. *Lancet* 1997; 350: 1366.
2. Bosch X. Henoch-Schönlein purpura induced by losartan therapy. *Arch Intern Med* 1998; 158: 191–2.
3. Brouard M, *et al.* Schönlein-Henoch purpura associated with losartan treatment and presence of antineutrophil cytoplasmic antibodies of x specificity. *Br J Dermatol* 2001; 145: 362–3.
4. Morton A, *et al.* Rash and acute nephritic syndrome due to candesartan. *BMJ* 2004; 328: 25.
5. Constable S, *et al.* Systemic illness with skin eruption, fever and positive lymphocyte transformation test in a patient on irbesartan. *Br J Dermatol* 2006; 155: 491–3.
6. Marquart-Elbaz C, *et al.* Sartans, angiotensin II receptor antagonists, can induce psoriasis. *Br J Dermatol* 2002; 147: 617–18.

Effects on taste. Taste disturbances, in some cases progressing to complete taste loss, have occurred[1,2] in patients receiving losartan for hypertension. In each case taste returned to normal after stopping losartan therapy. Taste impairment has also been reported with both candesartan[3,4] and valsartan[4] in healthy subjects.

1. Schlienger RG, *et al.* Reversible ageusia associated with losartan. *Lancet* 1996; 347: 471–2.
2. Heeringa M, van Puijenbroek EP. Reversible dysgeusia attributed to losartan. *Ann Intern Med* 1998; 129: 72.
3. Tsuruoka S, *et al.* Subclinical alteration of taste sensitivity induced by candesartan in healthy subjects. *Br J Clin Pharmacol* 2004; 57: 807–12.
4. Tsuruoka S, *et al.* Angiotensin II receptor blocker-induces blunted taste sensitivity: comparison of candesartan and valsartan. *Br J Clin Pharmacol* 2005; 60: 204–7.

Hypersensitivity. See Angioedema and Effects on the Skin, above.

Migraine. Severe migraine has been reported[1] in a patient after use of losartan. The patient had no history of migraine and symptoms recurred on rechallenge. However, angiotensin II receptor antagonists have also been reported to reduce the incidence of migraine (see under Uses and Administration, p. 1423.3).

1. Ahmad S. Losartan and severe migraine. *JAMA* 1995; 274: 1266–7.

Pancreatitis. Acute pancreatitis has been reported[1,2] in 2 patients receiving losartan. However, 1 of the patients subsequently developed pancreatitis unrelated to losartan.[3] The other patient[2] had also developed acute pancreatitis during enalapril therapy. Acute pancreatitis has also been reported[4] with irbesartan; the patient was also taking hydrochlorothiazide but in a dose lower than that usually associated with thiazide-induced pancreatitis. Biochemical alterations suggestive of acute pancreatitis have been reported after telmisartan overdosage.[5]

1. Bosch X. Losartan-induced acute pancreatitis. *Ann Intern Med* 1997; 127: 1043–4.
2. Birck R, *et al.* Pancreatitis after losartan. *Lancet* 1998; 351: 1178.
3. Bosch X. Correction: losartan, pancreatitis, and microlithiasis. *Ann Intern Med* 1998; 129: 755.
4. Fisher AA, Bassett ML. Acute pancreatitis associated with angiotensin II receptor antagonists. *Ann Pharmacother* 2002; 36: 1883–6.
5. Baffoni L, *et al.* Acute pancreatitis induced by telmisartan overdose. *Ann Pharmacother* 2004; 38: 1088.

Vasculitis. For mention of the development of Henoch-Schönlein purpura and other vasculitic disorders in patients receiving angiotensin II receptor antagonists see Effects on the Skin, above.

Precautions

Losartan is contra-indicated in pregnancy (see below) and in severe hepatic impairment. Lower doses should be considered in mild or moderate hepatic impairment (see Uses and Administration, p. 1422.2). Losartan should be used with caution in renal artery stenosis, and in patients with volume depletion (for example those who have received high-dose diuretic therapy), who are at risk of hypotension; volume depletion should be corrected before starting therapy, or a low initial dose should be used. Since hyperkalaemia may occur, serum-potassium concentrations should be monitored, especially in the elderly and patients with renal impairment, and potassium-sparing diuretics should generally be avoided.

Diabetes mellitus. After reports of reduced awareness of hypoglycaemia in type 1 diabetic patients receiving losartan, a study[1] in healthy subjects found that losartan slightly attenuated the symptomatic and hormonal responses to hypoglycaemia. Although the clinical significance was not established, the authors recommended that losartan should be used with caution in diabetics with reduced awareness of hypoglycaemia. However, losartan and other angiotensin II receptor antagonists may have a role in the management of some diabetic complications (see under Uses, p. 1423.1).

1. Deininger E, *et al.* Losartan attenuates symptomatic and hormonal responses to hypoglycemia in humans. *Clin Pharmacol Ther* 2001; 70: 362–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies losartan as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pregnancy. Losartan and other angiotensin II receptor antagonists are contra-indicated in all trimesters of pregnancy; they have been associated with fetal toxicity in *animal* studies and fetal toxicity has also occurred in humans.[1] The effects appear to be due to blockade of the renin-angiotensin system and are similar to those of ACE inhibitors (see p. 1288.1). Oligohydramnios with subsequent fetal death occurred in a patient given losartan during weeks 20 to 31 of pregnancy;[2] a number of similar cases have subsequently been reported with losartan,[3,4] candesartan,[3] and valsartan.[4,6,7] Angiotensin II receptor antagonists should be avoided in those planning pregnancy, and stopped immediately upon diagnosis of pregnancy. They should only be used in pregnant women where the benefit clearly outweighs the risk.[8]

1. Branch RL, Martin U. Adverse effects of angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers in pregnancy. *Adverse Drug React Bull* 2007; (Oct): 943–6.
2. Saji H, *et al.* Losartan and fetal toxic effects. *Lancet* 2001; 357: 363.
3. Lambot M-A, *et al.* Angiotensin-II-receptor inhibitors in pregnancy. *Lancet* 2001; 357: 1619–20.
4. Martinovic J, *et al.* Fetal toxic effects and angiotensin-II-receptor antagonists. *Lancet* 2001; 358: 241–2.
5. Hinsberger A, *et al.* Angiotensin-II-receptor inhibitors in pregnancy. *Lancet* 2001; 357: 1620.
6. Briggs GG, Nageotte MP. Fatal fetal outcome with the combined use of valsartan and atenolol. *Ann Pharmacother* 2001; 35: 859–61.
7. Bos-Thompson M-A, *et al.* Fetal toxic effects of angiotensin II receptor antagonists: case report and follow-up after birth. *Ann Pharmacother* 2005; 39: 157–61. Correction, *ibid.*: 389.
8. MHRA/CHM. ACE inhibitors and angiotensin II receptor antagonists: not for use in pregnancy. *Drug Safety Update* 2007; 1 (5): 8–9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2033217&RevisionSelectionMethod=LatestReleased (accessed 30/07/09)

Interactions

The antihypertensive effects of losartan may be potentiated by drugs or other agents that lower blood pressure. An additive hyperkalaemic effect is possible with potassium supplements, potassium-sparing diuretics, or other drugs that can cause hyperkalaemia; losartan and potassium-sparing diuretics should not generally be given together. NSAIDs should be used with caution in patients taking

losartan as the risk of renal impairment may be increased, particularly in those who are inadequately hydrated; use of NSAIDs may also attenuate the hypotensive effect of losartan. The use of losartan with an ACE inhibitor may increase the risk of hyperkalaemia, hypotension, and syncope, particularly in patients with atherosclerotic disease or heart failure, or in diabetics who have end-organ damage. Such combinations should be reserved for selected cases with close monitoring of renal function. Additionally, the use of angiotensin II receptor antagonists with the renin inhibitor aliskiren is generally not recommended, and should be avoided in some patients (see p. 1296.2). Losartan and some other angiotensin II receptor antagonists are metabolised by cytochrome P450 isoenzymes and interactions may occur with drugs that affect these enzymes.

Lithium. For reference to toxicity resulting from a possible interaction between lithium and angiotensin II receptor antagonists, see p. 431.3.

Pharmacokinetics

Losartan is readily absorbed from the gastrointestinal tract after oral doses, but undergoes substantial first-pass metabolism resulting in a systemic bioavailability of about 33%. It is metabolised to an active carboxylic acid metabolite E-3174 (EXP-3174), which has greater pharmacological activity than losartan; some inactive metabolites are also formed. Metabolism is mainly by cytochrome P450 isoenzymes CYP2C9 and CYP3A4. Peak plasma concentrations of losartan and E-3174 occur about 1 hour and 3 to 4 hours, respectively, after an oral dose. Both losartan and E-3174 are more than 98% bound to plasma proteins. Losartan is excreted in the urine, and in the faeces via bile, as unchanged drug and metabolites. About 4% of an oral dose is excreted unchanged in urine and about 6% is excreted in urine às the active metabolite. The terminal elimination half-lives of losartan and E-3174 are about 1.5 to 2.5 hours and 3 to 9 hours, respectively.

References.
1. Sica DA, *et al.* Clinical pharmacokinetics of losartan. *Clin Pharmacokinet* 2005; 44: 797–814.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Biablan; Cartan; Corticosan; Cozaarex; Enromic; Fabosic; Fensartan; Klosartan; Loctenk; Loplac; Losacor; Losargal; Losarlan†; Niten; Paxon; Presinor; Prisonil; Tacardia; Tacicul; Temisartan; Troezel; Vasexten; *Austral.*: Cozaar; *Austria*: Cosaar; *Belg.*: Cozaar; Loortan; *Braz.*: Anzacor; Aradois; Corus; Cozaar; Lanzacor; Lorsacor; Losaprin; Losartec; Losartion; Lotanol; Torlos; Valtrian; Zaarpress; *Canad.*: Cozaar; *Chile*: Aratan; Corodin; Cozaar; Lopren; Losapres; Losarbon; Sanipresin; Simperten; Valinor; *China*: Cozaar (科素亚); *Cz.*: Arionecs; Arionex; Cozaar; Giovax†; Lakea; Lorista; Losacor; Losagen; Losartic†; Losathia†; Lozap; Nopretens; Sangona; Sidok; *Denm.*: Ancozan; Cozaar; Licolos; Locardin; Losanin; Losarstad; Losatrix; Losindia†; Lostankal; Lotanec; *Fin.*: Cozaar; Losarstad; Losatrix; *Fr.*: Cozaar; *Ger.*: Lorzaar Protect; Lorzaar; Losargamma; *Gr.*: Cozaar; Cozapert; Golasan; Hypozar; Loben; Locardan; Lorfast; Lorotens; Losadrac; Losalet; Losametan; Losarb; Lozanel; Lozatan; Lyosan; Mozartan; Ozarium; Press-Down; Proelsartan; Rabolan; Rapifast; *Hong Kong*: Cozaar; Emlosar; Lopress; Zaart; *Hung.*: Arbartan; Artagert†; Cozaar; Lavestra; Lozarep; Portiron; Prelow; Rasoltan; Stadazar; Tervalon; *India*: Actilop; Alsartan; Angilo; Angilos; Angizaar; Arblos; Asipress; Biozaar; Blosar; Cardikare; Cosart; Covance; Czar; Czartan; Etotan; Giftan; Gosart; Hypart; Lanxes; Lap; Lara; Lartan; Lo; Loril; Lortan; Losacar; Losaday; Losaden; Losagard; Losain; Losakare; Losakind; Losamax; Losan; Losanorm; Losapot; Losar; Losarep; Losariv; Losartas; Losasun; Losatec; Losatrust; Losavas; Losavik; Loscard; Loscom; Losin; Losit; Losium; Lospi; Lospot; Lossar; Lostat; Lot; Lotace; Lotan; Lozitan; LSP; LTP; Miotin; Nusar; Osart; Zaart; *Indon.*: Acetensa; Angioten; Cozaar; Insaar; Kaftensar; Lifezar; Sartaxal; Tensaar†; *Irl.*: Cosartal; Cozaar; Cozatan; Lotanos; Lozitar; Myzaar; Solvatan; *Israel*: Losardex; Losarta; Lotan; Loxart†; Ocsaar; Tlasar; *Ital.*: Dalosar; Lortaan; Losaprex; Neo-Lotan; Precten; *Jpn*: Nu-Lotan; *Malaysia*: Cozaar; *Mex.*: Bimidal; Conciluk; Cozaar; Lodestar; Lopred; Lospotar; Punab; Saravanta; Takilpam; Tevalos; Viopexa; *Neth.*: Cozaar; Entrizen; Loridan†; Losafox; Losahelm; Losamater†; Losanox; Lozitan†; *Norw.*: Cozaar; *NZ*: Cozaar; *Philipp.*: Angisartan; Angizaar†; Anzar; ARA; Arbloc; Bepsar; Besartan; Cotenace; Cozaar; Doxar; Ecozar; Eseflah; Getzar; Hartzar; Hextan; Hylos; Hyperthree; Hyzart; Jensar; Kenzar; Lifezar; Lorzan; Losacar; Losargard; Losart; Lostar; Lozaris; Myotan; Myzar; Neosartan; Nipartan; Normoten; Provizar; Qxar; Wilopres; Xartan; Zarnat; Zarten; *Pol.*: Apo-Lozart; Cozaar; Lakea; Lorista; Losacor; Losagen; Losartic; Lozap; Presartan; Rasoltan; Sarve; Xartan; *Port.*: Aratis; Cozaar; Decara; Lortaan; Losab; Losarmed; Loteak; Monocer; Rogbaz; Sartal; Satarmed; Tarnasol†; Tlasar; Varsil; *Rus.*: Bloctran (Блоктран); Cardomin (Кардомин); Cozaar (Козаар); Lorista (Лориста); Losarel (Лозарел); Lozap (Лозап); Presartan (Презартан); Renicard (Реникард); Vasotenz (Вазотенз); Zysacar (Зисакар); *S.Afr.*: Ciplazar; Cozaar; Hytenza; Lepitrin; Los-Arb; Renicard; Zartan; *Singapore*: Angizaar; Cozaar; Losartas; *Spain*: Cozaar; Lavestra; Soluvass; *Swed.*: Cozaar; Losarstad; Losatrix; Lostankal; *Switz.*: Cosaar; Losartax; *Thai.*: Cozaar; Lanzaar; Loranta; Tanzaril; Tosan; *Turk.*: Aston; Cozaar; Eklips; Pelow; Hilos; Losartil; Loxibin; Sarilen; Sarvas; *UK*: Cozaar; *Ukr.*: Angizaar (Ангизар); Lorista (Лориста); Lozap (Лозап); Presartan (Пресартан); Sentor (Сентор); *USA*: Cozaar; *Venez.*: Biortan; Cormac; Cozaar; Hyzaar; Nefrotal; Presartan; Sortal.

Multi-ingredient Preparations. *Arg.*: Biablan D; Cartan D; Cozaarex D; Fensartan D; Klosartan-D; Loctenk D; Loplac-D; Losacor D; Niten D; Paxon D; Pelmec Max D; Pelmec Max; Presinor D; Prisonil D; Tacardia D; Temisartan Diur; Terloc Max; Vasexten-D; *Austria*: Cosaar Plus; Fortzaar; Losarcomp; *Belg.*: Co-Losartan; Cozaar Plus; Loortan Plus; *Braz.*: Aradois H; Branta; Corus H; Hyzaar; Lorsar + HCT; Lotar; Neopress; Torlos H; Valtrian HCT; Zaarpress HCT; *Canad.*: Hyzaar; *Chile*: Aratan D; Corodin D; Hyzaar; Lopren-D; Losapres-D; Sanipresin-D; Simperten-D; Tensivel-D; *China*: Hyzaar (海捷亚); *Cz.*: Apo-Combilos; Arionex Combi; Artager†; Giovax plus H; Hyzaar; Lorista H; Losagen Combi; Losaratio Plus H; Loscomb; Lozap H; Nopretens Plus H; Prelow; Sangona Combi; Zalarlos comp; *Denm.*: Anartan Comp; Cosaar Plus†; Cozaar Comp; Cozaar Plus; Esparaloz Comp; Fortzaar†; Forzaar†; Hyzaar†; Kemlosar comp†; Losapensa Compt; Losarstad Comp; Losatrix Compt; Losazid†; Marozid†; Tanlozid; Zalarlos comp; *Fin.*: Cozaar Comp; Losamyl Comp†; Losarstad Comp; Losatrix Comp; *Fr.*: Fortzaar; Hyzaar; *Ger.*: Fortzaar; Lorzaar plus; Losargamma HCT; Losarplus; Losartan comp; Losartan Plus; *Gr.*: CardZaar; Co-Rabolan; Faxiven; Hysadrac; Hyzaar; Loben Plus; Logika; Lopernal; Lorotens Plus; Lortazil Plus; Losachlor; Losalet Plus; Losarb Plus; Losazide; Maxartan; Normatens Plus; Press-Down-Plus; Sartafin Plus; Zotefox; *Hong Kong*: Hyzaar Plus; Hyzaar; *Hung.*: Co-Arbartan; Hyzaar; Lavestra H; Lost-HCT; Lostanorm Plus; Portiron HCT; Prelow Plus; Stadazar HCT; Tervalon HCT; *India*: Acord-L; Actilop-H; Adpace; Alsartan-AM; Alsartan-H; Amcard-LP; Amchek-Z; Amlokind-L; Amlokos L; Amlopres Z; Amlotin; Amlozaar; Angicam-LT; Angilo-AM; Angilo-H; Angilos-H; Angizaar-AT; Angizaar-H; Arblos-H; Asipress-H; Asomex-LT; Biozaar-AM; Cardikare-H; Cosart-H; Covamlo; Covance-D; Czar-AM; Czar-H; Envas-RB; Esam LT; Eslo Tan; Espin-LT; Etotan-AT; Etotan-H; Etotan-HR; Etotan-R; Giftan-HC; Hypart-H; Hysartas; Lanxes-A; Lanxes-H; Lap Plus; Lara-H; Lartan-AM; Lartan-H; Lo-E; Lo-H; Loar-H; Locin-H; Lok-H; Loram-H; Loram; Loril-HT; Losacar-A; Losacar-H; Losaday-H; Losaden-AM; Losaden-H; Losagen-H; Losain-H; Losakare-H; Losakind-H; Losamax-H; Losanorm-HR; Losapot-H; Losar-A; Losar-Beta-H; Losar-Beta; Losar-H; Losarep-H; Losartar H; Losartas-HT; Losasun-HT; Losatec-H; Losatrust-H; Losavas-H; Losavik-H; Loscard-H; Loscom-H; Loscom-R; Losium-H; Lospot-AM; Lospot-H; Lostat H; Lot-H; Lotace-H; Lotan-A; Lotemos-HT; Lozadip; LR; LSP Plus; LSR-H; LTP-H; Nicol-LS; Nusar-AM Low; Nusar-ATN; Nusar-H; Omnitan H; Osart-H; Zaart-H; *Indon.*: Hyzaar; *Irl.*: Cozaar Comp; Cozatan Comp; Lotanos Comp; Lozitar Comp; Myzaar Comp; *Israel*: Cotiasar; Losartan Plus; Lotan Plus†; Ocsaar Plus; *Ital.*: Forzaar; Hizaar; Kemlosar; Losazid; lozid; Neo-Lotan Plus; *Malaysia*: Fortzaar; Hyzaar; *Mex.*: Co-Tarsan; Hyzaar; Lodestar Zid; Proloscan; Saravanta D; *Neth.*: Cozaar Compt; Cozaar Plus; Entrizen/HCT; Fortzaar; Hyzaar; Lavesta†; Lodarin†; Lonita†; Losahelm/HCTZ; Losathia†; Losazid†; Lotazin†; Lozatin†; *Norw.*: Cozaar Comp; *NZ*: Hyzaar; *Philipp.*: 2Zaris; Angizaar-H†; AnzaPlus; Co-Normoten; Combizar; Duosar; Ecozar Plus; Hyzaar; Kenzar Plus; Losacar-H; Losargard Plus; Neosartan Plus; Nipartan-H; Tozam; Vazortan-H; Wilopres Plus; *Pol.*: Hyzaar; Lakea HCT; Lorista H; Lozap HCT; Presartan H; *Port.*: Arazid; Cotiasar; Cozaar Plus; Fortzaar; Hicloran; Hicortal; Hipara; Hiperozida†; Hizialos†; Hyzaar; Loziaze†; Lorista; Lortaan Plus; Losarbio; Losarerin; Odix; Rominguer; Siaara†; Tecnilor†; Vilbitan†; *Rus.*: Cardomin Plus (Кардомин Плюс); Hyzaar (Гизаар); Lorista H (Лориста H); Lorista HD (Лориста НД); Lozap Plus (Лозап Плюс); Vasotenz H (Вазотенз H); *S.Afr.*: Cozaar Comp; Fortzaar; Lohype Plus; Lohype Plus; Losaar Plus; Losaar Plus; Lozaan Co; Netrasol Co; Sartoc; Zartan Co; *Singapore*: Hyzaar; *Spain*: Cozaar Plus; Fortzaar; *Swed.*: Cozaar Comp; Losamyl Compt; Losarstad Comp; Losatrix Comp; Marozid; Tanlozid; *Switz.*: Co-Losartan; Cosaar Plus; *Thai.*: Fortzaar; Hyzaar; *Turk.*: Aston Plus; Co-Hilos; Eklips Fort; Eklips Plus; Hyzaar; Losapres Plus; Losartil Plus; Loxibin Plus; Sarilen Plus; Sarvastan; *UK*: Cozaar Comp; *Ukr.*: Angizaar Plus (Ангизар Плюс); Co-Sentor (Ко-Сентор); Lo-Asomex (Ло-Азомекс); Lorista H (Лориста H); Lorista HD (Лориста HD); Lozap Plus (Лозап Плюс); Sardip (Сардип); *USA*: Hyzaar; *Venez.*: Cormatic; Hyzaar Plus; Nefrotal H.

Pharmacopoeial Preparations
BP 2014: Losartan Potassium Tablets;
USP 36: Losartan Potassium and Hydrochlorothiazide Tablets; Losartan Potassium Tablets.

Lovastatin *(BAN, USAN, rINN)*

L-154803; Lovastatiini; Lovastatina; Lovastatinas; Lovastatine; Lovastatinum; Lovasztatin; MB-530B; 6α-Methylcompactin; Mevinolin; MK-803; Monacolin K; MSD-803; Ловастатин.

(3*R*,5*R*)-7-[(1*S*,2*S*,6*R*,8*S*,8a*R*)-1,2,6,7,8,8a-Hexahydro-2,6-dimethyl-8-[(*S*)-2-methylbutyryloxy]-1-naphthyl]-3-hydroxyheptan-5-olide.

$C_{24}H_{36}O_5$=404.5

CAS — 75330-75-5.

ATC — C10AA02.

ATC Vet — QC10AA02.

UNII — 9LHU78OQFD.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Lovastatin). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; soluble in acetone. Store under nitrogen at a temperature of 2 degrees to 8 degrees.

USP 36: (Lovastatin). A white to off-white crystalline powder. Insoluble in water; sparingly soluble in alcohol; practically insoluble in petroleum spirit; freely soluble in chloroform; soluble in acetone, in acetonitrile, and in methyl alcohol. Store under nitrogen in airtight containers at a temperature not exceeding 8 degrees.

Uses and Administration

Lovastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (a statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p. 1489.3).

Lovastatin is used to reduce cholesterol in the treatment of hyperlipidaemias (p. 1248.1), particularly in type IIa and IIb hyperlipoproteinaemias. It is also given for cardiovascular risk reduction (p. 1246.1) in both primary and secondary prevention of ischaemic heart disease.

Lovastatin is given in an initial oral dose of 10 to 20 mg daily in the evening with food, increased, if necessary, at intervals of 4 weeks or more to 80 mg daily as a single dose or in 2 divided doses. Lower doses of lovastatin should be used in patients at risk of myopathy, including patients with severe renal impairment (see below) and those taking drugs that interact with lovastatin; an initial dose of 10 mg daily is recommended in patients taking *ciclosporin* or *danazol*, and the daily dose should not exceed 20 mg in patients taking *ciclosporin, danazol, fibric acid derivatives*, or *nicotinic acid*, or 40 mg in those taking *amiodarone* or *verapamil*.

For the use of lovastatin in children, see below.

General reviews.
1. Curran MP, Goa KL. Lovastatin extended release: a review of its use in the management of hypercholesterolaemia. *Drugs* 2003; 63: 685–99.

Administration in children. Lovastatin reduces plasma-cholesterol concentrations in children and adolescents with heterozygous familial hypercholesterolaemia[1-3] and has been given safely for up to 48 weeks in boys,[2] and up to 24 weeks in girls.[3] In the USA it is licensed in children aged 10 to 17 years and is given orally in an initial dose of 10 to 20 mg once daily, increased at intervals of 4 weeks or more, if necessary, to a maximum dose of 40 mg once daily.

1. Lambert M, *et al.* Canadian Lovastatin in Children Study Group. Treatment of familial hypercholesterolemia in children and adolescents: effect of lovastatin. *Pediatrics* 1996; 97: 619–28.
2. Stein EA, *et al.* Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA* 1999; 281: 137–44.
3. Clauss SB, *et al.* Efficacy and safety of lovastatin therapy in adolescent girls with heterozygous familial hypercholesterolemia. *Pediatrics* 2005; 116: 682–8.

Administration in renal impairment. Patients with renal impairment may be at increased risk of myopathy and US licensed product information states that doses of lovastatin above 20 mg daily should be used cautiously in patients with a creatinine clearance below 30 mL/minute.

Adrenoleucodystrophy. A preliminary study[1] has shown that lovastatin may be useful in the treatment of adrenoleucodystrophy (see under Lorenzo's Oil, p. 2545.2). Lovastatin reduced the plasma levels of very-long-chain fatty acids which are known to be elevated in patients with this rare metabolic disorder.

1. Pai GS, *et al.* Lovastatin therapy for X-linked adrenoleukodystrophy: clinical and biochemical observations on 12 patients. *Mol Genet Metab* 2000; 69: 312–22.

Adverse Effects and Precautions

As for Simvastatin, p. 1492.1 and p. 1494.1, respectively.

Incidence of adverse effects. Adverse effects led to withdrawal of lovastatin in 21 of 745 patients receiving the drug for about 5 years.[1] They included asymptomatic elevation of hepatic aminotransferases in 10 patients, gastrointestinal symptoms in 3, rash in 2, myopathy in 2, myalgia in 1, arthralgia in 1, insomnia in 1, and weight gain in 1.

1. Lovastatin Study Groups. Lovastatin 5-year safety and efficacy study: Lovastatin Study Groups I through IV. *Arch Intern Med* 1993; 153: 1079–87.

Interactions

As for Simvastatin, p. 1494.2.

For specific dosage reductions in patients taking lovastatin with interacting drugs, see Uses and Administration, above.

Pharmacokinetics

Lovastatin is absorbed from the gastrointestinal tract and must be hydrolysed to its active β-hydroxyacid form. Three other metabolites have also been isolated. Lovastatin is a substrate for the cytochrome P450 isoenzyme CYP3A4 and undergoes extensive first-pass metabolism in the liver, its primary site of action; less than 5% of an oral dose has been reported to reach the circulation. Peak plasma concentrations occur within 2 to 4 hours, and steady-state concentrations are achieved after 2 to 3 days with daily dosage. Both lovastatin and its β-hydroxyacid metabolite are more than 95% bound to plasma proteins. Lovastatin is mainly excreted in the bile as metabolites; about 85% of a dose has been recovered from the faeces and about 10% from the urine. The half-life of the active metabolite is 1 to 2 hours.

General reviews.

1. Desager J-P, Horsmans Y. Clinical pharmacokinetics of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. *Clin Pharmacokinet* 1996; 31: 348–71.
2. Lennernäs H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors: similarities and differences. *Clin Pharmacokinet* 1997; 32: 403–25.
3. Neuvonen PJ, *et al.* Pharmacokinetic comparison of the potential over-the-counter statins simvastatin, lovastatin, fluvastatin and pravastatin. *Clin Pharmacokinet* 2008; 47: 463–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Hipovastin; Mevlor; *Austria*: Mevacor; *Braz.*: Lipoclin; Lovaton; Mevacor; Mevalip; Reducol; Redustatin; *Canad.*: Mevacor; *Chile*: Hiposterol; Lispor; Lovacol; Sanelor; *China*: Ai Le Ting (艾乐汀); Deolip (海立); Du Le (都乐); Gengxian (更先); Jun Ning (俊宁); Le Huo (乐活); Lefuxin (乐福欣); Luo Zhi Da (洛之达); Luohuaning (罗华宁); Meixinjie (美辛杰); Ming Wei Xin (明维欣); Su Er Qing (苏尔清); Su Xin (苏欣); Xin Lu (欣露); Xue Qing (雪庆); *Cz.*: Holetar†; Medostatin; Mevacor†; Rancor†; *Denm.*: Lovacodan; Lovastad; *Fin.*: Lovacol†; *Ger.*: Lovabeta; Lovagamma; Lovahexal†; Mevinacor†; *Gr.*: Aurostatin; Cecural; Ilopar; Liferzit; Lipidless; Lostin; Lovadrug; Lovapen; Lovasten; Lovatex; Lovatop; Lowlipid; Medovascin; Mevacor; Mevastin; Mevinol; Misodomin; Nabicortin; Terveson; Velkalov; Viking; *Hong Kong*: Ellanco†; Lomar†; Medostatin; Mevacor†; *Hung.*: Stoplip†; *India*: Aztatin; Elstatin; Favolip; Lestric; Lipistat; Lochol; Lostatin; Lotin; Lova; Lovacard; Lovadac; Lovalip; Lovameg; Lovastat; Lovastrol; Lovatin; Lovex; Pro HDL; Rovacor; *Indon.*: Cholvastin; Justin; Lipovas; Lofacol; Lotivas; Lotyn; Lovatrol; *Ital.*: Lovinacor; Rextat; Tavacor; *Malaysia*: Ellanco; Lestric; Lostatin†; Lovarem; Lovastin; Medostatin; *Mex.*: Casbame; Dilucid†; Liperol†; Mevacor; *Norw.*: Mevacor†; *Pol.*: Anlostin†; Apo-Lova†; Liprox; Lovasterol; Lovastin; *Port.*: Flozul†; Lipdaune; Lipus; Mevinacor; Mevlor; Tecnolip; *Rus.*: Apextatin (Апекстатин); Cardiostatin (Кардиостатин); Holetar (Холетар); Lovasterol (Ловастерол); Medostatin (Медостатин); Mevacor (Мевакор); Rovacor (Ровакор); *S.Afr.*: Lovachol; *Singapore*: Ellanco; Elstatin; Lochol; Lofacol; Lostatin; Lovastin; Medostatin; Mevacor; Rovacor; *Spain*: Aterkey†; Colesvir; Liposcler; Mevacor; Mevasterol†; Nergadan; Taucor; *USA*: Altoprev; Mevacor; *Venez.*: Levistan; Lovanil; Mevacor.

Multi-ingredient Preparations. *Canad.*: Advicor†; *USA*: Advicor.

Pharmacopoeial Preparations
USP 36: Lovastatin Tablets.

Low-molecular-weight Heparins

Depolymerised Heparins; Heparina Massae Molecularis Minoris; Heparinas de baja masa molecular; Heparinas de bajo peso molecular; Heparinas fraccionadas; Hepariner, lågmolekylära; Héparines de basse masse moléculaire; Heparíny nízkomolekulámí; LMW Heparins; Low-molecular-mass Heparins; Mažos molekulinės masės heparinai; Pienimolekyyliset hepariinit; Низкомолекулярные Гепарины

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Heparins, Low-molecular Mass; Low-molecular-weight Heparins BP 2014). Salts of sulfated glucosaminoglycans having a mass-average molecular mass less than 8000. They are obtained by fractionation or depolymerisation of heparin of natural origin and display different chemical structures at the reducing or the non-reducing end of the polysaccharide chains.

The potency is not less than 70 units of anti-factor Xa activity per mg with reference to the dried substance and the ratio of anti-factor Xa activity to anti-factor IIa (antithrombin) activity is not less than 1.5.

A white or almost white hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers.

Units

The second International Standard for low-molecular-weight heparin was agreed in 2003 and is used to calibrate products for both anti-factor Xa and anti-factor IIa activities. Potency is expressed in terms of units of anti-factor Xa activity per mg and the ratio of anti-factor Xa to anti-factor IIa activity. This ratio differs for individual low-molecular-weight heparins and neither they nor unfractionated heparin can be used interchangeably unit for unit.

Uses and Administration

Low-molecular-weight heparins are salts of fragments of heparin produced by chemical or enzymatic depolymerisation of the heparin molecule. Commercially available low-molecular-weight heparins differ in their method of production, molecular-weight range, and degree of sulfation. Those included in *Martindale* are:

- Ardeparin, p. 1307.1
- Bemiparin, p. 1314.2
- Certoparin, p. 1334.2
- Dalteparin, p. 1348.3
- Enoxaparin, p. 1372.3
- Nadroparin, p. 1443.2
- Parnaparin, p. 1464.2
- Reviparin, p. 1486.3
- Tinzaparin, p. 1514.2

Like heparin (p. 1397.1), these compounds enhance the action of antithrombin III but they are characterised by a higher ratio of anti-factor Xa to anti-factor IIa (antithrombin) activity than heparin. Low-molecular-weight heparins have less effect on platelet aggregation than heparin. They have no significant effect on blood coagulation tests such as activated partial thromboplastin time (APTT). Therapy may be monitored by measurement of plasma-anti-factor-Xa activity but monitoring is less frequently required than with heparin since low-molecular-weight heparins have a more predictable effect.

Low-molecular-weight heparins are used for the prophylaxis and treatment of venous thromboembolism (deep-vein thrombosis and pulmonary embolism, p. 1274.1). They are given by subcutaneous injection once or twice daily. They are also used intravenously to prevent coagulation during haemodialysis and other extracorporeal circulatory procedures. They may be given subcutaneously in the management of unstable angina (p. 1254.3) and both intravenously and subcutaneously in acute myocardial infarction (p. 1257.1).

Doses are expressed either in terms of the weight of low-molecular-weight heparin or in terms of units of anti-factor Xa activity. Since low-molecular-weight heparins differ in their relative inhibition of factor Xa and thrombin, doses, even when expressed in terms of anti-factor-Xa activity, cannot be equated. Different preparations of the same low-molecular-weight heparin may appear to have different doses depending on the reference preparation used.

References.

1. Hirsh J, *et al.* Parenteral anticoagulants: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133 (suppl): 141S–159S.
2. Canales JF, Ferguson JJ. Low-molecular-weight heparins: mechanisms, trials, and role in contemporary interventional medicine. *Am J Cardiovasc Drugs* 2008; 8: 15–25.
3. Jeske WP, *et al.* Differentiating low-molecular-weight heparins based on chemical, biological, and pharmacologic properties: implications for the development of generic versions of low-molecular-weight heparins. *Semin Thromb Hemost* 2008; 34: 74–85.
4. Gray E, *et al.* Heparin and low-molecular-weight heparin. *Thromb Haemost* 2008; 99: 807–18.
5. Nowak-Göttl U, *et al.* Pharmacokinetics, efficacy, and safety of LMWHs in venous thrombosis and stroke in neonates, infants and children. *Br J Pharmacol* 2008; 153: 1120–7.
6. Camporese G, Bernardi E. Low-molecular-weight heparin for thromboprophylaxis. *Curr Opin Pulm Med* 2009; 15: 443–54.
7. Lim W. Using low molecular weight heparin in special patient populations. *J Thromb Thrombolysis* 2010; 29: 233–40.
8. Kalyani BS, Roberts CS. Low molecular weight heparin: current evidence for its application in orthopaedic surgery. *Curr Vasc Pharmacol* 2011; 9: 19–23.

Diabetic foot ulcers. Subcutaneous injection of some low-molecular-weight heparins has been investigated, with some apparent benefit, in the management of diabetic foot ulceration (p. 464.2) in patients with diabetes mellitus.

References.

1. Kalani M, *et al.* Effect of dalteparin on healing of chronic foot ulcers in diabetic patients with peripheral arterial occlusive disease: a prospective, randomized, double-blind, placebo-controlled study. *Diabetes Care* 2003; 26: 2575–80.
2. Kalani M, *et al.* Beneficial effects of dalteparin on haemostatic function and local tissue oxygenation in patients with diabetes, severe vascular disease and foot ulcers. *Thromb Res* 2007; 120: 653–61.
3. Rullan M, *et al.* Treatment of chronic diabetic foot ulcers with bemiparin: a randomized, triple-blind, placebo-controlled, clinical trial. *Diabet Med* 2008; 25: 1090–5.

Inflammatory bowel disease. Modified-release oral preparations of low-molecular-weight heparin have been investigated in the treatment of ulcerative colitis, and may be of benefit in mild to moderate disease.[1] Subcutaneous low-molecular-weight heparin did not appear to be of value. The overall management of inflammatory bowel disease is discussed on p. 1811.3.

1. Chande N, *et al.* Unfractionated or low-molecular weight heparin for induction of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 10. Chichester: John Wiley; 2010 (accessed 06/04/11).

Sickle-cell disease. Thrombosis may be a frequent complication of sickle-cell disease. A placebo-controlled study[1] in 253 patients with sickle-cell crisis found that the severity and duration of acute crises were reduced by tinzaparin given in a subcutaneous dose of 175 units/kg once daily for 7 days. However, a review[2] concluded that the evidence of benefit with anticoagulants in such patients was insufficient to recommend their use.

The overall management of sickle-cell disease is described on p. 1123.2.

1. Qari MH, *et al.* Reduction of painful vaso-occlusive crisis of sickle cell anaemia by tinzaparin in a double-blind randomized trial. *Thromb Haemost* 2007; 98: 392–6.
2. Charneski L, Congdon HB. Effects of antiplatelet and anticoagulant medications on the vasoocclusive and thrombotic complications of sickle cell disease: A review of the literature. *Am J Health-Syst Pharm* 2010; 67: 895–900.

Adverse Effects

As for Heparin, p. 1398.3, although incidence of some adverse effects may be lower with the low-molecular-weight heparins.

Reviews.

1. Gouin-Thibault I, *et al.* Safety profile of different low-molecular weight heparins used at therapeutic dose. *Drug Safety* 2005; 28: 333–49.

Effects on the adrenal glands. Hyperkalaemia related to hypoaldosteronism has been reported in patients treated with low-molecular-weight heparins.[1-4] The UK CSM suggests[5] that plasma-potassium concentrations should be monitored in all patients with risk factors for hyperkalaemia, particularly those receiving low-molecular-weight heparins for more than 7 days (see Heparin, p. 1398.3).

1. Levesque R, *et al.* Low molecular weight heparins and hypoaldosteronism. *BMJ* 1990; 300: 1437–8.
2. Canova CR, *et al.* Effect of low-molecular-weight heparin on serum potassium. *Lancet* 1997; 349: 1447–8.
3. Wiggam MI, Beringer TRO. Effect of low-molecular-weight heparin on serum concentrations of potassium. *Lancet* 1997; 350: 292–3.
4. Gheno G, *et al.* Variations of serum potassium level and risk of hyperkalemia in inpatients receiving low-molecular-weight heparin. *Eur J Clin Pharmacol* 2003; 59: 373–7.
5. CSM/MCA. Suppression of aldosterone secretion by heparin. *Current Problems* 1999; 25: 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023236&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)

Effects on the blood. It was hoped that, because of their higher ratio of anti-factor Xa to anti-thrombin activity compared with heparin, low-molecular-weight heparins might cause less *bleeding* while maintaining their antithrombotic activity. Some large studies[1,2] have suggested less bleeding with low-molecular-weight heparins than with unfractionated heparin. However, meta-analyses and reviews[3,4] have been unable to confirm a significant reduction in major haemorrhage in patients treated with low-molecular-weight heparins, compared with heparin, for venous thromboembolism, although they confirmed that low-molecular-weight heparins are not associated with an increase in risk. There may be an increased risk of bleeding in patients with renal impairment,[5-7] (see Precautions, p. 1427.1) although the criterion of creatinine clearance 30 mL/minute or less as a guide to selecting patients at increased risk has been questioned;[8] pharmacokinetic response may vary according to the low-molecular-weight heparin used.

Like unfractionated heparin, low-molecular-weight heparins may cause *thrombocytopenia*, including the more severe, immune-mediated form known as heparin-induced thrombocytopenia (HIT). Incidence is much lower with the low-molecular-weight heparins, but platelet-count monitoring is recommended in certain patients depending on other risk factors.[9] The principles of management are the same as for unfractionated heparin, and are described under Heparin, p. 1399.1.

There have been reports[10] of the spontaneous development of spinal haematomas after the use of low-molecular-weight heparins.

1. Levine MN, *et al.* Prevention of deep vein thrombosis after elective hip surgery: a randomized trial comparing low molecular weight heparin with standard unfractionated heparin. *Ann Intern Med* 1991; 114: 545–51.
2. Hull RD, *et al.* Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med* 1992; 326: 975–82. Correction. *ibid.* 327: 1485.
3. Gould MK, *et al.* Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 1999; 130: 800–809.
4. Schulman S, *et al.* Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133 (suppl): 257S–298S.

5. Cestac P, *et al.* Utilisation and safety of low molecular weight heparins: prospective observational study in medical inpatients. *Drug Safety* 2003; 26: 197–207.
6. Lim W, *et al.* Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med* 2006; 144: 673–84.
7. Crowther M, Lim W. Low molecular weight heparin and bleeding in patients with chronic renal failure. *Curr Opin Pulm Med* 2007; 13: 409–13.
8. Nagge J, *et al.* Is impaired renal function a contraindication to the use of low-molecular-weight heparin? *Arch Intern Med* 2002; 162: 2605–9.
9. Warkentin TE, *et al.* American College of Chest Physicians. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133 (suppl): 340S–380S. Also available at: http://chestjournal.chestpubs.org/content/139/5/1261.full.pdf (accessed 25/10/11) Correction. *ibid.* 2011; 139: 1261. [dose]
10. Heppner PA, *et al.* Spontaneous spinal hematomas and low-molecular-weight heparin. Report of four cases and review of the literature. *J Neurosurg Spine* 2004; 1: 232–6.

Effects on the skin. Adverse effects of low-molecular-weight heparins on the skin have been reviewed.[1] Most low-molecular-weight heparins have been implicated. Urticarial rash or immediate hypersensitivity has been reported (see below). Delayed hypersensitivity skin reactions have occurred mainly in women. These women were generally postmenopausal, pregnant, or in the postpartum period, suggesting a hormonal influence on pathogenesis. About half of these patients also had a history of allergy to unfractionated heparin.[1] Cross-reactivity between heparins appears to be common.[2] Whether molecular weight influences cross-reactivity between the heparins and heparinoids has been a matter of debate.[3-4]

Skin necrosis reactions are usually localised to the subcutaneous injection site, although distant lesions have also been reported. There has been a report[7] of diffuse skin necrosis leading to fatality in a patient given enoxaparin.

1. Wüthschert R, *et al.* Adverse skin reactions to low molecular weight heparins: frequency, management and prevention. *Drug Safety* 1999; 20: 515–25.
2. Palacios Colom L, *et al.* Delayed-type hypersensitivity to heparins: different patterns of cross-reactivity. *Contact Dermatitis* 2008; 59: 375–7.
3. Grims RH, *et al.* Delayed-type hypersensitivity to low molecular weight heparins and heparinoids: cross-reactivity does not depend on molecular weight. *Br J Dermatol* 2007; 157: 514–17.
4. Ludwig RJ, *et al.* Molecular weight determines the frequency of delayed type hypersensitivity reactions to heparin and synthetic oligosaccharides. *Thromb Haemost* 2005; 94: 1265–9.
5. Gómez-Outes A, *et al.* Delayed-type hypersensitivity to low molecular weight heparins and heparinoids: cross-reactivity does not depend on molecular weight. Commentary. *Br J Dermatol* 2008; 158: 869–70.
6. Ludwig RJ, *et al.* The influence of heparin's molecular weight and the incidence of delayed type hypersensitivity reactions revisited: in response to Grims et al., *Br J Dermatol* 2008; 158: 849–51.
7. Nadir Y, *et al.* A fatal case of enoxaparin induced skin necrosis and thrombophilia. *Eur J Haematol* 2006; 77: 166–8.

Hypersensitivity. Hypersensitivity reactions to heparin and low-molecular-weight heparins are not uncommon,[1] and include urticaria,[2,3] angioedema,[2] and delayed hypersensitivity skin reactions (see above).

1. Jappe U. Allergy to heparins and anticoagulants with a similar pharmacological profile: an update. *Blood Coag Fibrinol* 2006; 17: 605–13.
2. Odeh M, Oliven A. Urticaria and angioedema induced by low-molecular-weight heparin. *Lancet* 1992; 340: 972–3.
3. Weber HO, *et al.* Recall urticaria induced by skin tests with heparin. *Br J Dermatol* 2009; 161: 187–9.

Treatment of Adverse Effects

Severe bleeding with low-molecular-weight heparins, usually caused by accidental overdosage, may be reduced by the slow intravenous injection of protamine sulfate (p. 1572.1). The recommended doses of protamine sulfate are given in the individual monographs and should completely neutralise the anti-thrombin effect of the low-molecular-weight heparin but will only partially neutralise the anti-factor-Xa effect.

Overdosage. A review[1] concluded that the use of eptacog alfa (recombinant factor VIIa) was of benefit in the management of refractory bleeding associated with certain anticoagulants, including low-molecular-weight heparins. Although the lowest effective dose was uncertain, 20 to 120 micrograms/kg had been reported to be effective for low-molecular-weight heparin reversal. Repeat doses of eptacog alfa were not recommended.

1. Vavra KA, *et al.* Recombinant factor VIIa to manage major bleeding from newer parenteral anticoagulants. *Ann Pharmacother* 2010; 44: 718–26.

Precautions

As for Heparin, p. 1399.3.

Low-molecular-weight heparins should not be given to patients who have developed thrombocytopenia with heparin and who have a positive *in-vitro* platelet aggregation test (that is, cross-reactivity) with the particular low-molecular-weight heparin to be used.

Monitoring of plasma-anti-factor-Xa activity may be considered in patients with an increased risk of bleeding, for example the elderly or those with renal impairment or extremes of body-weight, and in patients with active bleeding.

Licensed product information for some low-molecular-weight heparins contra-indicates their use in patients with prosthetic heart valves as they may not provide adequate prophylaxis against thromboembolism even at high doses (but see under Valvular Heart Disease, p. 1264.3, for references to their use).

Spinal anaesthesia. Spinal and epidural haematomas, sometimes leading to paralysis, have occurred in patients receiving low-molecular-weight heparins with spinal or epidural anaesthesia or analgesia (see p. 1400.1).

Interactions

As for Heparin, p. 1400.2.

Pharmacokinetics

Although the precise pharmacokinetic parameters of different low-molecular-weight heparins vary (see individual monographs), they generally have a greater bioavailability after subcutaneous injection and a longer half-life than heparin.

References.
1. Kandrotas RJ. Heparin pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 1992; 22: 359–74.
2. Samama MM, Gerotziafas GT. Comparative pharmacokinetics of LMWHs. *Semin Thromb Hemost* 2000; 26 (suppl 1): 31–8.

Lubeluzole *(BAN, USAN, rINN)*

Lubeluzol; Lubéluzole; Lubeluzolum; R-87926; Лубелузол.

(*S*)-1-{4-[1,3-Benzothiazol-2-yl(methyl)amino]piperidino}-3-(3,4-difluorophenoxy)propan-2-ol.

$C_{22}H_{25}F_2N_3O_2S$=433.5

CAS — 144665-07-6.

UNII — V2SIB71583.

Profile

Lubeluzole is a neuroprotectant that has been investigated for ischaemic stroke, but results have been disappointing.

References.
1. Gandolfo C, *et al.* Lubeluzole for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2002 (accessed 24/06/05).

Macitentan *(USAN, rINN)*

ACT-064992; Macitentán; Macitentanum; Мацитентан.

N-[5-(4-Bromophenyl)-6-{2-[(5-bromopyrimidin-2-yl)oxy]ethoxy}pyrimidin-4-yl]-*N'*-propylsulfuric diamide.

$C_{19}H_{20}Br_2N_6O_4S$=588.3

CAS — 441798-33-0.

UNII — Z9K9Y9WMVL.

Profile

Macitentan is an endothelin receptor antagonist used in the management of pulmonary hypertension (p. 1278.2). It is given orally in a usual dose of 10 mg once daily.

Macitentan may cause fetal harm and should not be taken by pregnant women. Effective contraception should be used by women who could become pregnant, and pregnancy should be excluded before, and monthly during, treatment. Other adverse effects include anaemia and hepatotoxicity.

The metabolism of macitentan is dependent on the cytochrome P450 isoenzyme system, mainly CYP3A4, and strong CYP3A4 inhibitors or inducers can affect exposure to macitentan.

References.
1. Patel T, McKeage K. Macitentan: first global approval. *Drugs* 2013. Available at: doi:10.1007/s40265-013-0156-6
2. Dingemanse J, *et al.* Efficacy, safety and clinical pharmacology of macitentan in comparison to other endothelin receptor antagonists in the treatment of pulmonary arterial hypertension. *Expert Opin Drug Safety* 2013. Available at: 10.1517/14740338.2014.859674

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK:* Opsumit; *USA:* Opsumit.

Manidipine Hydrochloride *(rINNM)*

CV-4093; Franidipine Hydrochloride; Hidrocloruro de manidipino; Manidipina Cloridrato; Manidipine, Chlorhydrate de; Manidipinhydrochlorid; Manidipini Hydrochloridum; Manidipino, hidrocloruro de; Манидипина гидрохлорид.

2-[4-(Diphenylmethyl)-1-piperazinyl]ethyl methyl (±)-1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate dihydrochloride.

$C_{35}H_{38}N_4O_6.2HCl$=683.6

CAS — 120092-68-4 (manidipine); 89226-75-5 (manidipine hydrochloride); 126229-12-7 (manidipine hydrochloride).

ATC — C08CA11.

ATC Vet — QC08CA11.

UNII — ZL507UZ6QL.

Pharmacopoeias. In *Jpn.*

Profile

Manidipine is a dihydropyridine calcium-channel blocker (see Nifedipine, p. 1447.2). It is given orally as the hydrochloride in the management of hypertension (p. 1251.1) in a usual dose of 10 to 20 mg once daily.

Reviews.
1. McKeage K, Scott LJ. Manidipine: a review of its use in the management of hypertension. *Drugs* 2004; 64: 1923–40.
2. Roca-Cusachs A, Triposkiadis F. Antihypertensive effect of manidipine. *Drugs* 2005; 65 (suppl 2): 11–19.
3. Richy FF, Laurent S. Efficacy and safety profiles of manidipine compared with amlodipine: a meta-analysis of head-to-head trials. *Blood Pressure* 2010; 20: 54–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.:* Manivasc; *Fr.:* Iperten; *Ger.:* Manyper; *Gr.:* Manyper; *Hung.:* Iperten; *Ital.:* Iperten; Vascoman; *Jpn:* Calslot; *Philipp.:* Caldine; *Spain:* Artedil; *Thai.:* Madiplot.

Multi-ingredient Preparations. *Austria:* Vivace†; *Braz.:* Hipertil; *Ger.:* Vivace; *Gr.:* Vivace; *Spain:* Bimade; Vivace.

Mannitol ⊗

Cordycepic Acid; E421; Fraxinina; Manita; Manitol; Manitolis; Manna Sugar; Mannit; Mannite; Mannitoli; Mannitolum; Маннит; Маннитол.

D-Mannitol.

$C_6H_{14}O_6$=182.2

CAS — 69-65-8.

ATC — A06AD16; B05BC01; B05CX04; R05CB16.

ATC Vet — QA06AD16; QB05BC01; QB05CX04; QR05CB16.

UNII — 3OWL53L36A.

Description. Mannitol is a hexahydric alcohol related to mannose ($C_6H_{12}O_6$= 180.2). It is isomeric with sorbitol (p. 2092.1).

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 8: (Mannitol). White or almost white crystals or powder. It exhibits polymorphism. Freely soluble in water; practically insoluble in alcohol.

USP 36: (Mannitol). A white odourless crystalline powder or free-flowing granules with a sweet taste. Soluble 1 in 5.5 of water; very slightly soluble in alcohol; practically insoluble in ether; slightly soluble in pyridine; soluble in alkaline solutions.

Incompatibility. Mannitol should never be added to whole blood for transfusion or given through the same set by which blood is being infused. For details of the adverse effects of mannitol on red blood cells, see Effects on the Blood under Adverse Effects, p. 1428.3.

Supersaturated solutions. Supersaturated aqueous solutions are prepared with the aid of heat. Any crystals that form during storage of the injection should be dissolved by warming before use; this may be a particular problem with the 20 and 25% injections which are supersaturated. A 5.07% solution in water is iso-osmotic with serum.

Uses and Administration

Mannitol is an osmotic agent. Although an isomer of sorbitol, it has little energy value, since it is largely eliminated from the body before any metabolism can take place.

Mannitol is mainly used, with adequate rehydration, to increase urine flow in patients with acute renal failure and to reduce raised intracranial pressure (p. 1271.3) and treat cerebral oedema (although it may be of no benefit or even harmful in patients with cerebral malaria—see p. 1428.3). It is also used in the short-term management of glaucoma (p. 1999.1), especially to reduce intra-ocular pressure before ophthalmic surgery, and to promote the excretion of toxic substances by forced diuresis.

Other indications include bladder irrigation during transurethral resection of the prostate in order to reduce haemolysis and it has been used as an oral osmotic laxative for bowel preparation. It is given by inhalation for a mucolytic effect in cystic fibrosis and in the diagnosis of bronchial hyperresponsiveness in asthma (see Respiratory Disorders, p. 1428.2). Mannitol is used as a diluent, a

bulking agent for freeze-drying, and an excipient in pharmaceutical preparations and as a bulk sweetener.

When given parenterally, mannitol raises the osmotic pressure of the plasma thus drawing water out of body tissues and producing an osmotic diuresis. Reduction of CSF and intra-ocular fluid pressure occurs within 15 minutes of the start of a mannitol infusion and lasts for 3 to 8 hours after the infusion is stopped; diuresis occurs after 1 to 3 hours.

When used as an osmotic diuretic, mannitol is given by intravenous infusion. Careful monitoring of fluid balance, electrolytes, renal function, and vital signs is necessary during infusion to prevent fluid and electrolyte imbalance, including circulatory overload and tissue dehydration. Solutions containing more than 15% of mannitol may crystallise during storage, particularly at low temperatures; crystals may be redissolved by warming before use; the giving set should include a filter.

Mannitol may be used to treat patients in the oliguric phase of **renal failure** or those suspected of inadequate renal function after correction of plasma volume, provided a test dose of about 200 mg/kg given by rapid intravenous infusion of a 15 to 25% solution over 3 to 5 minutes produces a diuresis of at least 30 to 50 mL/hour during the next 2 to 3 hours; a second test dose is permitted if the response to the first is inadequate. The usual adult dose of mannitol ranges from 50 to 100 g in a 24 hour period, given by intravenous infusion of a 5 to 20% solution. The rate of infusion is usually adjusted to maintain a urine flow of at least 30 to 50 mL/hour.

For doses in children, see below.

The total dosage, the concentration, and the rate of infusion depend on the fluid requirement, the urinary output, and the nature and severity of the condition being treated. Mannitol infusion has also been used to prevent acute renal failure during cardiovascular and other types of surgery, or after trauma.

To reduce **raised intracranial** or **intra-ocular pressure** mannitol may be given by intravenous infusion as a 15 to 25% solution in a dose of 0.25 to 2 g/kg over 30 to 60 minutes. Rebound increases in intracranial or intra-ocular pressure may occur but are less frequent than with urea.

During **transurethral prostatic resection** a 2.5 to 5% solution of mannitol has been used for irrigating the bladder.

In the management of **cystic fibrosis**, in patients aged 18 years and over, the initial dose of mannitol is given in an escalating dosage regimen to assess bronchial hyperresponsiveness. Baseline measures of FEV_1 and oxygen saturation in the blood (SpO_2) are followed by an inhaled bronchodilator. After a further 5 to 15 minutes mannitol powder is given by inhalation as:

- 40 mg, followed by SpO_2 measurement after 60 seconds, then
- 80 mg, followed by SpO_2 measurement after 60 seconds, then
- 120 mg, followed by FEV_1 and SpO_2 measurement after 60 seconds, then
- 160 mg, followed by FEV_1 and SpO_2 measurement after 60 seconds, then
- FEV_1 measured after 15 minutes

Hyperresponsiveness is defined as any of the following:

- ⩾ 10% fall from baseline in SpO_2 at any time during the assessment
- FEV_1 has fallen from baseline ⩾ 20% at a cumulative dose of 240 mg
- FEV_1 has fallen 20 to < 50% from baseline at the end of the assessment and does not return to < 20% below baseline within 15 minutes
- FEV_1 has fallen ⩾ 50% from baseline at the end of the assessment

Patients who are not hyperresponsive may be started on a maintenance dose of mannitol 400 mg inhaled twice daily. Doses should be given 5 to 15 minutes after an inhaled bronchodilator and before physiotherapy or exercise and any other inhaled treatments such as dornase alfa and inhaled antibacterials.

Inhaled mannitol is also used as a **bronchial provocation test** for asthma in patients aged 6 years and older who do not have clinically apparent asthma, and have a baseline FEV_1 of 70% or more of predicted value. Mannitol powder is given by inhalation in incremental doses of 5, 10, 20, 40, 80, 160, 160, and 160 mg. Each dose is followed by measurement of FEV_1, until a positive response occurs (a 15% fall in FEV_1 from baseline or a 10% incremental fall between doses) or a total of 635 mg has been given.

Administration in children. Mannitol may be given to children in the treatment of oliguria in acute renal failure, cerebral and peripheral oedema, ascites, and raised intra-ocular pressure. A test dose is first given, as in adults (see Uses and Administration, p. 1427.3).

In the oliguric phase of **renal failure**, children may be given a 0.25 to 2 g/kg or 60 g/m² intravenous infusion of a 15 to 20% solution over 2 to 6 hours.

For **raised intracranial** or **intra-ocular pressure**, a dose of 1 to 2 g/kg or 30 to 60 g/m² of a 15 to 25% solution may be infused over 30 to 60 minutes. In small or debilitated patients, a dose of 500 mg/kg may suffice. An alternative dose suggested by the *BNFC* for children aged 1 month to 12 years is 0.25 to 1.5 g/kg infused over 30 to 60 minutes and repeated once or twice after 4 to 8 hours if necessary.

In the treatment of **peripheral oedema** and **ascites**, the *BNFC* suggests that children aged 1 month to 18 years may be given an infusion of 1 to 2 g/kg over 2 to 6 hours.

Mannitol may be used as a **bronchial provocation test** in children (see Uses and Administration, p. 1427.3).

Ciguatera poisoning. Ciguatera poisoning occurs throughout the Caribbean and Indopacific as a result of the consumption of certain fish contaminated with ciguatoxin; it is increasingly seen elsewhere, in travellers returning from these areas or as a result of eating imported fish. Nausea, vomiting, diarrhoea, and abdominal pain usually start within 24 hours and resolve within about 4 days. Neurological symptoms generally develop after the acute gastrointestinal illness, and include paraesthesias of the extremities and oral region, and a bizarre reversal of hot and cold sensation. Some neurological symptoms, pruritus, arthralgia, and fatigue, may persist for years.[1,2] Painful ejaculation and dyspareunia have been reported, as well as the occurrence of symptoms in sexual partners, suggesting that ciguatoxin can been transferred during intercourse.[2]

Treatment is usually symptomatic since there is no specific antidote. Dramatic reversal of neuromuscular symptoms with slower resolution of gastrointestinal upset has been reported after giving mannitol 1 g/kg by intravenous infusion over 30 to 45 minutes in the acute phase of the illness.[3-5] Mannitol may also be beneficial up to a week after poisoning.[6] However, a double-blind study[7] found mannitol to be no better than normal saline at relieving symptoms at 24 hours. Despite the weak and conflicting evidence for its efficacy, mannitol has been recommended for patients who are diagnosed within 48 to 72 hours after fish consumption; repeat treatment may be necessary if symptoms recur. After 72 hours, mannitol may be considered on an individual basis.[1] Amitriptyline has been found on several occasions[8-10] to relieve neurological symptoms (dysaesthesias and paraesthesias) and pruritus. Gabapentin has also been reported to be of benefit.[11]

1. Friedman MA, *et al.* Ciguatera fish poisoning: treatment, prevention and management. *Mar Drugs* 2008; 6: 456–79.
2. Stewart I, *et al.* Emerging tropical diseases in Australia. Part 2. Ciguatera fish poisoning. *Ann Trop Med Parasitol* 2010; 104: 557–71.
3. Palafox NA, *et al.* Successful treatment of ciguatera fish poisoning with intravenous mannitol. *JAMA* 1988; 259: 2740–2.
4. Pearn JH, *et al.* Ciguatera and mannitol: experience with a new treatment regimen. *Med J Aust* 1989; 151: 77–80.
5. Williamson J. Ciguatera and mannitol: a successful treatment. *Med J Aust* 1990; 153: 306–7.
6. Fenner PJ, *et al.* A Queensland family with ciguatera after eating coral trout. *Med J Aust* 1997; 166: 473–5.
7. Schnoef H, *et al.* Ciguatera fish poisoning: a double-blind randomized trial of mannitol therapy. *Neurology* 2002; 58: 873–80.
8. Bowman PB. Amitriptyline and ciguatera. *Med J Aust* 1984; 140: 802.
9. Davis RT, Villar LA. Symptomatic improvement with amitriptyline in ciguatera fish poisoning. *N Engl J Med* 1986; 315: 65.
10. Calvert GM, *et al.* Treatment of ciguatera fish poisoning with amitriptyline and nifedipine. *J Toxicol Clin Toxicol* 1987; 25: 423–8.
11. Perez CM, *et al.* Treatment of ciguatera poisoning with gabapentin. *N Engl J Med* 2001; 344: 692–3.

Gastrointestinal disorders. *BOWEL PREPARATION.* Mannitol, 1000 mL of a 10% solution or 500 mL of 10 or 20% solution, given orally, has been used to prepare the bowel for surgical and diagnostic procedures.[1,2] The potential for formation of explosive gas in the bowel should be borne in mind (see Effects on the Gastrointestinal Tract, below).

1. Palmer KR, Khan AN. Oral mannitol: a simple and effective bowel preparation for barium enema. *BMJ* 1979; 2: 1038.
2. Newstead GL, Morgan BP. Bowel preparation with mannitol. *Med J Aust* 1979; 2: 582–3.

DIAGNOSIS AND TESTING. Mannitol has been used with lactulose[1,2] and with cellobiose[3,4] in the detection of abnormal small bowel permeability, particularly that occurring in coeliac disease. For further information on the use of differential sugar absorption tests, see Lactulose, p. 1854.1.

1. Pearson ADJ, *et al.* The gluten challenge—biopsy v permeability. *Arch Dis Child* 1983; 58: 653.
2. Cooper BT. Intestinal permeability in coeliac disease. *Lancet* 1983; i: 658–9.
3. Juby LD, *et al.* Cellobiose/mannitol sugar test—a sensitive tubeless test for coeliac disease: results on 1010 unselected patients. *Gut* 1989; 30: 476–80.
4. Hodges S, *et al.* Cellobiose: mannitol differential permeability in small bowel disease. *Arch Dis Child* 1989; 64: 853–5.

Respiratory disorders. Inhalation of dry powder mannitol improves mucus clearance and small studies have suggested it may be of benefit in bronchiectasis.[1,2] In patients with cystic fibrosis (p. 177.2) it can improve FEV_1 and reduce the risk of pulmonary exacerbations requiring intravenous antibacterial therapy.[3-5] Inhaled mannitol may also be used as a bronchial provocation test in the diagnosis of asthma.[6-9]

1. Wills P, Greenstone M. Inhaled hyperosmolar agents for bronchiectasis. *Available in The Cochrane Database of Systematic Reviews*; Issue . Chichester: John Wiley; 2006 (accessed 24/08/12).
2. Gjoerup J, *et al.* Inhaled mannitol in the treatment of non-cystic fibrosis bronchiectasis in adults. *Respirology* 2012; 17: 927–32.
3. Bilton D, *et al.* CF301 Study Investigators. Inhaled dry powder mannitol in cystic fibrosis: an efficacy and safety study. *Eur Respir J* 2011; 38: 1071–80.
4. Aitken ML, *et al.* CF302 Investigators. Long-term inhaled dry powder mannitol in cystic fibrosis: an international randomized study. *Am J Respir Crit Care Med* 2012; 185: 645–52.
5. Burness CB, Keating GM. Mannitol dry powder for inhalation: in patients with cystic fibrosis. *Drugs* 2012; 72: 1411–21.
6. Brannan JD, *et al.* The safety and efficacy of inhaled dry powder mannitol as a bronchial provocation test for airway hyperresponsiveness: a phase 3 comparison study with hypertonic (4.5%) saline. *Respir Res* 2005; 6: 144. Available at: http://respiratory-research.com/content/pdf/1465-9921-6-144.pdf (accessed 25/02/10)
7. Anderson SD, *et al.* A305 Study Group. Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. *Respir Res* 2009; 10: 4.
8. Sverrild A, *et al.* Diagnostic properties of inhaled mannitol in the diagnosis of asthma: a population study. *J Allergy Clin Immunol* 2009; 124: 928–32.
9. Sverrild A, *et al.* The use of inhaled mannitol in the diagnosis and management of asthma. *Expert Opin Pharmacother* 2012; 13: 115–23.

Adverse Effects and Precautions

The most common adverse effect associated with intravenous mannitol therapy is fluid and electrolyte imbalance including circulatory overload and acidosis at high doses. The expansion of extracellular volume can precipitate pulmonary oedema and congestive heart failure. The shift of fluid from the intracellular to extracellular compartment can cause tissue dehydration; dehydration of the brain, particularly in patients with renal failure, may give rise to CNS symptoms. Excessive diuresis can cause serious electrolyte imbalance.

Intravenous infusion of mannitol has been associated with nausea, vomiting, thirst, headache, dizziness, chills, fever, tachycardia, chest pain, hyponatraemia, dehydration, blurred vision, urticaria, and hypotension or hypertension. Large doses have been associated rarely with acute renal failure. Hypersensitivity reactions have occurred. Extravasation of the solution may cause oedema and skin necrosis; thrombophlebitis may occur.

Intravenous mannitol is contra-indicated in patients with severe pulmonary congestion or frank pulmonary oedema, intracranial bleeding (except during craniotomy), heart failure, severe dehydration, and in patients with renal failure unless a test dose has produced a diuretic response. All patients given mannitol should be carefully observed for signs of fluid and electrolyte imbalance and renal function should be monitored.

Mannitol should not be given with whole blood.

When given orally, mannitol causes diarrhoea.

Inhaled mannitol produces bronchospasm. Cough, wheezing, local irritation and pain, and headache are common; dizziness, nausea and vomiting, and haemoptysis can also occur.

Cerebral malaria. Mannitol has been used to treat raised intracranial pressure that is caused by oedema associated with cerebral malaria. However, a study in children found no benefit in measures of recovery or mortality,[1] and a study in adults reported that mannitol prolonged coma duration and may be harmful.[2]

1. Namutangula B, *et al.* Mannitol as adjunct therapy for childhood cerebral malaria in Uganda: a randomized clinical trial. *Malar J* 2007; 6: 138. Available at: *http://www.malariajournal.com/content/pdf/1475-2875-6-138.pdf* (accessed 28/08/12)
2. Mohanty S, *et al.* Brain swelling and mannitol therapy in adult cerebral malaria: a randomized trial. *Clin Infect Dis* 2011; 53: 349–55.

Effects on the blood. Agglutination and irreversible crenation of erythrocytes occurred when blood was mixed with varying proportions of a 10% mannitol solution.[1] It was suggested that intravenous infusions should be carefully controlled and given at a slow rate. This observation could have particular relevance to patients with sickle-cell disease.[2,3] Although agglutination and crenation had been seen *in vitro*, dilutional effects would make *in-vivo* interaction with blood cells less likely.[4]

1. Roberts BE, Smith PH. Hazards of mannitol infusions. *Lancet* 1966; ii: 421–2.
2. Konotey-Ahulu FID. Hazards of mannitol infusions. *Lancet* 1966; ii: 591.
3. Roberts BE, Smith PH. Hazards of mannitol infusions. *Lancet* 1966; ii: 591.
4. Samson JH. Hazards of mannitol infusions. *Lancet* 1966; ii: 1191.

Effects on the gastrointestinal tract. Potentially explosive intracolonic concentrations of hydrogen gas have been measured in patients given mannitol before colonoscopy,[1,2] and cases of colonic explosion, including fatalities, have been reported in patients undergoing colonoscopic electrocautery, who had received mannitol bowel preparation. However, the risk of explosion was considered to be small when air or carbon dioxide insufflation

and suction were used during the colonoscopy procedure.[2,3]

Colonic perforation and subsequent death has been attributed to the use of mannitol for the treatment of constipation.[4]

1. La Brooy SJ, *et al.* Potentially explosive colonic concentrations of hydrogen after bowel preparation with mannitol. *Lancet* 1981; i: 634–6.
2. Avgerinos A, *et al.* Bowel preparation and the risk of explosion during colonoscopic polypectomy. *Gut* 1984; 25: 361–4.
3. Trouman L, Walt R. Mannitol and explosions. *Lancet* 1981; i: 848.
4. Moses FM. Colonic perforation due to oral mannitol. *JAMA* 1988; 260: 640.

Effects on the kidneys. Focal osmotic nephrosis occurred in a patient given mannitol 20% intravenously.[1]

Acute oliguric renal failure has been associated with the use of large doses of mannitol in patients with previously normal renal function,[2-4] and acute renal failure developed[5] in a patient with diabetes mellitus complicated by nephropathy after he was given 420 g of mannitol intravenously over 4 days.

1. Goodwin WE, Latta H. Focal osmotic nephrosis due to the therapeutic use of mannitol: a case of perirenal hematoma after renal biopsy. *J Urol (Baltimore)* 1970; 103: 11–14.
2. Whelan TV, *et al.* Acute renal failure associated with mannitol intoxication. *Arch Intern Med* 1984; 144: 2053–5.
3. Goldwasser P, Fotino S. Acute renal failure following massive mannitol infusion: appropriate response of tubuloglomerular feedback? *Arch Intern Med* 1984; 144: 2214–16.
4. Rabetoy GM, *et al.* Where the kidney is concerned, how much mannitol is too much? *Ann Pharmacother* 1993; 27: 25–8.
5. Matsumura M. Mannitol-induced toxicity in a diabetic patient receiving losartan. *Am J Med* 2001; 110: 331.

Overdosage. Severe mannitol intoxication was reported in 8 patients with renal failure given large, and sometimes enormous, amounts of mannitol intravenously over 1 to 3 days.[1] These patients had CNS involvement out of proportion to uraemia, severe hyponatraemia, a large osmolality gap, and fluid overload. Six patients were treated with haemodialysis and this was considered to be more effective than peritoneal dialysis, which was used in 1 patient.

1. Borges HF, *et al.* Mannitol intoxication in patients with renal failure. *Arch Intern Med* 1982; 142: 63–6.

Pharmacokinetics

Only small amounts of mannitol are absorbed from the gastrointestinal tract or after inhalation. After intravenous injection mannitol is excreted rapidly by the kidneys before any very significant metabolism can take place in the liver. Mannitol does not cross the blood-brain barrier or penetrate the eye. An elimination half-life of about 100 minutes has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Aridol; Mede-Prep†; Osmitrol; ***Canad.***: Osmitrol; Resectisol; ***China***: Feng Hai Lu (丰海露); Pu Ke (普可); Shen Ning (伸宁); ***Cz.***: Ardeaosmosol MA; Mannisol†; ***Denm.***: Bronchitol; Osmohale; ***Fin.***: Aridol; ***Fr.***: Aridol; ***Ger.***: Aridol; Deltamannit; Mannit-Losung; Osmofundin 15% N; Osmosteril; ***Gr.***: Aridol; ***Hong Kong***: Osmitrol†; ***Hung.***: Mannisol; ***India***: Neurotol-M; Osmitrol; ***Indon.***: Infusan M; ***Irl.***: Osmohale; ***Israel***: Osmitrol; ***Ital.***: Isotol; Osmohale; ***Mex.***: Osmorol†; ***Neth.***: Bronchitol; Osmohale; Osmosteril; ***Norw.***: Aridol; ***Port.***: Aridol; Osmofundina; ***Singapore***: Osmitrol; ***Spain***: Osmofundina Concentrada; Osmohale; ***Swed.***: Aridol; ***Switz.***: Aridol; Mannite; ***Turk.***: Resectisol; Rezosel; ***UK***: Bronchitol; Osmohale; ***USA***: Aridol; Osmitrol.

Multi-ingredient Preparations. ***Chile***: Gelsolets; Solucion Irrigacion Vesical†; ***Denm.***: Pharmalgen Albumin; ***Ger.***: Flacar; Preka-Drainjet Purisole†; Hya-ject Plus; Infi-tract V; ***Hong Kong***: Osmofundin†; ***India***: Kratol; Mannigyl; Mengy; Neurotol; ***Ital.***: Levoplus; Naturalass; Plurilac; ***Mex.***: Jarabe de Manzanas; ***Pol.***: Purisole SM†; ***Port.***: Purisole; Xarope de Macas Reinetas; ***Rus.***: Rheogluman (Реоглюман); ***Singapore***: Osmofundin; ***Spain***: Hidrofundin; Osmofundina; Salmagne; ***Thai.***: Dimedon; ***Ukr.***: Turusol (Турусол).

Used as an adjunct in:. ***China***: Chen Ya (辰雅).

Pharmacopoeial Preparations
BP 2014: Mannitol Infusion;
USP 36: Chlorothiazide Sodium for Injection; Cisplatin for Injection; Mannitol in Sodium Chloride Injection; Mannitol Injection.

Mecamylamine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de mecamilamina; Mecamilamina, hidrocloruro de; Mecamine Hydrochloride; Mécamylamine; Chlorhydrate de; Mecamylamini Hydrochloridum; Мекамиламина Гидрохлорид.

N-Methyl-2,3,3-trimethylbicyclo[2.2.1]hept-2-ylamine hydrochloride.

$C_{11}H_{21}N,HCl$=203.8

CAS — 60-40-2 (mecamylamine); 826-39-1 (mecamylamine hydrochloride).

ATC — C02BB01.

ATC Vet — QC02BB01.

UNII — 4956DJR58O.

Pharmacopoeias. In *US*.

USP 36: (Mecamylamine Hydrochloride). Store in airtight containers.

Uses and Administration

Mecamylamine hydrochloride is a ganglion blocker that acts to reduce transmission of nerve impulses in sympathetic and parasympathetic ganglia, resulting via the former action in peripheral vasodilatation and a fall in blood pressure. It is given orally in the management of hypertension (p. 1251.1). However, it may be limited to patients with severe hypertension or uncomplicated malignant hypertension and other antihypertensives with fewer adverse effects are generally preferred.

The usual initial dose is 2.5 mg twice daily gradually adjusted, usually in steps of 2.5 mg at intervals of not less than 2 days, until a satisfactory dose is obtained. The average maintenance dose is 25 mg daily in three divided doses. Tolerance may develop. Sudden withdrawal of mecamylamine may cause rebound hypertension therefore a gradual withdrawal is recommended.

Reviews.
1. Young JM, *et al.* Mecamylamine: new therapeutic uses and toxicity/risk profile. *Clin Ther* 2001; 23: 532–65.

Smoking cessation. Mecamylamine acts centrally as a nicotinic antagonist and might be of some benefit in assisting withdrawal from smoking. Two studies[1,2] have shown that addition of low-dose oral mecamylamine (2.5 to 5 mg twice daily) appeared to enhance the efficacy of nicotine skin patches. However, a later controlled study[3] found that a patch containing both mecamylamine and nicotine was not significantly better than transdermal nicotine alone. Smoking cessation is discussed under Nicotine, p. 2570.2.

1. Rose JE, *et al.* Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicotine patch treatment alone. *Clin Pharmacol Ther* 1994; 56: 86–99.
2. Rose JE, *et al.* Nicotine-mecamylamine treatment for smoking cessation: the role of pre-cessation therapy. *Exp Clin Psychopharmacol* 1998; 6: 331–43.
3. Glover ED, *et al.* A randomized, controlled trial to assess the efficacy and safety of a transdermal delivery system of nicotine/mecamylamine in cigarette smokers. *Addiction* 2007; 102: 795–802.

Tourette's syndrome. Mecamylamine has been tried[1-3] in the management of Tourette's syndrome (see under Tics, p. 1030.1) although results have been mixed.

1. Sanberg PR, *et al.* Treatment of Tourette's syndrome with mecamylamine. *Lancet* 1998; 352: 705–6.
2. Silver AA, *et al.* Mecamylamine in Tourette's syndrome: a two-year retrospective case study. *J Child Adolesc Psychopharmacol* 2000; 10: 59–68.
3. Silver AA, *et al.* Multicenter, double-blind, placebo-controlled study of mecamylamine monotherapy for Tourette's disorder. *J Am Acad Child Adolesc Psychiatry* 2001; 40: 1103–10.

Adverse Effects and Precautions

The adverse effects of mecamylamine are mainly due to ganglionic blockade. A reduction in gastrointestinal motility may cause constipation or paralytic ileus (sometimes preceded by frequent liquid stools). Dry mouth, glossitis, and other gastrointestinal disturbances such as anorexia, nausea, or vomiting, may occur. Orthostatic hypotension and dizziness may be seen. Other adverse effects include blurred vision, urinary retention, erectile dysfunction, weakness, and fatigue. Pulmonary oedema and fibrosis have been reported. Mecamylamine crosses the blood-brain barrier and may also cause tremor, convulsions, choreiform movements, insomnia, sedation, dysarthria, and mental aberrations. Use is contra-indicated in patients with coronary insufficiency or recent myocardial infarction; it should also be avoided in those with glaucoma, pyloric stenosis, or marked renal impairment.

Pharmacokinetics

Mecamylamine hydrochloride is almost completely absorbed from the gastrointestinal tract. It crosses the placenta and the blood-brain barrier. About 50% of the dose is excreted unchanged in the urine over 24 hours, but the rate is diminished in alkaline urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Inversine†.

Pharmacopoeial Preparations
USP 36: Mecamylamine Hydrochloride Tablets.

Mefruside *(BAN, USAN, rINN)* ⊗

Bay-1500; FBA-1500; Mefrusid; Mefrusida; Méfruside; Mefrusidi; Mefrusidum; Мефрузид.

4-Chloro-*N*^{1}-methyl-*N*^{1}-(tetrahydro-2-methylfurfuryl)benzene-1,3-disulphonamide.

$C_{13}H_{19}ClN_2O_5S_2$=382.9

CAS — 7195-27-9.

ATC — C03BA05.

ATC Vet — QC03BA05.

UNII — X1NS9SNS92.

NOTE. The names Escaron and Mebread have been used as trade names for mefruside.

Pharmacopoeias. In *Jpn*.

Profile

Mefruside is a diuretic with properties similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1403.2) even though it does not contain a thiazide ring system. It is used for hypertension (p. 1251.1).

Diuresis begins about 2 to 4 hours after an oral dose and reaches a peak between 6 and 12 hours.

Mefruside is given with other antihypertensives in a usual oral dose of 10 to 50 mg daily, either as a single dose or in two divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Sali-Adalat; Sali-Prent.

Meldonium *(rINN)*

Meldonio; MET-88; 3-(2,2,2-Trimethylhydrazinium)propionate; Мельдоний.

3-(2,2,2-Trimethyldiazaniumyl)propanoate.

$C_6H_{14}N_2O_2$=146.2

CAS — 76144-81-5 (meldonium); 86426-17-7 (meldonium dihydrate).

UNII — 73H7UDN6EC.

Profile

Meldonium is an inhibitor of carnitine synthesis and is reported to have cardioprotective and anti-ischaemic effects. It has been used in a variety of disorders. In the management of ischaemic heart disease and ischaemic cerebrovascular disturbances typical oral doses have ranged from 500 mg to 1 g daily. A course of 500 mg given four times daily for 7 to 10 days has been used in alcohol abstinence syndrome. Meldonium has also been given intravenously in doses similar to those used orally.

References.
1. Dambrova M, *et al.* Mildronate: cardioprotective action through carnitine-lowering effect. *Trends Cardiovasc Med* 2002; 12: 275–9.
2. Sjakste N, *et al.* Mildronate: an antiischemic drug for neurological indications. *CNS Drug Rev* 2005; 11: 151–68.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Cardionate (Кардионат); Idrinol (Идринол); Midolat (Мидолат); Mildronate (Милдронат); Mildroxyn (Милдроксин); ***Ukr.***: Metamax (Метамакс); Methyldronat (Метилдронат)†; Metonat (Метонат); Mildronate (Милдронат); Trizipin (Тризипин); Vazonat (Вазонат); Vazopro (Вазопро).

Mephentermine Sulfate *(BANM, rINNM)* ⊗

Mefentermina, sulfato de; Méphentermine, Sulfate de; Mephentermine Sulphate; Mephentermini Sulfas; Mephetedrine Sulphate; Sulfato de mefentermina; Мефентермина Сульфат.

N,α,α-Trimethylphenethylamine sulphate dihydrate.

$(C_{11}H_{17}N)_2H_2SO_4.2H_2O$=460.6

CAS — 100-92-5 (mephentermine); 1212-72-2 (anhydrous mephentermine sulfate); 6190-60-9 (mephentermine sulfate dihydrate).

ATC — C01CA11.

ATC Vet — QC01CA11.

UNII — 580655Z8RR.

Uses and Administration

Mephentermine is a sympathomimetic (p. 1507.3) with mainly indirect effects on adrenergic receptors. It has alpha- and beta-adrenergic activity, and a slight stimulating effect on the CNS. It has an inotropic effect on the heart.

Mephentermine has been used to maintain blood pressure in hypotensive states, for example after spinal anaesthesia. It is given as the sulfate but doses are expressed in terms of the base; 21 mg of sulfate is equivalent to about

15 mg of base. Typical doses have ranged from 15 to 45 mg by slow intravenous or intramuscular injection.

References.
1. Kansal A, *et al.* Randomised trial of intravenous infusion of ephedrine or mephentermine for management of hypotension during spinal anaesthesia for Caesarean section. *Anaesthesia* 2005; 60: 28–34.
2. Mohta M, *et al.* Comparison of potency of ephedrine and mephentermine for prevention of post-spinal hypotension in caesarean section. *Anaesth Intensive Care* 2008; 36: 360–4.
3. Mohta M, *et al.* Potency of mephentermine for prevention of post-spinal hypotension. *Anaesth Intensive Care* 2009; 37: 568–70.

Adverse Effects, Treatment, and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3; adverse effects may be related to alpha- or beta-adrenergic stimulation. Mephentermine may produce CNS stimulation, especially in overdosage; anxiety, drowsiness, incoherence, hallucinations, and convulsions have been reported.

Interactions

As for Sympathomimetics, p. 1508.3.

Pharmacokinetics

Mephentermine acts in about 5 to 15 minutes after intramuscular injection and has a duration of action of up to about 4 hours; it acts almost immediately after intravenous injection with a duration of action of up to about 30 minutes. It is rapidly metabolised in the body by demethylation; hydroxylation may follow. It is excreted as unchanged drug and metabolites in the urine; excretion is more rapid in acidic urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Mephentine.

Multi-ingredient Preparations. *USA*: Emergent-Ez.

Metaraminol Tartrate *(BANM, rINNM)* ⊗

Bitartrato de metaraminol; Hydroxynorephedrine Bitartrate; Metaradrine Bitartrate; Metaraminol Acid Tartrate; Metaraminol Bitartrate; Métaraminol, Tartrate de; Metaraminol, tartrato de; Metaraminoli Tartras; Tartrato de metaraminol; Метараминола Тартрат.

(-)-2-Amino-1-(3-hydroxyphenyl)propan-1-ol hydrogen tartrate.

$C_9H_{13}NO_2,C_4H_6O_6$=317.3

CAS — 54-49-9 (metaraminol); 33402-03-8 (metaraminol tartrate).

ATC — C01CA09.

ATC Vet — QC01CA09.

UNII — ZC4202M9P3.

Pharmacopoeias. In *Br.*, *Chin.*, and *US.*

BP 2014: (Metaraminol Tartrate). An odourless or almost odourless, white, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform and in ether. A 5% solution in water has a pH of 3.2 to 3.5.

USP 36: (Metaraminol Bitartrate). A 5% solution in water has a pH of between 3.2 and 3.5. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Metaraminol is a sympathomimetic (p. 1507.3) with direct and indirect effects on adrenergic receptors. It has alpha-and beta-adrenergic activity, the former being predominant. Metaraminol has an inotropic effect and acts as a peripheral vasoconstrictor, thus increasing cardiac output, peripheral resistance, and blood pressure. Coronary blood flow is increased and the heart rate slowed.

Metaraminol tartrate is used for its pressor action in **hypotensive states** such as those that may occur after spinal anaesthesia. Doses are expressed in terms of the base; metaraminol tartrate 9.5 mg is equivalent to about 5 mg of metaraminol. An intravenous infusion of 15 to 100 mg of metaraminol in 500 mL of glucose 5% or sodium chloride 0.9% may be used for maintaining the blood pressure, the rate of infusion being adjusted according to blood pressure response. Higher concentrations have been given. As the maximum effects are not immediately apparent, at least 10 minutes should elapse before increasing the dose and the possibility of a cumulative effect should be borne in mind. In an emergency an initial dose of 0.5 to 5 mg may be given by direct intravenous injection followed by an intravenous infusion as above.

Metaraminol tartrate has also been given by intramuscular or subcutaneous injection for the prevention of hypotension in doses equivalent to 2 to 10 mg of metaraminol. Subcutaneous injection increases the risk of local tissue necrosis and sloughing.

Priapism. Priapism[1,2] or prolonged penile erection may occur due to either decreased venous outflow (low-flow priapism) or increased arterial inflow (high-flow priapism). Low-flow priapism is a medical emergency since inflow is also impaired, leading to the development of ischaemia. It may be related to the use of drugs that cause smooth muscle relaxation, such as alpha blockers; intraluminal obstruction, such as in sickle-cell disease, may also be a cause. It is usually treated with corporal aspiration, followed if necessary by irrigation with a low dosage of a dilute solution of an alpha agonist such as metaraminol.

Intracavernosal metaraminol has been used successfully to treat drug-induced priapism,[3] as well as priapism associated with chronic myeloid leukaemia,[4] haemodialysis,[5] spinal block,[6] or fentanyl-induced general anaesthesia.[6] It may also be used to reverse the effects of alprostadil or papaverine given intracavernosally for the management of some types of erectile dysfunction, although this has been associated with fatal hypertensive crisis (see also Alprostadil, p. 2353.2).

Alternative alpha agonists that are used include intracavernosal phenylephrine,[7] and intracavernosal adrenaline, again in a low dosage and dilute solution. Phenylpropanolamine,[7] or pseudoephedrine,[8] given orally, have also been used. In patients with priapism due to sickle-cell disease, intracavernosal irrigation with a dilute adrenaline solution (see p. 1294.1) or intracavernosal injection of etilefrine have been used; oral etilefrine has been given for prophylaxis. Many other drugs have been tried or suggested, including baclofen, gabapentin, terbutaline, and, paradoxically, low doses of phosphodiesterase type-5 inhibitors such as sildenafil or tadalafil.[2] Surgery is usually favoured in low-flow priapism unresponsive to drug therapy.

In high-flow priapism, which is less of an emergency, embolisation of the source of abnormal inflow is the usual treatment.

1. Maan Z, *et al.* Priapism—a review of the medical management. *Expert Opin Pharmacother* 2003; 4: 2271–7.
2. Yuan J, *et al.* Insights of priapism mechanism and rationale treatment for recurrent priapism. *Asian J Androl* 2008; 10: 88–101.
3. Brindley GS. New treatment for priapism. *Lancet* 1984; ii: 220–1.
4. Stanners A, Colin-Jones D. Metaraminol for priapism. *Lancet* 1984; ii: 978.
5. Branger B, *et al.* Metaraminol for haemodialysis-associated priapism. *Lancet* 1985; i: 641.
6. Tsai SK, Hong CY. Intracavernosal metaraminol for treatment of intraoperative penile erection. *Postgrad Med J* 1990; 66: 831–3.
7. Harmon WJ, Nehra A. Priapism: diagnosis and management. *Mayo Clin Proc* 1997; 72: 350–5.
8. Millard RJ, *et al.* Risks of self-injection therapy for impotence. *Med J Aust* 1996; 165: 117–18.

Adverse Effects, Treatment, and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3. The adverse effects of metaraminol mainly relate to its alpha-agonist action. Metaraminol has a longer duration of action than adrenaline or noradrenaline and therefore an excessive vasopressor response may cause a prolonged rise in blood pressure. Tissue necrosis can occur as a result of accidental extravasation during intravenous injection.

Interactions

As for Sympathomimetics, p. 1508.3. The interactions of metaraminol relate to both its direct and indirect actions.

Pharmacokinetics

Metaraminol acts about 10 minutes after intramuscular injection with a duration of action of up to about 1 hour. Effects are seen 1 to 2 minutes after intravenous injection with a duration of action of about 20 minutes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fadamine; *Austral.*: Aramine†; *Braz.*: Aramin; *NZ*: Aramine†; *Singapore*: Aramine; *Thai.*: Aramine; *USA*: Aramine†.

Pharmacopoeial Preparations
BP 2014: Metaraminol Injection;
USP 36: Metaraminol Bitartrate Injection.

Methoxamine Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de metoxamina; Methoxamedrine Hydrochloride; Méthoxamine, Chlorhydrate de; Methoxamini Hydrochloridum; Metoxamina, hidrocloruro de; Метоксамина Гидрохлорид.

2-Amino-1-(2,5-dimethoxyphenyl)propan-1-ol hydrochloride.

$C_{11}H_{17}NO_3,HCl$=247.7

CAS — 390-28-3 (methoxamine); 61-16-5 (methoxamine hydrochloride).

ATC — C01CA10.

ATC Vet — QC01CA10.

UNII — 8MB4MJ9R7L.

Pharmacopoeias. In *Br.* and *Chin.*

BP 2014: (Methoxamine Hydrochloride). Colourless crystals or white plate-like crystals or white crystalline powder; odourless or almost odourless. Freely soluble in water; soluble in alcohol; very slightly soluble in chloroform and in ether. A 2% solution in water has a pH of 4.0 to 6.0.

Profile

Methoxamine is a sympathomimetic (p. 1507.3) with mainly direct effects on adrenergic receptors. It has alpha-adrenergic activity entirely; beta-adrenergic activity is not demonstrable and beta-adrenoceptor blockade may occur at high doses. Methoxamine hydrochloride has been used parenterally for its pressor action in the management of hypotensive states, particularly in anaesthesia, and also in the management of paroxysmal supraventricular tachycardia. A typical dose, given by intramuscular injection is 10 to 15 mg. Alternatively, 3 to 10 mg may be given in emergencies by slow intravenous injection. It has also been used topically as a vasoconstrictor in the management of nasal congestion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Mexan†.

Pharmacopoeial Preparations
BP 2014: Methoxamine Injection.

Methyclothiazide *(BAN, USAN, rINN)* ⊗

Méthyclothiazide; Methyclothiazidum; Meticlotiazida; Metiklotiatsidi; Metyklotiazid; NSC-110431; Метиклотиазид.

6-Chloro-3-chloromethyl-3,4-dihydro-2-methyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_9H_{11}Cl_2N_3O_4S_2$=360.2

CAS — 135-07-9.

ATC — C03AA08.

ATC Vet — QC03AA08.

UNII — L3H46UAC61.

Pharmacopoeias. In *US.*

USP 36: (Methyclothiazide). A white or practically white crystalline powder, odourless or with a slight odour. Very slightly soluble to practically insoluble in water and in chloroform; soluble 1 in 92.5 of alcohol and 1 in 2700 of ether; freely soluble in acetone and in pyridine; sparingly soluble in methyl alcohol; very slightly soluble in benzene.

Profile

Methyclothiazide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (see p. 1403.2). It is given orally for oedema, including that associated with heart failure (p. 1262.3), and for hypertension (p. 1251.1).

Diuresis starts in about 2 hours, reaches a peak at about 6 hours, and lasts for 24 hours or more.

In the treatment of oedema the usual initial dose is 2.5 to 5 mg daily, increasing to a maximum dose of 10 mg daily if necessary. In the treatment of hypertension the usual dose is 2.5 to 5 mg daily, either alone, or with other antihypertensives. Doses of up to 10 mg daily have been suggested, but this may not result in an increased hypotensive effect.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies methyclothiazide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Enduron.

Multi-ingredient Preparations. *China*: Enduronyl (降压乐); *Fr.*: Isobar.

Pharmacopoeial Preparations
USP 36: Methyclothiazide Tablets.

Methyldopa (BAN, USAN, rINN)

Alpha-methyldopa; Methyldopa; Methyldopum; Methyldopum Hydratum; Metildopa; Metyldopa; Metylidopa; MK-351; Mervidona.

(-)-3-(3,4-Dihydroxyphenyl)-2-methyl-L-alanine sesquihydrate; (-)-2-Amino-2-(3,4-dihydroxybenzyl)propionic acid sesquihydrate.

$C_{10}H_{13}NO_4.1½H_2O$=238.2

CAS — 555-30-6 (anhydrous methyldopa); 41372-08-1 (methyldopa sesquihydrate).

ATC — C02AB01 (laevorotatary); C02AB02 (racemic).

ATC Vet — QC02AB01 (laevorotatary); QC02AB02 (racemic).

UNII — 56LH93261Y.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Methyldopa). Colourless or almost colourless crystals or a white to yellowish-white crystalline powder. Slightly soluble in water; very slightly soluble in alcohol; freely soluble in dilute mineral acids. Protect from light.

USP 36: (Methyldopa). A white to yellowish-white odourless fine powder which may contain friable lumps. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in ether; very soluble in 3N hydrochloric acid. Protect from light.

Methyldopate Hydrochloride (BANM, USAN)

Cloridrato de Metildopato; Metildopato, hidrocloruro de. The hydrochloride of the ethyl ester of anhydrous methyldopa; Ethyl (-)-2-amino-2-(3,4-dihydroxybenzyl) propionate hydrochloride.

$C_{12}H_{17}NO_4.HCl$=275.7

CAS — 2544-09-4 (methyldopate); 2508-79-4 (methyldopate hydrochloride).

UNII — 7PX435DNSA.

Pharmacopoeias. In *Br.* and *US*.

BP 2014: (Methyldopate Hydrochloride). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; slightly soluble in chloroform; practically insoluble in ether. A 1% solution in water has a pH of 3.0 to 5.0. Protect from light.

USP 36: (Methyldopate Hydrochloride). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; slightly soluble in chloroform; practically insoluble in ether. A 1% solution in water has a pH of between 3.0 and 5.0. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Incompatibility. A haze developed over 3 hours when methyldopate hydrochloride 1 mg/mL was mixed with amphotericin B 200 micrograms/mL in glucose; crystals were produced with methohexital sodium 200 micrograms/mL in sodium chloride, and a haze developed when they were mixed in glucose. A crystalline precipitate occurred with tetracycline hydrochloride 1 mg/mL in glucose, and with sulfadiazine sodium 4 mg/mL in glucose or sodium chloride.[1]

1. Riley BB. Incompatibilities in intravenous solutions. *J Hosp Pharm* 1970; **28**: 228–40.

Uses and Administration

Methyldopa is an antihypertensive that is thought to have a mainly central action. It is decarboxylated in the CNS to alpha-methylnoradrenaline, which is thought to stimulate $alpha_2$ adrenoceptors resulting in a reduction in sympathetic tone and a fall in blood pressure. It may also act as a false neurotransmitter, and have some inhibitory actions on plasma renin activity. Methyldopa reduces the tissue concentrations of dopamine, noradrenaline, adrenaline, and serotonin.

Methyldopa is used in the management of hypertension (p. 1251.1), although other drugs with fewer adverse effects are generally preferred. Methyldopa may, however, be the treatment of choice for hypertension in pregnancy. Oedema and tolerance sometimes associated with methyldopa therapy may be reduced when it is given with a thiazide diuretic.

Methyldopa is given orally as the sesquihydrate, but doses are usually expressed in terms of anhydrous methyldopa. Methyldopa sesquihydrate 1.13 g is equivalent to about 1 g of anhydrous methyldopa. For hypertensive crises, methyldopa has been given intravenously as methyldopate hydrochloride.

When methyldopa is given orally its effects reach a maximum in 4 to 6 hours after a single dose, although the maximum hypotensive effect may not occur until the second or third day of continuous treatment; some effect is usually apparent for 48 hours after withdrawal of methyldopa. When given intravenously the hypotensive effect may be obtained within 4 to 6 hours and last for 10 to 16 hours. It lowers the standing, and to a lesser extent the supine, blood pressure.

In hypertension, the usual initial adult oral dose is 250 mg of methyldopa two or three times daily for 2 days; this is then adjusted, not more frequently than every 2 days according to response, up to a usual maximum dose of 3 g daily. The usual maintenance dosage is 0.5 to 2 g of methyldopa daily. In the elderly an initial dose of 125 mg twice daily has been used; this dose may be increased gradually if necessary, but should not exceed 2 g daily.

References.

1. Mah GT, *et al.* Methyldopa for primary hypertension. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 09/03/10).

Administration in children. Children aged under 12 years may be given methyldopa in the management of hypertension at an initial oral dose of 10 mg/kg daily in 2 to 4 divided doses. This may be adjusted to a maximum daily dose of 65 mg/kg or 3 g, whichever is the smaller. It has been suggested that dosage adjustments are made at intervals of at least 2 days.

Adverse Effects

The adverse effects of methyldopa are mostly consequences of its pharmacological action. The incidence of adverse effects overall may be as high as 60% but most are transient or reversible. Drowsiness is common, especially initially and after an increase in dosage. Dizziness and lightheadedness may be associated with orthostatic hypotension; nausea, headache, weakness and fatigue, and decreased libido and impotence have also been reported quite often.

The mental and neurological effects of methyldopa have included impaired concentration and memory, mild psychoses, depression, disturbed sleep and nightmares, paraesthesias, Bell's palsy, involuntary choreoathetotic movements, and parkinsonism.

As well as orthostatic hypotension, methyldopa is often associated with fluid retention and oedema, which responds to diuretics but may rarely progress to heart failure. Angina pectoris may be aggravated. Bradycardia, syncope, and prolonged carotid sinus hypersensitivity have been reported. Intravenous methyldopate has been associated with a paradoxical rise in blood pressure.

Methyldopa may produce gastrointestinal disturbances including nausea and vomiting, diarrhoea, constipation, and rarely pancreatitis and colitis. A black or sore tongue, and inflammation of the salivary glands, have occurred, and dry mouth is quite common.

A positive Coombs' test may occur in 10 to 20% of all patients on prolonged therapy but only a small proportion develop haemolytic anaemia. Thrombocytopenia and leucopenia, notably granulocytopenia, have occurred and warrant prompt withdrawal. Other hypersensitivity effects have included myocarditis, fever, eosinophilia, and disturbances of liver function. Hepatitis may develop, particularly in the first 2 or 3 months of therapy, and is generally reversible on stopping, but fatal hepatic necrosis has occurred. Antinuclear antibodies may develop and cases of a lupus-like syndrome have been reported.

Other adverse effects that have been reported in patients taking methyldopa include rashes, lichenoid and granulomatous eruptions, toxic epidermal necrolysis, a flu-like syndrome (of fever, myalgia, and mild arthralgia), nocturia, uraemia, nasal congestion, and retroperitoneal fibrosis. Hyperprolactinaemia may occur, with breast enlargement or gynaecomastia, galactorrhoea, and amenorrhoea.

Methyldopa may occasionally cause urine to darken on exposure to the air because of the breakdown of the drug or its metabolites.

Reviews.

1. Furhoff A-K. Adverse reactions with methyldopa—a decade's reports. *Acta Med Scand* 1978; **203**: 425–8.
2. Lawson DH, *et al.* Adverse reactions to methyldopa with particular reference to hypotension. *Am Heart J* 1978; **96**: 572–9.

Effects on the blood. An analysis of drug-induced blood dyscrasias reported to the Swedish Adverse Drug Reaction Committee for the 10-year period 1966 to 1975 showed that haemolytic anaemia attributable to methyldopa had been reported on 69 occasions and had caused 3 deaths. This represented the vast majority of all the reports of drug-induced haemolytic anaemia.[1] However, the actual incidence of haemolytic anaemia in patients receiving methyldopa is quite low; data from the Boston Collaborative Drug Surveillance Program indicated that only 2 of 1067 patients receiving methyldopa developed haemolytic anaemia,[2] an incidence of about 0.2%. The proportion of patients with a positive Coombs' test is much higher, being variously reported[3-5] at 10 to 20%. It has been suggested that the high incidence of autoantibody formation may be due to inhibition of suppressor T-cells by methyldopa[4] while the relatively low incidence of resultant haemolysis may be due to drug-associated impairment of the reticuloendothelial system which would normally clear the antibody-sensitised cells from the circulation.[5] Although the use of methyldopa has now declined, reports of methyldopa-induced haemolytic anaemia still occasionally occur.[6]

Autoantibodies were detected in the neonate of a mother who took methyldopa during pregnancy—see Pregnancy under Precautions, p. 1432.2.

1. Böttiger LE, *et al.* Drug-induced blood dyscrasias. *Acta Med Scand* 1979; **205**: 457–61.
2. Lawson DH, *et al.* Adverse reactions to methyldopa with particular reference to hypotension. *Am Heart J* 1978; **96**: 572–9.
3. Carstairs K, *et al.* Methyldopa and haemolytic anaemia. *Lancet* 1966; **i**: 201.
4. Kirtland HH, *et al.* Methyldopa inhibition of suppressor-lymphocyte function: a proposed cause of autoimmune hemolytic anemia. *N Engl J Med* 1980; **302**: 825–32.
5. Kelton JG. Impaired reticuloendothelial function in patients treated with methyldopa. *N Engl J Med* 1985; **313**: 596–600.
6. Thomas A, *et al.* Methyldopa-induced autoimmune haemolytic anaemia revisited. *N Z Med J* 2009; **122**: 53–6.

Effects on the gastrointestinal tract. *COLITIS.* There has been a report of 6 cases of colitis associated with methyldopa.[1] An auto-immune mechanism was proposed.

1. Graham CF, *et al.* Acute colitis with methyldopa. *N Engl J Med* 1981; **304**: 1044–5.

DIARRHOEA. Severe chronic diarrhoea was associated with methyldopa over periods of 2 and 7 years;[1,2] it stopped in both cases on withdrawal of the drug.

1. Quart BD, Guglielmo BJ. Prolonged diarrhea secondary to methyldopa therapy. *Drug Intell Clin Pharm* 1983; **17**: 462.
2. Gloth FM, Busby MJ. Methyldopa-induced diarrhea: a case of iatrogenic diarrhea leading to request for nursing home placement. *Am J Med* 1989; **87**: 480–1.

PANCREATITIS. Increases in serum- and urinary-amylase activity accompanied by fever and suggestive of pancreatitis were associated with methyldopa in 2 patients,[1] one of whom had symptoms of severe pancreatitis. Symptoms reappeared on rechallenge in both patients. A further report of acute pancreatitis in a patient who had recently begun methyldopa therapy (with a diuretic) also confirmed a recurrence of symptoms on rechallenge.[2] In contrast to the acute form, chronic pancreatitis is not generally attributable to drug use.[3] However, a case of florid chronic pancreatitis, with exocrine and endocrine insufficiency and heavy calcification over 30 months, associated with 2 periods of methyldopa treatment, has been reported.[4] Symptoms in this patient, who was also receiving a thiazide, included severe diabetic ketoacidosis.

1. van der Heide H, *et al.* Pancreatitis caused by methyldopa. *BMJ* 1981; **282**: 1930–1.
2. Anderson JR, *et al.* Drug-associated recurrent pancreatitis. *Dig Surg* 1985; **2**: 24–6.
3. Banergee AK, *et al.* Drug-induced acute pancreatitis. *Med Toxicol Adverse Drug Exp* 1989; **4**: 186–98.
4. Ramsay LE, *et al.* Methyldopa-induced chronic pancreatitis. *Practitioner* 1982; **226**: 1166–9.

Effects on the heart. Sudden death in patients receiving methyldopa has been associated with myocarditis (often with hepatitis and pneumonitis).[1,2] The effect is thought to be due to hypersensitivity. Hypersensitivity myocarditis is generally marked by ECG changes, a slight rise in cardiac enzymes, cardiomegaly, and persistent sinus tachycardia, along with peripheral blood eosinophilia, and most patients will recover within days if the drug is withdrawn in time.[3]

1. Mullick FG, McAllister HA. Myocarditis associated with methyldopa therapy. *JAMA* 1977; **237**: 1699–1701. Correction. *ibid.*: **238**: 399.
2. Seeverens H, *et al.* Myocarditis and methyldopa. *Acta Med Scand* 1982; **211**: 233–5.
3. Anonymous. Myocarditis related to drug hypersensitivity. *Lancet* 1985; **ii**: 1165–6.

Effects on the liver. In a report of 6 cases of hepatitis in patients taking methyldopa, including a review of 77 cases from the literature,[1] most patients presented with symptoms including malaise, fatigue, anorexia, weight loss, nausea, and vomiting, and histopathological changes resembling those of viral hepatitis. Fever occurred in 28 of the 83 patients; rashes and eosinophilia occurred rarely. Symptoms usually began 1 to 4 weeks after the first dose of methyldopa. Clinically apparent jaundice occurred as early as 1 week and as late as 3 years after the start of therapy, although only 6 or 7 patients presented with jaundice later than 3 months. Liver damage was not dose-related and had features suggestive of an immunologically-mediated hypersensitivity reaction. The histological changes included chronic active hepatitis, massive fatal necrosis, and cirrhosis.

In a further analysis of 36 patients with liver damage due to methyldopa, hepatic injury tended to occur in 2 phases—acute and chronic.[2] Acute damage developed within a few months of starting treatment, and was considered to be an allergic reaction to methyldopa metabolites. The chronic form usually occurred at least a year after starting methyldopa, and was characterised by an accumulation of fat in the liver. Recovery after withdrawal of methyldopa was directly related to duration of exposure and degree of

liver damage. There was also a suggestion of genetic predisposition, as acute methyldopa-induced liver damage occurred in 4 members of a family. Idiosyncratic metabolism of methyldopa in susceptible patients may be responsible for expression of an antigen on the surface of liver cells with which circulating antibodies react.[3]

See also Fever, below.

1. Rodman JS, *et al.* Methyldopa hepatitis: a report of six cases and review of the literature. *Am J Med* 1976; 60: 941–8.
2. Sotaniemi EA, *et al.* Hepatic injury and drug metabolism in patients with alpha-methyldopa-induced liver damage. *Eur J Clin Pharmacol* 1977; 12: 429–35.
3. Neuberger J, *et al.* Antibody mediated hepatocyte injury in methyldopa induced hepatotoxicity. *Gut* 1985; 26: 1233–9.

Effects on mental function. Anecdotal reports have implicated methyldopa in disturbances of mental acuity including inability to concentrate, impaired calculating ability, and forgetfulness.[1-3] These have been confirmed to some extent by psychometric studies. Impaired verbal but not visual memory has been reported in 10 patients receiving methyldopa with a diuretic.[4] A crossover study in 16 patients also indicated impairment of cognitive function by methyldopa.[5]

1. Adler S. Methyldopa-induced decrease in mental activity. *JAMA* 1974; 230: 1428–9.
2. Ghosh SK. Methyldopa and forgetfulness. *Lancet* 1976; i: 202–3.
3. Fernandez PG. Alpha methyldopa and forgetfulness. *Ann Intern Med* 1976; 85: 128.
4. Solomon S, *et al.* Impairment of memory function by antihypertensive medication. *Arch Gen Psychiatry* 1983; 40: 1109–12.
5. Johnson B, *et al.* Effects of methyldopa on psychometric performance. *J Clin Pharmacol* 1990; 30: 1102–5.

DEPRESSION. Depression has been associated with methyldopa therapy, although the exact relationship is unclear.[1] One review[2] reported the incidence to be 3.6% and suggested that depression was more common in patients with a previous history.

1. Patten SB, Love EJ. Drug-induced depression. *Drug Safety* 1994; 10: 203–19.
2. Paykel ES, *et al.* Psychiatric side effects of antihypertensive drugs other than reserpine. *J Clin Psychopharmacol* 1982; 2: 14–39.

Effects on the nervous system. Involuntary choreoathetotic movements resembling those of Huntington's chorea began in a 59-year-old man with cerebrovascular disease after an increase of his methyldopa dose from 1 to 1.5 g daily. He recovered when the drug was withdrawn.[1] In another report methyldopa was associated with the development of bilateral choreiform movements in a patient without cerebrovascular disease but with chronic renal failure.[2]

1. Yamadori A, Albert ML. Involuntary movement disorder caused by methyldopa. *N Engl J Med* 1972; 286: 610.
2. Neil EM, Waters AK. Generalized choreiform movements as a complication of methyldopa therapy in chronic renal failure. *Postgrad Med J* 1981; 57: 732–3.

Effects on sexual function. Methyldopa has been associated with many cases of sexual dysfunction. In males failure to maintain erection, decreased libido, impaired ejaculation, and gynaecomastia have occurred, while in females decreased libido, painful breast enlargement, and delayed or absent orgasm have been reported.[1] The reported incidence varies and there is some evidence[2] that sexual dysfunction may be underreported: while only 2 of 30 men receiving methyldopa spontaneously reported erection failure the actual incidence on questioning was 16 of 30.

1. Stevenson JG, Umstead GS. Sexual dysfunction due to antihypertensive agents. *Drug Intell Clin Pharm* 1984; 18: 113–21.
2. Alexander WD, Evans JI. Side effects of methyldopa. *BMJ* 1975; 2: 501.

Fever. In a report of 78 cases of methyldopa-induced fever,[1] fever occurred 5 to 35 days after the first exposure to methyldopa in 77 patients and 1 day after restarting methyldopa in the remaining patient. Rigors, headache, and myalgia were common accompanying symptoms, but eosinophilia and skin rashes were not seen. The majority of patients did not appear seriously ill, but 4 patients presented with symptoms of septic shock. Biochemical evidence of liver damage was found in 61% of patients but jaundice was uncommon. In the majority of patients, symptoms were relieved within 48 hours of stopping the drug.

1. Stanley P, Mijch A. Methyldopa: an often overlooked cause of fever and transient hepatocellular dysfunction. *Med J Aust* 1986; 144: 603–5.

Lupus erythematosus. The incidence of antinuclear antibodies was 13% in 269 hypertensive patients taking methyldopa (irrespective of other medication), compared with 3.8% in 448 hypertensive patients not taking methyldopa.[1] However, methyldopa-induced lupus has been reported[2] only rarely.

1. Wilson JD, *et al.* Antinuclear antibodies in patients receiving non-practolol beta-blockers. *BMJ* 1978; 1: 14–16.
2. Dupont A, Six R. Lupus-like syndrome induced by methyldopa. *BMJ* 1982; 285: 693–4.

Overdosage. Ingestion of methyldopa 2.5 g produced coma, hypothermia, hypotension, bradycardia, and dry mouth in a 19-year-old man.[1] His serum-methyldopa concentration 10 hours after ingestion was 19.2 micrograms/mL compared with serum concentrations of about 2 micrograms/mL in patients receiving therapeutic doses of methyldopa. He recovered after treatment with intravenous fluids.

1. Shnaps Y, *et al.* Methyldopa poisoning. *J Toxicol Clin Toxicol* 1982; 19: 501–3.

Retroperitoneal fibrosis. A 60-year-old patient developed retroperitoneal fibrosis and a positive direct Coombs' test associated with methyldopa given in a daily dose of 750 mg with bendroflumethiazide 2.5 mg for about 5 years.[1]

1. Iversen BM, *et al.* Retroperitoneal fibrosis during treatment with methyldopa. *Lancet* 1975; ii: 302–4.

Treatment of Adverse Effects

Withdrawal of methyldopa or reduction in dosage causes the reversal of many adverse effects. If overdosage occurs, the benefit of gastric decontamination is uncertain, but patients who present within 1 hour may be given activated charcoal. Treatment is largely symptomatic, but if necessary, intravenous fluid infusions may be given to promote urinary excretion, and vasopressors given cautiously. Atropine may be given for bradycardia. Severe hypotension may respond to placing the patient in the supine position with the feet raised.

Methyldopa is dialysable.

Precautions

Methyldopa should be used with caution in the elderly, and in patients with hepatic or renal impairment or with a history of haemolytic anaemia, liver disease, or depression. Care is also advisable in patients with parkinsonism. It should not be given to patients with active liver disease or depression and it is not recommended for phaeochromocytoma.

It is advisable to make periodic blood counts and to perform liver function tests at intervals during the first 6 to 12 weeks of treatment or if the patient develops an unexplained fever. Patients taking methyldopa may produce a positive response to a direct Coombs' test; if blood transfusion is required, prior knowledge of a positive direct Coombs' test reaction will aid cross-matching.

Methyldopa may cause sedation; if affected, patients should not drive or operate machinery.

Breast feeding. Methyldopa is distributed into breast milk in small amounts.[1] In a study[2] of 3 breast-feeding women, concentrations of free methyldopa in the breast milk were found to be between 19 and 30% of those in the plasma after a 500-mg dose. Detectable concentrations were found in the plasma of only 1 infant and adverse effects were seen in none. It was estimated that the amount of methyldopa a breast-fed infant would receive would be about 0.02% of the maternal dose. In another study[3] over a 3-month period no adverse effects were found in a breast-feeding infant whose mother was taking methyldopa, although the drug was detectable in the infant's urine. The American Academy of Pediatrics considers[4] that methyldopa is therefore usually compatible with breast feeding.

1. Jones HMR, Cummings AJ. A study of the transfer of α-methyldopa to the human foetus and newborn infant. *Br J Clin Pharmacol* 1978; 6: 432–4.
2. White WB, *et al.* Alpha-methyldopa disposition in mothers with hypertension and in their breast-fed infants. *Clin Pharmacol Ther* 1985; 37: 387–90.
3. Hauser GJ, *et al.* Effect of α-methyldopa excreted in human milk on the breast-fed infant. *Helv Paediatr Acta* 1985; 40: 83–6.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/09/05)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies the laevo-isomer of methyldopa as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients. Racemic methyldopa is not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pregnancy. Methyldopa is commonly used in the management of hypertension during pregnancy (p. 1251.1). There is little evidence of adverse effects on fetal development. However, it crosses the placenta[1] and reduced blood pressure has been reported in infants born to mothers receiving the drug.[2] There has also been a report of tremor in 7 infants associated with maternal methyldopa use in pregnancy.[3] Depressed noradrenaline concentrations in the CSF were noted in the 3 infants examined leading to successful treatment of the other 4 infants with atropine: tremor was abolished in 2 and substantially reduced in the other 2. Suppurative parotitis occurred[4] in a CMV-infected neonate whose mother took methyldopa throughout pregnancy. Autoantibodies were detected[5] in another neonate whose mother had taken methyldopa throughout pregnancy, although it seemed likely that they had crossed the placenta from the mother, who also tested positive, rather than being produced by the fetus itself.

1. Jones HMR, Cummings AJ. A study of the transfer of α-methyldopa to the human foetus and newborn infant. *Br J Clin Pharmacol* 1978; 6: 432–4.
2. Whitelaw A. Maternal methyldopa treatment and neonatal blood pressure. *BMJ* 1981; 283: 471.
3. Bódis J, *et al.* Methyldopa in pregnancy hypertension and the newborn. *Lancet* 1982; ii: 498–9.
4. Todoroki Y, *et al.* Neonatal suppurative parotitis possibly associated with congenital cytomegalovirus infection and maternal methyldopa administration. *Pediatr Int* 2006; 48: 185–6.
5. Özdemir ÖMA, *et al.* A newborn with positive antiglobulin test whose mother took methyldopa in pregnancy. *Turk J Pediatr* 2008; 50: 592–.

Interactions

The hypotensive effects of methyldopa are potentiated by diuretics, other antihypertensives, and drugs with hypotensive effects. However, there have been reports of paradoxical antagonism of the hypotensive effects by tricyclic antidepressants, antipsychotics, and beta blocker. Sympathomimetics may also antagonise the hypotensive effects.

There may be an interaction between methyldopa and MAOIs and care is required if they are given together. Caution is also needed with catechol-*O*-methyltransferase inhibitors, such as entacapone, since they might reduce the metabolism of methyldopa.

Patients receiving methyldopa may require lower doses of general anaesthetics.

Alpha blockers. Urinary incontinence occurred when methyldopa was given with *phenoxybenzamine* in a patient who had undergone bilateral lumbar sympathectomy.[1]

1. Fernandez PG, *et al.* Urinary incontinence due to interaction of phenoxybenzamine and α-methyldopa. *Can Med Assoc J* 1981; 124: 174–5.

Antipsychotics. Antipsychotics may enhance the hypotensive effects of methyldopa but a paradoxical increase in blood pressure has also been reported. A woman with SLE taking *trifluoperazine* up to 15 mg daily and prednisone up to 120 mg daily was given methyldopa up to 2 g and triamterene for high blood pressure.[1] Her blood pressure rose further to 200/140 mmHg. After stopping trifluoperazine blood pressure returned to 160/100 mmHg.

In another report, 2 patients with essential hypertension who had been taking methyldopa for 3 years and 18 months respectively developed symptoms of dementia within days of taking *haloperidol* for anxiety.[2] In both patients the symptoms resolved rapidly on stopping haloperidol.

1. Westervelt FB, Atuk NO. Methyldopa-induced hypertension. *JAMA* 1974; 227: 557.
2. Thornton WE. Dementia induced by methyldopa with haloperidol. *N Engl J Med* 1976; 294: 1222.

Cephalosporins. A *pustular pruritic* eruption occurred after use of *cefazolin* by a patient taking methyldopa.[1] A previous similar case involved use of *cefradine* with methyldopa.

1. Stough D, *et al.* Pustular eruptions following administration of cefazolin: a possible interaction with methyldopa. *J Am Acad Dermatol* 1987; 16: 1051–2.

Digoxin. Syncope associated with carotid sinus hypersensitivity has been reported to be possibly enhanced by methyldopa in a patient taking digoxin and chlortalidone.[1] In another report,[2] sinus bradycardia developed in 2 patients taking methyldopa and digoxin.

1. Bauernfeind R, *et al.* Carotid sinus hypersensitivity with alpha-methyldopa. *Ann Intern Med* 1978; 88: 214–15.
2. Davis JC, *et al.* Sinus node dysfunction caused by methyldopa and digoxin. *JAMA* 1981; 245: 1241–3.

Iron. After results in healthy subjects indicated that the absorption of methyldopa was reduced by 73% and 61% respectively when taken with a dose of *ferrous sulfate* or *ferrous gluconate*, 5 hypertensive patients taking methyldopa were also given ferrous sulfate 325 mg three times daily for 2 weeks.[1] All patients had a rise in systolic pressure, and 4 had a rise in diastolic pressure, amounting to more than 15/10 mmHg in some patients after 2 weeks. Blood pressure fell again when the ferrous sulfate was stopped.

1. Campbell N, *et al.* Alteration of methyldopa absorption, metabolism, and blood pressure control caused by ferrous sulfate and ferrous gluconate. *Clin Pharmacol Ther* 1988; 43: 381–6.

Levodopa. For reference to a mutual interaction between methyldopa and levodopa, see Antihypertensives, under Levodopa, Interactions, p. 907.2.

Lithium. For reference to the development of lithium toxicity when given with methyldopa, see p. 432.2.

Sympathomimetics. A 31-year-old man whose hypertension was well controlled with methyldopa and oxprenolol suffered a severe hypertensive episode when he took a preparation containing *phenylpropanolamine* for a cold.[1]

1. McLaren EH. Severe hypertension produced by interaction of phenylpropanolamine with methyldopa and oxprenolol. *BMJ* 1976; 2: 283–4.

Pharmacokinetics

After oral use methyldopa is variably and incompletely absorbed, apparently by an amino-acid active transport system. The mean bioavailability has been reported to be about 50%. It is extensively metabolised and is excreted in urine mainly as unchanged drug and the *O*-sulfate conjugate. It crosses the blood-brain barrier and is decarboxylated in the CNS to active alpha-methylnoradrenaline.

The elimination is biphasic with a half-life of about 1.7 hours in the initial phase; the second phase is more prolonged. Clearance is decreased and half-life prolonged in renal impairment. Plasma protein binding is reported to be minimal. Methyldopa crosses the placenta; small amounts are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aldomet; Dopagrand; Dopatral; *Austral.*: Aldomet; Hydopa; *Austria*: Aldometil; *Belg.*: Aldomet; *Braz.*: Aldomet; Aldotensin; Alfuzina; Angimet†; Cardiodopa; Dimipress; Dopametil; Ductomet; Etildopanan; Kindomet†; Metil-DT†; Metilpress; Metilprod†; Tensioval; Tildomet†; Venopressin; *Canad.*: Novo-Medopa; Nu-Medopa; *Cz.*: Dopegyt; *Denm.*: Aldomet†; *Fr.*: Aldomet; *Ger.*: Dopegyt; Presinol; *Gr.*: Aldomet; Dopatens; *Hong Kong*: Dopamet; Dopatab†; Dopegyt; Hydopa†; *Hung.*: Dopegyt; *India*: Alphadopa; Dopagyt; Emdopa; Gynapres; *Indon.*: Dopamet; Medopa†; *Irl.*: Aldomet; *Israel*: Aldomin; *Ital.*: Aldomet; *Malaysia*: Dopegyt; *Mex.*: Aldomet; Amender; Hipermessel; Medopal†; Selm; Toparal; *Neth.*: Aldomet†; *Norw.*: Aldomet†; *NZ*: Prodopa; *Philipp.*: Aldomet; Dopamet; *Pol.*: Dopegyt; *Port.*: Aldomet; *Rus.*: Dopegyt (Допегит); *S.Afr.*: Aldomet†; Hy-Po-Tone; Normopress†; *Singapore*: Aldomet; *Spain*: Aldomet; *Swed.*: Aldomet†; *Switz.*: Aldomet; *Thai.*: Adomet; Aldomet; Aldomine; Dopamed; Dopasian; Dopegyt†; Isomet; Medopa; Mefpa; Metpata; Nudopa; Slamdopa; *Turk.*: Alfamet; *UK*: Aldomet; *Ukr.*: Dopegyt (Допегит); *Venez.*: Aldomet.

Multi-ingredient Preparations. *Braz.*: Hydromet; *Canad.*: Apo-Methazide; PMS-Dopazide; *Gr.*: Hydromet; Rabemylon; *Ital.*: Medozide†; *USA*: Aldoclor.

Pharmacopoeial Preparations
BP 2014: Methyldopa Tablets; Methyldopate Injection;
USP 36: Methyldopa and Chlorothiazide Tablets; Methyldopa and Hydrochlorothiazide Tablets; Methyldopa Oral Suspension; Methyldopa Tablets; Methyldopate Hydrochloride Injection.

Meticrane (rINN) ⊗

Méticrane; Meticrano; Meticranum; SD-17102; Метикран.
6-Methylthiochroman-7-sulphonamide 1,1-dioxide.
$C_{10}H_{13}NO_4S_2$=275.3
CAS — 1084-65-7.
ATC — C03BA09.
ATC Vet — QC03BA09.
UNII — I7EKN1924Q.

Pharmacopoeias. In *Jpn.*

Profile

Meticrane is a diuretic with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1403.2). It is used in the treatment of hypertension.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Arresten.

Metildigoxin (BAN, rINN)

Medigoxin; β-Methyl Digoxin; β-Methyldigoxin; Metildigoksiini; Metildigoxina; Métildigoxine; Metildigoxinum; Metyylidigoksiini; Метилдигоксин.
3β-[(O-2,6-Dideoxy-4-O-methyl-D-*ribo*-hexopyranosyl-(1→4)-O-2,6-dideoxy-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β,14β-card-20(22)-enolide.
$C_{42}H_{66}O_{14}$=795.0
CAS — 30685-43-9.
ATC — C01AA08.
ATC Vet — QC01AA08.
UNII — I7GG1YUC5V.

Pharmacopoeias. In *Chin.* In *Jpn.* as $C_{42}H_{66}O_{14}.\frac{1}{2}C_3H_6O$.

Uses and Administration

Metildigoxin is a cardiac glycoside with positive inotropic activity. It has actions similar to those of digoxin (p. 1353.3) and may be used in the treatment of some cardiac arrhythmias (p. 1266.1) and in heart failure (p. 1262.3).

The onset of action of metildigoxin is more rapid than that of digoxin. When metildigoxin is given orally an effect may appear within 5 to 20 minutes and a maximum effect on the myocardium may be seen in 15 to 30 minutes. The duration of action is similar to or a little longer than that of digoxin; therapeutic plasma concentrations are also similar. In stabilised patients on oral therapy a dose of 300 micrograms of metildigoxin is as effective as 500 micrograms of digoxin.

Metildigoxin may be given orally or intravenously. Initial oral doses of 100 to 600 micrograms daily may be given depending upon whether rapid or slow digitalisation is desired; digitalisation is usually performed over about 2 to 5 days and the larger doses are given in divided daily doses. Similar doses may also be given intravenously. Oral maintenance therapy is continued with 50 to 400 micrograms daily in single or divided doses.

Dosage should be reduced in patients with renal impairment (see below).

Administration in renal impairment. Fairly good non-linear correlation was found between creatinine clearance and metildigoxin half-life in a study of 15 patients with chronic renal impairment, including 8 undergoing haemodialysis, and 4 patients with heart failure and unimpaired renal function. The mean elimination half-life was 5.62 days in patients undergoing dialysis (clearance essentially 0 mL/minute) and 3.41 days in the other patients with chronic renal impairment (clearance 15 to 50 mL/minute) compared with 1.49 days in patients with normal renal function (clearance 62 to 96 mL/minute). It was recommended that patients undergoing dialysis should be given 30 to 50% of the usual dose initially.[1] Other studies have suggested[2] that dose reduction may be necessary in renal impairment when creatinine clearance is below 50 mL/minute per 1.48 m^2.

1. Trovato GM, *et al.* Relationship between β-methyl-digoxin pharmacokinetic and degree of renal impairment. *Curr Ther Res* 1983; 33: 158–64.
2. Tsutsumi K, *et al.* Pharmacokinetics of beta-methyldigoxin in subjects with normal and impaired renal function. *J Clin Pharmacol* 1993; 33: 154–60.

Adverse Effects, Treatment, and Precautions

As for Digoxin, p. 1354.3.

Interactions

As for Digoxin, p. 1356.1.

Calcium-channel blockers. For a report of an interaction between metildigoxin and *diltiazem*, see Calcium-channel Blockers, under Interactions of Digoxin, p. 1357.2.

Pharmacokinetics

Metildigoxin is rapidly and almost completely absorbed from the gastrointestinal tract and at steady state has a half-life of 36 to 47.5 hours. Demethylation to digoxin occurs. About 60% of an oral or intravenous dose is excreted in the urine as unchanged drug and metabolites over 7 days.

Hepatic impairment. Hepatic demethylation of metildigoxin was reduced in 12 patients with cirrhosis of the liver compared with 12 healthy subjects. This resulted in a reduction in metildigoxin clearance, a smaller volume of distribution, and a significantly higher serum concentration.[1]

1. Rameis H, *et al.* Changes in metildigoxin pharmacokinetics in cirrhosis of the liver: a comparison with β-acetyldigoxin. *Int J Clin Pharmacol Ther Toxicol* 1984; 22: 145–51.

Renal impairment. For reference to the pharmacokinetics of metildigoxin in patients with renal impairment, see under Uses and Administration, above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Lanitop; *Belg.*: Lanitop; *China*: Beikeli (贝可力); *Ger.*: Lanitop; *Gr.*: Lanitop; *Hong Kong*: Lanitop†; *Ital.*: Lanitop; *Jpn*: Lanirapid; *Pol.*: Bemecor; Medigox†; *Port.*: Lanitop; *Spain*: Lanirapid; *Venez.*: Lanitop.

Metipamide ⊗

Metiparnid; Metiparnidum; VUFB-14429.
3-(Aminosulfonyl)-4-chlorobenzoic acid 2-methyl-2-phenylhydrazide.
$C_{14}H_{14}ClN_3O_3S$=339.8
CAS — 85683-41-6.

Profile

Metipamide is a diuretic structurally related to indapamide (p. 1409.2); it is used as an antihypertensive.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Hypotylin.

Metirosine (BAN, rINN)

L-588357-0; Metirosilni; Metirosin; Metirosina; Métirosine; Metirosinum; Metyrosine (USAN); MK-781; Метирозин.
(-)-α-Methyl-L-tyrosine; 4-Hydroxy-α-methylphenylalanine.
$C_{10}H_{13}NO_3$=195.2
CAS — 672-87-7 (metirosine); 620-30-4 (racemetirosine).
ATC — C02KB01.
ATC Vet — QC02KB01.
UNII — DOQ0J0TPF7.

NOTE. The term α-methyltyrosine (α-MPT; α-MT; α-methyl-*p*-tyrosine; AMPT) is used below since although metirosine, the (-)-isomer, is the active form the manufacturers state that some racemate (racemetirosine; (±)-α-methyl-DL-tyrosine) is produced during synthesis but that the material supplied contains mainly (-)-isomer with a small amount of (+)-isomer.

The code name MK-781, applied to earlier investigational material, may have described a racemate or a preparation containing a smaller proportion of (-)-isomer than the product now available commercially.

Potency of the proprietary preparation (*Demser*) is expressed in terms of metirosine.

Pharmacopoeias. In *US*.

Uses and Administration

α-Methyltyrosine is an inhibitor of the enzyme tyrosine hydroxylase, and consequently of the synthesis of catecholamines. It is used to control the symptoms of excessive sympathetic stimulation in patients with phaeochromocytoma (p. 1278.1) and decreases the frequency and severity of hypertensive attacks and related symptoms in most patients. It may be given for pre-operative preparation, or for long-term management in those for whom surgery is contra-indicated or who have malignant phaeochromocytoma.

In the management of phaeochromocytoma, α-methyltyrosine is given orally in a dose of 250 mg four times daily, increased daily by 250 mg or 500 mg to a maximum of 4 g daily in divided doses. The optimum dose, achieved by monitoring clinical symptoms and catecholamine excretion, is usually in the range of 2 to 3 g daily and when used pre-operatively it should be given for at least 5 to 7 days before surgery. The use of alpha blockers may also be necessary.

α-Methyltyrosine is not effective in controlling essential hypertension.

α-Methyltyrosine has also been tried in patients with schizophrenia.

Adverse Effects

Sedation occurs in almost all patients receiving α-methyltyrosine. Other adverse effects include extrapyramidal symptoms, such as trismus and frank parkinsonism; anxiety, depression, and psychic disturbances including hallucinations, disorientation, and confusion; and diarrhoea, which may be severe. Crystalluria, transient dysuria, and haematuria have been seen in a few patients. There have also been occasional reports of slight swelling of the breast, galactorrhoea, nasal congestion, decreased salivation, gastrointestinal disturbances, headache, impotence or failure of ejaculation, and hypersensitivity reactions. Eosinophilia, raised serum aspartate aminotransferase, and peripheral oedema have been reported rarely.

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome occurred after the use of the dopamine-deplet-

ing drugs tetrabenazine and α-methyltyrosine in a patient with Huntington's chorea.[1]

1. Burke RE, *et al.* Neuroleptic malignant syndrome caused by dopamine-depleting drugs in a patient with Huntington disease. *Neurology* 1981; 31: 1022–6.

Precautions

To minimise the risk of crystalluria, patients receiving α-methyltyrosine should have a fluid intake sufficient to maintain a urine volume of at least 2 litres daily and their urine should be examined regularly for the presence of crystals.

α-Methyltyrosine has sedative effects and patients should be warned of the hazards of driving a motor vehicle or operating machinery while receiving the drug. Symptoms of psychic stimulation and insomnia may occur when α-methyltyrosine is withdrawn.

When α-methyltyrosine is used pre-operatively in patients with phaeochromocytoma, blood pressure and the ECG should be monitored continuously during surgery as the danger of hypertensive crises and arrhythmias is not eliminated. Concomitant alpha blockade (e.g. with phentolamine) may be required: a beta blocker or lidocaine may be needed for the management of arrhythmias. Blood volume must be maintained during and after surgery, particularly if an alpha blocker is used, to avoid hypotension.

Interactions

The sedative effects of α-methyltyrosine may be potentiated by alcohol and other CNS depressants. Use with phenothiazines or haloperidol may exacerbate extrapyramidal effects.

Pharmacokinetics

α-Methyltyrosine is well absorbed from the gastrointestinal tract and is excreted mainly unchanged by the kidneys. A plasma half-life of 3.4 to 7.2 hours has been reported. Less than 1% of a dose may be excreted as the metabolites α-methyldopa, α-methyldopamine, α-methylnoradrenaline, and α-methyltyramine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA:* Demser.

Pharmacopoeial Preparations
USP 36: Metyrosine Capsules.

Metolazone *(BAN, USAN, rINN)* ⊗

Metolatsoni; Metolazon; Metolazona; Métolazone; Metolazonum; SR-720-22; Метолазон.
7-Chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-3-o-tolylquinazoline-6-sulphonamide.
$C_{16}H_{16}ClN_3O_3S$=365.8
CAS — 17560-51-9.
ATC — C03BA08.
ATC Vet — QC03BA08.
UNII — TZ7V40X7VX.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Metolazone). A white or slightly yellowish, crystalline powder. It exhibits polymorphism. Very slightly soluble in water and dichloromethane; sparingly soluble in methyl alcohol; slightly soluble in ethyl acetate. Protect from light.

USP 36: (Metolazone). Store in airtight containers. Protect from light.

Uses and Administration

Metolazone is a diuretic with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1403.2) even though it does not contain a thiazide ring system. It is given orally for oedema, including that associated with heart failure (p. 1262.3), and for hypertension (p. 1251.1).

Unlike thiazides in general, metolazone is reported to be effective in patients with a glomerular filtration rate of less than 20 mL/minute. Diuresis starts in about 1 hour, reaches a peak in about 2 hours, and lasts for 12 to 24 hours depending on the dose.

In the treatment of **oedema** the usual dose is 5 to 10 mg daily; in some cases doses of 20 mg or more may be required. No more than 80 mg should be given in any 24-hour period. In refractory cases, metolazone has been used with furosemide or other loop diuretics, but the electrolyte balance should be monitored closely.

For doses in children, see below.

In the treatment of **hypertension** the usual dose is 2.5 to 5 mg daily either alone, or with other antihypertensives. An initial dose of 1.25 mg has also been used. The dosage may be adjusted after 3 to 4 weeks according to response. A maintenance dose of 5 mg on alternate days may be used.

A formulation with enhanced bioavailability has also been available and was given in doses of 0.5 to 1 mg daily in the treatment of hypertension.

Administration in children. A study in 14 children aged from 1.5 to 14 years with furosemide-resistant oedema found that the addition of metolazone at an oral dose of 400 to 800 micrograms/kg daily in 2 divided doses safely induced diuresis. The two drugs appeared to work synergistically.[1]

Although metolazone is unlicensed in the UK for children, the *BNFC* suggests that it may be given in the treatment of oedema at the following oral doses according to age:

- 1 month to 12 years: 100 to 200 micrograms/kg once or twice daily
- 12 to 18 years: 5 to 10 mg once daily in the morning, increased to 5 to 10 mg twice daily in resistant oedema

1. Arnold WC. Efficacy of metolazone and furosemide in children with furosemide-resistant edema. *Pediatrics* 1984; 74: 872–5.

Adverse Effects and Treatment

As for Hydrochlorothiazide, p. 1404.2. Metolazone has also been reported to cause palpitations, chest pain, and chills.

Effects on the blood. Profound neutropenia was seen in a 58-year-old woman within 10 days of starting treatment with metolazone.[1] Neutropenia persisted for a further 10 days after metolazone was withdrawn. No other haematological abnormalities were seen.

1. Donovan KL. Neutropenia and metolazone. *BMJ* 1989; 299: 981.

Effects on the nervous system. Two patients had acute muscle cramps with impairment of consciousness and epileptiform movements after taking metolazone 5 mg (single dose) or 2.5 mg daily for 3 days.[1]

1. Fitzgerald MX, Brennan NJ. Muscle cramps, collapse, and seizures in two patients taking metolazone. *BMJ* 1976; 1: 1381–2.

Precautions

As for Hydrochlorothiazide, p. 1406.1.

Interactions

As for Hydrochlorothiazide, p. 1406.1. Severe electrolyte disturbances may occur when metolazone and furosemide are used together.

ACE inhibitors. Deterioration in renal function occurred in a 65-year-old woman when metolazone 5 mg [daily] was added to *captopril*, furosemide, spironolactone, and digoxin for heart failure.[1] An interaction between captopril and metolazone was suspected and both drugs were stopped with a subsequent return to normal renal function. It was suggested that natriuresis and a fall in blood pressure caused by the diuretic may have compromised an already low renal perfusion pressure when autoregulatory mechanisms were blocked by captopril.

1. Hogg KJ, Hillis WS. Captopril/metolazone induced renal failure. *Lancet* 1986; i: 501–2.

Antidiabetics. Hypoglycaemia occurred in a patient with type 2 diabetes mellitus controlled with *glibenclamide* 40 hours after starting therapy with metolazone 5 mg daily.[1] Studies of protein binding *in vitro* did not reveal any evidence of displacement of glibenclamide from binding sites.

1. George S, *et al.* Possible protein binding displacement interaction between glibenclamide and metolazone. *Eur J Clin Pharmacol* 1990; 38: 93–5.

Ciclosporin. An increase in serum-creatinine concentration in a renal transplant patient was attributed to a toxic drug interaction between metolazone and ciclosporin.[1] Serum-creatinine concentrations returned to pretreatment values when metolazone was stopped.

1. Christensen P, Leski M. Nephrotoxic drug interaction between metolazone and cyclosporin. *BMJ* 1987; 294: 578.

Pharmacokinetics

Metolazone is slowly and incompletely absorbed from the gastrointestinal tract. An average of about 65% of a dose has been reported to be absorbed after oral doses in healthy subjects, and an average of about 40% in patients with cardiac disease. In some countries a formulation with enhanced bioavailability is available. About 95% of the drug is bound in the circulation: about 50 to 70% to the red blood cells and between 15 and 33% to plasma proteins. The half-life has been reported to be 8 to 10 hours in whole blood, and 4 to 5 hours in plasma, but the diuretic effect persists for up to 24 hours or more. About 70 to 80% of the amount of metolazone absorbed is excreted in the urine, of which 80 to 95% is excreted unchanged. The remainder is excreted in the bile and some enterohepatic circulation has been reported. Metolazone crosses the placenta and is distributed into breast milk.

References.

1. Tillstone WJ, *et al.* Pharmacokinetics of metolazone in normal subjects and in patients with cardiac or renal failure. *Clin Pharmacol Ther* 1974; 16: 322–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Zaroxolyn; *Chile*: Pavedal; *Gr.*: Metenix; *Hong Kong*: Zaroxolyn; *India*: Diurem; Melatadure; Metoral; Metoz; *Israel*: Zaroxolyn; *Ital.*: Zaroxolyn; *Port.*: Diulo; *Singapore*: Metenix; *UK*: Metenix†; *USA*: Mykrox; Zaroxolyn.

Pharmacopoeial Preparations
USP 36: Metolazone Oral Suspension; Metolazone Tablets.

Metoprolol *(BAN, USAN, rINN)* ⊗

Métoprolol; Metoprololi; Metoprololum; Метопролол.
(±)-1-Isopropylamino-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol.
$C_{15}H_{25}NO_3$=267.4
CAS — 54163-88-1; 37350-58-6.
ATC — C07AB02.
ATC Vet — QC07AB02.
UNII — GEB06NHM23.

Metoprolol Fumarate *(BANM, USAN, rINNM)* ⊗

CGP-2175C; Fumarato de metoprolol; Métoprolol, Fumarate de; Metoprolol, fumarato de; Metoprololi Fumaras; Метопролола Фумарат.
$(C_{15}H_{25}NO_3)_2.C_4H_4O_4$=650.8
CAS — 119637-66-0.
ATC — C07AB02.
ATC Vet — QC07AB02.
UNII — IO1C09Z674.

Pharmacopoeias. In *US.*

USP 36: (Metoprolol Fumarate). A 10% solution in water has a pH of between 5.5 and 6.5. Store in airtight containers Protect from light.

Metoprolol Succinate *(BANM, USAN, rINNM)* ⊗

Métoprolol, succinate de; Metoprolol, succinato de; Metoprolol Süksinat; Metoprololi Succinas; Metoprololio sukcinatas; Metoprololisuksinaatti; Metoprololsuccinat; Metoprolol-sukcinát; Metoprolol-szukcinát; Succinato de metoprolol; Метопролола Сукцинат.
$(C_{15}H_{25}NO_3)_2.C_4H_6O_4$=652.8
CAS — 98418-47-4.
ATC — C07AB02.
ATC Vet — QC07AB02.
UNII — TH2SPD4CCB.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Metoprolol Succinate). A white or almost white crystalline powder. Freely soluble in water; soluble in methyl alcohol; slightly soluble in alcohol; very slightly soluble in ethyl acetate. A 2% solution in water has a pH of between 7.0 and 7.6. Protect from light.

USP 36: (Metoprolol Succinate). A white to off-white powder. Freely soluble in water; soluble in methyl alcohol; sparingly soluble in alcohol; slightly soluble in isopropyl alcohol. A 6.5% solution in water has a pH of between 7.0 and 7.6. Store in airtight containers at controlled room temperature.

Metoprolol Tartrate *(BANM, USAN, rINNM)* ⊗

CGP-2175E; H-93/26; Metoprolol Tartarat; Metoprolol tartarát; Métoprolol, Tartrate de; Metoprolol, tartrato de; Metoprololi Tartras; Metoprololio tartratas; Metoprololitartraatti; Metoprolol-tartarát; Metoprololtartrat; Tartrato de metoprolol; Метопролола Тартрат.
$(C_{15}H_{25}NO_3)_2.C_4H_6O_6$=684.8
CAS — 56392-17-7.
ATC — C07AB02.
ATC Vet — QC07AB02.
UNII — W5S57Y3A5L.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Metoprolol Tartrate). A white or almost white crystalline powder or colourless crystals. It exhibits polymorphism. Very soluble in water; freely soluble in alcohol. A 2% solution in water has a pH of between 6.0 and 7.0. Protect from light.

USP 36: (Metoprolol Tartrate). A white crystalline powder. Very soluble in water; freely soluble in alcohol, in

chloroform, and in dichloromethane; slightly soluble in acetone; insoluble in ether. A 10% solution in water has a pH of between 6.0 and 7.0. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Stability. Metoprolol tartrate 400 micrograms/mL in glucose 5% or sodium chloride 0.9% was stable for 36 hours when stored at 24 degrees in PVC bags.[1]

1. Belliveau PP, *et al.* Stability of metoprolol tartrate in 5% dextrose injection or 0.9% sodium chloride injection. *Am J Hosp Pharm* 1993; 50: 950–2.

Uses and Administration

Metoprolol is a cardioselective beta blocker (p. 1316.3). It is reported to lack intrinsic sympathomimetic activity and to have little or no membrane-stabilising activity.

It is used in the management of hypertension (p. 1251.1), angina pectoris (p. 1254.3), cardiac arrhythmias (p. 1266.1), myocardial infarction (p. 1257.1), and heart failure (p. 1262.3). It is also used in the management of hyperthyroidism (p. 2332.2) and in the prophylactic treatment of migraine (p. 670.3).

Metoprolol is given orally and intravenously as the tartrate. Modified-release tablets usually contain the tartrate or the succinate, but the fumarate has also been used. Doses are usually expressed in terms of the tartrate; 95 mg of metoprolol fumarate or metoprolol succinate is equivalent to about 100 mg of metoprolol tartrate.

The bioavailability of metoprolol is increased if taken with food and it has been recommended that some preparations are taken with or immediately after a meal.

Reduced doses should be given to patients with hepatic impairment.

In **hypertension** metoprolol tartrate is usually given in an initial oral dose of 100 mg daily, as a single dose or in two divided doses. The dose may be increased weekly, according to response; the usual maintenance dose is 100 to 200 mg daily, but up to 400 mg daily may be given.

The usual oral dose for **angina pectoris** is 50 to 100 mg two or three times daily.

In the treatment of **cardiac arrhythmias** the usual oral dose is 50 mg two or three times daily, increased if necessary up to 300 mg daily in divided doses.

For the emergency treatment of cardiac arrhythmias metoprolol tartrate may be given intravenously in an initial dose of up to 5 mg, at a rate of 1 to 2 mg/minute; this may be repeated, if necessary, at intervals of 5 minutes to a total dose of 10 to 15 mg.

Arrhythmias may be prevented on induction of anaesthesia, or controlled during anaesthesia, by the slow intravenous injection of 2 to 4 mg; further injections of 2 mg may be repeated as necessary to a maximum total dose of 10 mg.

Metoprolol is also used as an adjunct in the early management of acute **myocardial infarction.** Treatment should be given within 12 hours of the onset of chest pain; metoprolol tartrate 5 mg should be given intravenously at 2-minute intervals to a total of 15 mg, where tolerated. After 15 minutes, in patients who have received the full intravenous dose, oral treatment should be started; 50 mg is given every 6 hours for 2 days. In patients who have failed to tolerate the full intravenous dose a reduced oral dose should be given as, and when, their condition permits. Subsequent oral maintenance dosage is 100 mg given twice daily. In patients not given metoprolol by intravenous injection as part of the early management of myocardial infarction, metoprolol may be started once the clinical condition of the patient stabilises, in a dose of 200 mg daily in 2 or 4 divided doses.

In the management of stable, symptomatic **heart failure** metoprolol succinate may be given as an oral modified-release preparation. The initial dose is the equivalent of metoprolol tartrate 12.5 to 25 mg once daily, increased as tolerated, at intervals of 2 weeks, with a target dose of 200 mg once daily.

As an adjunct in the treatment of **hyperthyroidism** metoprolol tartrate may be given in oral doses of 50 mg four times daily. Doses of 100 to 200 mg are given daily in divided doses for **migraine** prophylaxis.

General references.

1. Plosker GL, Clissold SP. Controlled release metoprolol formulations: a review of their pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and ischaemic heart disease. *Drugs* 1992; 43: 382–414.
2. Prakash A, Markham A. Metoprolol: a review of its use in chronic heart failure. *Drugs* 2000; 60: 647–78.
3. Tangeman HJ, Patterson JH. Extended-release metoprolol succinate in chronic heart failure. *Ann Pharmacother* 2003; 37: 701–10.
4. Papadopoulos DP, Papademetriou V. Metoprolol succinate combination in the treatment of hypertension. *Angiology* 2009; 60: 608–13.

Administration in children. Metoprolol has been used in children, although experience is limited. A study[1] in children aged 6 to 16 years with hypertension found that modified-release metoprolol succinate was well tolerated in doses of up to the equivalent of metoprolol tartrate 2 mg/kg daily, although efficacy was not established. US licensed product information nevertheless allows the use of oral doses of metoprolol succinate once daily in children aged 6 to 16 years; the initial dose is the equivalent of metoprolol tartrate 1 mg/kg daily (maximum 50 mg), adjusted according to response to a maximum of 2 mg/kg (not more than 200 mg) daily.

The *BNFC* recommends that for hypertension children aged 1 month to 12 years may be given standard formulations of metoprolol tartrate in an initial dose of 1 mg/kg twice daily orally, increased if necessary to a maximum dose of 8 mg/kg daily in 2 to 4 divided doses. Children over 12 years may be given the adult dose (see above).

1. Batisky DL, *et al.* Efficacy and safety of extended release metoprolol succinate in hypertensive children 6 to 16 years of age: a clinical trial experience. *J Pediatr* 2007; 150: 134–9.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Breast feeding. Studies[1-3] have shown that the concentration of metoprolol distributed into breast milk is higher than that in plasma. However, the amount ingested by an infant is likely to be small, and the concentration of metoprolol in infant plasma has been found[3] to be undetectable or very low. No adverse effects have been seen in breast-fed infants whose mothers were given metoprolol and the American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding.

1. Sandström B, Regårdh C-G. Metoprolol excretion into breast milk. *Br J Clin Pharmacol* 1980; 9: 518–19.
2. Liedholm H, *et al.* Accumulation of atenolol and metoprolol in human breast milk. *Eur J Clin Pharmacol* 1981; 20: 229–31.
3. Kulas J, *et al.* Atenolol and metoprolol: a comparison of their excretion into human breast milk. *Acta Obstet Gynecol Scand Suppl* 1984; 118: 65–9.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Effects on hearing. Loss of hearing in a patient receiving metoprolol appeared to be dose-related;[1] hearing gradually improved over several months once the drug was withdrawn.

1. Fäldt R, *et al.* β Blockers and loss of hearing. *BMJ* 1984; 289: 1490–2.

Effects on lipid metabolism. Beta blockers may increase serum-triglyceride concentrations. For a report of acute pancreatitis provoked by severe hypertriglyceridaemia in a patient taking metoprolol followed by atenolol, see p. 1320.1.

Effects on the liver. Acute hepatitis associated with metoprolol has been reported in a 56-year-old woman.[1] The hepatotoxicity could not be explained by deficient oxidation of metoprolol; drug oxidation phenotyping showed she was an extensive metaboliser of debrisoquine and hence metoprolol.

For a discussion of the relationship between polymorphic oxidation of metoprolol and the incidence of adverse effects, see Metabolism, under Pharmacokinetics, below.

1. Larrey D, *et al.* Metoprolol-induced hepatitis: rechallenge and drug oxidation phenotyping. *Ann Intern Med* 1988; 108: 67–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies metoprolol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Surgery. The oral bioavailability, rate of absorption, AUC, and peak plasma concentrations of metoprolol were significantly reduced in 12 patients after coronary artery bypass surgery, and did not return to their pre-operative levels *until the third postoperative day.*[1] The authors warned of the possibility of inducing beta-blocker withdrawal syndrome (p. 1321.2), and suggested that the intravenous route may be more appropriate in surgical patients requiring beta blockers.

1. Valtola A, *et al.* Does coronary artery bypass surgery affect metoprolol bioavailability. *Eur J Clin Pharmacol* 2007; 63: 471–8.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Antivirals. US licensed product information for *ritonavir* warns that ritonavir may increase concentrations of metoprolol and that the dose of metoprolol may need to be reduced if used together.

Pharmacokinetics

Metoprolol is readily and completely absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism, with a bioavailability of about 50%. Peak plasma concentrations vary widely and occur about 1.5 to 2 hours after a single oral dose. It is moderately lipid-soluble.

Metoprolol is widely distributed; it crosses the blood-brain barrier and the placenta, and is distributed into breast milk. It is about 12% bound to plasma protein. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP2D6, and undergoes oxidative deamination, *O*-dealkylation followed by oxidation, and aliphatic hydroxylation. The metabolites are excreted in the urine with only small amounts of unchanged metoprolol. The rate of metabolism by CYP2D6 is determined by genetic polymorphism; the half-life of metoprolol in fast hydroxylators is stated to be 3 to 4 hours, whereas in poor hydroxylators it is about 7 hours.

The elderly. Several studies[1-3] indicate that age-related physiological changes have negligible effects on the pharmacokinetics of metoprolol.

1. Quarterman CP, *et al.* The effect of age on the pharmacokinetics of metoprolol and its metabolites. *Br J Clin Pharmacol* 1981; 11: 287–94.
2. Regårdh CG, *et al.* Pharmacokinetics of metoprolol and its metabolite α-OH-metoprolol in healthy, non-smoking, elderly individuals. *Eur J Clin Pharmacol* 1983; 24: 221–6.
3. Larsson M, *et al.* Pharmacokinetics of metoprolol in healthy, elderly, non-smoking individuals after a single dose and two weeks of treatment. *Eur J Clin Pharmacol* 1984; 27: 217–22.

Metabolism. Metoprolol is metabolised by the cytochrome P450 isoenzyme CYP2D6 and therefore shows a debrisoquine-type genetic polymorphism.[1-3] Poor, intermediate, extensive, and ultrarapid metabolisers of metoprolol have been identified, and studies[4-6] have confirmed that plasma-metoprolol concentrations correlate with metaboliser status. However, the clinical relevance of these differences is less clear. Subtherapeutic levels have been reported[7] in extensive metabolisers, while a fivefold higher risk of adverse effects[8] and significantly greater reductions in heart rate and blood pressure[9] have been reported among poor metabolisers. However, other studies[10,11] have found no correlation between the incidence of adverse effects and metaboliser status, and controlled studies in patients with hypertension[5] and in healthy subjects[4] have found that there is little or no relationship between plasma concentrations or metaboliser status and either the incidence of adverse effects or the response to therapy.

The subject may be further confused by variations in the phenotype between ethnic groups. Although the incidence of the poor metaboliser phenotype in whites of European origin is reported to be about 9%, a study in 138 Nigerians[12] failed to identify evidence of polymorphic metabolism, and the authors caution against extrapolation of data between different racial groups.

1. Lennard MS, *et al.* Defective metabolism of metoprolol in poor hydroxylators of debrisoquine. *Br J Clin Pharmacol* 1982; 14: 301–3.
2. Lennard MS, *et al.* Oxidation phenotype—a major determinant of metoprolol metabolism and response. *N Engl J Med* 1982; 307: 1558–60.
3. McGourty JC, *et al.* Metoprolol metabolism and debrisoquine oxidation polymorphism—population and family studies. *Br J Clin Pharmacol* 1985; 20: 555–66.
4. Kirchheiner J, *et al.* Impact of the ultrarapid metabolizer genotype of cytochrome P450 2D6 on metoprolol pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 2004; 76: 302–12.
5. Zineh I, *et al.* Pharmacokinetics and CYP2D6 genotypes do not predict metoprolol adverse events or efficacy in hypertension. *Clin Pharmacol Ther* 2004; 76: 536–44.
6. Ismail R, Teh LK. The relevance of CYP2D6 genetic polymorphism on chronic metoprolol therapy in cardiovascular patients. *J Clin Pharm Ther* 2006; 31: 99–109.
7. Goryachkina K, *et al.* CYP2D6 is a major determinant of metoprolol disposition and effects in hospitalized Russian patients treated for acute myocardial infarction. *Eur J Clin Pharmacol* 2008; 64: 1163–73.
8. Wuttke H, *et al.* Increased frequency of cytochrome P450 2D6 poor metabolizers among patients with metoprolol-associated adverse effects. *Clin Pharmacol Ther* 2002; 72: 429–37.
9. Rau T, *et al.* Impact of the CYP2D6 genotype on the clinical effects of metoprolol: a prospective longitudinal study. *Clin Pharmacol Ther* 2009; 85: 269–72.
10. Clark DWJ, *et al.* Adverse effects from metoprolol are not generally associated with oxidation status. *Br J Clin Pharmacol* 1984; 18: 965–6.
11. Pux R, *et al.* Impact of CYP2D6 genotype on adverse effects during treatment with metoprolol: a prospective clinical study. *Clin Pharmacol Ther* 2005; 78: 378–87.
12. Iyun AO, *et al.* Metoprolol and debrisoquin metabolism in Nigerians: lack of evidence for polymorphic oxidation. *Clin Pharmacol Ther* 1986; 40: 387–94.

Pregnancy. The clearance of metoprolol was increased fourfold in 5 pregnant women during the last trimester, compared with that some months after delivery; this was probably due to enhanced hepatic metabolism in the pregnant state.[1]

The disposition of metoprolol was investigated in neonates of mothers treated with metoprolol 50 to 100 mg twice daily.[2] In 15 of the 17 neonates plasma-metoprolol concentrations increased in the first 2 to 5 hours of the postnatal period, then declined over the next 15 hours; 5 of these infants had no detectable metoprolol concentrations

in the umbilical plasma. No infant showed signs of beta blockade.

1. Högstedt S, *et al.* Increased oral clearance of metoprolol in pregnancy. *Eur J Clin Pharmacol* 1983; 24: 217–20.
2. Lundborg P, *et al.* Disposition of metoprolol in the newborn. *Br J Clin Pharmacol* 1981; 12: 598–600.

Renal impairment. A single dose of a modified-release tablet of metoprolol produced similar plasma-metoprolol concentrations and values for the area under the concentration/time curve in both normal subjects and those with renal impairment.[1] Mean plasma concentrations of the metabolite α-hydroxymetoprolol were increased two to threefold in subjects with renal impairment compared with normal subjects but such a rise was not considered likely to contribute to beta blockade.

1. Lloyd P, *et al.* The effect of impaired renal function on the pharmacokinetics of metoprolol after single administration of a 14/190 metoprolol OROS system. *Am Heart J* 1990; 120: 478–82.

Surgery. Oral bioavailability of metoprolol may be significantly reduced after surgery—see under Adverse Effects, Treatment, and Precautions, p. 1435.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Belozok; Lopresor; *Austral.*: Betaloc; Lopresor; Metohexal; Metrol; Minax; Toprol; *Austria*: Beloc; Lanoc; Metohexal; Seloken; *Belg.*: Lopresor; Selo-Zok; Seloken; Slow-Lopresor; *Braz.*: Lopressor; Miclox; Selo-Zok; Seloken; *Canad.*: Betaloc; Lopresor; Novo-Metoprol†; Nu-Metop; *Chile*: Betaloc Zok; *China*: Betaloc (倍他乐克); JunQing (均青); Meng De Kang (蒙得康); Shumeng (舒梦); Tuo Xi Er Kang (托西尔康); *Cz.*: Belenzok†; Betaloc; Egilok; Emzok; Lidazoc; Vasocardin; *Denm.*: Betaloc Zok†; Isalok; Mepronet; Mertolok; Metocar; Metomylan; Metoratio; Metostad; Rukolok; Selo-Zok; Seloken; *Fin.*: Metohexal; Metomylan; Metoprolin; Seloken ZOC; Seloken; Selopral; Spesicor; Spesimax; *Fr.*: Lopressor; Seloken; Selozok; *Ger.*: Beloc-Zok; Beloc; Jeprolol; Jutabloc†; Lopresor; Meprolol; Meto-Succinat†; Meto-Tablinen†; Meto; Metobeta; Metodoc†; Metohexal†; Metoprogamma; Prelis; *Gr.*: Inophylin; Lofarbil; Lopresor; Styralonax; Venolone; *Hong Kong*: Betaloc; CP-Metolol†; Minax; Novo-Metoprol†; Sefloc†; *Hung.*: Betaloc; Egilok; *India*: Actiblok-IPR; Betacon; Betaloc; Betaone; Blumet; CGRol; Embeta; Gudpres; Intramet; Kimet; Libmet; Lopresor; Lopressor; Mepol; Met; Metapro; Meto; Metocard; Metocare; Metofin; Metolar; Metomac; Metosafe; Metzok; Mexes; Motoblock; MT-Loc; Revelol; Selopres; *Indon.*: Cardiosel†; Lopresor; Loprolol; Seloken; *Irl.*: Betaloc; Lopresor†; Metocor; Metop; *Israel*: Lopresor; Neobloc; *Ital.*: Lopresor; Seloken; *Jpn*: Seloken; *Malaysia*: Betaloc; Betawin; Denex; *Mex.*: Bioprol; Eurolol; Futaline; Kenaprol; Lopresor; Metopresol; Proken M; Prolaken†; Promiced; Prontol; Rimtolol; Selectadril; Seloken; Sermetrol; Tiazidol†; *Neth.*: Selokeen; *Norw.*: Selo-Zok; Seloken; *NZ*: Betaloc; Lopresor; Myloc; Slow-Lopresor; *Philipp.*: Angimet; Angiobloc; Angionorm; Betaloc; Betaryx; Betazok; Cardiosel; Cardiostat; Cardiotab; Carditec; Gerbloc; Hypetor; Hyprofil; Metobloc; Metocare; Metoprim; Metospec; Metostad; Montebloc; Neobloc; Prolohext†; Valvexin; Zionel; *Pol.*: Betaloc; Beto; Metocard; *Metogen*; *Metohexal*†; *Port.*: Lopresor; *Rus.*: Betaloc (Беталок ЗОК); Corvitol (Корвалол); Egilok (Эгилок); Emzok (Энзок); Metocard (Метокард); Serdol (Сердол); Vasocardin (Вазокардин); *S.Afr.*: Lopresor; *Singapore*: Betaloc†; Denex; Sefloc; *Spain*: Beloken; Lopresor; *Swed.*: Metomylan; Metoratio†; Seloken ZOC; Seloken; *Switz.*: Beloc-Zok; Beloc; Lopresor; Meto Zerok; Metopress; *Thai.*: Betaloc; Cardeloc; Cardoxone; Meloc; Melol; *Metoblock*; *Metolol*†; Metprolol; *Minax*†; Sefloc; *Turk.*: Beloc; Lopresor; Probiok; Sanelox; *UK*: Betaloc; Lopresor; *Ukr.*: Anepro (Анепро)†; Betaloc (Беталок); Corvitol (Корвитол); Egilok (Эгилок); *USA*: Lopressor; Toprol; *Venez.*: Lopresor.

Multi-ingredient Preparations. *Austria*: Beloc comp†; Metoprolol compositum; Seloken retard Plus; Triloc†; *Belg.*: Logimat; Logroton; Zok-Zid; *Braz.*: Selopress; *Denm.*: Logimax; Zok-Zid; *Fin.*: Logimax; Selocomp ZOC; *Fr.*: Logimax; Logroton; *Ger.*: Belnif; Beloc-Zok comp; Meto-Succinat HCT†; Metobeta comp; Metohexal comp†; Metoprolol comp; Metoprolol HCT†; Metoprololsuccinat plus†; Metostad Comp†; Mobloc; Prelis comp; *Gr.*: Logimax; *Hong Kong*: CP-Metolol Co†; Logimax; *Hung.*: Logimax; *India*: Amlovas-M; Betaloc H; Meto ER HT; Metolar-H; Motoblock-AM; Olsar-M; *Irl.*: Co-Betaloc†; *Israel*: Logimax†; *Ital.*: Igroton-Lopresor; *Malaysia*: Logroton; *Mex.*: Logimax; Selopres; *Neth.*: Selokomb; *Philipp.*: Betazide†; Logimax; *Rus.*: Logimax (Логимакс); *Singapore*: Logroton; *Spain*: Higrotensin†; Logimax; *Swed.*: Logimax; *Switz.*: Logimax; Logroton; *Turk.*: Meprolol; *USA*: Dutoprol; Lopressor HCT.

Pharmacopoeial Preparations

BP 2014: Metoprolol Injection; Metoprolol Tartrate Tablets; Prolonged-release Metoprolol Tartrate Tablets;

USP 36: Metoprolol Succinate Extended-Release Tablets; Metoprolol Tartrate and Hydrochlorothiazide Tablets; Metoprolol Tartrate Injection; Metoprolol Tartrate Oral Solution; Metoprolol Tartrate Oral Suspension; Metoprolol Tartrate Tablets.

Metreleptin *(USAN, rINN)*

Metreleptina; Métréleptine; Metreleptinum; r-metHuLeptin; Метрелептин.

N-Methionylleptin (human).

$C_{714}H_{1167}N_{191}O_{221}S_6$

CAS — 186018-45-1.

UNII — TL60C27RLH.

Profile

Metreleptin is a recombinant methionyl analogue of human leptin. It is given by subcutaneous injection in the treatment of lipodystrophy. Starting doses of 20 to 40 micrograms/kg daily are increased to a maintenance dose of 40 to 80 micrograms/kg daily within 1 month.

References.
1. Chan JL, *et al.* Clinical effects of long-term metreleptin treatment in patients with lipodystrophy. *Endocr Pract* 2011; 17: 922–32.
2. Chou K, Perry CM. Metreleptin: first global approval. *Drugs* 2013; 73: 989–97.
3. Frank S, *et al.* Long-term stabilization effects of leptin on brain functions in a leptin-deficient patient. *PLoS One* 2013; 8: e65893.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Metreleptin.

Mexiletine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de mexiletina; Kö-1173; Meksiletiinihydrokloridi; Meksiletin Hidroklorür; Meksiletino hidrochloridas; Mexiletina, hidrocloruro de; Mexilétine, chlorhydrate de; Mexiletin-hidroklorid; Mexiletin-hydrochlorid; Mexiletinhydrochlorid; Mexiletinhydroklorid; Mexiletini Hydrochloridum; Мексилетина Гидрохлорид.

1-Methyl-2-(2,6-xylyloxy)ethylamine hydrochloride.

$C_{11}H_{17}NO,HCl=215.7$

CAS — 31828-71-4 (mexiletine); 5370-01-4 (mexiletine hydrochloride).

ATC — C01BB02.

ATC Vet — QC01BB02.

UNII — 606D60I538.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Mexiletine Hydrochloride). A white or almost white, crystalline powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; sparingly soluble in dichloromethane. A 10% solution in water has a pH of 4.0 to 5.5.

USP 36: (Mexiletine Hydrochloride). A white powder. Freely soluble in water and in dehydrated alcohol; practically insoluble in ether; slightly soluble in acetonitrile. A 10% solution in water has a pH of between 3.5 and 5.5. Store in airtight containers.

Uses and Administration

Mexiletine is a class Ib antiarrhythmic (p. 1243.1) with actions similar to those of lidocaine (p. 1992.2), to which it is structurally related. Unlike lidocaine it undergoes little hepatic first-pass metabolism and can be given orally.

Mexiletine is used for the treatment of ventricular **arrhythmias** (p. 1266.1). It is given orally or intravenously as the hydrochloride.

Mexiletine hydrochloride is given orally in a usual loading dose of 400 mg followed by 200 to 300 mg three times daily, starting 2 to 8 hours after the loading dose. The usual maintenance dosage is 600 to 900 mg daily in divided doses; doses up to 1.2 g daily may be given. Oral doses should be taken with food and swallowed with plenty of liquid to avoid oesophageal ulceration. Modified-release preparations have been used. Higher loading doses have been given to patients after myocardial infarction to overcome delayed absorption, especially if they have received an opioid analgesic.

Mexiletine hydrochloride has also been given by slow intravenous injection and infusion.

Mexiletine has been tried in the treatment of refractory neuropathic pain (see below).

Administration in children. Mexiletine may be effective for ventricular arrhythmias in children; a study[1] of 42 children and young adults (age range 5 months to 34 years) found that mexiletine, given orally in a dose of 1.4 to 5 mg/kg every 8 hours, was effective in 30 patients (71%), with long-term control reported in 18. Treatment was more effective in children with congenital heart disease than in those with cardiomyopathy or no heart disease. Another report[2] found that young children required higher mg/kg doses than adults; a 2-week-old girl and a 20-month-old boy required oral doses of 25 and 15 mg/kg daily, respectively, to produce therapeutic plasma concentrations and control of tachycardia.

1. Moak JP, *et al.* Mexiletine: an effective antiarrhythmic drug for treatment of ventricular arrhythmias in congenital heart disease. *J Am Coll Cardiol* 1987; 10: 824–9.
2. Holt DW, *et al.* Paediatric use of mexiletine and disopyramide. *BMJ* 197 ; 2: 1476–7.

Administration in the elderly. The rate of absorption of mexiletine was slower in a group of 7 elderly subjects compared with 8 young subjects given mexiletine 100 mg orally, but the extent of absorption was probably not affected.[1] Elimination of mexiletine was not significantly different between the 2 groups and there was no pharmacokinetic basis for dosage modification of mexiletine in the elderly. An observational study[2] in patients receiving mexiletine found a small decrease in clearance with age, but again this was not considered to warrant dosage adjustment.

1. Grech-Bélanger O, *et al.* Pharmacokinetics of mexiletine in the elderly. *J Clin Pharmacol* 1989; 29: 311–15.
2. Ueno K, *et al.* Pharmacokinetics of mexiletine in middle-aged and elderly patients. *Clin Pharm* 1993; 12: 768–70.

Administration in renal impairment. The pharmacokinetics of mexiletine do not appear to be affected by renal impairment,[1] although one study[2] found that in patients with creatinine clearance below 10 mL/minute the steady-state plasma concentration and half-life were increased, suggesting that dosage should be adjusted according to plasma concentrations in such patients. Haemodialysis[1] and continuous ambulatory peritoneal dialysis[3] do not appear to affect mexiletine clearance.

1. Wang T, *et al.* Pharmacokinetics and nondialyzability of mexiletine in renal failure. *Clin Pharmacol Ther* 1985; 37: 649–53.
2. El Allaf D, *et al.* Pharmacokinetics of mexiletine in renal insufficiency. *Br J Clin Pharmacol* 1982; 14: 431–5.
3. Guay DRP, *et al.* Mexiletine clearance during peritoneal dialysis. *Br J Clin Pharmacol* 1985; 19: 857–8.

Myotonia. Reference[1] to the use of mexiletine in the management of myotonic dystrophy type 1. Oral doses of 150 or 200 mg three times daily appeared to be of benefit in relieving myotonia and were well tolerated in small placebo-controlled crossover groups.

1. Logigian EL, *et al.* Mexiletine is an effective antimyotonia treatment in myotonic dystrophy type 1. *Neurology* 2010; 74: 1441–8.

Pain. Neuropathic pain (p. 10.1) is often insensitive to opioid analgesics; alternatives that have been tried include mexiletine. Mexiletine may be of benefit in diabetic neuropathy,[1] although studies have given conflicting results; two of the studies that reported no difference between treatment and placebo found that a subset of patients (those with stabbing or burning pain, heat sensations, and formication) appeared to benefit.[2,3] There have also been reports of improvement in patients with central post-stroke pain (thalamic pain syndrome),[4] and in neuropathic pain associated with cancer,[5-7] and a systematic review[8] concluded that mexiletine was safe and effective in various types of neuropathic pain.

Other painful states in which mexiletine has been reported to be of benefit include: Dercum's disease (a condition involving painful fatty deposits),[9] and erythromelalgia.[10-12] It has also been tried in refractory chronic daily headache.[13] However, it proved ineffective in a study in patients with postamputation pain.[14]

1. Jarvis B, Coukell AJ. Mexiletine: a review of its therapeutic use in painful diabetic neuropathy. *Drugs* 1998; 56: 691–707.
2. Stracke H, *et al.* Mexiletine in the treatment of diabetic neuropathy. *Diabetes Care* 1992; 15: 1550–5.
3. Wright JM, *et al.* Mexiletine in the symptomatic treatment of diabetic peripheral neuropathy. *Ann Pharmacother* 1997; 31: 29–34.
4. Awerbuch GI, Sandyk R. Mexiletine for thalamic pain syndrome. *Int J Neurosci* 1990; 55: 129–33.
5. Colclough G, *et al.* Mexiletine for chronic pain. *Lancet* 1993; 342: 1484–5.
6. Sloan P, *et al.* Mexiletine as an adjuvant analgesic for the management of neuropathic cancer pain. *Anesth Analg* 1999; 89: 760–1.
7. Fassoulaki A, *et al.* The analgesic effect of gabapentin and mexiletin after breast surgery for cancer. *Anesth Analg* 2002; 95: 985–91.
8. Challapalli V, *et al.* Systemic administration of local anesthetic agents to relieve neuropathic pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 24/01/07).
9. Petersen P, *et al.* Treating the pain of Dercum's disease. *BMJ* 1984; 288: 1880.
10. Kuhnert SM, *et al.* Lidocaine and mexiletine therapy for erythromelalgia. *Arch Dermatol* 1999; 135: 1447–9.
11. Nathan A, *et al.* Primary erythromelalgia in a child responding to intravenous lidocaine and oral mexiletine treatment. Abstract: *Pediatrics* 2005; 115: 1066. Full version: http://pediatrics.aappublications.org/cgi/content/full/115/4/e504 (accessed 10/07/07)
12. Iqbal J, *et al.* Experience with oral mexiletine in primary erythromelalgia in children. *Ann Saudi Med* 2009; 29: 316–8.
13. Marmura MJ, *et al.* Mexiletine for refractory chronic daily headache: a report of nine cases. *Headache* 2008; 48: 1506–10.
14. Wu CL, *et al.* Morphine versus mexiletine for treatment of postamputation pain: a randomized, placebo-controlled, crossover trial. *Anesthesiology* 2008; 109: 289–96.

Adverse Effects and Treatment

Mexiletine has a narrow therapeutic ratio; although many of its adverse effects are dose-related and will respond to

dosage reduction they may be severe enough to force treatment to be stopped and symptomatic and supportive therapy to be given. Toxicity is common with oral or parenteral loading doses when plasma concentrations are high.

The most common adverse effects involve the gastrointestinal tract and CNS. Effects on the gastrointestinal tract include nausea, vomiting, constipation, and diarrhoea; oesophageal ulceration has also been reported. Effects on the nervous system include tremor, confusion, lightheadedness, dizziness, blurred vision and other visual disturbances, sleep disturbances, and speech difficulties. The most frequent cardiovascular effects are hypotension, sinus bradycardia, heart block and AV dissociation, and atrial fibrillation. As with other antiarrhythmics mexiletine may exacerbate arrhythmias. Other adverse effects that have been reported include rashes, abnormal liver function tests, thrombocytopenia, positive antinuclear factor titres, and convulsions. The Stevens-Johnson syndrome has been reported rarely.

Incidence of adverse effects. In a study involving 100 patients with ventricular arrhythmias, mexiletine had to be stopped in 49 patients because of intolerable adverse effects.[1] The most common of these affected the gastrointestinal system (27%) and included nausea (10%), vomiting (6%), heartburn (6%), and oesophageal spasm (3%). Intolerable effects on the CNS occurred in 10% of patients and these were most commonly tremor (4%), ataxia (2%), dyskinesia (1%), and tinnitus (1%). When mexiletine was used with another antiarrhythmic, the incidence of intolerable effects was 56%.

Tolerable adverse effects with mexiletine alone were transient and dose-dependent and occurred in 18% of patients. They most often affected the gastrointestinal tract. No irreversible adverse effects were reported and no proarrhythmic effects were seen.

1. Kerin NZ, *et al.* Mexiletine: long-term efficacy and side effects in patients with chronic drug-resistant potentially lethal ventricular arrhythmias. *Arch Intern Med* 1990; 150: 381–4.

Effects on the lungs. Pulmonary fibrosis has been reported in an elderly patient receiving mexiletine; the manufacturer was aware of 3 other cases.[1] A case of the hypersensitivity syndrome DRESS (drug rash with eosinophilia and systemic symptoms), manifesting as eosinophilic pneumonia, has also been reported[2] in a patient given mexiletine.

1. Bero CJ, Riha TL. Possible association of pulmonary fibrosis with mexiletine. *DICP Ann Pharmacother* 1991; 25: 329–31.
2. Lee S-P, *et al.* A case of mexiletine-induced hypersensitivity syndrome presenting as eosinophilic pneumonia. *J Korean Med Sci* 2010; 25: 148–51.

Precautions

Mexiletine is contra-indicated in cardiogenic shock and in second- or third-degree AV block (unless the patient has a pacemaker). It should be used with caution in patients with sinus node dysfunction, other conduction disorders, bradycardia, hypotension, heart failure, or hepatic impairment. ECG and blood pressure monitoring should be carried out during treatment.

Absorption of oral mexiletine may be delayed in situations where gastric emptying is slowed, such as acute myocardial infarction.

Breast feeding. Mexiletine is distributed into human breast milk in higher concentrations than in maternal serum. A woman[1] given 200 mg of mexiletine three times daily during the last trimester of pregnancy (see below), went on to breast feed the infant. Concentrations of mexiletine in the maternal milk and serum were found to be 600 and 300 nanograms/mL respectively on the second day postpartum, and 800 and 700 nanograms/mL respectively after 6 weeks. This represented a milk to serum ratio of 2.0 and 1.1 respectively. However, mexiletine was undetectable in the infant's serum on both occasions and no adverse effects were seen. In another report[2] a woman taking a similar dose of mexiletine for the last 5 months of her pregnancy also breast fed her infant. In samples of maternal milk and blood collected between the second and fifth day postpartum the milk to plasma ratio varied between 0.78 and 1.89 with a mean of 1.45. It was considered unlikely that the infant would ingest more than 1.25 mg of mexiletine in any 24-hour period, and this amount was not thought to be enough to cause adverse effects. Failure to feed was noted[3] in the first 17 days in an infant whose mother was taking 750 mg daily of mexiletine and 50 mg daily of atenolol. After maternal education and formula supplementation an acceptable growth curve was established. Breast feeding continued until the infant was 3 months old, and no adverse effects were seen at 10 months. The American Academy of Pediatrics[4] therefore considers that mexiletine is usually compatible with breast feeding.

1. Timmis AD, *et al.* Mexiletine for control of ventricular dysrhythmias in pregnancy. *Lancet* 1980; ii: 647–8.
2. Lewis AM, *et al.* Mexiletine in human blood and breast milk. *Postgrad Med J* 1981; 57: 546–7.
3. Lownes HE, Ives TJ. Mexiletine use in pregnancy and lactation. *Am J Obstet Gynecol* 1987; 157: 446–7.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mexiletine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pregnancy. Mexiletine crosses the placenta but there have been several reports of its use in pregnant women with no apparent long-term effects on the infants. A normal infant was born to a woman given mexiletine with propranolol for the control of ventricular tachycardia during the third trimester of pregnancy.[1] During the first 6 hours after delivery the infant had a heart rate of only 90 beats/minute, probably due to the propranolol; it was normal thereafter. At delivery the serum concentration of mexiletine in mother and infant was the same. A woman[2] who received mexiletine and atenolol throughout pregnancy also delivered a normal infant; failure to feed was noted at 17 days but at 10 months no adverse effects were seen. In another case[3] where the mother took mexiletine throughout pregnancy, the infant had a low Apgar score at 1 minute and hypoglycaemia was also noted, but the relationship to mexiletine was unclear; cord and maternal blood concentrations at the time of delivery were 400 nanograms/mL and 600 nanograms/mL, respectively.

1. Timmis AD, *et al.* Mexiletine for control of ventricular dysrhythmias in pregnancy. *Lancet* 1980; ii: 647–8.
2. Lownes HE, Ives TJ. Mexiletine use in pregnancy and lactation. *Am J Obstet Gynecol* 1987; 157: 446–7.
3. Gregg AR, Tomich PG. Mexilitene [sic] use in pregnancy. *J Perinatol* 1988; 8: 33–5.

Interactions

Mexiletine undergoes extensive metabolism in the liver particularly by the cytochrome P450 isoenzymes CYP1A2 and CYP2D6, and possibly CYP3A4, and interactions may occur with other drugs metabolised by the same enzymes. Plasma concentrations of mexiletine may be reduced by hepatic enzyme inducers such as phenytoin and rifampicin; increased plasma concentrations may occur with enzyme inhibitors.

Absorption of mexiletine may be delayed by drugs that slow gastric emptying such as opioid analgesics and atropine. The rate of absorption may be increased by metoclopramide; the extent of absorption is unaffected.

Drugs that acidify or alkalinise the urine enhance or reduce the rate of elimination of mexiletine, respectively.

There may be an increased risk of arrhythmias if mexiletine is used with other antiarrhythmics or with arrhythmogenic drugs.

Mexiletine has been reported to increase theophylline concentrations (see Antiarrhythmics, p. 1234.1) and to precipitate lidocaine toxicity (p. 1995.1).

Pharmacokinetics

Mexiletine is readily and almost completely absorbed from the gastrointestinal tract, with a bioavailability of about 90%, although absorption may be delayed in situations where gastric emptying is slowed, such as acute myocardial infarction.

Mexiletine is metabolised in the liver to several metabolites; metabolism may involve cytochrome P450 isoenzymes CYP1A2, CYP2D6, and CYP3A4, and genetic polymorphism in relation to CYP2D6 has been identified. Mexiletine is excreted in the urine, mainly in the form of its metabolites with about 10% excreted unchanged; clearance is increased in acid urine.

Mexiletine is widely distributed throughout the body and is about 50 to 70% bound to plasma proteins. Mexiletine crosses the placenta and is distributed into breast milk. It has an elimination half-life of about 10 hours in healthy subjects but this may be prolonged in patients with heart disease, hepatic impairment, or severe renal impairment. Its therapeutic effect has been correlated with plasma concentrations of 0.5 to 2 micrograms/mL, but the margin between therapeutic and toxic concentrations is narrow, and severe toxicity may occur within this range.

References.

1. Labbé L, Turgeon J. Clinical pharmacokinetics of mexiletine. *Clin Pharmacokinet* 1999; 37: 361–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Mexitilen; *Austral.*: Mexitil†; *Belg.*: Mexitil†; *Braz.*: Mexitil; *Cz.*: Katen†; *Ger.*: Mexitil†; *Gr.*: Antiaril; Mexitil; Myovek; *Hung.*: Ritalmex; *India*: Mexitil; *Irl.*: Mexitil†; *Ital.*: Mexitil; *Jpn*: Mexitil; *Malaysia*: Meletin; *NZ*: Mexitil; *Pol.*: Mexicord†; *Rus.*: Ritalmex (Риталмекс); *Turk.*: Mexitil; *Ukr.*: Mexaritm (Мексаритм); *USA*: Mexitil; *Venez.*: Tumetil.

Pharmacopoeial Preparations

BP 2014: Mexiletine Capsules; Mexiletine Injection;
USP 36: Mexiletine Hydrochloride Capsules.

Midodrine Hydrochloride

(BANM, USAN, rINNM) ⊗

Hidrocloruro de midodrina; Midodrina, hidrocloruro de; Midodrine, Chlorhydrate de; Midodrini Hydrochloridum; ST-1085 (midodrine or midodrine hydrochloride); Мидодрина Гидрохлорид.

2-Amino-*N*-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide hydrochloride; (*RS*)-*N*^{1}-(β-Hydroxy-2,5-dimethoxyphenethyl) glycinamide hydrochloride.

$C_{12}H_{18}N_2O_4HCl$=290.7

CAS — 42794-76-3 (midodrine); 3092-17-9 (midodrine hydrochloride).

ATC — C01CA17.

ATC Vet — QC01CA17.

UNII — 59JV96YTXV.

Pharmacopoeias. In *US.*

USP 36: (Midodrine Hydrochloride). A white crystalline powder. Soluble in water; sparingly soluble in methyl alcohol. A 5% solution in water has a pH of 4.0 to 5.0. Store in airtight containers.

Uses and Administration

Midodrine is a direct-acting sympathomimetic (p. 1507.3) with selective alpha-agonist activity; the main active moiety has been stated to be its major metabolite, deglymidodrine. It acts as a peripheral vasoconstrictor but has no direct cardiac stimulatory effects.

Midodrine hydrochloride is used in the treatment of hypotensive states (p. 1277.2) and in particular of orthostatic hypotension (p. 1634.3). Alpha-agonist drugs such as midodrine have also been used as an adjunct in the management of urinary incontinence (p. 2349.2).

In **hypotensive states**, the usual initial oral dose of midodrine hydrochloride is 2.5 mg two or three times daily, adjusted gradually according to response; up to 10 mg three times daily may be required. The potential for supine hypertension is reduced by taking the last dose of the day at least 4 hours before bedtime.

An oral dose for **urinary incontinence** is 2.5 to 5 mg two or three times daily.

Midodrine hydrochloride has also been given in similar doses by slow intravenous injection. It has also been used orally or by injection in the treatment of **retrograde ejaculation.**

References.

1. McClellan KJ, *et al.* Midodrine: a review of its therapeutic use in the management of orthostatic hypotension. *Drugs Aging* 1998; 12: 76–86.
2. Prakash S, *et al.* Midodrine appears to be safe and effective for dialysis-induced hypotension: a systematic review. *Nephrol Dial Transplant* 2004; 19: 2553–8.
3. Karwa R, Woodis CB. Midodrine and octreotide in treatment of cirrhosis-related hemodynamic complications. *Ann Pharmacother* 2009; 43: 692–9.
4. Safarinejad MR. Midodrine for the treatment of organic anejaculation but not spinal cord injury: a prospective randomized placebo-controlled double-blind clinical study. *Int J Impot Res* 2009; 21: 213–20.
5. Soler JM, *et al.* Oral midodrine for prostaglandin E1 induced priapism in spinal cord injured patients. *J Urol (Baltimore)* 2009; 182: 1096–1100.

Adverse Effects, Treatment, and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3. Midodrine has mainly alpha-agonist properties and the most serious adverse effect of midodrine is supine hypertension. Paraesthesias, dysuria, pilomotor reaction (goose flesh), pruritus and rashes have been reported.

Interactions

As for Sympathomimetics, p. 1508.3.

Pharmacokinetics

Midodrine is well absorbed from the gastrointestinal tract and undergoes enzymatic hydrolysis in the systemic circulation to its active metabolite, deglymidodrine (desglymidodrine; ST-1059). Midodrine itself reaches its peak plasma concentrations about half an hour after an oral dose, and has a plasma half-life of about 25 minutes. The active metabolite reaches its peak plasma concentration

about an hour after oral dosage and has a terminal elimination half-life of about 3 hours. Deglymidodrine undergoes some further metabolism in the liver. Midodrine is mainly excreted in the urine as metabolites and a small amount of unchanged drug.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Gutron; *Austria*: Gutron; *Canad.*: Amatine†; *Chile*: Gutron; *China*: An De Lin (安得林); Gutron (管通); Mi Wei (米维); *Cz.*: Gutron; *Fr.*: Gutron; *Ger.*: Gutron; *Gr.*: Gutron; *Hong Kong*: Gutron; *Hung.*: Gutron; *Irl.*: Midon; *Israel*: Gutron†; *Ital.*: Gutron; Xerotil; *Jpn*: Metligine; *Neth.*: Gutron; *NZ*: Gutron; *Pol.*: Gutron; *Port.*: Gutron; *Rus.*: Gutron (Гутрон); *Singapore*: Gutron; *Spain*: Gutron; *Switz.*: Gutron; *USA*: ProAmatine.

Pharmacopoeial Preparations
USP 36: Midodrine Hydrochloride Tablets.

Milrinone *(BAN, USAN, rINN)*

Milrinona; Milrinonum; Win-47203-2; YM-018; Мильринон.
1,6-Dihydro-2-methyl-6-oxo[3,4′-bipyridine]-5-carbonitrile.
$C_{12}H_9N_3O$=211.2
CAS — 78415-72-2.
ATC — C01CE02.
ATC Vet — QC01CE02.
UNII — JU9YAX04C7.

Pharmacopoeias. In *US*.

USP 36: (Milrinone). A white to tan, hygroscopic, crystalline solid. Practically insoluble in water and in chloroform; very slightly soluble in methyl alcohol; freely soluble in dimethyl sulfoxide. Store in airtight containers.

Milrinone Lactate *(BANM, rINNM)*

Lactato de milrinona; Milrinona, lactato de; Milrinone, Lactate de; Milrinoni Lactas; Мильринона Лактат.
$C_{12}H_9N_3O.C_3H_6O_3$=301.3
ATC — C01CE02.
ATC Vet — QC01CE02.
UNII — 9K8XR81MO8.

Incompatibility. UK licensed product information states that milrinone lactate injection is incompatible with furosemide and bumetanide, and it should not be diluted with sodium bicarbonate injection. Physical incompatibility with imipenem-cilastatin sodium has also been reported.[1]

1. Veltri MA, Conner KG. Physical compatibility of milrinone lactate injection with intravenous drugs commonly used in the pediatric intensive care unit. *Am J Health-Syst Pharm* 2002; 59: 452–4.

Uses and Administration

Milrinone is a phosphodiesterase type 3 inhibitor similar to amrinone (p. 1305.1) with positive inotropic and vasodilator activity. It is, however, reported to have greater positive inotropic activity than amrinone. It is given intravenously, as the lactate, in the short-term management of severe heart failure unresponsive to other forms of therapy and in acute heart failure after cardiac surgery. In some longer-term studies milrinone was given orally, but an increased mortality rate was reported.

Doses of milrinone lactate are expressed in terms of the base; milrinone lactate 1.43 mg is equivalent to about 1 mg of milrinone. The initial loading dose is the equivalent of milrinone 50 micrograms/kg given over 10 minutes followed by a continuous maintenance infusion. The maintenance infusion may be titrated between 375 and 750 nanograms/kg per minute but a total daily dose of 1.13 mg/kg should not be exceeded.

Dosage should be reduced in patients with renal impairment (see below).

Use of milrinone by inhalation is being investigated in the management of pulmonary hypertension.

Administration in children. Milrinone has been used in children with septic shock or heart failure after cardiac surgery. Pharmacokinetic studies[1,2] have suggested that steady-state plasma concentrations of milrinone are lower in children than in adults given similar doses, and that milrinone clearance is faster in children. Higher doses in proportion to body-weight may therefore be necessary in children than in adults. For neonates and children aged 1 month to 18 years with heart failure, low cardiac output after cardiac surgery, or shock, the *BNFC* recommends an initial dose of 50 to 75 micrograms/kg by intravenous infusion over 30 to 60 minutes, followed by continuous intravenous infusion at a dose of 30 to 45 micrograms/kg per hour (500 to 750 nanograms/kg per minute). The infusion may be continued for 2 to 3 days, but is usually given for 12 hours after cardiac surgery.

Milrinone also appears to be effective for the prevention of low cardiac output in children undergoing cardiac surgery.[3] It has been tried for the prevention of low systemic blood flow in premature infants, but further studies are needed to confirm its role.[4]

A study[5] of adverse effects in children given milrinone has suggested that arrhythmias are less common than in adults whereas thrombocytopenia is more common.

1. Lindsay CA, *et al.* Pharmacokinetics and pharmacodynamics of milrinone lactate in pediatric patients with septic shock. *J Pediatr* 1998; 132: 329–34.
2. Ramamoorthy C, *et al.* Pharmacokinetics and side effects of milrinone in infants and children after open heart surgery. *Anesth Analg* 1998; 86: 283–9.
3. Hoffman TM, *et al.* Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation* 2003; 107: 996–1002.
4. Paradisis M, *et al.* Pilot study of milrinone for low systemic blood flow in very preterm infants. *J Pediatr* 2006; 148: 306–13.
5. Watson S, *et al.* Use of milrinone in the pediatric critical care unit. *Pediatrics* 1999; 104 (suppl): 681–2.

Administration in renal impairment. Doses of milrinone should be reduced in patients with renal impairment. The following doses for maintenance infusion are recommended based on creatinine clearance (CC):

- CC 50 mL/min per 1.73 m²: 430 nanograms/kg per minute
- CC 40 mL/min per 1.73 m²: 380 nanograms/kg per minute
- CC 30 mL/min per 1.73 m²: 330 nanograms/kg per minute
- CC 20 mL/min per 1.73 m²: 280 nanograms/kg per minute
- CC 10 mL/min per 1.73 m²: 230 nanograms/kg per minute
- CC 5 mL/min per 1.73 m²: 200 nanograms/kg per minute

Heart failure. Milrinone is one of several drugs that may be used in heart failure (p. 1262.3), but because of an increased mortality rate reported after long-term oral use of phosphodiesterase type 3 inhibitors[1] it is usually only given intravenously for short-term management of heart failure unresponsive to other treatments. The PROMISE (Prospective Randomized Milrinone Survival Evaluation) study[2] showed that oral milrinone increased morbidity and mortality in patients with severe chronic heart failure. However, longer-term continuous intravenous use for up to 8 weeks was subsequently studied in patients awaiting heart transplantation and appeared to be well tolerated.[3] Intermittent use on several days a week has also been tried.[4]

In patients with acute exacerbation of heart failure, a prospective study[5] found no benefit from the routine use of short-term intravenous milrinone.

1. Amsallem E, *et al.* Phosphodiesterase III inhibitors for heart failure. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 29/04/10).
2. Packer M, *et al.* Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med* 1991; 325: 1468–75.
3. Mehra MR, *et al.* Safety and clinical utility of long-term intravenous milrinone in advanced heart failure. *Am J Cardiol* 1997; 80: 61–4.
4. Cesario D, *et al.* Beneficial effects of intermittent home administration of the inotrope/vasodilator milrinone in patients with end-stage congestive heart failure: a preliminary study. *Am Heart J* 1998; 135: 121–9.
5. Cuffe MS, *et al.* Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA* 2002; 287: 1541–7.

Adverse Effects and Precautions

Prolonged oral use of milrinone has increased the mortality rate and milrinone is now only used intravenously for short-term use.

Supraventricular and ventricular arrhythmias (including torsade de pointes), hypotension, angina-like chest pain, and headache have been reported. Hypokalaemia, tremor, thrombocytopenia, bronchospasm, anaphylaxis, and infusion site reactions may occur. The incidence of arrhythmias may be lower in *children* whereas the risk of thrombocytopenia may be higher (see Administration in Children, above).

Milrinone should be used with caution in patients with severe obstructive aortic or pulmonary valvular disease or with hypertrophic cardiomyopathy. Since milrinone may facilitate conduction through the atrioventricular node it can increase the ventricular response rate in patients with atrial flutter or fibrillation. Digitalisation should be considered in these patients before milrinone therapy is started.

Blood pressure, heart rate, ECG, fluid and electrolyte balance, and renal function should be monitored during milrinone therapy.

Milrinone should be given in reduced doses to patients with renal impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies milrinone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pharmacokinetics

Although milrinone is rapidly and almost completely absorbed from the gastrointestinal tract, it is only given intravenously. It is about 70% bound to plasma proteins. Elimination occurs mainly via the urine; about 83% of a dose is excreted as unchanged drug. The elimination half-life is about 2.3 hours.

General references.

1. Rocci ML, Wilson H. The pharmacokinetics and pharmacodynamics of newer inotropic agents. *Clin Pharmacokinet* 1987; 13: 91–109. Correction. *ibid.* 1988; 14:(contents page).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Corotrope; *Austria*: Primacor; *Austria*: Corotrop; *Belg.*: Corotrope; *Braz.*: Primacor; *Chile*: Corotrope; *China*: Lunan Likang (鲁南力康); Primacor (伊克维); *Cz.*: Corotrop; *Fr.*: Corotrope; *Ger.*: Corotrop†; *Gr.*: Corotrope; *Hong Kong*: Primacor; *Hung.*: Corotrope; *Ind.*: Milicor; Milron; Myolong; *Indon.*: Coritrope; Inovad; *Israel*: Primacor; *Jpn*: Milrila; *Malaysia*: Primacor; *Mex.*: Primacor; *Neth.*: Corotrope; *NZ*: Primacor; *Pol.*: Corotrope; *Port.*: Corotrope; *Singapore*: Primacor; *Spain*: Corotrope; *Swed.*: Corotrop; *Switz.*: Corotrop; *Thai.*: Primacor; *UK*: Primacor; *USA*: Primacor†; *Venez.*: Corotrope.

Minoxidil *(BAN, USAN, rINN)*

Minoksidiili; Minoksidilis; Minoxidilum; U-10858; Миноксидил.
2,6-Diamino-4-piperidinopyrimidine 1-oxide.
$C_9H_{15}N_5O$=209.3
CAS — 38304-91-5.
ATC — C02DC01; D11AX01.
ATC Vet — QC02DC01.
UNII — 5965120SH1.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Minoxidil). A white or almost white crystalline powder. Slightly soluble in water; soluble in methyl alcohol and in propylene glycol. Protect from light.

USP 36: (Minoxidil). A white or off-white crystalline powder. Slightly soluble in water; soluble in alcohol and in propylene glycol; practically insoluble in acetone, in chloroform, in ethyl acetate, and in petroleum spirit; sparingly soluble in methyl alcohol.

Uses and Administration

Minoxidil is an antihypertensive that acts mainly by causing direct peripheral vasodilatation of the arterioles. It produces effects on the cardiovascular system similar to those of hydralazine (p. 1401.2). Minoxidil is given orally for the treatment of severe hypertension unresponsive to standard therapy (p. 1251.1). When applied topically to the scalp minoxidil may stimulate hair growth to a limited extent and is used in the treatment of alopecia.

In the treatment of **hypertension** minoxidil is given with a beta blocker, or with methyldopa, to diminish the cardiac-accelerating effects, and with a diuretic, usually a loop diuretic, to control oedema. After a single oral dose, the maximum hypotensive effect usually occurs after 2 to 8 hours, although the full effects may not occur until after 3 to 7 days of continuous treatment. An initial dose of 5 mg of minoxidil daily (or 2.5 mg daily in the elderly) is gradually increased at intervals of not less than 3 days to 40 or 50 mg daily according to response; in exceptional circumstances up to 100 mg daily has been given. If more rapid control of blood pressure is required, dosage increments of 5 mg may be made every 6 hours with careful monitoring. The daily dose may be given as a single dose or in 2 divided doses.

For doses in children, see below.

Reduced doses may be required in patients with renal impairment (see below).

In the treatment of **alopecia androgenetica** (male pattern baldness) 1 mL of a 2% solution or gel or 5% solution of minoxidil is applied twice daily to the scalp. The 5% solution is not recommended for women.

Administration in children. Minoxidil may be used in children aged 12 years and under to treat severe hypertension unresponsive to standard therapy. The initial oral dose is 200 micrograms/kg daily in 1 or 2 divided doses, increased according to response by 100 to 200 micrograms/kg increments at intervals of not less than 3 days to a maximum daily dose of 1 mg/kg or 50 mg.

Administration in renal impairment. A study of the pharmacokinetics of minoxidil in patients with varying degrees

of renal impairment found that the non-renal clearance was also impaired as renal function worsened.[1] Substantial accumulation of minoxidil might occur in these patients during multiple-dose therapy. It was advised that minoxidil be started with smaller doses or at longer dosage intervals in patients with renal impairment.

1. Halstenson CE, *et al.* Disposition of minoxidil in patients with various degrees of renal function. *J Clin Pharmacol* 1989; 29: 798–802.

Alopecia. Minoxidil is used topically to stimulate hair growth in alopecia (p. 1682.3), although its mechanism of action is poorly understood.[1] Increases in pigmented non-vellus hair may be due to thickening and pigmentation of existing vellus rather than new growth.[2] Measurement over 96 weeks showed[3] that minoxidil in solutions of 2 or 5% had a greater effect on hair weight than number of hairs in men with androgenetic alopecia (male-pattern baldness) with the 5% solution being more effective; 24 weeks after treatment was stopped both values had returned to baseline. Another study[4] also showed that 5% minoxidil had a greater effect than 2%, and produced an earlier response. However, 5% minoxidil has been found[5] less effective than oral finasteride. Even with continued use there is a waning of effect with minoxidil.[6,7] It may be more effective in retarding the progression of male-pattern baldness than in reversing it,[2] and users are advised to abandon treatment if there is insufficient benefit after a year.[8]

Minoxidil has also been used in women with female pattern hair loss,[9] and as with men the 5% solution has been found[10] more effective than the 2%. In women with no evidence of biochemical hyperandrogenism minoxidil 2% was more effective[11] than oral cyproterone; where there was such evidence, cyproterone was superior.

Topical minoxidil has been shown to be safe in a large prospective study[12] of men and women with androgenetic alopecia.

Minoxidil appeared to have no beneficial effect on alopecia areata,[13] although one study indicated that topical minoxidil with 0.5% dithranol cream was more effective than either treatment alone.[14]

1. Messenger AG, Rundegren J. Minoxidil: mechanisms of action on hair growth. *Br J Dermatol* 2004; 150: 186–94.
2. Katz HI. Topical minoxidil: review of efficacy and safety. *Cutis* 1989; 43: 94–8.
3. Price VH, *et al.* Changes in hair weight and hair count in men with androgenetic alopecia, after application of 5% and 2% topical minoxidil, placebo, or no treatment. *J Am Acad Dermatol* 1999; 41: 717–21.
4. Olsen EA, *et al.* A randomized clinical trial of 5% topical minoxidil versus 2% topical minoxidil and placebo in the treatment of androgenetic alopecia in men. *J Am Acad Dermatol* 2002; 47: 377–85.
5. Arca E, *et al.* An open, randomized, comparative study of oral finasteride and 5% topical minoxidil in male androgenetic alopecia. *Dermatology* 2004; 209: 117–25.
6. de Groot AC, *et al.* Minoxidil: hope for the bald? *Lancet* 1987; i: 1019–22.
7. Anonymous. Topical minoxidil does little for baldness. *Drug Ther Bull* 1989; 27: 74–5.
8. Shrank AB. Treating young men with hair loss. *BMJ* 1989; 298: 847–8.
9. Camacho-Martínez FM. Hair loss in women. *Semin Cutan Med Surg* 2009; 28: 19–32.
10. Lucky AW, *et al.* A randomized, placebo-controlled trial of 5% and 2% topical minoxidil solutions in the treatment of female pattern hair loss. *J Am Acad Dermatol* 2004; 50: 541–53.
11. Vexiau P, *et al.* Effects of minoxidil 2% vs. cyproterone acetate treatment on female androgenetic alopecia: a controlled, 12-month randomized trial. *Br J Dermatol* 2002; 146: 992–9.
12. Shapiro J. Safety of topical minoxidil solution: a one-year, prospective, observational study. *J Cutan Med Surg* 2003; 7: 322–9.
13. Anonymous. Topical minoxidil for baldness: a reappraisal. *Med Lett Drugs Ther* 1994; 36: 9–10.
14. Fiedler VC, *et al.* Treatment-resistant alopecia areata. *Arch Dermatol* 1990; 126: 756–9.

CHEMOTHERAPY-INDUCED ALOPECIA. Minoxidil 2% solution was applied daily to the scalp of a boy with acute lymphoblastic leukaemia whose hair had failed to regrow satisfactorily after intensive chemotherapy.[1] Almost normal hair growth, achieved over a 9-month period, was attributed to the use of minoxidil.

A small study[2] in women undergoing combination chemotherapy including doxorubicin found that topical minoxidil applied throughout therapy and for up to 4 months afterwards reduced the duration of alopecia by an average of 50 days.

Other methods for reducing chemotherapy-induced alopecia are described under the Treatment of Adverse Effects of Antineoplastics, p. 730.3.

1. Vickers MA, Barton CJ. Minoxidil induced hair growth after leukaemia treatment? *Arch Dis Child* 1995; 73: 184.
2. Duvic M, *et al.* A randomized trial of minoxidil in chemotherapy-induced alopecia. *J Am Acad Dermatol* 1996; 35: 74–8.

Adverse Effects and Treatment

Adverse effects commonly caused by minoxidil include reflex tachycardia, fluid retention accompanied by weight gain, oedema, and sometimes deterioration of existing heart failure and changes in the ECG. Hypertrichosis develops in up to 80% of patients within 3 to 6 weeks of the start of minoxidil therapy but is slowly reversible on stopping. Pericardial effusion, sometimes with associated tamponade, has been reported in about 3% of patients. Pericarditis may also occur. Minoxidil may aggravate or uncover angina pectoris. Other less frequent adverse effects include headache, nausea, gynaecomastia and breast tenderness, polymenorrhoea, allergic rashes, Stevens-Johnson syndrome, and thrombocytopenia.

Reflex tachycardia can be overcome by the use of a beta blocker, or alternatively methyldopa, and a diuretic (usually a loop diuretic) is used to reduce fluid retention. If excessive hypotension occurs, an intravenous infusion of sodium chloride 0.9% can be given to maintain the blood pressure. If a pressor agent is necessary, drugs such as adrenaline, which can aggravate tachycardia, should be avoided; phenylephrine, angiotensinamide, vasopressin, or dopamine may be given if there is evidence of inadequate perfusion of a vital organ.

Topical application of minoxidil may be associated with contact dermatitis, pruritus, local burning, and flushing; sufficient may be absorbed to produce systemic adverse effects. Changes in hair colour or texture may occur.

Effects on the eyes. Bilateral optic neuritis and retinitis occurred in a patient during treatment with minoxidil for hypertension after a renal transplant.[1] The patient was also taking prednisolone and azathioprine.

1. Gombos GM. Bilateral optic neuritis following minoxidil administration. *Ann Ophthalmol* 1983; 15: 259–61.

Effects on the hair. The hypertrichosis frequently associated with oral minoxidil makes it generally unsuitable for women. There have also been reports of changes in hair colour.[1] In addition a case has been reported of increased hair loss, followed by subsequent regrowth of differently-coloured hair.[2] Substantial hair loss occurred in a woman after withdrawal of minoxidil and she had to wear a wig.[3]

Severe hypertrichosis has also been reported in 5 of 56 women applying minoxidil 5% solution topically for androgenetic alopecia.[4] Facial, arm, and leg hypertrichosis were reported 2 to 3 months after starting treatment. Hypertrichosis had disappeared 5 months after stopping minoxidil.

1. Traub YM, *et al.* Treatment of severe hypertension with minoxidil. *Isr J Med Sci* 1975; 11: 991–8.
2. Ingles RM, Kahn T. Unusual hair changes with minoxidil therapy. *Int J Dermatol* 1983; 22: 120–2.
3. Kidwai BJ, George M. Hair loss with minoxidil withdrawal. *Lancet* 1992; 340: 609–10.
4. Peluso AM, *et al.* Diffuse hypertrichosis during treatment with 5% topical minoxidil. *Br J Dermatol* 1997; 136: 118–20.

Effects on skeletal muscle. A polymyalgia syndrome, manifesting as fatigue, anorexia, weight loss, and severe pain in the shoulders and pelvic girdle, was seen in 4 men using topical minoxidil.[1] All symptoms improved within 2 to 4 weeks of stopping the drug. In 2 of the patients rechallenge produced a recurrence of symptoms.

1. Colamarino R, *et al.* Polymyalgia and minoxidil. *Ann Intern Med* 1990; 113: 256–7.

Effects on the skin. Skin reactions to systemic minoxidil do not appear to be common. However, fatal toxic epidermal necrolysis has been associated with minoxidil,[1] and cases of classic Stevens-Johnson syndrome have also been reported.[2,3] Stevens-Johnson syndrome generally responds to withdrawal and corticosteroid therapy; in one case[2] subsequent rechallenge provoked a recurrence. In another patient an extensive erythematous weeping rash with lesions consistent with actinic keratosis also appeared to be due to minoxidil; bullous lesions recurred on re-exposure.[4] After topical application itching, scaling, flushing, and dermatitis have been the most common adverse effects; allergic contact dermatitis has been reported in rare instances.[5,6]

For other lesions associated with Kaposi's sarcoma and angioma, see Neoplasms, below, and for effects on the hair, see above.

1. Karaoui LR, Chahine-Chakhtoura C. Fatal toxic epidermal necrolysis associated with minoxidil. *Pharmacotherapy* 2009; 29: 460–7.
2. DiSantis DJ, Flanagan J. Minoxidil-induced Stevens-Johnson syndrome. *Arch Intern Med* 1981; 141: 1515.
3. Callen EC, *et al.* Stevens-Johnson syndrome associated with oral minoxidil: a case report. *J Nephrol* 2007; 20: 91–3.
4. Ackerman BH, *et al.* Pruritic rash with actinic keratosis and impending exfoliation in a patient with hypertension managed with minoxidil. *Drug Intell Clin Pharm* 1988; 22: 702–3.
5. Clissold SP, Heel RC. Topical minoxidil: a preliminary review of its pharmacodynamic properties and therapeutic efficacy in alopecia areata and alopecia androgenetica. *Drugs* 1987; 33: 107–22.
6. Rodríguez-Martín M, *et al.* Pustular allergic contact dermatitis from topical minoxidil 5%. *J Eur Acad Dermatol Venereol* 2007; 21: 701–2.

Neoplasms. Two haemorrhagic lesions with Kaposi's features appeared on the forehead, an unusual location for HIV-associated Kaposi's sarcoma, in an HIV-positive patient who had applied topical minoxidil there for 3 months.[1] In a healthy patient an angioma of the scalp developed after 2 months of topical minoxidil therapy. The patient had had a similar lesion as a baby. Minoxidil may induce angiogenesis or may stimulate endothelial cells, fibroblasts, and muscle cells to proliferate. Care should be taken when minoxidil is applied to the skin of people who are predisposed to neo-angiogenesis, or who are HIV-positive.

For other effects of minoxidil on the skin following topical application, see above.

1. Pavlovitch JH, *et al.* Angiogenesis and minoxidil. *Lancet* 1990; 336: 889.

Precautions

Minoxidil is contra-indicated in phaeochromocytoma. It should be used with caution after a recent myocardial infarction, and in patients with pulmonary hypertension, angina pectoris, chronic heart failure, and significant renal impairment.

Topical application of minoxidil should be restricted to the scalp; it should not be applied to inflamed scalp skin or areas affected by psoriasis, severe sunburn, or severe excoriations, because of the risk of increased absorption. Patients being treated for hypertension should be monitored if topical minoxidil is used concurrently.

AIDS. For recommendations that topical minoxidil should be used with caution in HIV-positive patients, see Neoplasms under Adverse Effects, above.

Breast feeding. Study[1] of a breast-feeding mother showed that minoxidil was rapidly distributed into breast milk, achieving similar concentrations to those in the maternal plasma. No adverse effects were seen in the infant after 2 months and the American Academy of Pediatrics considers[2] that minoxidil is therefore usually compatible with breast feeding.

1. Valdivieso A, *et al.* Minoxidil in breast milk. *Ann Intern Med* 1985; 102: 135.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/09/05)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies the dermatological form of minoxidil as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients. The oral form is not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pregnancy. There are reports of uneventful pregnancies that resulted in healthy infants when *oral* minoxidil was taken throughout pregnancy with either propranolol and furosemide[1] or metoprolol and prazosin,[2] although temporary hypertrichosis was seen in one infant.[2] However, multiple congenital abnormalities and hypertrichosis occurred in another infant whose mother took minoxidil, propranolol, and captopril throughout pregnancy,[3] and congenital cardiac abnormalities were fatal in an infant whose mother took minoxidil, methyldopa, hydralazine, furosemide, and phenobarbital.[3] Caudal agenesis requiring second-trimester termination occurred after *topical* maternal application of 2% minoxidil solution daily, 2 weeks of co-trimoxazole, and 1 week of erythromycin during pregnancy.[4] Multiple abnormalities were also detected in another fetus whose mother applied 2% minoxidil daily throughout pregnancy, but had taken no other medications except a single dose of paracetamol.[5]

1. Valdivieso A, *et al.* Minoxidil in breast milk. *Ann Intern Med* 1985; 102: 135.
2. Rosa FW, *et al.* Fetal minoxidil exposure. *Pediatrics* 1987; 80: 120.
3. Kaler SG, *et al.* Hypertrichosis and congenital anomalies associated with maternal use of minoxidil. *Pediatrics* 1987; 79: 434–6.
4. Rojansky N, *et al.* Extreme caudal agenesis. Possible drug-related etiology? *J Reprod Med* 2002; 47: 241–5.
5. Smorlesi C, *et al.* Topically applied minoxidil may cause fetal malformation: a case report. *Birth Defects Res A Clin Mol Teratol* 2003; 67: 997–1001.

Interactions

The antihypertensive effect of minoxidil may be enhanced by use of other hypotensive drugs. Severe orthostatic hypotension may occur if minoxidil and sympathetic blocking drugs such as guanethidine are given concurrently.

Topical minoxidil should not be used with other topical agents known to enhance absorption, such as corticosteroids, retinoids, or occlusive ointment bases.

Tretinoin. Percutaneous absorption of minoxidil is enhanced by tretinoin as a result of increased stratum corneum permeability.[1]

1. Ferry JJ, *et al.* Influence of tretinoin on the percutaneous absorption of minoxidil from an aqueous topical solution. *Clin Pharmacol Ther* 1990; 47: 439–46.

Pharmacokinetics

About 90% of an oral dose of minoxidil is absorbed from the gastrointestinal tract. The plasma half-life is about 4.2 hours although the haemodynamic effect may persist for up to 75 hours, presumably due to accumulation at its site of action. Minoxidil is not bound to plasma proteins. It is distributed into breast milk. Minoxidil is extensively metabolised by the liver. It requires sulfation to become active, but the major metabolite is a glucuronide conjugate. Minoxidil is excreted chiefly in the urine mainly in the form of metabolites. Minoxidil and its metabolites are dialysable, although the pharmacological effect is not reversed.

About 0.3 to 4.5% of a topical dose of minoxidil is absorbed from intact scalp.

References.
1. Pacifici GM, *et al.* Minoxidil sulphation in human liver and platelets: a study of interindividual variability. *Eur J Clin Pharmacol* 1993; 45: 337–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Anagen; Ivix; Locemix; Macbirs Minoxidil; Minoxile; Tricolocion; Tricoplus; Ylox; *Austral.*: Hair A-Gain; Hair Retreva; Loniten; Regaine; *Austria*: Loniten; Regaine; Rogaine; *Belg.*: Alopexy; Neoxidil; Regaine†; *Braz.*: Loniten; Regaine; *Canad.*: Apo-Gain; Hair Regrowth; Loniten; Minox; Rogaine; *Chile*: Alopek; Regaine†; Tricoxane; *China*: Da Fei Xin (达霏欣); Si Bi Shen (斯必申); Xue Rui (学瑞); *Cz.*: Neocapil; Regaine; *Denm.*: Regaine; *Fin.*: Recrea; Rogaine; *Fr.*: Alopexy; Alostil; Lonoten; Regaine†; Unipexil; *Ger.*: Alopexy; Lonolox; Regaine; *Gr.*: Axelan; Botafex; Dermolantyl; Dilaine; Ebersedin; Hairway; Hamarityl; Loniten; Lonoten; Lotorin; Minodril; Monoxidil; Neo-Pruristam; Nherea; Oxofenil; Regaine; Stemeral; Vius; *Hong Kong*: Hairgrow; Hargro†; Headway; Loniten†; Minoxi†; Regaine; Regro; Renew†; *Hung.*: Neocapil; Regaine; *India*: Coverit; Gromane; Hair 4 U; Hairex; Hygaine; Inoxi; Manexil; Minscalp; Mintop; Morr; Multigain; *Indon.*: Aloxid; Eminox; Regaine†; Regrou; *Irl.*: Loniten; Regaine; *Israel*: Alopexy; Hair-Treat; Hairgain; Minoxi; Noxidil; Regaine; *Ital.*: Aloxidil; Carexidil; Loniten; Minovital; Minoximen; Regaine; Tricoxidil; *Malaysia*: Apo-Gain; Headway†; Regaine; Regro; *Mex.*: Folcres; Regaine; *Neth.*: Alopexy†; Lonoten; Regaine; *Norw.*: Recrea; Rogaine†; *NZ*: Headway†; Loniten; Rogaine; *Philipp.*: Regroe; Relive; *Pol.*: Loxon; Piloxidil; Regaine; *Port.*: Biocrinal; Crinalsofex; Folcare; Hairtene†; Mantai; Minocalve; Minox; Neoxidil; Regaine; Tricovivax; Zeldilon; *Rus.*: Cosilon (Косилон); Regaine (Регейн); *S.Afr.*: Loniten; Regaine; *Singapore*: Growell; Loniten; Minoxi; Minoxitrim†; Regaine; Regro; *Spain*: Alopexy; Aloxidil; Carexidil†; Dinaxcinco; Dinaxil Capilar; Lacovin; Loniten; Regaine†; Regaxidil; *Swed.*: Recrea; Rogaine; *Switz.*: Alopexy; Loniten; Neocapil; Regaine; *Thai.*: Loniten; Manoxidil; Minodil; Minor; Modil; Noxidil; Nuhair; Regaine; Regrowth; Reten; SM; *Turk.*: Rogan; *UK*: Loniten; Regaine; *Ukr.*: Pilfud (Пилфуд); Regaine (Регейн)†; *USA*: Rogaine; *Venez.*: Guayaten; Topixidil; Zitoxil.

Pharmacopoeial Preparations
BP 2014: Minoxidil Scalp Application;
USP 36: Minoxidil Tablets; Minoxidil Topical Solution.

Mipomersen *(rINN)*

Mipomersen; Mipomersenum; Мипомерсен.
$C_{230}H_{305}N_{67}O_{122}P_{19}S_{19}$=7158.0
CAS — 1000120-98-8.
ATC — C10AX11.
ATC Vet — QC10AX11.
UNII — 9GJBS4GU0M.

Mipomersen Sodium *(USAN, rINNM)*

Isis-301012; Mipomersen sódico; Mipomersen Sodique; Natrii Mipomersenum; Натрий Мипомерсен.
$C_{230}H_{305}N_{67}Na_{19}O_{122}P_{19}S_{19}$=7594.8
CAS — 629167-92-6.
ATC — C10AX11.
ATC Vet — QC10AX11.
UNII — 18EAY4870E.

Uses and Administration

Mipomersen is an antisense oligonucleotide that inhibits apolipoprotein B synthesis. It is used, as an adjunct to other lipid regulating drugs and dietary modification, to reduce low-density lipoprotein (LDL)-cholesterol and other lipoproteins in patients with homozygous familial hypercholesterolaemia (see Hyperlipidaemias, p. 1248.1). Mipomersen sodium 200 mg is given by subcutaneous injection once weekly. If a dose is missed it should be given at least 3 days before the next weekly dose. The patient should be assessed after 6 months of treatment to determine whether the achieved reduction in LDL-cholesterol is sufficient to warrant ongoing therapy, when balanced against the risk of liver toxicity.

References.
1. Geisinger C, *et al.* Therapeutic potential of mipomersen in the management of familial hypercholesterolaemia. *Drugs* 2012; 72: 1445–55.
2. Visser ME, *et al.* Antisense oligonucleotides for the treatment of dyslipidaemia. *Eur Heart J* 2012; 33: 1451–8.
3. Stein EA, *et al.* Apolipoprotein B synthesis inhibition with mipomersen in heterozygous familial hypercholesterolemia: results of a randomized, double-blind, placebo-controlled trial to assess efficacy and safety as add-on therapy in patients with coronary artery disease. *Circulation* 2012; 126: 2283–92.
4. Hair P, *et al.* Mipomersen sodium: first global approval. *Drugs* 2013; 73: 487–93.

Adverse Effects and Precautions

Elevation of serum transaminases and hepatic fat accumulation occur in a significant proportion of patients given mipomersen. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin should be measured before starting treatment; ALT and AST should be monitored monthly during the first year of therapy and three-monthly thereafter. Mipomersen is contra-indicated in patients with moderate to severe hepatic impairment or active liver disease.

Flu-like symptoms, typically occurring within 2 days after a dose, and injection-site reactions are very common in patients given mipomersen. Other adverse effects include gastrointestinal disturbances, headache, and insomnia. Cardiovascular effects such as hypertension, angina, and palpitations have also been reported.

The EMA refused marketing authorisation for mipomersen in 2012, which was reconfirmed in 2013. There was uncertainty about the long-term cardiovascular safety of mipomersen, and concerns about hepatotoxicity and high rates of withdrawal from studies because of intolerance.

Effects on the liver. Hepatic steatosis occurred in the majority of patients given mipomersen in phase 3 studies for familial hypercholesterolaemia. This effect is inherent to the drug's mode of action, which results in impaired excretion of triglycerides and hence accumulation of fat in the liver. Steatosis is a risk factor for advanced liver disease including steatohepatitis and cirrhosis, although it has been suggested that the fat accumulation associated with mipomersen differs from that associated with these conditions. Follow-up of about 141 patients treated for more than 2 years found that hepatic fat content plateaued between 6 and 12 months, then decreased despite continuing mipomersen therapy. Nevertheless, safety data from large numbers of patients treated long term are lacking.[1]

The elevation of hepatic transaminases (mainly alanine aminotransferase; ALT), without elevation of bilirubin or jaundice, is a common adverse effect of mipomersen. It has been reported to be reversible despite continuing treatment, and might correlate with hepatic fat content.[1]

1. Sjouke B, *et al.* Is mipomersen ready for clinical implementation? A transatlantic dilemma. *Curr Opin Lipidol* 2013; 24: 301–6.

Pharmacokinetics

A peak plasma concentration of mipomersen is usually reached within 3 to 4 hours after subcutaneous injection, and the estimated bioavailability over a dose range of 50 to 400 mg ranges from 54 to 78%. Mipomersen is highly bound to plasma proteins and has a distribution plasma half-life of 2 to 5 hours. Steady state is usually achieved within 6 months with weekly dosing. Mipomersen is metabolised in tissues by endonucleases to form shorter oligonucleotides that are substrates for exonucleases, and both mipomersen and its metabolites are eliminated mainly in the urine. The elimination half-life of mipomersen after subcutaneous injection is about 1 to 2 months.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Kynamro.

Mivazerol *(rINN)*

Mivazérol; Mivazerolum; UCB-22073; Мивазерол.
α-Imidazol-4-yl-2,3-cresotamide.
$C_{11}H_{11}N_3O_2$=217.2
CAS — 125472-02-8.
UNII — W5P1SSA8KD.

Profile

Mivazerol is an alpha$_2$-adrenoceptor agonist that has been investigated for the prevention of perioperative complications resulting from myocardial ischaemia in patients with ischaemic heart disease undergoing non-cardiac surgery.

References.
1. Oliver MF, *et al.* Effect of mivazerol on perioperative cardiac complications during non-cardiac surgery in patients with coronary heart disease: the European Mivazerol Trial (EMIT). *Anesthesiology* 1999 91: 951–61.

Moexipril Hydrochloride

(BANM, USAN, rINNM)

CI-925; Hidrocloruro de moexipril; Moeksipril Hidroklorür; Moexipril, Chlorhydrate de; Moexipril, hidrocloruro de; Moexipril Hydrochloridum; RS-10085-197; SPM-925; Моэксиприла Гидрохлорид.
(3*S*-[2[*R**(*R**)],3*R**])-2-(2-[[1-(Ethoxycarbonyl)-3-phenylpropyl] amino]-1-oxopropyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinoline-carboxylic acid hydrochloride.
$C_{27}H_{34}N_2O_7$,HCl=535.0
CAS — 103775-10-6 (moexipril); 82586-52-5 (moexipril hydrochloride).
ATC — C09AA13.
ATC Vet — QC09AA13.
UNII — Q1UMG3UH45.

Uses and Administration

Moexipril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1).

Moexipril owes its activity to moexiprilat, to which it is converted after oral doses. The haemodynamic effects are seen about 1 hour after an oral dose and the maximum effect occurs after about 3 to 6 hours, although the full effect may not develop for 2 to 4 weeks during chronic dosing. Moexipril is given orally as the hydrochloride.

The usual initial dose of moexipril hydrochloride is 7.5 mg once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. An initial dose of 3.75 mg once daily, given under close medical supervision, is suggested for patients who are taking a *diuretic*; if possible the diuretic should be withdrawn 2 or 3 days before moexipril is started and resumed later if necessary. An initial dose of 3.75 mg once daily is also recommended for patients with renal or hepatic impairment and for the elderly.

The usual maintenance dose is 7.5 to 30 mg daily, which may be given in 2 divided doses if control is inadequate with a single dose.

Reviews.
1. Brogden RN, Wiseman LR. Moexipril: a review of its use in the management of essential hypertension. *Drugs* 1998; 55: 845–60.
2. Chrysant SG, Chrysant GS. Pharmacological and clinical profile of moexipril: a concise review. *J Clin Pharmacol* 2004; 44: 827–36.

Administration in renal impairment. In patients with renal impairment (creatinine clearance 40 mL/minute or less) an initial dose of moexipril hydrochloride 3.75 mg is given; in the USA it is required that the maximum dose in such patients should not exceed 15 mg daily.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies moexipril as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Moexipril acts as a prodrug of the diacid moexiprilat, its active metabolite. After oral doses moexipril is rapidly but incompletely absorbed and is metabolised to moexiprilat in the gastrointestinal mucosa and liver. Absorption is reduced in the presence of food. The bioavailability of moexiprilat is about 13% after oral doses of moexipril, and peak plasma concentrations of moexiprilat occur in about 1.5 hours. Both moexipril and moexiprilat are moderately bound to plasma proteins. Moexipril is excreted mainly in the urine as moexiprilat, unchanged drug, and other metabolites; some moexiprilat may also be excreted in the faeces. The functional elimination half-life of moexiprilat is about 12 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Moex; *Fr.*: Moex; *Ger.*: Pempress; *Gr.*: Tensotec; *Hong Kong*: Moex†; *Israel*: Perdix; *Ital.*: Femipres; *Mex.*: Renoprotec; *Philipp.*: Univasc; *Pol.*: Cardiotensin†; *Port.*: Tensotec†; *Rus.*: Моех (Моэкс); *S.Afr.*: Perdix†;

Turk.: Univasc; *UK*: Perdix; *Ukr.*: Moex (Моэкс); *USA*: Univasc.

Multi-ingredient Preparations. *Ger.*: Fempress Plus; *Ital.*: Enulid; Femipres Plus; *Philipp.*: Uniretic; *Rus.*: Moex Plus (Моэкс Плюс); *Turk.*: Uniretic; *USA*: Uniretic.

Molsidomine *(BAN, USAN, rINN)*

CAS-276; Molsidomiini; Molsidomin; Molsidomina; Molsidominum; Morsydomine; SIN-10; Молсидомин.

N-Ethoxycarbonyl-3-morpholinosydnonimine.

$C_9H_{14}N_4O_4$=242.2

CAS — 25717-80-0.

ATC — C01DX12.

ATC Vet — QC01DX12.

UNII — D46583G77X.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Molsidomine). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in anhydrous alcohol and in dichloromethane. A 1% solution in water has a pH of 5.5 to 7.5. Protect from light.

Profile

Molsidomine is a nitrovasodilator used in angina pectoris (p. 1254.3). It may also be used in heart failure (p. 1262.3) and after myocardial infarction (below).

Molsidomine is given in usual oral doses of 1 to 4 mg two to four times daily. Modified-release preparations are also available. It is also given intravenously in single doses of 2 to 4 mg and doses of 2 mg may be repeated at intervals of at least 2 hours if necessary; total doses of up to 40 mg daily have been given. Infusions may be given at a rate of up to 3 mg/hour.

Molsidomine is metabolised to linsidomine (p. 1420.3), an active metabolite.

Carcinogenicity. Molsidomine tends to degrade into morpholine (even when protected from the light), a compound considered potentially carcinogenic. This finding led to the suspension of marketing of one molsidomine formulation;[1] an earlier temporary suspension was related to evidence of carcinogenicity in some *animals*, although this has not been confirmed in humans.

1. Anonymous. Corvaton Tropfen. *Dtsch Apotheker Ztg* 1989; 129 (49): VI.

Myocardial infarction. Although intravenous nitrates (glyceryl trinitrate or sodium nitroprusside) may be used in the management of acute myocardial infarction (p. 1257.1), molsidomine and its active metabolite linsidomine (a nitric oxide donor) had no effect on mortality.[1]

1. European Study of Prevention of Infarct with Molsidomine (ESPRIM) Group. The ESPRIM trial: short-term treatment of acute myocardial infarction with molsidomine. *Lancet* 1994; 344: 91–7.

Pharmacokinetics. The pharmacokinetics of molsidomine have been reviewed.[1] Molsidomine is metabolised in the liver to linsidomine and other morpholine derivatives. Prolonged elimination half-lives of molsidomine and linsidomine due to reduced plasma clearance have been reported in patients with liver cirrhosis.[2]

1. Rosenkranz B, *et al.* Clinical pharmacokinetics of molsidomine. *Clin Pharmacokinet* 1996; 30: 372–84.
2. Spreux-Varoquaux O, *et al.* Pharmacokinetics of molsidomine and its active metabolite, linsidomine, in patients with liver cirrhosis. *Br J Clin Pharmacol* 1991; 32: 399–401.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Molsicor†; Molsidaine; *Austria*: Molsidolat; Molsihexal†; *Belg.*: Coruno; Corvaton; *Cz.*: Corvaton; Molsihexal; Molsiket; *Fr.*: Corvasal; *Ger.*: Corvaton†; Molsi-Puren†; Molsibeta; Molsigamma; Molsihexal†; molsiket; *Hung.*: Corvaton; *Ital.*: Corvalgan; Sidomol; *Rus.*: Corvamin (Корвамин); Corvaton (Корватон); Dilasidom (Диласидом); Sydnopharm (Сиднофарм); *Spain*: Corpea†; Molsidain; *Switz.*: Corvaton; *Turk.*: Molsicor; *Ukr.*: Dilasidom (Диласидом)†; Sydnopharm (Сиднофарм).

Multi-ingredient Preparations. *Ukr.*: Advocard (Адвокард).

Monteplase *(rINN)*

E-6010; Monteplasa; Monteplase; Monteplasum; Монтеплаза.

$C_{2569}H_{3896}N_{746}O_{783}S_{39}$=59010.2

CAS — 156616-23-8.

Profile

Monteplase is a thrombolytic related to alteplase (p. 1296.3) that is used in acute myocardial infarction (p. 1257.1) and pulmonary embolism (see Venous Thromboembolism, p. 1274.1). For acute myocardial infarction, the usual dose is 27 500 units/kg given by intravenous injection as soon as possible after the onset of symptoms. For pulmonary embolism, the usual dose is 13 750 units/kg to 27 500 units/kg.

References.

1. Kawai C, *et al.* A prospective, randomized, double-blind multicenter trial of a single bolus injection of the novel modified t-PA E6010 in the treatment of acute myocardial infarction: comparison with native t-PA. *J Am Coll Cardiol* 1997; 29: 1447–53.
2. Inoue T, *et al.* A new thrombolytic agent, monteplase, is independent of the plasminogen activator inhibitor in patients with acute myocardial infarction: initial results of the COmbining Monteplase with Angioplasty (COMA) trial. *Am Heart J* 2002; 144: E5.
3. Inoue T, *et al.* Long-term benefits of monteplase before coronary angioplasty in acute myocardial infarction. *Am J Cardiol* 2005; 95: 506–8.
4. Inoue T, *et al.* Therapeutic potential of monteplase in acute myocardial infarction. *Am J Cardiovasc Drugs* 2005; 5: 225–31.
5. Yamamoto T, *et al.* Thrombolysis with a novel modified tissue-type plasminogen activator, monteplase, combined with catheter-based treatment for major pulmonary embolism. *Circ J* 2009; 73: 106–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Cleactor.

Moracizine *(BAN, rINN)*

EN-313; Moracizina; Moracizinum; Moricizine (USAN); Морацизин.

Ethyl [10-(3-morpholinopropionyl)phenothiazin-2-yl]carbamate.

$C_{22}H_{25}N_3O_4S$=427.5

CAS — 31883-05-3.

ATC — C01BG01.

ATC Vet — QC01BG01.

UNII — 2GT1D0TMX1.

Moracizine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de moracizina; Moracizina, hidrocloruro de; Moracizine, Chlorhydrate de; Moracizinhydroklorid; Moracizini Hydrochloridum; Morasitsilnihydroklorid; Морацизина гидрохлорид.

$C_{22}H_{25}N_3O_4S$,HCl=464.0

CAS — 29560-58-5.

ATC — C01BG01.

ATC Vet — QC01BG01.

UNII — 71OK3Z1ESP.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Moricizine Hydrochloride). A white to off-white crystalline powder. Soluble in water and in alcohol. Store in airtight containers.

Uses and Administration

Moracizine is a phenothiazine compound that has class I antiarrhythmic activity (p. 1243.1) but does not readily fall into the subclasses a, b, or c. It has been given orally as the hydrochloride in the treatment of serious symptomatic ventricular arrhythmias.

Reviews.

1. Clyne CA, *et al.* Moricizine. *N Engl J Med* 1992; 327: 255–60.

Cardiac arrhythmias. Like other class I antiarrhythmics (see Cardiac Arrhythmias under Flecainide, p. 1383.2), moracizine has been associated with increased mortality when used prophylactically after myocardial infarction.[1] However, limited evidence suggested that it might be useful in some patients with supraventricular arrhythmias.[2,3]

1. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992; 327: 227–33.
2. Mehta AV, *et al.* Experience with moricizine HCl in children with supraventricular tachycardia. *Int J Cardiol* 1996; 57: 31–5.
3. Geller JC, *et al.* Efficacy and safety of moricizine in the maintenance of sinus rhythm in patients with recurrent atrial fibrillation. *Am J Cardiol* 2001; 87: 172–7.

Adverse Effects and Precautions

As for Flecainide Acetate, p. 1383.3.

Like other antiarrhythmics moracizine can provoke or worsen arrhythmias. This may range from an increase in the frequency of premature ventricular contractions to induction or worsening of ventricular tachycardia.

An increased mortality rate occurred when moracizine was tested in the control of asymptomatic ventricular arrhythmias in post-infarction patients (see Cardiac Arrhythmias under Uses and Administration, above).

Effects on body temperature. Fever with elevated creatine phosphokinase and hepatic transaminase concentrations was associated with moracizine in 2 patients.[1] The fever abated within 48 hours of stopping moracizine and recurred within 24 hours of rechallenge in both patients. Results suggested a similarity to the neuroleptic malignant syndrome that is associated with other phenothiazine derivatives.

1. Miura DS, *et al.* Ethmozine toxicity: fever of unknown origin. *J Clin Pharmacol* 1986; 26: 153–5.

Interactions

Use of moracizine with other antiarrhythmics or arrhythmogenic drugs may increase the incidence of cardiac arrhythmias. Moracizine undergoes metabolism in the liver and its activity may be influenced by other drugs affecting the enzymes responsible for its metabolism; it is itself an inducer of those enzymes and may thus affect the activity of other drugs.

Pharmacokinetics

Moracizine is readily and almost completely absorbed from the gastrointestinal tract. It undergoes significant first-pass hepatic metabolism so that the oral bioavailability is about 38%. Moracizine is extensively metabolised and some of its many metabolites may be active. It induces its own metabolism; the plasma elimination half-life is about 2 hours after multiple doses. Although plasma concentrations are reduced with multiple dosing, clinical response is not affected. It is about 95% bound to plasma proteins. Moracizine is distributed into breast milk. About 56% of a dose is excreted in the faeces and about 39% in the urine.

References.

1. Benedek IH, *et al.* Enzyme induction by moricizine: time course and extent in healthy subjects. *J Clin Pharmacol* 1994; 34: 167–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Etmozine (Этмозин).

Pharmacopoeial Preparations

USP 36: Moricizine Hydrochloride Tablets.

Moxisylyte Hydrochloride *(BANM, rINNM)*

Hidrocloruro de moxisilita; Moksisylyyttihydrokloridi; Moxisilita Clorhidrato; Moxisilita, hidrocloruro de; Moxisylyte, Chlorhydrate de; Moxisylythydrokloridi; Moxisylyti Hydrochloridum; Moxisylytum Hydrochloridum; Thymoxamine Hydrochloride; Моксизилита гидрохлорид.

4-(2-Dimethylaminoethoxy)-5-isopropyl-2-methylphenyl acetate hydrochloride.

$C_{16}H_{25}NO_3$,HCl=315.8

CAS — 54-32-0 (moxisylyte); 964-52-3 (moxisylyte hydrochloride).

ATC — C04AX10; G04BE06.

ATC Vet — QC04AX10; QG04BE06.

UNII — WK2KZM9V6X.

NOTE. MOX, formerly THY, is a code approved by the BP 2014 for use on single unit doses of eye drops containing moxisylyte hydrochloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Br.*

BP 2014: (Moxisylyte Hydrochloride). A white, odourless or almost odourless, crystalline powder. Freely soluble in water and in chloroform; soluble in alcohol; practically insoluble in ether and in petroleum spirit. A 5% solution in water has a pH of 4.5 to 5.5. Protect from light.

Uses and Administration

Moxisylyte is an alpha-adrenoceptor blocker with vasodilating activity. It is used orally in the treatment of peripheral vascular disorders (p. 1272.3) and has been self-administered by intracavernosal injection in erectile dysfunction (p. 2348.2).

Moxisylyte is given as the hydrochloride but the dose may be expressed in terms of the base. Moxisylyte hydrochloride 45.2 mg is equivalent to about 40 mg of moxisylyte.

In the management of **peripheral vascular disease**, the usual oral dose is the equivalent of 40 mg of moxisylyte four times daily increased if necessary to 80 mg four times daily. It should be withdrawn if there is no response in 2 weeks.

Moxisylyte has been used locally in the eye to reverse the mydriasis caused by phenylephrine and other sympathomimetics. It has also been used orally in benign prostatic hyperplasia, although such use has been associated with hepatotoxicity; the doses used in prostatic hyperplasia were generally higher than those in peripheral vascular disease.

Reviews.

1. Marquer C, Bressolle F. Moxisylyte: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in impotence. *Fundam Clin Pharmacol* 1998; 12: 377–87.

Adverse Effects

Moxisylyte hydrochloride may cause nausea, diarrhoea, headache, vertigo, flushing of the skin, dry mouth, and nasal congestion. Hepatotoxicity has been reported. Overdosage may cause hypotension.

Transient ptosis has occurred occasionally after ophthalmic application. Prolonged erections or priapism have occurred rarely after intracavernosal injection and systemic effects may also occur.

Effects on the liver. Hepatic adverse reactions with moxisylyte first appeared in France after its use in benign prostatic hyperplasia, a condition in which relatively high doses were used (up to 480 mg daily compared with up to 320 mg daily for peripheral vascular disease). The UK CSM subsequently received reports associated with lower doses.[1] Thirteen hepatic reactions, accounting for 17% of all reports of suspected adverse reactions to moxisylyte, had been received as of November 1993. These comprised 3 cases of hepatic function abnormalities, 3 of jaundice, 4 of cholestatic jaundice, 2 of hepatitis, and 1 of hepatitis with jaundice. In most cases the reaction occurred within 5 weeks of the start of treatment and resolved on drug withdrawal. In 9 cases the dosage of moxisylyte was known and varied from 80 to 320 mg daily with 7 patients receiving 160 mg or less daily.

1. CSM/MCA. Hepatic reactions with thymoxamine (Opilon). *Current Problems* 1993; 19: 11–12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20244566&RevisionSelectionMethod=LatestReleased (accessed 10/04/08)

Precautions

Moxisylyte hydrochloride should not be given to patients with active liver disease; monitoring of liver function is recommended, especially if therapy is prolonged or if high doses are being used. It should be given with care to patients with diabetes mellitus as it may theoretically decrease insulin requirements. Intracavernosal injection of moxisylyte is contra-indicated in patients with conditions that predispose to priapism.

Interactions

Moxisylyte may enhance the effects of antihypertensives and the hypotensive effect of moxisylyte may be enhanced by tricyclic antidepressants.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Carlytene; *Irl.*: Opilon†; *UK*: Opilon.

Pharmacopoeial Preparations
BP 2014: Moxisylyte Tablets.

Moxonidine *(BAN, USAN, rINN)*

BDF-5895; BDF-5896; BE-5895; LY-326869; Moksonidi; Moksonidiini; Moksonidin; Moksonidinas; Moxonid; Moxonidin; Moxonidina; Moxonidinum; Moxonidum; Моксонидин.
4-Chloro-5-(2-imidazolin-2-ylamino)-6-methoxy-2-methylpyrimidine.
$C_9H_{12}ClN_5O$=241.7
CAS — 75438-57-2.
ATC — C02AC05.
ATC Vet — QC02AC05.
UNII — CC6X0L40GW.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Moxonidine). A white or almost white powder. Very slightly soluble in water and in acetonitrile; slightly soluble in dichloromethane; sparingly soluble in methyl alcohol.

Uses and Administration

Moxonidine is a centrally acting antihypertensive structurally related to clonidine (p. 1339.1). It appears to act through stimulation of central imidazoline receptors to reduce sympathetic tone, and also has alpha$_2$-adrenoceptor agonist activity. It is used in the treatment of hypertension (p. 1251.1) and has also been investigated for heart failure (but see below).

In the treatment of hypertension, moxonidine is given orally in a usual initial dose of 200 micrograms once daily. The dose may be increased if necessary, after 3 weeks, to 400 micrograms daily as a single dose or in 2 divided doses, and after a further 3 weeks, to a maximum dose of 600 micrograms daily in 2 divided doses. The dose should be reduced in patients with renal impairment (see below).

References.

1. Chrisp P, Faulds D. Moxonidine: a review of its pharmacology, and therapeutic use in essential hypertension. *Drugs* 1992; 44: 993–1012.
2. Schachter M, *et al.* Safety and tolerability of moxonidine in the treatment of hypertension. *Drug Safety* 1998; 19: 191–203.
3. Bousquet P, Feldman J. Drugs acting on imidazoline receptors: a review of their pharmacology, their use in blood pressure control and their potential interest in cardioprotection. *Drugs* 1999; 58: 799–812.
4. Schachter M. Moxonidine. *Prescribers' J* 1999; 39: 113–17.
5. Fenton C, *et al.* Moxonidine: a review of its use in essential hypertension. *Drugs* 2006; 66: 477–96.

Administration in renal impairment. UK licensed product information states that in patients with moderate renal impairment (GFR 30 to 60 mL/minute) single doses of moxonidine should not exceed 200 micrograms and the daily dose should not exceed 400 micrograms; moxonidine should not be given in severe impairment (GFR less than 30 mL/minute).

Heart failure. Heart failure is usually treated with diuretics, ACE inhibitors, and beta blockers (see p. 1262.3). Beta blockers are thought to act by suppressing the sympathetic nervous system, which is activated in heart failure. Centrally-acting antihypertensives such as moxonidine also suppress sympathetic activation and might therefore have a role in heart failure. A study[1] in patients with heart failure found that moxonidine reduced plasma noradrenaline concentrations and increased left ventricular ejection fraction, but also led to an increase in adverse effects. A further study[2] was stopped early due to increased mortality in the group receiving moxonidine.

1. Swedberg K, *et al.* Effects of sustained-release moxonidine, an imidazoline agonist, on plasma norepinephrine in patients with chronic heart failure. *Circulation* 2002; 105: 1797–1803.
2. Cohn JN, *et al.* Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). *Eur J Heart Fail* 2003; 5: 659–67.

Adverse Effects and Treatment

Moxonidine has similar adverse effects to clonidine (p. 1341.2) but causes less sedation. The incidence of dry mouth may also be lower.

Precautions

Moxonidine should not be used in patients with conduction disorders, bradycardia, severe arrhythmias, severe heart failure, severe ischaemic heart disease, severe hepatic or renal impairment, or a history of angioedema. Licensed product information suggests that it should also be avoided in patients with intermittent claudication or Raynaud's disease, Parkinson's disease, epilepsy, glaucoma, and depression. Moxonidine is distributed into breast milk and should not be used during breast feeding.

Although rebound hypertension has not been reported after moxonidine withdrawal it should not be stopped abruptly but should be withdrawn gradually over 2 weeks. As for clonidine (p. 1341.3), if patients are also receiving a beta blocker, this should be stopped several days before moxonidine is withdrawn.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies moxonidine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The hypotensive effect of moxonidine may be enhanced by other antihypertensives and drugs that cause hypotension. The effect of sedatives and hypnotics, including benzodiazepines, may be enhanced by moxonidine.

Pharmacokinetics

Moxonidine is well absorbed when given orally and has a bioavailability of about 88%. Peak plasma concentrations occur 0.5 to 3 hours after an oral dose. It is excreted almost entirely in the urine as unchanged drug and metabolites; about 50 to 75% of an oral dose is excreted as unchanged drug. The mean plasma elimination half-life is 2 to 3 hours and is prolonged in renal impairment. Moxonidine is about 7% bound to plasma proteins. It is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Physiotens; ***Austria***: Moxonibene; Normohex; ***Belg.***: Moxon; ***Braz.***: Cynt; ***Chile***: Norcynt; ***Cz.***: Cynt; Moxogamma; Moxostad; Physiotens†; ***Denm.***: Moxonat; Physiotens†; ***Fin.***: Physiotens; ***Fr.***: Physiotens; ***Ger.***: Cynt; Moxobeta; Moxocard†; Moxogamma; Physiotens; ***Gr.***: Cynt; Fisiotens; Gilutensin; ***Hong Kong***: Physiotens†; ***Hung.***: Cynt; Moxogamma; Moxostad; Physiotens; ***Indon.***: Physiotens; ***Ital.***: Fisiotens; ***Malaysia***: Physiotens; ***Mex.***: Norcynt; ***Neth.***: Jacomox†; Moxamar; Moxavivt†; Moxoham†; Moxonur; Moxovasc†; ***Norw.***: Physiotens; ***Philipp.***: Physiotens; ***Pol.***: Moxogamma†; Physiotens; ***Port.***: Moxon; ***Rus.***: Cynt (Цинт); Moxonitex (Моксонитекс); Physiotens (Физиотенз); Tenzotran (Тензотран); ***S.Afr.***: Cynt; Moxotens; Physiotens; ***Singapore***: Physiotens†; ***Spain***: Moxon; ***Swed.***: Physiotens; ***Switz.***: Physiotens; ***Turk.***: Cynt; Physiotens; ***UK***: Physiotens; ***Ukr.***: Moxogamma (Моксогамма); Moxonid (Моксонид)†; Physiotens (Физиотенз).

Nadolol *(BAN, USAN, rINN)* ⊗

Nadololi; Nadololis; Nadololum; SQ-11725; Надолол.
(2*R*,3*S*)-5-(3-*tert*-Butylamino-2-hydroxypropoxy)-1,2,3,4-tetrahydronaphthalene-2,3-diol.
$C_{17}H_{27}NO_4$=309.4
CAS — 42200-33-9.
ATC — C07AA12.
ATC Vet — QC07AA12.
UNII — FEN504330V.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Nadolol). A white or almost white crystalline powder. Slightly soluble in water; freely soluble in alcohol; practically insoluble in acetone.

USP 36: (Nadolol). A white or off-white, practically odourless, crystalline powder. Soluble in water at pH 2; slightly soluble in water at pH 7 to 10; freely soluble in alcohol and in methyl alcohol; insoluble in acetone, in ether, in petroleum spirit, in trichloroethane, and in benzene; slightly soluble in chloroform, in dichloromethane, and in isopropyl alcohol.

Uses and Administration

Nadolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to lack intrinsic sympathomimetic and membrane-stabilising activity. Nadolol is given orally in the management of hypertension (p. 1251.1), angina pectoris (p. 1254.3), and cardiac arrhythmias (p. 1266.1). It is also used in the management of hyperthyroidism (p. 2332.2) and in the prophylactic treatment of migraine (p. 670.3).

In the treatment of **hypertension**, nadolol is usually given in an initial dose of 40 to 80 mg once daily, increased weekly according to response to 240 mg or more daily.

In **angina pectoris**, the usual initial dose is 40 mg once daily, increased weekly according to response to usual doses of up to 160 mg daily; some patients may require up to 240 mg daily. Doses of 40 to 160 mg once daily have also been given for **cardiac arrhythmias**.

Doses of 40 to 160 mg once daily are used in **migraine** prophylaxis.

As an adjunct in the treatment of **hyperthyroidism**, doses of 80 to 160 mg once daily have been given; most patients are reported to require the higher dose.

Patients with renal impairment may require a reduction in dose (see below).

Administration in renal impairment. Nadolol is excreted mainly in the urine and doses should be reduced in patients with renal impairment, usually by increasing the dosage interval. For patients with hypertension or angina pectoris, US licensed product information recommends the following dosage intervals, based on creatinine clearance (CC):

- CC between 31 and 50 mL/minute per 1.73 m^2: give every 24 to 36 hours
- CC between 10 and 30 mL/minute per 1.73 m^2: give every 24 to 48 hours
- CC less than 10 mL/minute per 1.73 m^2: give every 40 to 60 hours.

Variceal haemorrhage. References[1-7] to the use of nadolol, alone or with isosorbide mononitrate, in the management of variceal haemorrhage (p. 2563.1).

1. Merkel C, *et al.* Gruppo Triveneto per l'Ipertensione Portale. A placebo-controlled clinical trial of nadolol in the prophylaxis of growth of small esophageal varices in cirrhosis. *Gastroenterology* 2004; 127: 476–84.
2. Mann NS. Nadolol versus band ligation for prevention of variceal bleeding. *Gastrointest Endosc* 2004; 60: 1036–7.
3. de la Peña J, *et al.* Variceal ligation plus nadolol compared with ligation for prophylaxis of variceal rebleeding: a multicenter trial. *Hepatology* 2005; 41: 572–8.
4. Romero G, *et al.* Comparative study between nadolol and 5-isosorbide mononitrate vs. endoscopic band ligation plus sclerotherapy in the prevention of variceal rebleeding in cirrhotic patients: a randomized controlled trial. *Aliment Pharmacol Ther* 2006; 24: 601–11.
5. Wang HM, *et al.* Comparison of endoscopic variceal ligation and nadolol plus isosorbide-5-mononitrate in the prevention of first variceal bleeding in cirrhotic patients. *J Chin Med Assoc* 2006; 69: 453–60.
6. Villanueva C, *et al.* Clinical trial: a randomized controlled study on prevention of variceal rebleeding comparing nadolol + ligation vs. hepatic venous pressure gradient-guided pharmacological therapy. *Aliment Pharmacol Ther* 2009; 29: 397–408.
7. García-Pagán JC, *et al.* Spanish Variceal Bleeding Study Group. Nadolol plus isosorbide mononitrate alone or associated with band ligation in the prevention of recurrent bleeding: a multicentre randomised controlled trial. *Gut* 2009; 58: 1144–50.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Breast feeding. Concentrations of nadolol distributed into breast milk are higher than those in maternal plasma. In a study[1] in 12 normotensive women given nadolol 80 mg daily by mouth for 5 days, the mean nadolol concentration in milk for the 24 hours after the last dose was 357 nanograms/mL; the equivalent mean serum-nadolol concentration was only 77 nanograms/mL. It was calculated that a 5-kg infant would therefore ingest about 2 to 7% of an equivalent adult dose. No adverse effects have been seen in breast-fed infants whose mothers were given nadolol and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Devlin RG, *et al.* Nadolol in human serum and breast milk. *Br J Clin Pharmacol* 1981; **12**: 393–6.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Hypersensitivity. Hypersensitivity pneumonitis was associated with nadolol in a patient given the drug for migraine.[1] Symptoms improved when nadolol was withdrawn.

1. Levy MB, *et al.* Nadolol and hypersensitivity pneumonitis. *Ann Intern Med* 1986; **105**: 806–7.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Nadolol is incompletely absorbed from the gastrointestinal tract to give peak plasma concentrations about 3 or 4 hours after a dose. It has low lipid solubility. Nadolol is widely distributed and concentrations found in breast milk have been higher than those in serum. It is only about 30% bound to plasma proteins. It does not appear to be metabolised and is excreted mainly in the urine. The plasma half-life has been reported as ranging from about 12 to 24 hours. Nadolol is reported to be dialysable.

In 4 patients with mild hypertension given nadolol 2 mg orally or intravenously, the elimination half-life from plasma was an average of 10 to 12 hours (a range of 5.9 to 12.2 hours after intravenous doses, and a range of 9.6 to 14.2 hours after oral doses). Calculations based on urinary excretion and plasma concentration data suggested that about 33% was absorbed after oral dosage. There was evidence of biliary as well as urinary excretion since after intravenous dosage about 73% was excreted in urine and 23% in faeces. Nadolol did not appear to be metabolised.[1] In a similar study of therapeutic oral doses, terminal half-lives ranging from 14 to 17 hours were reported for nadolol 80 mg given as a single dose and the same dose daily in a multiple dosage regimen.[2]

1. Dreyfuss J, *et al.* Metabolic studies in patients with nadolol: oral and intravenous administration. *J Clin Pharmacol* 1977; **17**: 300–7.
2. Dreyfuss J, *et al.* Pharmacokinetics of nadolol, a beta-receptor antagonist: administration of therapeutic single- and multiple-dosage regimens to hypertensive patients. *J Clin Pharmacol* 1979; **19**: 712–20.

Children. The pharmacokinetics of nadolol given intravenously and orally were studied in six children aged 3 months to 14 years.[1] The elimination half-lives for the two oldest children aged 10 and 14 years were 7.3 and 15.7 hours, respectively. These values are similar to those reported for adults whereas in the children 22 months of age or younger, shorter half-lives of 3.2 to 4.3 hours were found. The shorter half-lives were probably a result of a reduction in the total apparent volume of distribution of nadolol in the youngest children. Elimination rates were similar after either intravenous or oral dosage.

1. Mehta AV, *et al.* Pharmacokinetics of nadolol in children with supraventricular tachycardia. *J Clin Pharmacol* 1992; **32**: 1023–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Corgard; *Belg.*: Corgard†; *Braz.*: Corgard; *Canad.*: Apo-Nadol; *Chile*: Corgard; *Fr.*: Corgard; *Gr.*: Corgard; *Ital.*: Corgard†; *Mex.*: Corgard; *NZ*: Corgard; *S.Afr.*: Corgard†; *Spain*: Solgol; *UK*: Corgard; *USA*: Corgard; *Venez.*: Corgard.

Multi-ingredient Preparations. *Gr.*: Corzide; *Mex.*: Corgaretic; *S. Afr.*: Corgaretic†; *USA*: Corzide.

Pharmacopoeial Preparations

USP 36: Nadolol and Bendroflumethiazide Tablets; Nadolol Tablets.

Nadroparin Calcium (BAN, rINN)

CY-216; CY-216D; Nadroparinkalsiumi; Nadroparin-Calcium; Nadroparin Kalsiyum; Nadroparin vápenatá sůl; Nadroparina cálcica; Nadroparine calcique; Nadroparin-kalcium; Nadroparinkalcium; Nadroparino kalcio druska; Nadroparinum Calcicum; Надропарин Кальций.

ATC — B01AB06.

ATC Vet — QB01AB06.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Nadroparin Calcium). It is prepared by nitrous acid depolymerisation of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-*O*-sulfo-2,5-anhydro-D-mannitol structure at the reducing end of their chain. The mass-average molecular mass ranges between 3600 and 5000, with a characteristic value of 4300. The mass percentage of chains lower than 2000 is not more than 15%. The degree of sulfation is about 2 per disaccharide unit.

The potency is not less than 95 units and not more than 130 units of anti-factor Xa activity per mg with reference to the dried substance, and the ratio of anti-factor Xa activity to anti-factor IIa (antithrombin) activity is between 2.5 and 4.0.

Profile

Nadroparin calcium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant properties. It is used in the treatment and prophylaxis of venous thromboembolism (p. 1274.1) and to prevent clotting during extracorporeal circulation. It is also used in the management of unstable angina (p. 1254.3).

Doses are expressed in terms of anti-factor Xa activity (anti-Xa units) although different values may be encountered in the literature depending upon the reference preparation used. For *prophylaxis* of **venous thromboembolism** during surgery, patients at moderate risk of thrombosis are given 2850 units of nadroparin calcium by subcutaneous injection daily for at least 7 days or until the patient is ambulant; the first dose is given 2 to 4 hours before the procedure. For patients at high risk of thrombosis the dose is adjusted according to body-weight. Usual doses are 38 units/kg 12 hours before surgery, 12 hours post-operatively and then daily until 3 days after the procedure; the dose is then increased by 50% to 57 units/kg daily. The total duration of treatment should be at least 10 days.

For the *treatment* of thromboembolism, nadroparin calcium is given in a dose of 171 units/kg once daily. For patients at increased risk of bleeding, the total daily dose may be given in 2 divided doses.

For prevention of clotting in the extracorporeal circulation during **haemodialysis** sessions lasting less than 4 hours, a single dose of nadroparin calcium is given into the arterial line of the circuit at the beginning of the dialysis session. The usual dose is 2850 units for patients weighing less than 50 kg, 3800 units for patients weighing 50 to 69 kg, and 5700 units for patients weighing 70 kg or more. Doses should be halved in patients at high risk of haemorrhage.

In the management of unstable **angina**, nadroparin calcium is given in an initial intravenous injection of 86 units/kg, followed by a subcutaneous dose of 86 units/kg every 12 hours for about 6 days. Low-dose aspirin should also be given.

Elimination of nadroparin is prolonged in renal impairment, and doses may need to be reduced in moderate or severe impairment.

References.

1. Barradell LB, Buckley MM. Nadroparin calcium: a review of its pharmacology and clinical applications in the prevention and treatment of thromboembolic disorders. *Drugs* 1992; **44**: 858–88.
2. Davis R, Faulds D. Nadroparin calcium: a review of its pharmacology and clinical use in the prevention and treatment of thromboembolic disorders. *Drugs Aging* 1997; **10**: 299–322.
3. Egger B, *et al.* Efficacy and safety of weight-adapted nadroparin calcium vs. heparin sodium in prevention of clinically evident thromboembolic complications in 1,190 general surgical patients. *Dig Surg* 2000; **17**: 602–9.
4. Makatsaria AD, *et al.* Use of the low-molecular-weight heparin nadroparin during pregnancy: a review. *Curr Med Res Opin* 2003; **19**: 4–12.
5. Simonneau G, *et al.* FX140 Study Investigators. A randomized study comparing the efficacy and safety of nadroparin 2850 IU (0.3 mL) vs. enoxaparin 4000 IU (40 mg) in the prevention of venous thromboembolism after colorectal surgery for cancer. *J Thromb Haemost* 2006; **4**: 1693–1700.
6. van Ommen CH, *et al.* Nadroparin therapy in pediatric patients with venous thromboembolic disease. *J Pediatr Hematol Oncol* 2008; **30**: 230–4.
7. Agnelli G, *et al.* PROTECHT Investigators. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. *Lancet Oncol* 2009; **10**: 943–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nadroparin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fraxiparine; *Austria*: Fraxiparin; *Belg.*: Fraxiparine; Fraxodi; *Braz.*: Fraxiparina; *Canad.*: Fraxiparine; *Chile*: Fraxiparine; *China*: Fraxiparine (速碧林); Fraxodi (速碧劲); *Cz.*: Fraxiparine; *Fr.*: Fraxiparine; Fraxodi; *Ger.*: Fraxiparin; Fraxodi; *Gr.*: Fraxiparine; *Hong Kong*: Fraxiparine; *Hung.*: Fraxiparine; Fraxodi; *India*: Cardioparin; Fraxiparine; Fraxodi; Nadrohep; *Indon.*: Fraxiparine; *Israel*: Fraxiparine; *Ital.*: Fraxiparina; Fraxodi; Seledie; Seleparina; *Malaysia*: Fraxiparine; *Mex.*: Fraxiparine; Fraxodi†; *Neth.*: Fraxiparine; Fraxodi; *Philipp.*: Fraxiparine; *Pol.*: Fraxiparine; Fraxodi; *Port.*: Fraxiparina; Fraxodi; *Rus.*: Fraxiparine (Фраксипарин); *S.Afr.*: Fraxiparine; *Singapore*: Fraxiparine; *Spain*: Fraxiparina; *Switz.*: Fraxiforte; Fraxiparine; *Thai.*: Fraxiparine; *Turk.*: Fraxiparine; Fraxodi; *Ukr.*: Fraxiparine (Фраксипарин); *Venez.*: Praxiparina.

Naftidrofuryl Oxalate (BANM, rINNM)

EU-1806; LS-121; Nafronyl Oxalate (USAN); Nafronyl Oxalate; Naftidrofuril-hidrogén-oxalát; Naftidrofurilio-vandenilio oksalatas; Naftidrofurilo, oxalato de; Naftidrofuryl Hydrogen Oxalate; Naftidrofuryl, hydrogénooxalate de; Naftidrofuryl, Oxalate de; Naftidrofurylhydrogenoxalat; Naftidrofuryli Hydrogenooxalas; Naftidrofuryli Oxalas; Naftidrofuryl-oxalát; Naftidrofurylvätеoxalat; Naftidrofuryylivetyoksalaatti; Oxalato de naftidrofurilo; Нафтидрофурила Оксалат.

2-Diethylaminoethyl 3-(1-naphthyl)-2-tetrahydrofurfurylpropionate hydrogen oxalate.

$C_{24}H_{33}NO_3.C_2H_2O_4$=473.6

CAS — 31329-57-4 (naftidrofuryl); 3200-06-4 (naftidrofuryl oxalate).

ATC — C04AX21.

ATC Vet — QC04AX21.

UNII — 5ADB8D9388.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Naftidrofuryl Hydrogen Oxalate; Naftidrofuryl Oxalate BP 2014). A white or almost white powder. Freely soluble in water; freely soluble or soluble in alcohol; slightly or sparingly soluble in acetone.

Uses and Administration

Naftidrofuryl oxalate is used as a vasodilator in the treatment of peripheral (p. 1272.3) and cerebral vascular disorders (p. 1269.2). It is also claimed to enhance cellular oxidative capacity thereby protecting cells against the results of ischaemia.

Naftidrofuryl oxalate is given orally in usual doses of 100 to 200 mg three times daily for peripheral vascular disorders and 100 mg three times daily for cerebrovascular disorders.

Naftidrofuryl oxalate has also been given parenterally. However, intravenous use has been associated with serious adverse effects (see below) and intravenous preparations have been withdrawn.

References.

1. De Backer TLM, *et al.* Naftidrofuryl for intermittent claudication. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 08/05/08).

Adverse Effects

Naftidrofuryl oxalate given orally may cause nausea and epigastric pain. Rash has been reported occasionally. Hepatitis or hepatic failure has occurred rarely. Convulsions and depression of cardiac conduction may occur after overdosage. After intravenous use cardiac arrhythmias, hypotension, and convulsions have been reported and intravenous preparations have been withdrawn from the market (see below).

In early 1995 the UK CSM published details of adverse reactions to naftidrofuryl.[1] After parenteral doses of naftidrofuryl 47 reports of 79 reactions had been received, the most serious consequences being 9 cases of cardiac arrhythmias, 3 of convulsions, and 2 of hypotension. It was also noted that 2 fatal cases of cardiac arrest had occurred in Germany after bolus intravenous doses and it was stressed that the drug must not be given as a bolus but as a slow intravenous infusion. Additionally, 16 reports, including one fatality, of hepatitis or hepatic failure associated with oral naftidrofuryl had been received although this appeared to be a rare reaction.

Later in 1995, after a review conducted in the UK and Europe, it was announced by the CSM that intravenous naftidrofuryl was to be withdrawn.[2] It was considered that the risks of cardiac and neurological toxicity outweighed the benefits of intravenous dosage in peripheral vascular

disease. The oral form of naftidrofuryl would remain available.

1. CSM/MCA. Adverse reactions with naftidrofuryl (Praxilene). *Current Problems* 1995; 21: 2. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 08/05/08)
2. CSM/MCA. Withdrawal of naftidrofuryl infusion (Praxilene Forte). *Current Problems* 1995; 21: 7. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 08/05/08)

Effects on the kidneys. Calcium oxalate crystals in the renal tubules of 2 patients with acute renal failure[1] were associated with the high amounts of oxalate they had received when naftidrofuryl oxalate was given intravenously.

1. Moesch C, *et al.* Renal intratubular crystallisation of calcium oxalate and naftidrofuryl oxalate. *Lancet* 1991; 338: 1219–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Dusodril; ***Belg.***: Praxilene; ***Braz.***: Iridux; ***Cz.***: Enelbin; ***Fr.***: Di-Actane; Gevatran; Naftilux; Praxilene; ***Ger.***: Dusodril; Nafti; Naftilong†; ***Gr.***: Praxilene; ***Hong Kong***: Praxilene; ***Hung.***: Naftilong; ***Indon.***: Frilix; Nafoxal; Praxilene; Vascuprax; ***Irl.***: Praxilene; ***Ital.***: Praxilene; ***Mex.***: Iridus; ***Philipp.***: Praxilene; ***Port.***: Praxilene; ***Rus.***: Dusopharm (Дузофарм); Enelbin (Энелбин); ***Singapore***: Praxilene; ***Spain***: Praxilene; ***Switz.***: Praxilene; Sodipryl retard; ***Thai.***: Praxilene; ***UK***: Praxilene; ***Venez.***: Iridus.

Pharmacopoeial Preparations
BP 2014: Naftidrofuryl Capsules.

Natriuretic Peptides ⊗

Péptidos natriuréticos; Натрийуретические Пептиды.

Profile

Natriuretic peptides are endogenous substances that possess diuretic, natriuretic, and vasodilator properties. Three types are known. *Atrial natriuretic peptide* (ANP), also known as atrial natriuretic factor (ANF), atriopeptin, auriculin, or cardionatrin, is produced mainly in the cardiac atria, although another form, ularitide (urodilatin), is produced in the kidney. *Brain natriuretic peptide* (BNP, B-type natriuretic peptide) was originally isolated from brain tissue but is now known to be mainly produced by the cardiac ventricles. *C-type natriuretic peptide* (CNP) is produced by the endothelium and appears to act locally as a vasodilator but has little natriuretic effect.

Natriuretic peptides have an important physiological role in fluid and electrolyte homoeostasis and in the regulation of blood pressure, and they interact closely with other complex systems such as the renin-angiotensin-aldosterone cascade. Plasma concentrations of atrial natriuretic peptide and brain natriuretic peptide are altered in some pathological states and have been used as indicators of cardiac function. Natriuretic peptides that have been investigated for therapeutic use include anaritide, a synthetic form of atrial natriuretic peptide, and ularitide; both have been studied in acute renal failure, and ularitide has also been studied in heart failure. Recombinant forms of atrial natriuretic peptide (carperitide, p. 1332.3) and brain natriuretic peptide (nesiritide, below) are used in the management of acute heart failure.

The currently available natriuretic peptides have short half-lives and have to be given parenterally. Other approaches to manipulating their effects have been investigated, including the use of atriopeptidase inhibitors (neutral endopeptidase inhibitors; neutral metalloendopeptidase inhibitors), such as candoxatrilat and ecadotril (sinorphan) to prolong the half-life of endogenous atrial natriuretic peptide. Compounds such as omapatrilat (p. 1460.1) that inhibit both neutral endopeptidase and angiotensin-converting enzyme are also being studied.

References.

1. Tan ACITL, *et al.* Atrial natriuretic peptide: an overview of clinical pharmacology and pharmacokinetics. *Clin Pharmacokinet* 1993; 24: 28–45.
2. Richards AM. The renin-angiotensin-aldosterone system and the cardiac natriuretic peptides. *Heart* 1996; 76 (suppl 3): 36–44.
3. Forssmann W, *et al.* The renal urodilatin system: clinical implications. *Cardiovasc Res* 2001; 51: 450–62.
4. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart* 2006; 92: 843–9.
5. Mitrovic V, *et al.* Haemodynamic and clinical effects of ularitide in decompensated heart failure. *Eur Heart J* 2006; 27: 2823–32.
6. Lüss H, *et al.* Renal effects of ularitide in patients with decompensated heart failure. *Am Heart J* 2008; 155: 1012.e1–8.
7. Rubattu S, *et al.* Natriuretic peptides: an update on bioactivity, potential therapeutic use, and implication in cardiovascular diseases. *Am J Hypertens* 2008; 21: 733–41.
8. Jankowski M. B-type natriuretic peptide for diagnosis and therapy. *Recent Pat Cardiovasc Drug Discov* 2008; 3: 77–83.
9. Das BB, Solinger R. Role of natriuretic peptide family in cardiovascular medicine. *Cardiovasc Hematol Agents Med Chem* 2009; 7: 29–42.
10. Shimada M, *et al.* Role of natriuretic peptides in cardiovascular surgery. *Expert Rev Cardiovasc Ther* 2009; 7: 515–19.
11. Nigwekar SU, *et al.* Atrial natriuretic peptide for preventing and treating acute kidney injury. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 26/10/09).
12. Krupička J, *et al.* Natriuretic peptides — physiology, pathophysiology and clinical use in heart failure. *Physiol Res* 2009; 58: 171–7.

Nebivolol *(BAN, USAN, rINN)* ⊗

Narbivolol; Nébivolol; Nebivololi; Nebivololum; R-65824; Небиволол.

(1*RS*,1′*RS*)-1,1′-[(2*RS*,2′*SR*)-Bis(6-fluorochroman-2-yl)]-2,2′-iminodiethanol.

$C_{22}H_{25}F_2NO_4$=405.4

CAS — 99200-09-6; 118457-14-0.

ATC — C07AB12.

ATC Vet — QC07AB12.

UNII — 030Y90569U.

Nebivolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Hidrocloruro de nebivolol; Nébivolol, Chlorhydrate de; Nebivolol, hidrocloruro de; Nebivololi Hydrochloridum; R-067555; R-67555; Небиволола Гидрохлорид.

$C_{22}H_{25}F_2NO_4$.HCl=441.9

CAS — 169293-50-9; 152520-56-4.

ATC — C07AB12.

ATC Vet — QC07AB12.

UNII — JG534J7L9I.

Uses and Administration

Nebivolol is a cardioselective beta blocker (p. 1316.3). It has vasodilating activity, which appears to be due to a direct action on the endothelium, possibly involving nitric oxide release. It is reported to lack intrinsic sympathomimetic and membrane-stabilising activity.

Nebivolol is used in the management of hypertension (p. 1251.1), and as an adjunct to standard therapy in patients aged 70 years and older with stable chronic heart failure (p. 1262.3). It is given orally as the hydrochloride although doses are expressed in terms of the base; 5.45 mg of nebivolol hydrochloride is equivalent to about 5 mg of base.

In **hypertension** the usual initial dose of nebivolol is 5 mg once daily. US licensed product information allows the dose to be increased, if necessary, at intervals of 2 weeks, to a maximum dose of 40 mg once daily. Dosage reduction may be necessary in the elderly and in patients with hepatic or renal impairment (see below).

In **heart failure** the initial dose of nebivolol is 1.25 mg once daily. If tolerated, the dose should be doubled every 1 to 2 weeks up to a maximum of 10 mg once daily.

Reviews.

1. Moen MD, Wagstaff AJ. Nebivolol: a review of its use in the management of hypertension and chronic heart failure. *Drugs* 2006; 66: 1389–1409.
2. Veverka A, *et al.* Nebivolol: a third-generation β-adrenergic blocker. *Ann Pharmacother* 2006; 40: 1353–60.
3. Agabiti Rosei E, Rizzoni D. Metabolic profile of nebivolol, a β-adrenoceptor antagonist with unique characteristics. *Drugs* 2007; 67: 1097–1107.
4. Veverka A, Salinas JL. Nebivolol in the treatment of chronic heart failure. *Vasc Health Risk Manag* 2007; 3: 647–54.
5. Prisant LM. Nebivolol: pharmacologic profile of an ultraselective, vasodilatory β_1-blocker. *J Clin Pharmacol* 2008; 48: 225–39.
6. Cheng JW. Nebivolol: a third-generation beta-blocker for hypertension. *Clin Ther* 2009; 31: 447–62.
7. Münzel T, Gori T. Nebivolol: the somewhat-different beta-adrenergic receptor blocker. *J Am Coll Cardiol* 2009; 54: 1491–9.

Administration in the elderly. Some UK licensed product information state that, for hypertension, patients over 65 years of age should be given an initial dose of 2.5 mg of nebivolol once daily, increased to 5 mg once daily if required.

Administration in hepatic impairment. UK licensed product information contra-indicates the use of nebivolol in patients with hepatic impairment. In the USA, licensed product information also contra-indicates nebivolol in severe hepatic impairment (Child-Pugh higher than class B) but patients with moderate hepatic impairment may be given nebivolol for hypertension in an initial oral dose of 2.5 mg once daily, increased with caution if required.

Administration in renal impairment. UK licensed product information states that in hypertension the initial dose of nebivolol should be reduced to 2.5 mg once daily in patients with renal impairment, increased to 5 mg once daily for maintenance if required. US licensed product information similarly recommends an initial dose of 2.5 mg once daily in patients with severe renal impairment (creatinine clearance below 30 mL/minute); the dose may be increased cautiously if required.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Nebivolol is rapidly absorbed after oral doses. It is extensively metabolised in the liver by alicyclic and aromatic hydroxylation, *N*-dealkylation, and glucuronidation; the hydroxy metabolites are reported to be active. The rate of aromatic hydroxylation by cytochrome P450 isoenzyme CYP2D6 is subject to genetic polymorphism, and bioavailability and half-life vary widely. In fast metabolisers the elimination half-life of nebivolol is about 10 hours and that of the hydroxy metabolites is about 24 hours. Peak plasma concentrations of unchanged drug plus active metabolites are 1.3 to 1.4 times higher in slow metabolisers and the half-lives of nebivolol and its hydroxy metabolites are prolonged.

Nebivolol is about 98% bound to plasma proteins. It has high lipid solubility. It is excreted in the urine and faeces, almost entirely as metabolites. Nebivolol is distributed into breast milk in *animals*.

Metabolism. Despite wide variations in nebivolol bioavailability, peak plasma concentrations, and elimination half-life in 37 patients identified as either poor or extensive metabolisers of CYP2D6, metaboliser status did not significantly affect the nature and frequency of adverse effects nor the clinical response during treatment of essential hypertension.[1]

1. Lefebvre J, *et al.* The influence of CYP2D6 phenotype on the clinical response of nebivolol in patients with essential hypertension. *Br J Clin Pharmacol* 2007; 63: 575–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Nabila; Nebilet; Syncrocor; ***Austral.***: Nebilet; ***Austria***: Hypoloc; Nebilan; Nomexor; ***Belg.***: Hypoloc; Nobiten; ***Braz.***: Nebilet; ***Chile***: Anfibol; Nebilet; Pertium; ***Cz.***: Ezocem; Nebilan†; Nebilet; Nebinorm; Nebiscal; Nebispes†; Nebitrix; ***Denm.***: Dublock; Hypoloc; Lobivon; Nebicon; Nebidelta; Nebithan; ***Fin.***: Hypoloc; Nebilet; ***Fr.***: Nebilox; Temerit; ***Ger.***: Nebilet; ***Gr.***: Bivol; Dublock; Hypoloc; Lobibeta; Lobivon; Nebicur; Noviblock; Nozac; ***Hung.***: Esteban; Ezocem; Nebacop; Nebaletor; Nebibeta; Nebilet; Nebispes; Nebivep; Nebivogen; Nevotens; ***India***: Endolol; Nebest; Nebicard; Nebilol; Nebilong; Nebimac; Nebinex; Nebipil; Nebistar; Nebiten; Nebivas; Nebula; Nevol; Niavas; Nodon; Nubeta; NYFE; ***Irl.***: Nebilet; Nebimel; Nebol; Nebtev†; Nelet; ***Ital.***: Lobivon; Nebilox; ***Malaysia***: Nebilet; ***Neth.***: Ebivol†; Hypoloc; Lobivon; Nebilet; Nebiloc; Nebilostad; ***Philipp.***: Nebicar; Nebicard; ***Pol.***: Ebivol; Ezocem; Nebicard; Nebilenin; Nebilet; Nebinad; Nebispes; Nebitrix; Nebivor; Nedal; ***Port.***: Blokat; Hypoloc; Nebilet; Nebimarin; ***Rus.***: Binelol (Бинелол); Nebilet (Небилет); Nebivator (Небиватор); ***S.Afr.***: Nebilet; ***Singapore***: Nebilet; ***Spain***: Lobivon; Silostar; ***Swed.***: Hypoloc; ***Switz.***: Nebilet; ***Thai.***: Nebilet; ***Turk.***: Nebinorm; Nexivol; Vasoxen; ***UK***: Nebilet; ***Ukr.***: Nebilet (Небилет); Nebilong (Небилонг); Nebival (Небивал); ***USA***: Bystolic; ***Venez.***: Nebilet.

Multi-ingredient Preparations. ***Austria***: Nomexor plus HCT; ***Belg.***: Hyporetic Nobiretic; ***Cz.***: Nebilet Plus H; ***Denm.***: Nebilet Comp†; ***Fin.***: Hypoloc Comp; ***Fr.***: Conebilox; Temeritduo; ***Gr.***: Hypoloc Plus; Lobivon-Plus; ***India***: Amlopres-NB; Amlovas-SN; Nebest-H; Nebicard-H; Nebicard-SM; Nebicard-V; Nebilol-H; Nebilong-AM; Nebilong-H; Nebimac-H; Nebinex-AM; Nebipril-SA; Nebistar-SA; Nebiten-H; Nebivas-H; Nebivas-SA; Nevol-H; Niavas-D; Nodon-AM; Nodon-H; Nubeta-H; Nubeta-SM; NYFE-SA; ***Irl.***: Nebilet Plus; ***Neth.***: Hyporetic; Lobiretic; Nebiretic; ***Spain***: Lobivon Plus; Silostar Plus; ***Switz.***: Nebilet Plus.

Nesiritide Citrate *(USAN, rINNM)* ⊗

Citrato de nesiritida; Nésiritide, Citrate de; Nesiritidi Citras; Nesitirida, citrato de; Незиритида Цитрат.

$C_{149}H_{244}N_{50}O_{62}S_4xC_6H_8O_7$

CAS — 124584-08-3 (nesiritide); 189032-40-4 (nesiritide citrate).

ATC — C01DX19.

ATC Vet — QC01DX19.

UNII — EL5U85UKD2.

Incompatibility. The manufacturer states that nesiritide injection is physically and/or chemically incompatible with heparin, insulin, sodium etacrynate, bumetanide, enalaprilat, hydralazine, furosemide, and the preservative sodium metabisulfite. Nesiritide binds to heparin and should not be given through heparin-coated central catheters.

Uses and Administration

Nesiritide is a recombinant brain natriuretic peptide (see p. 1444.1) used in the management of acutely decompensated heart failure (below). It is given intravenously as the citrate, but dosage is expressed in terms of the base. The initial dose of nesiritide is 2 micrograms/kg by intravenous injection over 1 minute, followed by a maintenance infusion of 10 nanograms/kg per minute.

Heart failure. The use of nesiritide in acute decompensated heart failure (p. 1262.3) has been reviewed.[1-4] It may be used for short-term treatment as an alternative to standard intravenous therapy with vasodilators, inotropes, or diuretics, and appears to have no proarrhythmic effects; however, its effects on mortality are controversial (see under Adverse Effects and Precautions, below) and its role in therapy remains unclear. There is some evidence that it may be safely used in addition to standard therapy[5-7] and may have a role as a more prolonged treatment in patients awaiting cardiac transplantation.[8] Nesiritide has also been given intermittently for outpatient management of chronic heart failure,[9,10] but some have advised against such use.[11]

1. Vichiendilokkul A, *et al.* Nesiritide: a novel approach for acute heart failure. *Ann Pharmacother* 2003; 37: 247–58.
2. Keating GM, Goa KL. Nesiritide: a review of its use in acute decompensated heart failure. *Drugs* 2003; 63: 47–70.
3. Yancy CW. Benefit-risk assessment of nesiritide in the treatment of acute decompensated heart failure. *Drug Safety* 2007; 30: 765–81.
4. Tong AT, Rozner MA. The role of nesiritide in heart failure. *Expert Opin Drug Metab Toxicol* 2009; 5: 823–34.
5. O'Dell KM, *et al.* Nesiritide for secondary pulmonary hypertension in patients with end-stage heart failure. *Am J Health-Syst Pharm* 2005; 62: 606–9.
6. Smull DL, Jorde UP. Concomitant use of nesiritide and milrinone in decompensated congestive heart failure. *Am J Health-Syst Pharm* 2005; 62: 291–5.
7. Sakr A, *et al.* Nesiritide in the initial management of acute decompensated congestive heart failure. *Conn Med* 2008; 72: 517–23.
8. Witteles R, *et al.* B-type natriuretic peptide is effective therapy before care. *Ann Intern Med* 2004; 141: 895.
9. Sheikh-Taha M. Intermittent nesiritide therapy in outpatients with chronic heart failure. *Am J Health-Syst Pharm* 2005; 62: 196–8.
10. Schwarz ER, *et al.* Intermittent outpatient nesiritide infusion reduces hospital admissions in patients with advanced heart failure. *J Cardiovasc Pharmacol Ther* 2007; 12: 232–6.
11. Bauer JB, Randazzo MA. Nesiritide for outpatient treatment of heart failure. *Am J Health-Syst Pharm* 2005; 62: 2639–42.

Adverse Effects and Precautions

The most common adverse effects of nesiritide relate to vasodilatation and include hypotension, headache, and dizziness. Nausea and vomiting, abdominal pain, back pain, angina pectoris, insomnia, and anxiety, have also been reported. Cardiac arrhythmias have occurred but may be associated with the underlying condition. Adverse effects on renal function have been reported. If hypotension occurs the infusion of nesiritide should be stopped or the dose reduced and general supportive measures should be used; the hypotension may persist for several hours.

Nesiritide should not be used as primary therapy in patients with cardiogenic shock or with hypotension. It is not recommended in patients with low cardiac filling pressures or in those for whom vasodilators are inappropriate, such as those with significant valvular stenosis, restrictive or obstructive cardiomyopathy, constrictive pericarditis, or pericardial tamponade.

Effects on the kidneys. Nesiritide has both haemodynamic and neurohormonal effects on the kidneys and has been reported to worsen renal function. A meta-analysis[1] found that nesiritide significantly increased the risk of worsening renal function in patients with acute heart failure, and there is some evidence[2] that this may be related to the duration of treatment. However, a randomised study[3] in patients with acute heart failure and pre-existing renal impairment found that the effect of nesiritide on renal function was neutral. A review[4] of the data concluded that nesiritide should nevertheless be used with extreme caution in those with renal dysfunction; it has been suggested[5] that omission of the initial bolus dose might lessen renal hypoperfusion.

1. Sackner-Bernstein JD, *et al.* Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation* 2005; 111: 1487–91. Correction. *ibid.*: 2274.
2. Chow SL, *et al.* Effect of nesiritide infusion duration on renal function in acutely decompensated heart failure patients. *Ann Pharmacother* 2007; 41: 556–61.
3. Witteles RM, *et al.* Impact of nesiritide on renal function in patients with acute decompensated heart failure and pre-existing renal dysfunction: a randomized, double-blind, placebo-controlled clinical trial. *J Am Coll Cardiol* 2007; 50: 1835–40.
4. Dontas IO, *et al.* Impact of nesiritide on renal function and mortality in patients suffering from heart failure. *Cardiovasc Drugs Ther* 2009; 23: 221–33.
5. Witteles RM. Nesiritide, heart failure, and renal dysfunction: irrational exuberance or throwing the baby out with the bathwater. *Cardiovasc Drugs Ther* 2009; 23: 183–6.

Effects on mortality. Although nesiritide improves haemodynamics in patients with acute decompensated heart failure, its effects on mortality are controversial.[1] A retrospective study[2] comparing nesiritide with inotrope therapy or glyceryl trinitrate in patients with acute decompensated heart failure found a similar risk of in-hospital mortality with nesiritide and glyceryl trinitrate, which was significantly lower than the risk with inotrope therapy. However, a meta-analysis[3] of controlled studies comparing nesiritide with non-inotrope control therapy found that there was a trend to higher mortality at 30 days in patients given nesiritide; the results were not statistically significant, but became so after correction of the number of deaths in one of the studies.[4] A later meta-analysis[5] also found a trend towards increased mortality with nesiritide at 30 days, but the results again were not statistically significant, and there was no difference in mortality between nesiritide and control patients at 180 days.

1. Yancy CW. Benefit-risk assessment of nesiritide in the treatment of acute decompensated heart failure. *Drug Safety* 2007; 30: 765–81.
2. Abraham WT, *et al.* In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol* 2005; 46: 57–64.
3. Sackner-Bernstein JD, *et al.* Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA* 2005; 293: 1900–5.
4. Aaronson KD, Sackner-Bernstein J. Risk of death associated with nesiritide in patients with acutely decompensated heart failure. *JAMA* 2006; 296: 1465–6.
5. Arora RR, *et al.* Short and long-term mortality with nesiritide. *Am Heart J* 2006; 152: 1084–90.

Interactions

The risk of hypotension may be increased in patients receiving nesiritide with other drugs that lower blood pressure.

Pharmacokinetics

Nesiritide is cleared from the circulation by 3 mechanisms: uptake into cells; proteolytic cleavage by endopeptidases; and excretion by the kidneys. It has a biphasic elimination, with a terminal elimination half-life of 18 minutes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Natrecor; *Canad.*: Natrecor; *Indon.*: Natrecor†; *Israel*: Noratak; *Singapore*: Natrecor†; *Switz.*: Noratak†; *USA*: Natrecor; *Venez.*: Natrecor.

Nicardipine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de nicardipino; Nicardipina Cloridrato; Nicardipine, Chlorhydrate de; Nicardipini Hydrochloridum; Nicardipino, hidrocloruro de; Nikardipiinihydrokloridi; Nikardipin Hidroklorür; Nikardipinhydroklorid; RS-69216; RS-69216-XX-07-0; YC-93; Никардипина Гидрохлорид.

2-[Benzyl(methyl)amino]ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate hydrochloride.

$C_{26}H_{29}N_3O_6$,HCl=516.0

CAS — 55985-32-5 (nicardipine); 54527-84-3 (nicardipine hydrochloride).

ATC — C08CA04.

ATC Vet — QC08CA04.

UNII — K5BC5011K3.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

USP 36: (Nicardipine Hydrochloride). Store in airtight containers. Protect from light.

Incompatibility. Licensed product information recommends that a solution containing nicardipine hydrochloride 100 micrograms/mL is used for intravenous infusion. Suitable diluents are solutions of glucose or sodium chloride. Sodium bicarbonate and lactated Ringer's are incompatible with nicardipine infusion. Nicardipine hydrochloride (1 mg/mL in glucose 5%) has also been reported[1] to be visually incompatible with furosemide, heparin, and thiopental.

1. Chiu MP, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; 54: 64–5.

Uses and Administration

Nicardipine is a dihydropyridine calcium-channel blocker with actions and uses similar to nifedipine (p. 1447.2). It is used in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3).

Nicardipine hydrochloride is generally given orally although the intravenous route has been used for the short-term treatment of hypertension.

Oral doses of nicardipine hydrochloride are similar for both **hypertension and angina**. The initial dose is 20 mg three times daily and may be increased at intervals of at least 3 days until the required effect is achieved. The usual maintenance dose is 30 mg three times daily, but daily doses of between 60 and 120 mg in divided doses may be given. Modified-release preparations of nicardipine hydrochloride for dosage twice daily are also available.

Nicardipine hydrochloride may be given by slow intravenous infusion as a 100 micrograms/mL solution in the short-term treatment of hypertension. An initial infusion rate of 5 mg/hour is recommended, increased, as necessary, up to a maximum of 15 mg/hour and subsequently reduced to 3 mg/hour. For more information regarding suitable diluents and incompatibilities, see Incompatibility, above. For intravenous use in children, see below.

Reduced oral doses of nicardipine hydrochloride and longer dosing intervals may be necessary in patients with hepatic or renal impairment (see below).

Reviews.

1. Curran MP, *et al.* Intravenous nicardipine: its use in the short-term treatment of hypertension and various other indications. *Drugs* 2006; 66: 1755–82.

Administration in children. Intravenous infusion of nicardipine has been used in both infants and children for the management of hypertension. In studies[1-4] in patients aged between 2 days and 17 years, initial doses ranged from 0.2 to 5 micrograms/kg per minute, with maintenance infusions of 0.15 to 6 micrograms/kg per minute. Adverse effects were rare; one study[4] reported adverse effects in 5 of 31 treatment courses, including tachycardia, flushing, palpitations, and hypotension. There has also been a report[5] of the successful use of intravenous infusion of nicardipine in 8 preterm infants (gestational age 28 to 36 weeks). Infusions were given at a dose of 0.5 to 2 micrograms/kg per minute and continued for periods of 3 to 36 days. Hypotension, oedema, or tachycardia were not seen.

The *BNFC* suggests that neonates and children up to age 18 years may be given nicardipine hydrochloride by continuous intravenous infusion for the management of hypertensive crises. The initial dose is 500 nanograms/kg per minute, adjusted according to response; the usual maintenance dose is 1 to 4 micrograms/kg per minute, with a maximum dose of 250 micrograms/minute.

1. Treluyer JM, *et al.* Intravenous nicardipine in hypertensive children. *Eur J Pediatr* 1993; 152: 712–4.
2. Sartori SC, *et al.* Intravenous nicardipine for treatment of systemic hypertension in children. *Pediatrics* 1999; 104 (suppl): 676–7.
3. Tobias JD. Nicardipine to control mean arterial pressure after cardiothoracic surgery in infants and children. *Am J Ther* 2001; 8: 3–6.
4. Flynn JT, *et al.* Intravenous nicardipine for treatment of severe hypertension in children. *J Pediatr* 2001; 139: 38–43.
5. Gouyon JB, *et al.* Intravenous nicardipine in hypertensive preterm infants. *Arch Dis Child* 1997; 76: F126–F127.

Administration in hepatic or renal impairment. Reduced doses of nicardipine hydrochloride and longer dosing intervals may be necessary in patients with hepatic or renal impairment. US licensed product information has recommended an initial oral dose of 20 mg twice daily in patients with hepatic impairment.

Cerebrovascular disorders. Nimodipine (p. 1455.3) is the dihydropyridine calcium-channel blocker that is usually used for cerebrovascular disorders. Nicardipine is also a potent cerebral vasodilator[1,2] and has been investigated for the vasospasm after subarachnoid haemorrhage, as well as for controlling acute hypertension after ischaemic stroke or intracerebral haemorrhage (for these conditions see Stroke, p. 1269.2). It has also been tried in cerebrovascular insufficiency and vascular dementia.

Some studies have reported positive or favourable results in *subarachnoid haemorrhage*[1,3] although a systematic review (which assessed oral and intravenous use) concluded that there was no evidence that nicardipine has a significant effect on functional outcome.[2] The use of nicardipine prolonged-release implants (into the basal cistern) may, however, be of benefit.[4,5] Other preliminary observations in patients with refractory vasospasm after subarachnoid haemorrhage have suggested that alternative routes such as intraventricular[6] and intra-arterial[7] use should be investigated in more detail.

Both oral and intravenous nicardipine have also been studied for the reduction of hypertension after acute *ischaemic stroke*. Although some studies have shown positive results,[3] the data are too limited to draw firm conclusions[1,3,8] and a review considered that it should be used only in patients who cannot be given a better established alternative such as labetalol.[8] A similar conclusion was reached about the use of nicardipine for hypertension after *intracerebral haemorrhage*.[8]

Comparison of studies in different clinical situations in patients with *cerebrovascular insufficiency* or *vascular dementia* is difficult but a review considered that there does appear to

be a favourable effect on cognitive function with nicardipine.[1,3]

1. Amenta F, *et al.* Nicardipine: a hypotensive dihydropyridine-type calcium antagonist with a peculiar cerebrovascular profile. *Clin Exp Hypertens* 2008; 30: 808–26.
2. Dorhout Mees S, *et al.* Calcium antagonists for aneurysmal subarachnoid haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 25/07/08).
3. Amenta F, *et al.* Nicardipine use in cerebrovascular disease: a review of controlled clinical studies. *J Neurol Sci* 2009; 283: 219–23.
4. Barth M, *et al.* Effect of nicardipine prolonged-release implants on cerebral vasospasm and clinical outcome after severe aneurysmal subarachnoid hemorrhage: a prospective, randomized, double-blind phase IIa study. *Stroke* 2007; 38: 330–6.
5. Krischek B, *et al.* Nicardipine prolonged-release implants for preventing cerebral vasospasm after subarachnoid hemorrhage: effect and outcome in the first 100 patients. *Neurol Med Chir (Tokyo)* 2007; 47: 389–94.
6. Goodson K, *et al.* Intraventricular nicardipine for refractory cerebral vasospasm after subarachnoid hemorrhage. *Neurocrit Care* 2008; 8: 247–52.
7. Tejada JG, *et al.* Safety and feasibility of intra-arterial nicardipine for the treatment of subarachnoid hemorrhage-associated vasospasm: initial clinical experience with high-dose infusions. *AJNR Am J Neuroradiol* 2007; 28: 844–8.
8. Reddy P, Yeh YC. Use of injectable nicardipine for neurovascular indications. *Pharmacotherapy* 2009; 29: 398–409.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Pharmacokinetics

Nicardipine is rapidly and completely absorbed from the gastrointestinal tract but is subject to saturable first-pass hepatic metabolism. Bioavailability of about 35% has been reported after a 30-mg dose at steady state. The pharmacokinetics of nicardipine are non-linear due to the saturable first-pass hepatic metabolism and an increase in dose may produce a disproportionate increase in plasma concentration. There is also considerable interindividual variation in plasma-nicardipine concentrations. Nicardipine is more than 95% bound to plasma proteins. Nicardipine is extensively metabolised in the liver and is excreted in the urine and faeces, mainly as inactive metabolites. The terminal plasma half-life is about 8.6 hours, thus steady-state plasma concentrations occur after 2 to 3 days of dosing three times daily.

References.
1. Graham DJM, *et al.* Pharmacokinetics of nicardipine following oral and intravenous administration in man. *Postgrad Med J* 1984; 60 (suppl 4): 7–10.
2. Graham DJM, *et al.* The metabolism and pharmacokinetics of nicardipine hydrochloride in man. *Br J Clin Pharmacol* 1985; 20: 235–285.
3. Razak TA, *et al.* The effect of hepatic cirrhosis on the pharmacokinetics and blood pressure response to nicardipine. *Clin Pharmacol Ther* 1990; 47: 463–9.
4. Porchet HC, Dayer P. Serum concentrations and effects of (±)-nicardipine compared with nifedipine in a population of healthy subjects. *Clin Pharmacol Ther* 1990; 48: 155–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Rydene; ***China***: A Fa Duo Xin (阿法多欣); Bei Er Ping (贝尔平); Bei Li Ning (贝立宁); Ka Ni Ya (卡尼亚); Ka Shu Tai (卡舒泰); Perdipine (佩尔); Xian Li (仙立); Xin Shu Li Da (欣舒力达); Yu Luo Tong (毓罗通); ***Fr.***: Loxen; ***Ger.***: Antagonil†; ***Indon.***: Blistra; Perdipine; ***Ital.***: Bionicard; Cardioten†; Cardip†; Lisanirc; Nicapress†; Nicardal; Nicarpin†; Nicaven; Perdipina; Vasodin; ***Jpn***: Perdipine; ***Malaysia***: Cardepine; ***Neth.***: Cardene; ***Philipp.***: Cardepine; Perdipine; ***Port.***: Nerdipina; ***Singapore***: Cardibloc; ***Spain***: Dagan; Fluse-mide; Lecibral; Lincil; Lucenfal†; Nerdipina; Vasonase; ***Thai.***: Cardepine; ***Turk.***: Loxen; ***UK***: Cardene; ***USA***: Cardene.

Niceritrol *(BAN, rINN)*

Niceritrol; Niceritrolum; Nikeritroli; PETN; Ницеритрол.
Pentaerythritol tetranicotinate; 2,2-Bis(hydroxymethyl)propane-1,3-diol tetranicotinate.
$C_{29}H_{24}N_4O_8$=556.5
CAS — 5868-05-3.
ATC — C10AD01.
ATC Vet — QC10AD01.
UNII — FS4EHJ34MV.

NOTE. The synonym PETN has been applied to both niceritrol and pentaerithrityl tetranitrate.

Pharmacopoeias. In *Jpn*.

Profile

Niceritrol, an ester of pentaerythritol and nicotinic acid, has general properties similar to those of nicotinic acid (p. 2083.1), to which it is slowly hydrolysed. Niceritrol has been used as a lipid regulating drug in hyperlipidaemias and as a vasodilator in the treatment of peripheral vascular disease.

References.
1. Owada A, *et al.* Antiproteinuric effect of niceritrol, a nicotinic acid derivative, in chronic renal disease with hyperlipidemia: a randomized trial. *Am J Med* 2003; 114: 347–53.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Perycit.

Nicomol *(rINN)*

K-31; Nicomolum; Никомол.
2-Hydroxy-1,1,3,3-cyclohexanetetramethanol 1,1,3,3-tetranicotinate.
$C_{34}H_{32}N_4O_9$=640.6
CAS — 27959-26-8.
UNII — 215U8X2R44.

Pharmacopoeias. In *Jpn*.

Profile

Nicomol is a derivative of, and has general properties similar to, nicotinic acid (p. 2083.1) to which it is hydrolysed. It is used as a lipid regulating drug in hyperlipidaemias, and as a vasodilator in the treatment of peripheral circulatory disorders such as chilblains, Raynaud's syndrome, and limb arterial occlusive disease. The usual oral dosage is 600 to 1200 mg daily in 3 divided doses after food.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Cholexamin.

Nicorandil *(BAN, USAN, rINN)*

Nicorandilum; SG-75; Никорандил.
N-[2-(Nitroxy)ethyl]-3-pyridinecarboxamide.
$C_8H_9N_3O_4$=211.2
CAS — 65141-46-0.
ATC — C01DX16.
ATC Vet — QC01DX16.
UNII — 260456HAM0.

Pharmacopoeias. In *Br*. and *Jpn*.

BP 2014: (Nicorandil). A white crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in methyl alcohol. Store in airtight containers at a temperature of 2 degrees to 8 degrees.

Uses and Administration

Nicorandil is a nitrate derivative of nicotinamide (p. 2083.1) and acts as a vasodilator. It is a potassium-channel opener (p. 1245.2) providing vasodilatation of arterioles and large coronary arteries and its nitrate component produces venous vasodilatation through stimulation of guanylate cyclase. It thus reduces both preload and afterload, and improves coronary blood flow.

Nicorandil is given orally for prevention and long-term treatment of **angina pectoris**, including reduction of the risk of acute coronary events in high-risk patients (p. 1254.3). The usual initial oral dose is 10 mg twice daily (or 5 mg twice daily in patients susceptible to headache), increased as necessary to a maximum of 30 mg twice daily; the usual therapeutic dose is in the range of 10 to 20 mg twice daily.

Nicorandil is also given intravenously in the management of **unstable angina** and **acute heart failure** (p. 1262.3). For unstable angina, a solution containing 100 to 300 micrograms/mL is given by intravenous infusion in a dose of 2 mg/hour, adjusted according to response, to a maximum dose of 6 mg/hour. For acute heart failure, a solution containing 400 to 2500 micrograms/mL is used; the usual dose is 200 micrograms/kg given by intravenous injection over 5 minutes, followed by continuous intravenous infusion at a dose of 200 micrograms/kg per hour. The dosage should be adjusted according to response, within the range of 50 to 200 micrograms/kg per hour.

General references.
1. Markham A, *et al.* Nicorandil: an updated review of its use in ischaemic heart disease with emphasis on its cardioprotective effects. *Drugs* 2000; 60: 955–74.
2. Gomma AH, *et al.* Potassium channel openers in myocardial ischaemia: therapeutic potential of nicorandil. *Drugs* 2001; 12: 1705–10.
3. Anonymous. Nicorandil for angina – an update. *Drug Ther Bull* 2003; 41: 86–8.
4. Simpson D, Wellington K. Nicorandil: a review of its use in the management of stable angina pectoris, including high-risk patients. *Drugs* 2004; 64: 1941–55.

Ischaemic heart disease. A large multicentre double-blind randomised placebo-controlled study[1] suggested that nicorandil, in addition to its anti-anginal effects, may have cardioprotective properties. The incidence of major coronary events, particularly unplanned admission for chest pain, was significantly reduced in patients with stable angina at high risk of future adverse events. Mortality may also be reduced.[2] Nicorandil may mimic the mechanism of ischaemic pre-conditioning, whereby a brief period of ischaemia makes the myocardium resistant to damage from a further episode,[3] but it is not clear how much this mechanism contributes to its effects. There is some evidence[4-9] that nicorandil improves outcomes when given at the time of percutaneous coronary intervention, although a large study[10] in patients with myocardial infarction failed to confirm a benefit. It has been suggested[6] that an antioxidant effect may be part of the mechanism involved.

1. The IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet* 2002; 359: 1269–75. Correction. *ibid.*; 360: 806.
2. Horinaka S, *et al.* JCAD Study Investigators. Effects of nicorandil on cardiovascular events in patients with coronary artery disease in the Japanese Coronary Artery Disease (JCAD) study. *Circ J* 2010; 74: 503–9.
3. Lesnefsky EJ. The IONA study: preparing the myocardium for ischaemia? *Lancet* 2002; 359: 1262–3.
4. Matsuo H, *et al.* Evidence of pharmacologic preconditioning during PTCA by intravenous pretreatment with ATP-sensitive K+ channel opener nicorandil. *Eur Heart J* 2003; 24: 1296–1303.
5. Ikeda N, *et al.* Nicorandil versus isosorbide dinitrate as adjunctive treatment to direct balloon angioplasty in acute myocardial infarction. *Heart* 2004; 90: 181–5.
6. Ono H, *et al.* Nicorandil improves cardiac function and clinical outcome in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: role of inhibitory effect on reactive oxygen species formation. *Am Heart J* 2004; 148: E15.
7. Ishii H, *et al.* Impact of a single intravenous administration of nicorandil before reperfusion in patients with ST-segment-elevation myocardial infarction. *Circulation* 2005; 112: 1284–8.
8. Ishii H, *et al.* Effects of intravenous nicorandil before reperfusion for acute myocardial infarction in patients with stress hyperglycemia. *Diabetes Care* 2006; 29: 202–6.
9. Iwakura K, *et al.* Nicorandil treatment in patients with acute myocardial infarction: a meta-analysis. *Circ J* 2009; 73: 925–31.
10. Kitakaze M, *et al.* J-WIND investigators. Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials. *Lancet* 2007; 370: 1483–93.

Adverse Effects and Precautions

Adverse effects reported with nicorandil are headache (which is usually transitory and seen at the start of therapy), cutaneous vasodilatation and flushing, nausea, vomiting, dizziness, and weakness. Rarely reported effects include myalgia, rashes, and oral ulceration, and there have been very rare reports of angioedema and hepatic function abnormalities. A reduction in blood pressure and/or an increase in heart rate may occur with high doses.

Nicorandil is contra-indicated in patients with cardiogenic shock, left ventricular failure with low filling pressures, and hypotension. In patients with hypovolaemia, low systolic blood pressure, acute pulmonary oedema, or acute myocardial infarction with acute left ventricular failure and low filling pressures, nicorandil should preferably be avoided but may be used with caution.

Incidence of adverse effects. Postmarketing surveillance for nicorandil was carried out by prescription-event monitoring[1] of 13 620 patients, and showed that adverse reactions occurred in 175. The most frequent was headache, occurring in 58 patients, mainly in the first month of treatment. Unspecified adverse effects occurred in 36 patients. Other effects included dizziness (19 patients), nausea (17 patients), malaise (13 patients), palpitations (8 patients), flushing and vomiting (6 patients each), and lassitude (4 patients). Rare adverse effects included 3 cases each of angioedema and photosensitivity.

1. Dunn N, *et al.* Safety profile of nicorandil—prescription-event monitoring (PEM) study. *Pharmacoepidemiol Drug Safety* 1999; 8: 197–205.

Ulceration. Nicorandil has been associated with ulceration of mucosal surfaces. Painful, large aphthous ulcers on the *tongue* and *oral mucosa* have been reported[1-3] in patients receiving nicorandil for angina. The ulcers were usually resistant to treatment but all healed when nicorandil was withdrawn. Colchicine or thalidomide treatment has improved ulcers associated with nicorandil in a few patients, but relapse occurred when the colchicine or thalidomide was stopped.[3] However, a large study[4] casts some doubt on the evidence for a causal link between nicorandil and oral ulceration, although it was suggested that this could be further investigated.

Anal ulceration has been reported[5-7] in patients taking nicorandil. Healing of the ulcers occurred in those patients in whom nicorandil was withdrawn.

Multiple ulcers of the upper and lower *gastrointestinal tract*, in addition to oral and anal ulceration, have been reported[8] in a patient taking nicorandil; all of the ulcers healed when nicorandil was stopped. There have also been several cases of *peristomal* ulceration, which resolved after stopping nicorandil.[9]

Perivulval[10-13] and vaginal[12,14] ulceration has also been reported, and may be associated with *cutaneous*[10] or inguinal[13] ulceration. Another patient[15] developed both perianal and leg ulcers, both of which improved rapidly when nicorandil was stopped.

1. *Cribier B, et al.* Chronic buccal ulceration induced by nicorandil. *Br J Dermatol* 1998; 138: 372–3.
2. Desruelles P, *et al.* Giant oral aphthous ulcers induced by nicorandil. *Br J Dermatol* 1998; 138: 712–13.
3. Agbo-Godeau S, *et al.* Association of major aphthous ulcers and nicorandil. *Lancet* 1998; 352: 1598–9.
4. Dunn N, *et al.* Safety profile of nicorandil—prescription-event monitoring (PEM) study. *Pharmacoepidemiol Drug Safety* 1999; 8: 197–205.
5. Watson A, *et al.* Nicorandil associated anal ulceration. *Lancet* 2002; 360: 546–7.
6. Vella M, Molloy RG. Nicorandil-associated anal ulceration. *Lancet* 2002; 360: 1979.
7. Passeron T, *et al.* Chronic anal ulceration due to nicorandil. *Br J Dermatol* 2004; 150: 394–6.
8. Egred M, *et al.* Nicorandil may be associated with gastrointestinal ulceration. *BMJ* 2006; 332: 889.
9. Ogden S, *et al.* Nicorandil-induced peristomal ulcers: is nicorandil also associated with gastrointestinal fistula formation? *Br J Dermatol* 2007; 156: 608–9.
10. Claeys A, *et al.* Cutaneous, perivulvar and perianal ulcerations induced by nicorandil. *Br J Dermatol* 2006; 155: 494–6.
11. Fraser SJ, *et al.* Vulval ulceration induced by the potassium-channel activator Nicorandil: a case series of five patients. *BJOG* 2009; 116: 1400–2.
12. Chan SK, *et al.* Vulvovaginal ulceration during prolonged treatment with nicorandil. *BJOG* 2009; 116: 1403–5.
13. El-Dars LD, *et al.* Nicorandil associated vulval and inguinal ulceration. *J Obstet Gynaecol* 2009; 29: 674–5.
14. van de Nieuwenhof HP, *et al.* Never forget medication as a cause: vaginal ulceration caused by nicorandil. *Am J Obstet Gynecol* 2009; 201: e5–e6.
15. McKenna DJ, *et al.* Nicorandil-induced leg ulceration. *Br J Dermatol* 2007; 156: 394–6.

Interactions

Nicorandil should not be used with phosphodiesterase type-5 inhibitors such as sildenafil as the hypotensive effect of nicorandil may be significantly enhanced.

Pharmacokinetics

Nicorandil is well absorbed from the gastrointestinal tract and peak plasma concentrations occur 30 to 60 minutes after oral doses. Metabolism is mainly by denitration and about 20% of a dose is excreted in the urine mainly as metabolites. The elimination half-life is about 1 hour. Nicorandil is only slightly bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Ikorel; *Austria*: Dancor; *China*: Sigmart (喜格迈); *Denm.*: Angicor; Dancor; Ikorel; *Fr.*: Adancor; Ikorel; *Gr.*: Ikotril; *India*: Av-Cor; Corflo; Dilnicon; Duorandil; K-Cor; Korandil; Nicoduce; Nikoran; Nucoril; Zynicor; *Irl.*: Ikorel; Nicozone; *Jpn*: Sigmart; *Neth.*: Dancor†; Doranic; Ikorel; *NZ*: Ikorel; *Philipp.*: Aprior; Nikoran; *Port.*: Dancor; Nikoril†; *Switz.*: Dancor; *Turk.*: Ikorel; *UK*: Ikorel.

Pharmacopoeial Preparations
BP 2014: Nicorandil Tablets.

Nicotinyl Alcohol *(BAN, USAN)*

3-Hydroxymethylpyridine; Nicomethanol; Nicotinic Alcohol; Nicotinílico, alcohol; NSC-526046; NU-2121†; 3-Pyridinemethanol; β-Pyridylcarbinol; Ro-1-5155; Никотиниловый Спирт.

3-Pyridylmethanol.

C_6H_7NO=109.1

CAS — 100-55-0.

ATC — C04AC02; C10AD05.

ATC Vet — QC04AC02; QC10AD05.

UNII — 9TF312056Y.

Nicotinyl Alcohol Tartrate *(BANM)*

Alcohol nicotinílico, tartrato de; Nicotinyl Tartrate.

3-Pyridylmethanol hydrogen (2*R*,3*R*)-tartrate.

$C_6H_7NO,C_4H_6O_6$=259.2

CAS — 6164-87-0.

ATC — C04AC02; C10AD05.

ATC Vet — QC04AC02; QC10AD05.

UNII — 5G605ZIE90.

Pharmacopoeias. In *Br.*

BP 2014: (Nicotinyl Alcohol Tartrate). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. A 5% solution in water has a pH of 2.8 to 3.7.

Profile

Nicotinyl alcohol is a vasodilator and lipid regulating drug with general properties similar to those of nicotinic acid (p. 2083.1), to which it is partly hydrolysed.

Nicotinyl alcohol has been given orally, as the tartrate, in the management of peripheral vascular disease, and has also been used in Ménière's disease and in hyperlipidaemias. The hydrofluoride derivative, nicomethanol hydrofluoride, is used as a fluoride source in oral hygiene products.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Cetacol†.

Multi-ingredient Preparations. *Braz.*: Lipofacton†.

Pharmacopoeial Preparations
BP 2014: Nicotinyl Alcohol Tablets.

Nifedipine *(BAN, USAN, rINN)*

Bay-a-1040; Nifedipiini; Nifedipin; Nifedipina; Nifedipinas; Nifédipine; Nifedipino; Nifedipinum; Нифедипин.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate.

$C_{17}H_{18}N_2O_6$=346.3

CAS — 21829-25-4.

ATC — C08CA05.

ATC Vet — QC08CA05.

UNII — I9ZF7L6G2L.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Nifedipine). A yellow crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone. When exposed to daylight or to certain wavelengths of artificial light it is converted to a nitrosophenylpyridine derivative, while exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Solutions should be prepared in the dark or under light of wavelength greater than 420 nm, immediately before use. Protect from light.

USP 36: (Nifedipine). A yellow powder. Practically insoluble in water; soluble 1 in 10 of acetone. When exposed to daylight or to certain wavelengths of artificial light it is converted to a nitrosophenylpyridine derivative, while exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Store in airtight containers. Protect from light.

Stability. Yellow food colourings such as curcumin have been used[1] to slow photodegradation of nifedipine solutions. An extemporaneously prepared solution of nifedipine in a peppermint-flavoured vehicle was reported[2] to be stable for at least 35 days when stored in amber glass bottles.

1. Thoma K, Klimek R. Photostabilization of drugs in dosage forms without protection from packaging materials. *Int J Pharmaceutics* 1991; 67: 169–75.
2. Dentinger PJ, *et al.* Stability of nifedipine in an extemporaneously compounded oral solution. *Am J Health-Syst Pharm* 2003; 60: 1019–22.

Uses and Administration

Nifedipine is a dihydropyridine calcium-channel blocker (p. 1244.2). It is a peripheral and coronary vasodilator, but, unlike the rate-limiting calcium-channel blockers verapamil or diltiazem, has little or no effect on cardiac conduction and negative inotropic activity is rarely seen at therapeutic doses. Use of nifedipine results primarily in vasodilatation, with reduced peripheral resistance, blood pressure, and afterload, increased coronary blood flow, and a reflex increase in heart rate. This in turn results in an increase in myocardial oxygen supply and cardiac output. Nifedipine has no antiarrhythmic activity. Nicardipine and newer dihydropyridines such as amlodipine, felodipine, isradipine, and lacidipine may be even more selective than nifedipine for vascular smooth muscle. Nimodipine acts particularly on cerebral blood vessels. Most of the dihydropyridine calcium-channel blockers (nifedipine and lacidipine are exceptions) are chiral compounds used as racemic mixtures.

Nifedipine may be used in the management of hypertension; in the management of angina pectoris particularly when a vasospastic element is present, as in Prinzmetal's angina, though it is not suitable for relief of an acute attack; and in the treatment of Raynaud's syndrome. Nifedipine has also been tried in many non-vascular disorders. For further information on its uses see below.

Nifedipine is usually given orally. It is available in several formulations. Liquid-filled capsules with a relatively rapid onset but short duration of action are given three times daily. This short-acting preparation is not recommended for the management of hypertension or angina in adults. There are also tablets and capsules with a slower onset and longer duration of action, enabling twice-daily dosage; although these are often referred to by nomenclature implying extended or sustained release they should be distinguished from the true extended-release preparations available in some countries that allow dosage once daily.

Doses of nifedipine are dependent upon the formulation used; they may need to be reduced in the elderly or those with impaired liver function.

For **hypertension** a long-acting preparation of nifedipine may be given in doses of 10 to 40 mg twice daily, or 20 to 90 mg once daily, depending on the preparation used.

For **angina pectoris**, nifedipine may be given as a long-acting preparation in a dose of 10 to 40 mg twice daily or 30 to 90 mg once daily, depending on the preparation. Although the liquid-filled capsules have been given in a dose of 5 to 20 mg three times daily, this is no longer recommended and longer-acting preparations are preferred.

Nifedipine has been given by injection via a coronary catheter for the treatment of coronary spasm during coronary angiography and balloon angioplasty. Blood pressure and heart rate should be monitored carefully.

In the management of **Raynaud's syndrome**, nifedipine may be given as liquid-filled capsules in a dose of 5 to 20 mg three times daily.

For the use of nifedipine in children, see below.

General references.

1. Croom KF, Wellington K. Modified-release nifedipine: a review of the use of modified-release formulations in the treatment of hypertension and angina pectoris. *Drugs* 2006; 66: 497–528.
2. Meredith PA, Elliott HL. Benefits of nifedipine GITS in stable coronary artery disease: further analysis of the "ACTION" database. *Adv Therapy* 2010; 27: 297–306.

Administration in children. Nifedipine has been used in the management of various disorders in children. The *BNFC* recommends the following oral doses:

Hypertension; angina in Kawasaki disease or progeria:

- age 1 month to 12 years: 200 to 300 micrograms/kg 3 times daily, increased to a maximum daily dose of 3 mg/kg or 90 mg
- age 12 to 18 years: 5 to 20 mg 3 times daily, increased to a maximum daily dose of 90 mg

Dosage frequency may vary depending on the preparation used

Hypertensive crises; acute angina in Kawasaki disease or progeria:

- age 1 month to 18 years: 250 to 500 micrograms/kg (maximum 20 mg) as a single dose

(although such use is deprecated in adults, the *BNFC* considers that for rapid effect an immediate-release liquid-filled capsule may be bitten and the contents swallowed; a liquid preparation may be used if the unit doses available in such capsules are inappropriate)

Raynaud's syndrome:

- age 2 to 18 years: 2.5 to 10 mg 2 to 4 times daily; treatment should start with low doses at night, increased gradually to avoid orthostatic hypotension

Neonatal hyperinsulinaemic hypoglycaemia:

- see p. 1448.2

Use of nifedipine capsules for acute hypertension is no longer recommended in adults because of the risk of severe adverse effects related to precipitous reductions in blood pressure (see Effects on Mortality under Adverse Effects, p. 1450.2). Although there have been reports of adverse effects in children,[1-3] they may be less susceptible than adults, and the use of nifedipine capsules may still be appropriate.[4] A study[5] in 12 children aged 6 to 15 years with acute severe hypertension reported that sublingual nifedipine in a mean dose of 240 micrograms/kg (range 180 to 320 micrograms/kg) was safe and effective. A retrospective study[6] in 182 children also found that short-acting nifedipine in a mean dose of 220 micrograms/kg (range 43 to 670 micrograms/kg) was safe and effective, while another retrospective study[1] in 117 children found that nifedipine safely reduced blood pressure, and that precipitous declines only occurred with doses higher than 250 micrograms/kg; a third retrospective study[2] in 166 children found that nifedipine in a mean dose of 300 micrograms/kg (range 40 to 1300 micrograms/kg) was generally safe, although children with acute CNS injury were at higher risk of neurological adverse effects.

Other routes that have been used include rectal[7] and intranasal,[8] but these are less established.

1. Blaszak RT, *et al.* The use of short-acting nifedipine in pediatric patients with hypertension. *J Pediatr* 2001; 139: 34–7.
2. Egger DW, *et al.* Evaluation of the safety of short-acting nifedipine in children with hypertension. *Pediatr Nephrol* 2002; 17: 35–40.
3. Flynn JT. Nifedipine in the treatment of hypertension in children. *J Pediatr* 2002; 140: 787–8.
4. Sahney S. A review of calcium channel antagonists in the treatment of pediatric hypertension. *Pediatr Drugs* 2006; 8: 357–73.
5. Evans JHC, *et al.* Sublingual nifedipine in acute severe hypertension. *Arch Dis Child* 1988; 63: 975–7.
6. Yiu V, *et al.* The safety and use of short-acting nifedipine in hospitalized hypertensive children. *Pediatr Nephrol* 2004; 19: 644–50.
7. Uchiyama M, Ogawa L. Rectal nifedipine in acute severe hypertension in young children. *Arch Dis Child* 1989; 64: 632–3.

8. Lopez-Herce J, *et al.* Treatment of hypertensive crisis with intranasal nifedipine. *Crit Care Med* 1988; 9: 914.

Amaurosis fugax. Amaurosis fugax is a form of monocular visual loss that is usually attributed to a transient ischaemic attack and is treated with antiplatelet drugs or anticoagulants (see Stroke, p. 1269.2). Vasospasm may be an alternative cause and might explain the efficacy of the calcium-channel blockers nifedipine and verapamil reported[1] in a few patients unresponsive to standard therapy.

1. Winterkorn JMS, *et al.* Brief report: treatment of vasospastic amaurosis fugax with calcium-channel blockers. *N Engl J Med* 1993; 329: 396–8.

Anal fissure. Topical nitrates have commonly been used in the management of chronic anal fissure (p. 2017.3) because of their ability to relax the anal sphincter. Calcium-channel blockers, including nifedipine, have also been tried with success. Both oral[1] and topical[2] treatment have been tried, although most studies have used the latter. Oral nifedipine[3] was not as effective as surgery and compliance was poor. Topical nifedipine 0.2% was found[4] to be more effective and cause fewer adverse effects than glyceryl trinitrate, and appeared to be safe and effective in the long term,[5] although recurrences were common. Aggressive treatment with nifedipine 0.5% ointment has shown improved responses in terms of recurrence rate[6] and has compared favourably with surgery,[7] leading to the view that it might be considered a first-line treatment.

1. Cook TA, *et al.* Oral nifedipine reduces resting anal pressure and heals chronic anal fissure. *Br J Surg* 1999; 86: 1269–73.
2. Perrotti P, *et al.* Topical nifedipine with lidocaine ointment vs. active control for treatment of chronic anal fissure: results of a prospective, randomized, double-blind study. *Dis Colon Rectum* 2002; 45: 1468–75.
3. Ho KS, Ho YH. Randomized clinical trial comparing oral nifedipine with lateral anal sphincterotomy and tailored sphincterotomy in the treatment of chronic anal fissure. *Br J Surg* 2005; 92: 403–8.
4. Ezri T, Susmallian S. Topical nifedipine vs. topical glyceryl trinitrate for treatment of chronic anal fissure. *Dis Colon Rectum* 2003; 46: 805–8.
5. Lysy J, *et al.* Long-term results of "chemical sphincterotomy" for chronic anal fissure: a prospective study. *Dis Colon Rectum* 2006; 49: 858–64.
6. Katsinelos P, *et al.* Aggressive treatment of acute anal fissure with 0.5% nifedipine ointment prevents its evolution to chronicity. *World J Gastroenterol* 2006; 12: 6203–6.
7. Katsinelos P, *et al.* Topical 0.5% nifedipine vs. lateral internal sphincterotomy for the treatment of chronic anal fissure: long-term follow-up. *Int J Colorectal Dis* 2006; 21: 179–83.

Angina pectoris. Both dihydropyridines (such as nifedipine) and rate-limiting calcium-channel blockers (diltiazem and verapamil) may be used in the management of angina (p. 1254.3), with choice depending on individual patient characteristics and adverse effects. Short-acting preparations of nifedipine have been associated with increased mortality and are not recommended in adults (see under Adverse Effects, p. 1450.2) though they may be used in children (p. 1447.3).

Atherosclerosis. The use of drugs that interfere with atherogenesis (the development of atheromas) has been suggested as a means of reducing diseases associated with atherosclerosis (p. 1250.2). Calcium is thought to be necessary for several steps in atherogenesis and studies in *animals* have shown that calcium-channel blockers slow the development and progression of atherosclerotic lesions. However, studies in humans have been less convincing.[1] In a placebo-controlled study,[2] amlodipine had no demonstrable effect on angiographic progression of coronary atherosclerosis or the risk of major cardiovascular events although it was associated with fewer admissions to hospital for unstable angina and revascularisation. Similar results have been reported with nisoldipine.[3] Results with nifedipine have been mixed: no significant effect was seen on plaque progression,[4,5] although it may improve coronary endothelial function.[5] In a study[6] comparing lacidipine with a beta blocker, there was less progression of atherosclerosis in those receiving lacidipine and also a trend towards fewer cardiovascular events.

Calcium-channel blockers have also been tried in the prevention of restenosis after percutaneous coronary interventions. A meta-analysis[7] found that addition of calcium-channel blockers to standard therapy reduced the risk of restenosis and the occurrence of clinical events.

1. Borcherding SM, *et al.* Calcium-channel antagonists for prevention of atherosclerosis. *Ann Pharmacother* 1993; 27: 61–7.
2. Pitt B, *et al.* Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation* 2000; 102: 1503–10.
3. Dens JA, *et al.* Long term effects of nisoldipine on the progression of coronary atherosclerosis and the occurrence of clinical events: the NICOLE study. *Heart* 2003; 89: 887–92.
4. Motro M, *et al.* Tracking coronary calcification and atherosclerotic lesions in patients with stable angina pectoris undergoing nifedipine therapy. *Cardiology* 2007; 107: 165–71.
5. Lüscher TF, *et al.* A randomized placebo-controlled study on the effect of nifedipine on coronary endothelial function and plaque formation in patients with coronary artery disease: the ENCORE II study. *Eur Heart J* 2009; 30: 1590–7.
6. Zanchetti A, *et al.* Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. *Circulation* 2002; 106: 2422–7.
7. Dens J, *et al.* An updated meta-analysis of calcium-channel blockers in the prevention of restenosis after coronary angioplasty. *Am Heart J* 2003; 145: 404–8.

Cardiomyopathies. Calcium-channel blockers may have a role in some forms of cardiomyopathy (p. 1261.3). In *hypertrophic cardiomyopathy* verapamil is probably the calcium-channel blocker of choice (see p. 1522.3). Nifedipine does not appear to reduce left ventricular outflow tract obstruction, and has produced conflicting results with respect to improvement in the diastolic function abnormality.[1] The use of calcium-channel blockers is not standard therapy in *dilated cardiomyopathy* although symptomatic improvement has been reported[2] with diltiazem.

1. Richardson PJ. Calcium antagonists in cardiomyopathy. *Br J Clin Pract* 1988; 42 (suppl 60): 33–7.
2. Figulla HR, *et al.* Diltiazem improves cardiac function and exercise capacity in patients with idiopathic dilated cardiomyopathy: results of the Diltiazem in Dilated Cardiomyopathy Trial. *Circulation* 1996; 94: 346–52.

Cough. Nifedipine has been reported to reduce the severity of cough induced by captopril,[1] possibly by inhibiting prostaglandin synthesis. For further details on cough associated with ACE inhibitors, see p. 1285.3.

1. Fogari R, *et al.* Effects of nifedipine and indomethacin on cough induced by angiotensin-converting enzyme inhibitors: a double-blind, randomized, cross-over study. *J Cardiovasc Pharmacol* 1992; 19: 670–3.

Hiccup. Hiccups (p. 1046.3) result from involuntary spasmodic contraction of the diaphragm. Intractable hiccups resolved completely with nifedipine 20 mg every 8 hours in a patient.[1] In a further 7 such patients,[2] nifedipine in doses of 20 to 80 mg daily stopped hiccups in 4 and improved them in another. Resolution of intractable hiccups has also been reported[3] in 2 patients given nimodipine; the drug was given orally in one patient and intravenously in the other.

For the treatment of hiccups in palliative care the *BNF* suggests that nifedipine at a dose of 10 mg three times daily can be tried.

1. Mukhopadhyay P, *et al.* Nifedipine for intractable hiccups. *N Engl J Med* 1986; 314: 1256.
2. Lipps DC, *et al.* Nifedipine for intractable hiccups. *Neurology* 1990; 40: 531–2.
3. Hernández JL, *et al.* Nimodipine treatment for intractable hiccups. *Am J Med* 1999; 106: 600.

High-altitude disorders. Nifedipine lowers pulmonary artery pressure and is one of several drugs that are used in high-altitude disorders (p. 1276.2), success being reported for both the treatment[1,2] and prevention[2,3] of symptoms of pulmonary oedema.

In a study conducted at 4559 m above sea-level[1] nifedipine 10 mg sublingually and 20 mg as a modified-release dosage form was given to 6 subjects to treat symptoms of high-altitude pulmonary oedema. The sublingual dose was repeated if tolerated after 15 minutes and the subjects subsequently received modified-release nifedipine 20 mg every 6 hours while they remained at high altitude. Symptoms of high-altitude pulmonary oedema were relieved within 1 hour of beginning nifedipine and radiographic signs of oedema regressed during treatment despite remaining at high altitude for 36 hours and participating in mountaineering activities. Raised pulmonary arterial pressure was also reduced to control values by nifedipine.

Successful treatment of pulmonary oedema in a climber at 6550 m has been described with doses of 20 mg every 8 hours for 36 hours and such doses also prevented the development of symptoms in 2 climbers who had taken nifedipine from the start of the climb.[2] Doses of 20 mg every 8 hours have been reported to allow rapid ascent to 4559 m without development of pulmonary oedema in 9 of 10 subjects who received nifedipine compared with 4 of 11 who received only placebo.[3] Some consider that prophylactic treatment with nifedipine 60 mg daily in divided doses, as a modified-release oral preparation, should be started the day before ascent in climbers with a history of high-altitude pulmonary oedema and continued until descent or until 5 days has been spent at the target elevation.[4] Drug prophylaxis is not generally recommended in those without such a history, and although it is reasonable that many climbers carry nifedipine in case of an attack,[5] prophylactic nifedipine is not an alternative to slow ascent and acclimatisation.[4,5]

1. Oelz O, *et al.* Nifedipine for high altitude pulmonary oedema. *Lancet* 1989; ii: 1241–4. Correction. *ibid.* 1991; 337: 556.
2. Jamieson A, Kerr GW. Treatment of high-altitude pulmonary oedema. *Lancet* 1992; 340: 1468.
3. Bärtsch P, *et al.* Prevention of high-altitude pulmonary oedema by nifedipine. *N Engl J Med* 1991; 325: 1284–9.
4. Luks AM, *et al.* Wilderness Medical Society consensus guidelines for the prevention and treatment of acute altitude illness. *Wilderness Environ Med* 2010; 21: 146–55. Correction. *ibid.*; 386.
5. A'Court CHD, *et al.* Doctor on a mountaineering expedition. *BMJ* 1995; 310: 1248–52.

Hyperinsulinaemic hypoglycaemia. Nifedipine may have effects on blood-glucose levels due to inhibition of insulin release[1] (see Effects on Carbohydrate Metabolism, under Adverse Effects, p. 1451.1). There have been reports[1–4] of the successful use of nifedipine to increase blood-glucose levels in infants with hyperinsulinaemic hypoglycaemia (see under Uses of Glucagon, p. 1554.3), and it may have a role[5,6] as adjunctive therapy in such patients. The *BNFC* suggests that neonates with persistent hyperinsulinaemic hypoglycaemia may be given oral nifedipine in a dose of 100 to 200 micrograms/kg 4 times daily, increased to a maximum of 600 micrograms/kg 4 times daily if required.

1. Lindley KJ, *et al.* Ionic control of beta cell function in nesidioblastosis: a possible therapeutic role for calcium channel blockade. *Arch Dis Child* 1996; 74: 373–8.
2. Eichmann D, *et al.* Treatment of hyperinsulinaemic hypoglycaemia with nifedipine. *Eur J Pediatr* 1999; 158: 204–6.
3. Bas F, *et al.* Successful therapy with calcium channel blocker (nifedipine) in persistent neonatal hyperinsulinemic hypoglycemia of infancy. *J Pediatr Endocrinol Metab* 1999; 12: 873–8.
4. Shanbag P, *et al.* Persistent hyperinsulinemic hypoglycemia of infancy—successful therapy with nifedipine. *Indian J Pediatr* 2002; 69: 271–2.
5. Aynsley-Green A, *et al.* Practical management of hyperinsulinism in infancy. *Arch Dis Child Fetal Neonatal Ed* 2000; 82: F98–F107.
6. Müller D, *et al.* Should nifedipine be used to counter low blood sugar levels in children with persistent hyperinsulinaemic hypoglycaemia? *Arch Dis Child* 2004; 89: 83–5.

Hypertension. Long-acting calcium-channel blockers are among the drug groups that may be used as first-line therapy in uncomplicated hypertension (p. 1251.1); meta-analyses[1,2] and large studies[3] have shown them to be broadly comparable in safety and efficacy to other first-line antihypertensives, and they are particularly recommended in older patients. One systematic review[2] suggested that diuretics were associated with fewer cardiovascular events than calcium-channel blockers, but that the latter were superior to beta blockers. Dihydropyridine calcium-channel blockers are also useful in patients who require combination therapy[4,5] and are particularly effective when given with a beta blocker or an ACE inhibitor. However, the use of short-acting calcium-channel blockers is not recommended since they may increase mortality (see under Adverse Effects, p. 1450.2).

Calcium-channel blockers may also be used in **hypertensive crises**, particularly in hypertensive urgencies where oral therapy is suitable. Nifedipine has been given sublingually, or by biting the capsule and swallowing the contents, but such use may cause dangerous hypotension and is no longer recommended in adults, although the *BNFC* considers it appropriate in children. In hypertensive emergencies, where parenteral antihypertensives are required, intravenous nicardipine may be used. One study concluded that intravenous nicardipine was as effective as sodium nitroprusside in the treatment of postoperative hypertension.[6]

For **hypertension in pregnancy**, first-line treatment is usually methyldopa or a beta blocker but calcium-channel blockers may also be used. Nifedipine is reported to be teratogenic in *animals* and may inhibit labour, but it has been tried in a limited number of patients with pre-eclampsia. Although a high rate of caesarean deliveries, premature births, and small-for-date infants was reported[7] in patients given nifedipine as a second-line drug, assessment of the role of nifedipine is difficult because outcome is often poor in such severely compromised pregnancies.[8] Fetal nifedipine concentrations have been reported to be 75% of maternal values 2 to 3 hours after sublingual doses.[9] However, nifedipine in a single 20-mg oral dose lowered blood pressure without compromising blood flow in the fetus in 9 women in the third trimester with normal haemodynamics.[8] This is in line with other reports,[10] although there has also been a report[11] of severe hypotension and fetal distress after sublingual nifedipine. In a randomised controlled study,[12] nifedipine 10 to 30 mg sublingually followed by 10 mg orally as capsules every 6 hours, increasing to 20 mg every 4 hours if necessary, was compared with hydralazine 12.5 mg intravenously as required followed by 20 to 30 mg orally every 6 hours, with added methyldopa if necessary. Both groups also received intravenous magnesium sulfate. Effective control of blood pressure was achieved in 23 of 24 patients given nifedipine compared with only 17 of 25 given hydralazine and 9 nifedipine patients achieved term delivery compared with only 2 of those receiving hydralazine. The average gestational age was greater in infants in the nifedipine group; hence these neonates weighed more and had fewer neonatal complications when compared with neonates from the hydralazine treated group.

1. Opie LH, Schall R. Evidence-based evaluation of calcium channel blockers for hypertension: equality of mortality and cardiovascular risk relative to conventional therapy. *J Am Coll Cardiol* 2002; 39: 315–22. Correction. *ibid.*; 1409–10.
2. Chen N, *et al.* Calcium channel blockers versus other classes of drugs for hypertension. Available in The Cochrane Database of Systematic Reviews: Issue 8. Chichester: John Wiley; 2010 (accessed 24/11/10).
3. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2981–97. Correction. *ibid.*; 289: 178.

4. Epstein BJ, *et al.* Dihydropyridine calcium channel antagonists in the management of hypertension. *Drugs* 2007; 67: 1309–27.
5. Haller H. Effective management of hypertension with dihydropyridine calcium channel blocker-based combination therapy in patients at high cardiovascular risk. *Int J Clin Pract* 2008; 62: 781–90.
6. Halpern NA, *et al.* Postoperative hypertension: a multicenter, prospective, randomized comparison between intravenous nicardipine and sodium nitroprusside. *Crit Care Med* 1992; 20: 1637–43.
7. Constantine G, *et al.* Nifedipine as a second line antihypertensive drug in pregnancy. *Br J Obstet Gynaecol* 1987; 94: 1136–42.
8. Hanretty KP, *et al.* Effect of nifedipine on Doppler flow velocity waveforms in severe pre-eclampsia. *BMJ* 1989; 299: 1205–6.
9. Pirhonen JP, *et al.* Single dose of nifedipine in normotensive pregnancy: nifedipine concentrations, hemodynamic responses, and uterine and fetal flow velocity waveforms. *Obstet Gynecol* 1990; 76: 807–11.
10. Pirhonen JP, *et al.* Uterine and fetal flow velocity wave forms in hypertensive pregnancy: the effect of a single dose of nifedipine. *Obstet Gynecol* 1990; 76: 37–41.
11. Impey L. Severe hypotension and fetal distress following sublingual administration of nifedipine to a patient with severe pregnancy induced hypertension at 33 weeks. *Br J Obstet Gynaecol* 1993; 100: 959–61.
12. Penakel K, *et al.* Nifedipine in the treatment of severe preeclampsia. *Obstet Gynecol* 1991; 77: 331–7.

Kidney disorders. Although nifedipine can adversely affect renal function (see under Adverse Effects, p. 1451.2) there is evidence that calcium-channel blockers may be of benefit in some kidney disorders. Proteinuria is an important indicator of glomerular kidney disease (p. 1604.3) of various causes and the effects of calcium-channel blockers on proteinuria and renal dysfunction have been studied in a variety of patients. Results have been mixed and if there is a protective effect of calcium-channel blockers on renal function it is not clear if this is due to their antihypertensive action or whether they also have additional effects. Monotherapy with dihydropyridine calcium-channel blockers has not been shown to adequately protect renal function in patients with non-diabetic proteinuria, despite good blood pressure control,[1] whereas the renal benefits of ACE inhibitors and angiotensin II receptor antagonists are somewhat better established (see p. 1284.1 and p. 1423.3, respectively). However, reviews[2-5] have concluded that a calcium-channel blocker may safely be added when first-line therapy is insufficient in reducing blood pressure in patients with diabetic or non-diabetic proteinuria. Calcium-channel blockers may also delay the progression of chronic renal insufficiency although non-dihydropyridine calcium-channel blockers appear to slow renal decline and reduce proteinuria more consistently than dihydropyridines in patients with diabetic or non-diabetic renal disease, even at similar rates of blood pressure reduction.[2,6-9]

Nifedipine has also been used in the management of renal calculi (see p. 1450.1), and has been reported to protect against ciclosporin-induced nephrotoxicity in renal transplant patients (see Transplantation, p. 1450.2).

1. Ziakka S, *et al.* Calcium channels blockers and progression of kidney disease. *Ren Fail* 2007; 29: 1003–12.
2. Toto RD. Management of hypertensive chronic kidney disease: role of calcium channel blockers. *J Clin Hypertens (Greenwich)* 2005; 7 (4 suppl 1): 15–20.
3. Segura J, *et al.* Calcium channel blockers and renal protection: insights from the latest clinical trials. *J Am Soc Nephrol* 2005; 16 (suppl 1): S64–S66.
4. Rahn KH. The role of calcium antagonists in patients with chronic renal failure. *Pediatr Nephrol* 2005; 20: 1208–13.
5. Nosadini R, Tonolo G. Cardiovascular and renal protection in type 2 diabetes mellitus: the role of calcium channel blockers. *J Am Soc Nephrol* 2002; 13 (suppl 3): S216–S223.
6. Nathan S, *et al.* Calcium antagonists: effects on cardio-renal risk in hypertensive patients. *Hypertension* 2005; 46: 637–42.
7. Bakris GL, *et al.* Differential effects of calcium antagonist subclasses on markers of nephropathy progression. *Kidney Int* 2004; 65: 1991–2002.
8. Derwa A, *et al.* Calcium channel blockers in the prevention of end stage renal disease: a review. *Acta Clin Belg* 2004; 59: 44–56.
9. Toto RD. Reducing cardiovascular events in high-risk patients: the challenge of managing hypertension in patients with diabetic renal disease. *J Clin Hypertens (Greenwich)* 2007; 9 (11 suppl 4): 16–25.

Migraine and cluster headache. Drugs with calcium-channel blocking activity have been given in the management of headaches considered to have a vascular component such as migraine (p. 670.3) and cluster headache (p. 670.1).

In migraine prophylaxis, of those drugs with calcium-channel blocking activity studied, flunarizine (p. 630.1) has the best documented efficacy, and verapamil may be useful. Other calcium-channel blockers such as diltiazem, nifedipine, and nimodipine have been tried, but results have been conflicting. Verapamil has also been used successfully in patients with hemiplegic migraine, both intravenously to abort attacks,[1,2] and orally for prophylaxis.[2]

Beneficial effects have been reported[3-7] with calcium-channel blockers in the prevention of cluster headache during cluster periods. Verapamil appears to have been the most widely used. In one double-blind study it was found to be of similar efficacy to lithium[8] and appeared to produce fewer adverse effects. High doses of oral verapamil (up to 1.2 g daily in some patients) have been used;[7] the mode of action is unclear. There have also been reports[9] of the successful use of nimodipine in patients with thunderclap headache.

1. Ng TMH, *et al.* The effect of intravenous verapamil on cerebral hemodynamics in a migraine patient with hemiplegia. *Ann Pharmacother* 2000; 34: 39–43.
2. Yu W, Horowitz SH. Treatment of sporadic hemiplegic migraine with calcium-channel blocker verapamil. *Neurology* 2003; 60: 120–1.
3. Jónsdóttir M, *et al.* Efficacy, side effects and tolerance compared during headache treatment with three different calcium blockers. *Headache* 1987; 27: 364–9.
4. Gabai IJ, Spierings ELH. Prophylactic treatment of cluster headache with verapamil. *Headache* 1989; 29: 167–8.
5. Leone M, *et al.* Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. *Neurology* 2000; 54: 1382–5.
6. Matharu MS, *et al.* Management of trigeminal autonomic cephalgias and hemicrania continua. *Drugs* 2003; 63: 1637–77.
7. Tfelt-Hansen P, Tfelt-Hansen J. Verapamil for cluster headache: clinical pharmacology and possible mode of action. *Headache* 2009; 49: 117–25.
8. Bussone G, *et al.* Double blind comparison of lithium and verapamil in cluster headache prophylaxis. *Headache* 1990; 30: 411–17.
9. Lu S-R, *et al.* Nimodipine for treatment of primary thunderclap headache. *Neurology* 2004; 62: 1414–16.

Oesophageal motility disorders. Results from a number of studies have indicated that nifedipine, usually in doses of 10 to 20 mg sublingually, may be of benefit in patients with achalasia, reducing lower oesophageal sphincter pressure and producing some symptomatic improvement.[1-5] Nifedipine has a role when mechanical dilatation of the sphincter or surgery are not feasible (see Oesophageal Motility Disorders, p. 1816.2).

See also Effects on the Oesophagus under Adverse Effects, p. 1451.3.

1. Bortolotti M, Labò G. Clinical and manometric effects of nifedipine in patients with esophageal achalasia. *Gastroenterology* 1981; 80: 39–44.
2. Gelfond M, *et al.* Isosorbide dinitrate and nifedipine treatment of achalasia: a clinical, manometric and radionuclide evaluation. *Gastroenterology* 1982; 83: 963–9.
3. Traube M, *et al.* Effects of nifedipine in achalasia and in patients with high-amplitude peristaltic esophageal contractions. *JAMA* 1984; 252: 1733–6.
4. Román FJ, *et al.* Effects of nifedipine in achalasia and patients with high-amplitude peristaltic esophageal contractions. *JAMA* 1985; 253: 2046.
5. Coccia G, *et al.* Prospective clinical and manometric study comparing pneumatic dilatation and sublingual nifedipine in the treatment of oesophageal achalasia. *Gut* 1991; 32: 604–6.

Parkinson's disease. Case-control studies[1,2] have found that long-term use of calcium-channel blockers (but not of ACE inhibitors, angiotensin II receptor antagonists, or beta blockers) may be associated with a significantly reduced risk of developing Parkinson's disease, although other studies have reported no benefit.[3] The authors of one study[2] that differentiated between types of calcium-channel blocker suggested that only centrally acting L-type calcium-channel blockers might be expected to have an effect. They reported a 26 to 30% risk reduction with all dihydropyridines except amlodipine, which does not easily cross the blood-brain barrier. No risk reduction was seen with verapamil or diltiazem.

1. Becker C, *et al.* Use of antihypertensives and the risk of Parkinson disease. *Neurology* 2008; 70: 1438–44.
2. Ritz B, *et al.* L-type calcium channel blockers and Parkinson disease in Denmark. *Ann Neurol* 2010; 67: 600–6.
3. Simon KC, *et al.* Calcium channel blocker use and risk of Parkinson's disease. *Mov Disord* 2010; 25: 1818–22.

Peripheral vascular disease. Vasospastic arterial diseases (p. 1275.3) such as Raynaud's syndrome are due to an inappropriate response to temperature, usually cold, when vasoconstriction and/or vasospasm occurs. Calcium-channel blockers have been of benefit in Raynaud's syndrome, and are usually the first choice if drug therapy is needed, but it is not entirely clear which of their pharmacological actions is responsible. The most widely used and studied is nifedipine. Evidence of subjective benefit has been seen both in primary idiopathic disease[1] and in Raynaud's phenomenon secondary to systemic sclerosis,[2-5] SLE,[2,3] rheumatoid arthritis,[3] and cancer chemotherapy,[6] or associated with breast feeding.[7-9] Objective improvement as shown by evidence of improved digital blood flow has been seen in some[10-13] but not all[4] studies. Patients with Raynaud's syndrome usually receive an immediate-release formulation of nifedipine; however, a modified-release preparation has also been tried[14] and may reduce the incidence of adverse effects.

Nifedipine in doses of 20 to 60 mg daily has also been reported to be of benefit in the treatment of another vasospastic condition, chilblains, both for established chilblains and in the prevention of relapse.[15,16] Diltiazem appears to be less effective.[16]

1. Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud's phenomenon: a meta-analysis. *Rheumatology (Oxford)* 2005; 44: 145–50.
2. Smith CD, McKendry RJR. Controlled trial of nifedipine in the treatment of Raynaud's phenomenon. *Lancet* 1982; ii: 1299–1301.
3. Kahan A, *et al.* Nifedipine for Raynaud's phenomenon. *Lancet* 1983; i: 131.
4. Rademaker M, *et al.* Comparison of intravenous infusions of iloprost and oral nifedipine in treatment of Raynaud's phenomenon in patients with systemic sclerosis: a double blind randomised study. *BMJ* 1989; 298: 561–4.
5. Thompson AE, *et al.* Calcium-channel blockers for Raynaud's phenomenon in systemic sclerosis. *Arthritis Rheum* 2001; 44: 1841–7.
6. Hantel A, *et al.* Nifedipine and oncologic Raynaud phenomenon. *Ann Intern Med* 1988; 108: 767.
7. Garrison CP. Nipple vasospasms, Raynaud's syndrome, and nifedipine. *J Hum Lact* 2002; 18: 382–5.
8. Anderson JE, *et al.* Raynaud's phenomenon of the nipple: a treatable cause of painful breastfeeding. *Pediatrics* 2004; 113: e360–4.
9. Page SM, McKenna DS. Vasospasm of the nipple presenting as painful lactation. *Obstet Gynecol* 2006; 108: 806–8.
10. Gasser P. Reaction of capillary blood cell velocity in nailfold capillaries to nifedipine and ketanserin in patients with vasospastic disease. *J Int Med Res* 1991; 19: 24–31.
11. Thomas RHM, *et al.* Nifedipine in the treatment of Raynaud's phenomenon in patients with systemic sclerosis. *Br J Dermatol* 1987; 117: 237–41.
12. Nilsson H, *et al.* Treatment of digital vasospastic disease with the calcium-entry blocker nifedipine. *Acta Med Scand* 1984; 215: 135–9.
13. Finch MB, *et al.* The peripheral vascular effects of nifedipine in Raynaud's disease. *Br J Clin Pharmacol* 1986; 21: 100P–101P.
14. Raynaud's Treatment Study Investigators. Comparison of sustained-release nifedipine and temperature biofeedback for treatment of primary Raynaud phenomenon: results from a randomized clinical trial with 1-year follow-up. *Arch Intern Med* 2000; 160: 1101–8.
15. Rustin MHA, *et al.* The treatment of chilblains with nifedipine: the results of a pilot study, a double-blind placebo-controlled randomized study and a long-term open trial. *Br J Dermatol* 1989; 120: 267–75.
16. Patra AK, *et al.* Diltiazem vs. nifedipine in chilblains: a clinical trial. *Indian J Dermatol Venereol Leprol* 2003; 69: 209–11.

Phaeochromocytoma. Pharmacological management of phaeochromocytoma (p. 1278.1) is mainly with alpha-adrenergic blockade, and tachycardia may subsequently be controlled by cautious addition of a beta blocker. There have also been some reports[1-4] of the use of nifedipine to treat cardiovascular symptoms in adults and children with phaeochromocytoma.

1. Serfas D, *et al.* Phaeochromocytoma and hypertrophic cardiomyopathy: apparent suppression of symptoms and noradrenaline secretion by calcium-channel blockade. *Lancet* 1983; ii: 711–13.
2. Lenders JWM, *et al.* Treatment of a phaeochromocytoma of the urinary bladder with nifedipine. *BMJ* 1985; 290: 1624–5.
3. Favre L, Vallotton MB. Nifedipine in pheochromocytoma. *Ann Intern Med* 1986; 104: 125.
4. Deal JE, *et al.* Phaeochromocytoma—investigation and management of 10 cases. *Arch Dis Child* 1990; 65: 269–74.

Premature labour. Calcium-channel blockers (of which nifedipine is the most studied) have become increasingly favoured[1-3] as first-line tocolytics to postpone premature labour (p. 2131.1) over more traditionally-used drugs such as $beta_2$ agonists or magnesium. Meta-analyses and systematic reviews[4-7] have concluded that calcium-channel blockers were at least as effective as $beta_2$ agonists for tocolysis and caused fewer maternal adverse effects, although atosiban may be safer than either.[8] A meta-analysis[7] also found nifedipine to be as effective as, and associated with fewer adverse effects than, magnesium sulfate for tocolysis. The role of calcium-channel blockers in maintenance therapy is much less clear,[7,9,10] and some have found them to be ineffective.[7] There is also no evidence that nifedipine tocolysis is of value in facilitating external cephalic version (unlike $beta_2$ agonists) in women with breech or transverse presentation of the fetus.[11] A systematic review[12] that examined 31 studies of the efficacy of nifedipine in premature labour concluded that their overall quality was poor. Others[13] have expressed concern about the safety of calcium-channel blockers, reviewing cases of dyspnoea and pulmonary oedema in particular. They suggest that these drugs should not be used with intravenous beta agonists, that high doses should be avoided in women with cardiovascular compromise or multiple gestations, and that blood pressure and fetal heart rate should be monitored during use of short-acting preparations, which should not be chewed.

1. Tsatsaris V, Carbonne B. Tocolyse par les inhibiteurs calciques. *J Gynecol Obstet Biol Reprod (Paris)* 2001; 30: 246–51.
2. Papatsonis DNM, *et al.* Update on the controversies of tocolytic therapy for the prevention of preterm birth. *Acta Obstet Gynecol Scand* 2004; 83: 414.
3. Simhan HN, Caritis SN. Prevention of preterm delivery. *N Engl J Med* 2007; 357: 477–87.
4. Ray JG. Meta-analysis of nifedipine versus beta-sympathomimetic agents for tocolysis during preterm labour. *J Soc Obstet Gynaecol Can* 1998; 20: 259–69.
5. Tsatsaris V, *et al.* Tocolysis with nifedipine or beta-adrenergic agonists: a meta-analysis. *Obstet Gynecol* 2001; 97: 840–7.
6. King JF, *et al.* Calcium channel blockers for inhibiting preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 03/03/09).
7. Conde-Agudelo A, *et al.* Nifedipine in the management of preterm labor: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2011; 204: 134.e1–134.e20.
8. de Heus R, *et al.* Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study. *BMJ* 2009; 338: b744.
9. Gaunekar NN, Crowther CA. Maintenance therapy with calcium channel blockers for preventing preterm birth after threatened preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 03/03/09).
10. Kim A, Shim JY. Emerging tocolytics for maintenance therapy of preterm labour: oxytocin antagonists and calcium channel blockers. *BJOG* 2006; 113 (suppl 3): 113–15.
11. Wilcox C, *et al.* Effectiveness of nifedipine tocolysis to facilitate external cephalic version: a systematic review. *BJOG* 2011; 118: 423–8.
12. Lamont RF, *et al.* Steering Group of the International Preterm Labour Council. The quality of nifedipine studies used to assess tocolytic efficacy: a systematic review. *J Perinat Med* 2005; 33: 287–95.
13. Oei SG. Calcium channel blockers for tocolysis: a review of their role and safety following reports of serious adverse events. *Eur J Obstet Gynecol Reprod Biol* 2006; 126: 137–45.

Pulmonary hypertension. Vasodilators have been tried in pulmonary arterial hypertension (p. 1278.2) on the premise that pulmonary vasoconstriction is an important component of the condition, and calcium-channel blockers have been widely used. However, in practice only a small proportion (<10%)[1-3] of patients respond to calcium-channel blockers, and their empirical use in pulmonary hypertension is not recommended. Instead, the subset of responders may be identified using an acute response test in which a short-acting vasodilator such as inhaled nitric oxide or intravenous epoprostenol is given.[2] (The use of calcium-channel blockers themselves is no longer recommended for acute testing as severe adverse effects, including fatalities, have occurred.[4]) Cautious treatment with calcium-channel blockers may be started in those who respond.[1-3,5] Improved survival was seen in a study[6] in patients treated with high doses of nifedipine (120 to 240 mg daily) or diltiazem (540 to 900 mg daily) over a 5-year period, and these remain the drugs with which most experience lies. Choice may be influenced by baseline heart rate, nifedipine usually being given to those with relative bradycardia and diltiazem to those with relative tachycardia. Amlodipine has also been tried; verapamil is too strong a negative inotrope and should be avoided.[3,5] Patients should be monitored closely as the dose is titrated and assessed after 1 and 3 months, and additional or alternative therapy tried if the response is inadequate.[1,3,5]

1. National Pulmonary Hypertension Centres of the UK and Ireland. Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland. *Thorax* 2008; 63 (suppl 2): ii1–ii41. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Pulmonary%20hypertension/PulmHyper_ThoraxMarch08.pdf (accessed 04/03/09)
2. Sitbon O, *et al.* Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005; 111: 3105–11.
3. McLaughlin VV, *et al.* ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association. *Circulation* 2009; 119: 2250–94. Available at: http://circ.ahajournals.org/cgi/reprint/119/16/2250.pdf (accessed 29/03/11)
4. Badesch DB, *et al.* American College of Chest Physicians. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004; 126 (1 suppl): 35S–62S. Also available at: http://chestjournal.chestpubs.org/content/126/1_suppl/35S.full.pdf (accessed 29/03/11)
5. Badesch DB, *et al.* Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. *Chest* 2007; 131: 1917–28. Also available at: http://www.chestjournal.org/cgi/reprint/131/6/1917 (accessed 04/03/09)
6. Rich S, *et al.* The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992; 327: 76–81.

Renal calculi. There is some interest in the possible use of drug treatment to ease the spontaneous passage of renal calculi (p. 2350.3) in patients with uncomplicated lower ureteral stones. It has been suggested that the combination of a calcium-channel blocker (to reduce ureteral spasm) with a corticosteroid (to reduce oedema) may be useful. Small studies[1-3] have used modified-release preparations of nifedipine, given in oral doses of 30 mg daily for up to 28 days, with oral deflazacort 30 mg daily for up to 10 days. If the stone had not been expelled within 28 days, the patient was treated with extracorporeal shock wave lithotripsy or ureteroscopy. Treatment with nifedipine and deflazacort was found to improve the rate of stone expulsion and expulsion time, and to reduce analgesic requirements.

The use of a 10-day course of nifedipine and deflazacort has also been studied[4] as adjunctive therapy after lithotripsy. It was found to ease the passage of stone fragments, reduce analgesic requirements, and increase the number of patients who were stone-free after 45 days. A 14-day course of nifedipine with ketoprofen after lithotripsy also resulted[5] in improved stone-free rates at 1 and 2 months, and a lower percentage of patients needing re-treatment compared with controls.

1. Porpiglia P, *et al.* Effectiveness of nifedipine and deflazacort in the management of distal ureter stones. *Urology* 2000; 56: 579–83.
2. Porpiglia F, *et al.* Nifedipine versus tamsulosin for the management of lower ureteral stones. *J Urol (Baltimore)* 2004; 172: 568–71.
3. Deflabella M, *et al.* Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureteral calculi. *J Urol (Baltimore)* 2005; 174: 167–72.
4. Porpiglia F, *et al.* Role of adjunctive medical therapy with nifedipine and deflazacort after extracorporeal shock wave lithotripsy of ureteral stones. *Urology* 2002; 59: 835–8.
5. Micali S, *et al.* Efficacy of expulsive therapy using nifedipine or tamsulosin, both associated with ketoprofene, after shock wave lithotripsy of ureteral stones. *Urol Res* 2007; 35: 133–7.

Tardive dyskinesia. Calcium-channel blockers have been tried in the treatment of tardive dyskinesia (p. 1049.3). However, a systematic review[1] concluded that their effects are unclear and they should not be used.

1. Soares-Weiser K, Rathbone J. Calcium channel blockers for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 28/03/06).

Transplantation. The main adverse effect of ciclosporin is reversible, dose-related nephrotoxicity. There is some evidence that nifedipine may be of value in protecting against this effect. Retrospective analysis[1] of 106 ciclosporin-treated renal transplant patients found that patients taking nifedipine for hypertension had better graft function, despite having shorter graft duration and therefore requiring higher dosage of ciclosporin, than hypertensive patients given other drug treatment. Subsequent studies have similarly reported improved graft function[2] in patients receiving nifedipine and suggest that graft survival is also improved.[3,4] A nephroprotective effect has also been reported with amlodipine,[5] felodipine,[6] isradipine,[7] lacidipine,[8] and nitrendipine,[9] and with the non-dihydropyridines diltiazem and verapamil (see p. 1360.1 and p. 1523.3 respectively), although a study[10] with nicardipine failed to show any improvement in graft function. However, a systematic review[11] concluded that although calcium-channel blockers given in the perioperative period appear to reduce the incidence of acute tubular necrosis in renal transplant patients, the results should be viewed cautiously due to the lack of good quality data.

For a report of adverse effects attributed to reduced metabolism of nifedipine in patients taking ciclosporin, see Immunosuppressants, under Interactions, p. 1454.1.

1. Peehally J, *et al.* Does nifedipine ameliorate cyclosporin A nephrotoxicity? *BMJ* 1987; 295: 310.
2. Shin GT, *et al.* Effect of nifedipine on renal allograft function and survival beyond one year. *Clin Nephrol* 1997; 47: 33–6.
3. Weinrauch LA, *et al.* Role of calcium channel blockers in diabetic renal transplant patients: preliminary observations on protection from sepsis. *Clin Nephrol* 1995; 44: 185–92.
4. Mehrens T, *et al.* The beneficial effects of calcium channel blockers on long-term kidney transplant survival are independent of blood-pressure reduction. *Clin Transplant* 2000; 14: 257–61.
5. Venkat Raman G, *et al.* Renal effects of amlodipine in normotensive renal transplant recipients. *Nephrol Dial Transplant* 1999; 14: 384–8.
6. Madsen JK, *et al.* The effect of felodipine on renal function and blood pressure in cyclosporin-treated renal transplant recipients during the first three months after transplantation. *Nephrol Dial Transplant* 1998; 13: 2327–34.
7. van Riemsdijk IC, *et al.* Addition of isradipine (Lomir) results in a better renal function after kidney transplantation: a double-blind, randomized, placebo-controlled, multi-center study. *Transplantation* 2000; 70: 122–6.
8. Kuypers DR, *et al.* Lacidipine Study Group. Calcium channel blockade and preservation of renal graft function in cyclosporine-treated recipients: a prospective randomized placebo-controlled 2-year study. *Transplantation* 2004; 78: 1204–11.
9. Rahn K-H, *et al.* Effect of nitrendipine on renal function in renal-transplant patients treated with cyclosporin: a randomised trial. *Lancet* 1999; 354: 1415–20.
10. Kessler M, *et al.* Influence of nicardipine on renal function and plasma cyclosporin in renal transplant patients. *Eur J Clin Pharmacol* 1989; 36: 637–8.
11. Shilliday IR, Sherif M. Calcium channel blockers for preventing acute tubular necrosis in kidney transplant recipients. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 05/03/09).

Urticaria. Oral antihistamines are the main drugs used in the management of urticaria (p. 1689.2). Addition of a calcium-channel blocker, such as nifedipine, has been suggested for patients unresponsive to treatment with oral antihistamines alone, but results have been mixed.[1,2]

1. Lawlor F, *et al.* Calcium antagonist in the treatment of symptomatic dermographism: low-dose and high-dose studies with nifedipine. *Dermatologica* 1988; 177: 287–91.
2. Bressler RB, *et al.* Therapy of chronic idiopathic urticaria with nifedipine: demonstration of beneficial effect in a double-blinded, placebo-controlled, crossover trial. *J Allergy Clin Immunol* 1989; 83: 756–63.

Adverse Effects

The most common adverse effects of nifedipine are associated with its vasodilator action and often diminish on continued therapy. They include dizziness, flushing, headache, hypotension, peripheral oedema, tachycardia, and palpitations. Nausea, constipation, and other gastrointestinal disturbances, micturition disorders including increased frequency, lethargy, eye pain, visual disturbances, syncope, vertigo, migraine, and mood disturbances have also occurred. A paradoxical increase in ischaemic chest pain may occur at the start of treatment and in a few patients excessive fall in blood pressure has led to cerebral or myocardial ischaemia or transient blindness.

There have been reports of rashes (including erythema multiforme), fever, and abnormalities in liver function, including cholestasis, due to hypersensitivity reactions. Gingival hyperplasia, pruritus, myalgia, tremor, gynaecomastia, and impotence have been reported.

Some tablets formulated for once-daily use are covered in a membrane which is not digested and may cause gastrointestinal obstruction; bezoars may rarely occur.

Overdosage may be associated with bradycardia and hypotension; hyperglycaemia, metabolic acidosis, and coma may also occur.

Nifedipine has been reported to be teratogenic in *animals*.

Effects on mortality. In the mid-1990s a series of reports and reviews raised concerns about calcium-channel blockers (particularly short-acting nifedipine and high doses) in increasing cardiovascular and overall mortality. Possible links with cancer, haemorrhage, and depression and suicide are discussed separately (see Carcinogenicity and Effects on the Blood, below, and Effects on Mental Function, p. 1451.3, respectively).

In response, the US National Heart, Lung, and Blood Institute issued a statement warning that short-acting nifedipine should be used with great caution (if at all), especially at higher doses, in the treatment of hypertension, angina, and myocardial infarction,[1] and in some countries short-acting nifedipine preparations were withdrawn. Short-acting calcium-channel blockers can cause a dangerous rebound sympathetic stimulation, but the recommendations were occasionally extrapolated to include long-acting preparations and the general use of calcium-channel blockers fell out of favour. However, a review by the WHO/ISH pointed out that much of the evidence for adverse effects came from observational studies or small randomised studies (many of which had used the older short-acting calcium-channel blockers) and concluded that, as there was insufficient evidence to confirm either benefit or harm, recommendations on the management of angina, hypertension, and myocardial infarction should remain unchanged.[2] Since then, several large studies have found compelling evidence for the use of long-acting calcium-channel blockers in hypertension[3-6] and angina,[5] including an improvement of morbidity and mortality outcomes such as stroke[4] (although calcium-channel blockers do not have a role in myocardial infarction). The use of short-acting preparations of calcium-channel blockers such as nifedipine is no longer recommended for these indications; the once commonplace practice of biting a short-acting nifedipine capsule for the rapid reduction of acute hypertension should also be avoided.

More recently, a retrospective observational study has suggested that the use of dihydropyridine calcium-channel blockers was associated with higher 30-day mortality in patients undergoing surgery for aortic aneurysm.[7]

1. McCarthy M. US NIH issues warning on nifedipine. *Lancet* 1995; 346: 689–90.
2. Ad Hoc Subcommittee of the Liaison Committee of the World Health Organisation and the International Society of Hypertension. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. *J Hypertens* 1997; 15: 105–15.
3. Grossman E, Messerli FH. Are calcium antagonists beneficial in diabetic patients with hypertension? *Am J Med* 2004; 116: 44–9.
4. Basile J. The role of existing and newer calcium channel blockers in the treatment of hypertension. *J Clin Hypertens (Greenwich)* 2004; 6: 621–9.
5. Croom KF, Wellington K. Modified-release nifedipine: a review of the use of modified-release formulations in the treatment of hypertension and angina pectoris. *Drugs* 2006; 66: 497–528.
6. Epstein BJ, *et al.* Dihydropyridine calcium channel antagonists in the management of hypertension. *Drugs* 2007; 67: 1309–27.
7. Kertai MD, *et al.* Dihydropiridine calcium-channel blockers and perioperative mortality in aortic aneurysm surgery. *Br J Anaesth* 2008; 101: 458–65.

Carcinogenicity. An observational study carried out between 1988 and 1992 suggested that calcium-channel blockers were associated with an increased risk of cancer.[1] Subsequent studies have failed to support this finding.[2-7] A review by the WHO/ISH concluded that there is no good evidence that calcium-channel blockers increase cancer risk,[8] and the biological basis for an effect of calcium-channel blockers on cancer risk has also been questioned.[9] The large, long-term, randomised Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT)[10] found no increase in the incidence of cancer in patients receiving a calcium-channel blocker (amlodipine) compared with those receiving a diuretic (chlortalidone).

1. Pahor M, *et al.* Calcium-channel blockade and incidence of cancer in aged populations. *Lancet* 1996; 348: 493–7.
2. Jick H, *et al.* Calcium-channel blockers and risk of cancer. *Lancet* 1997; 349: 525–8.
3. Rosenberg L, *et al.* Calcium channel blockers and the risk of cancer. *JAMA* 1998; 279: 1000–4.
4. Braun S, *et al.* Calcium channel blocking agents and risk of cancer in patients with coronary heart disease. *J Am Coll Cardiol* 1998; 31: 804–8.
5. Sajadieh A, *et al.* Verapamil and risk of cancer in patients with coronary artery disease. *Am J Cardiol* 1999; 83: 1419–22.
6. Meier CR, *et al.* Angiotensin-converting enzyme inhibitors, calcium channel blockers, and breast cancer. *Arch Intern Med* 2000; 160: 349–53.
7. Cohen HJ, *et al.* Calcium channel blockers and cancer. *Am J Med* 2000; 108: 210–15.
8. Ad Hoc Subcommittee of the Liaison Committee of the World Health Organisation and the International Society of Hypertension. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. *J Hypertens* 1997; 15: 105–15.
9. Mason RP. Calcium channel blockers, apoptosis and cancer: is there a biologic relationship? *J Am Coll Cardiol* 1999; 34: 1857–66.
10. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2981–97. Correction. *ibid.*; 289: 178.

Effects on the blood. Treatment with nifedipine significantly reduces platelet aggregation *in vitro*[1] and inhibition of platelet function has been reported in healthy subjects given oral (but not intravenous) nifedipine.[2,3] There has therefore been concern[4] that calcium-channel blockers

might produce **haemorrhagic complications** in surgical patients (specifically, those undergoing coronary bypass surgery). Major surgical bleeding was associated with nimodipine in patients undergoing cardiac valve replacement,[5] although it has been used in other situations apparently without an increased risk of bleeding.[6] A later systematic review[7] found that dihydropyridines significantly increased endogenous fibrinolytic activity, although not in healthy subjects; the authors suggested that the effect might be due to interaction with anticoagulant or fibrinolytic drugs.

Conflicting results have been reported with regard to the risk of gastrointestinal bleeding. A prospective cohort study in 1636 elderly hypertensive patients,[8] and a subsequent case-control study,[9] reported that calcium-channel blockers were associated with an increased risk of gastrointestinal haemorrhage compared with beta blockers. However, it was suggested[10] that this may have been due to a protective effect of beta blockers rather than an adverse effect of calcium-channel blockers, and another study[11] also suggested that the risk of gastrointestinal bleeding was not materially increased by calcium-channel blockers.

Calcium-channel blockers have also been associated with **blood dyscrasias**; there have been case reports of aplastic anaemia with nifedipine,[12] and of thrombocytopenia with amlodipine[13] and with diltiazem.[14,15]

1. Ośmiałowska Z, *et al.* Effect of nifedipine monotherapy on platelet aggregation in patients with untreated essential hypertension. *Eur J Clin Pharmacol* 1990; 39: 403–4.
2. Winther K, *et al.* Dose-dependent effects of verapamil and nifedipine on in vivo platelet function in normal volunteers. *Eur J Clin Pharmacol* 1990; 39: 291–3.
3. Walley TJ, *et al.* The effects of intravenous and oral nifedipine on ex vivo platelet function. *Eur J Clin Pharmacol* 1989; 37: 449–52.
4. Becker RC, Alpert JS. The impact of medical therapy on hemorrhagic complications following coronary artery bypass grafting. *Arch Intern Med* 1990; 150: 2016–21.
5. Wagenknecht LE, *et al.* Surgical bleeding: unexpected effect of a calcium antagonist. *BMJ* 1993; 310: 776–7.
6. Öhman J and others. Surgical bleeding and calcium antagonists. *BMJ* 1995; 311: 388–9. [Several letters.]
7. Vergouwen MDI, *et al.* Dihydropyridine calcium antagonists increase fibrinolytic activity: a systematic review. *J Cereb Blood Flow Metab* 2007; 27: 1293–1308.
8. Pahor M, *et al.* Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old. *Lancet* 1996; 347: 1061–5.
9. Kaplan RC, *et al.* Use of calcium channel blockers and risk of hospitalized gastrointestinal tract bleeding. *Arch Intern Med* 2000; 160: 1849–55.
10. Suissa S, *et al.* Antihypertensive drugs and the risk of gastrointestinal bleeding. *Am J Med* 1998; 105: 230–5.
11. Kelly JP, *et al.* Major upper gastrointestinal bleeding and the use of calcium channel blockers. *Lancet* 1999; 353: 559.
12. Laporte J-R, *et al.* Fatal aplastic anaemia associated with nifedipine. *Lancet* 1998; 352: 619–20.
13. Usalan C, *et al.* Severe thrombocytopenia associated with amlodipine treatment. *Ann Pharmacother* 1999; 33: 1126–7.
14. Lahav M, Arav R. Diltiazem and thrombocytopenia. *Ann Intern Med* 1989; 110: 327.
15. Michalets EL, Jackson DV. Diltiazem-associated thrombocytopenia. *Pharmacotherapy* 1997; 17: 1345–8.

Effects on the bone and joints. For reports of arthralgia associated with calcium-channel blockers see under Effects on the Neuromuscular System, below.

Effects on the brain. Cerebral ischaemia[1,2] has been reported in small numbers of patients given nifedipine.

1. Nobile-Orazio E, Sterzi R. Cerebral ischaemia after nifedipine treatment. *BMJ* 1981; 283: 948.
2. Schwartz M, *et al.* Oral nifedipine in the treatment of hypertensive urgency: cerebrovascular accident following a single dose. *Arch Intern Med* 1990; 150: 686–7.

Effects on carbohydrate metabolism. There are reports of deterioration of diabetes,[1] reduction in glucose tolerance,[2] and development of diabetes[1,3] in patients given nifedipine. Nifedipine has also been reported to increase plasma-glucose concentrations.[3,4] However, other reports and studies have found no change in glucose tolerance in either diabetic or non-diabetic patients taking nifedipine.[5-10]

See also Diabetes Mellitus under Precautions, p. 1453.1.

1. Bhatnagar SK, *et al.* Diabetogenic effects of nifedipine. *BMJ* 1984; 289: 19.
2. Giugliano D, *et al.* Impairment of insulin secretion in man by nifedipine. *Eur J Clin Pharmacol* 1980; 18: 395–8.
3. Zezulka AV, *et al.* Diabetogenic effects of nifedipine. *BMJ* 1984; 289: 437–8.
4. Charles S, *et al.* Hyperglycaemic effect of nifedipine. *BMJ* 1981; 283: 19–20.
5. Harrower ADB, Donnelly T. Hyperglycaemic effect of nifedipine. *BMJ* 1981; 283: 796.
6. Greenwood RH. Hyperglycaemic effect of nifedipine. *BMJ* 1982; 284: 50.
7. Abadie E, Passa P. Diabetogenic effects of nifedipine. *BMJ* 1984; 289: 438.
8. Dante A. Nifedipine and fasting glycemia. *Ann Intern Med* 1986; 104: 125–6.
9. Whitcroft I, *et al.* Calcium antagonists do not impair long-term glucose control in hypertensive non-insulin dependent diabetics (NIDDS). *Br J Clin Pharmacol* 1986; 22: 208P.
10. Tentorio A, *et al.* Insulin secretion and glucose tolerance in non-insulin dependent diabetic patients after chronic nifedipine treatment. *Eur J Clin Pharmacol* 1989; 36: 311–13.

Effects on the ears. There have been isolated reports[1] of tinnitus associated with several calcium-channel blockers including nifedipine, nicardipine, nitrendipine, diltiazem, verapamil, and cinnarizine.

1. Narvárez M, *et al.* Tinnitus with calcium-channel blockers. *Lancet* 1994; 343: 1229–30.

Effects on the eyes. Individual reports have implicated nifedipine in the development of transient retinal ischaemia and blindness,[1] and of periorbital oedema.[2] In a post-marketing survey painful or stinging eyes were more common in patients receiving nifedipine (178 of 757 evaluable) than in those given captopril (45 of 289), although the cause was uncertain.[3] Nifedipine has also been suggested as a risk factor in the development of cataract,[4,5] but the numbers involved in this analysis are small[6] and it is possible that the risk, if it exists,[7] relates to hypertension rather than nifedipine treatment.[6]

1. Pitlik S, *et al.* Transient retinal ischaemia induced by nifedipine. *BMJ* 1983; 287: 1845–6.
2. Silverstone PH. Periorbital oedema caused by nifedipine. *BMJ* 1984; 288: 1654.
3. Coulter DM. Eye pain with nifedipine and disturbance of taste with captopril: a mutually controlled study showing a method of postmarketing surveillance. *BMJ* 1988; 296: 1086–8.
4. van Heyningen R, Harding JJ. Do aspirin-like analgesics protect against cataract? *Lancet* 1986; i: 1111–13.
5. Harding JJ, van Heyningen R. Drugs, including alcohol, that act as risk factors for cataract, and possible protection against cataract by aspirin-like analgesics and cyclopenthiazide. *Br J Ophthalmol* 1988; 72: 809–14.
6. van Heyningen R, Harding JJ. Aspirin-like analgesics and cataract. *Lancet* 1986; ii: 283.
7. Kewitz H, *et al.* Aspirin and cataract. *Lancet* 1986; ii: 689.

Effects on the heart. The use of nifedipine has been associated with the development of heart disorders in some patients. Complete heart block has been reported in an elderly patient who had previously developed heart block with verapamil,[1] and sudden circulatory collapse has been reported in 4 patients receiving nifedipine who underwent routine coronary bypass surgery.[2] One patient died despite all attempts at resuscitation.[2] However, most reports seem to have concerned the development or aggravation of cardiac ischaemia, up to and including frank myocardial infarction after use of short-acting nifedipine.[3-6] Such cases appear to be chiefly associated with a too-rapid fall in blood pressure after the use of sublingual nifedipine for hypertensive urgencies or emergencies,[5,6] or occur in patients with a history of ischaemic heart disease.[3,4] The use of short-acting preparations of nifedipine, especially sublingually in the treatment of hypertensive crises, is no longer recommended (see Hypertension, p. 1251.1).

For discussion of the effects of calcium-channel blockers on cardiovascular mortality, see p. 1450.2.

1. Chopra DA, Maxwell RT. Complete heart block with low dose nifedipine. *BMJ* 1984; 288: 760.
2. Goiti JJ. Calcium channel blocking agents and the heart. *BMJ* 1985; 291: 1505.
3. Sia STB, *et al.* Aggravation of myocardial ischaemia by nifedipine. *Med J Aust* 1985; 142: 48–50.
4. Boden WE, *et al.* Nifedipine-induced hypotension and myocardial ischemia in refractory angina pectoris. *JAMA* 1985; 253: 1131–5.
5. O'Mailia JJ, *et al.* Nifedipine-associated myocardial ischemia or infarction in the treatment of hypertensive urgencies. *Ann Intern Med* 1987; 107: 185–6.
6. Leavitt AD, Zweifler AJ. Nifedipine, hypotension, and myocardial injury. *Ann Intern Med* 1988; 108: 305–6.

WITHDRAWAL. Exacerbation of coronary ischaemia and thrombosis of arteriovenous graft could have resulted from withdrawal of nifedipine in a patient.[1] Abrupt withdrawal of nisoldipine from 15 patients with stable angina pectoris after 6 weeks of therapy resulted in severe unstable angina in 2 patients and acute myocardial infarction in another.[2] It was postulated that the withdrawal effect could be due to an increase in sensitivity of vascular α_2 adrenoceptors to circulating adrenaline.

1. Mysliwiec M, *et al.* Calcium antagonist withdrawal syndrome. *BMJ* 1983; 286: 1898.
2. Mehta J, Lopez LM. Calcium-blocker withdrawal phenomenon: increase in affinity of alpha$_2$ adrenoceptors for agonist as a potential mechanism. *Am J Cardiol* 1986; 58: 242–6.

Effects on the kidneys. Calcium-channel blockers may be of benefit in some kidney disorders (see under Uses and Administration, p. 1449.1). However, reversible deterioration in renal function without any noticeable decline in systemic arterial blood pressure has been reported[1] in 4 patients with underlying renal insufficiency taking nifedipine,[1] and in another report[2] nifedipine increased urinary protein excretion and exacerbated renal impairment in 14 type 2 diabetic patients.

Excessive diuresis occurred in a patient given nifedipine for angina pectoris,[3] and nocturia in 9 patients referred for prostatic surgery was also attributed to nifedipine.[4]

1. Diamond JR, *et al.* Nifedipine-induced renal dysfunction: alterations in renal hemodynamics. *Am J Med* 1984; 77: 905–9.
2. Demarie BK, Bakris GL. Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; 113: 987–8.
3. Antonelli D, *et al.* Excessive nifedipine diuretic effect. *BMJ* 1984; 288: 760.
4. Williams G, Donaldson RM. Nifedipine and nocturia. *Lancet* 1986; i: 738.

Effects on the liver. Cases of hepatitis, apparently due to a hypersensitivity reaction, and frequently accompanied by fever, sweating, chills, rigor, and arthritic symptoms, have been reported in patients receiving nifedipine.[1-4]

1. Romensch HH, *et al.* Lymphocyte sensitisation in nifedipine-induced hepatitis. *BMJ* 1980; 281: 976–7.
2. Davidson AR. Lymphocyte sensitisation in nifedipine-induced hepatitis. *BMJ* 1980; 281: 1354.
3. Abramson M, Littlejohn GO. Hepatic reactions to nifedipine. *Med J Aust* 1985; 142: 47–8.
4. Shaw DR, *et al.* Nifedipine hepatitis. *Aust N Z J Med* 1987; 17: 447–8.

Effects on the menstrual cycle. Menorrhagia in 2 women[1] and menstrual irregularity with heavy bleeding in another[2] have been reported with nifedipine treatment.

1. Rodger JC, Torrance TC. Can nifedipine provoke menorrhagia? *Lancet* 1983; ii: 460.
2. Singh G, *et al.* Can nifedipine provoke menorrhagia? *Lancet* 1983; ii: 1022.

Effects on mental function. Insomnia, hyperexcitability, pacing, agitation, and depression were reported[1] in a patient receiving nifedipine. The symptoms disappeared within 2 days of stopping the drug. Four further cases of major depression, which developed within a week of starting nifedipine and resolved within a week of stopping the drug, have been reported.[2]

Although 2 epidemiological studies suggested that calcium-channel blockers may promote suicide,[3] a subsequent study[4] found no evidence of an association between depression and the use of calcium-channel blockers, and the number of suicides was low. Further studies[5-7] have also failed to find an increased risk of suicide with calcium-channel blockers compared with other antihypertensive drugs.

1. Ahmad S. Nifedipine-induced acute psychosis. *J Am Geriatr Soc* 1984; 32: 408.
2. Hullett PJ, *et al.* Depression associated with nifedipine-induced calcium channel blockade. *Am J Psychiatry* 1988; 145: 1277–9.
3. Lindberg G, *et al.* Use of calcium channel blockers and risk of suicide: ecological findings confirmed in population based cohort study. *BMJ* 1998; 316: 741–5.
4. Dunn NR, *et al.* Cohort study on calcium channel blockers, other cardiovascular agents, and the prevalence of depression. *Br J Clin Pharmacol* 1999; 48: 230–3.
5. Gasse C, *et al.* Risk of suicide among users of calcium channel blockers: population based, nested case-control study. *BMJ* 2000; 320: 1251.
6. Sørensen HT, *et al.* Risk of suicide in users of beta-adrenoceptor blockers, calcium channel blockers and angiotensin converting enzyme inhibitors. *Br J Clin Pharmacol* 2001; 52: 313–8.
7. Callréus T, *et al.* Cardiovascular drugs and the risk of suicide: a nested case-control study. *Eur J Clin Pharmacol* 2007; 63: 591–6.

Effects on the mouth. *GINGIVAL HYPERPLASIA.* Gingival hyperplasia has been reported with many of the calcium-channel blockers, particularly the dihydropyridines.[1,2] Of 114 reports of gingival overgrowth in the Australian Adverse Drug Reactions Advisory Committee database[1] in 1999, nifedipine accounted for 25 cases, amlodipine 22 cases, and felodipine 14 cases. Onset ranged from a few days to more than 4 years after starting treatment, and the effect was usually reversible on stopping the drug.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Drug-induced gingival overgrowth. *Aust Adverse Drug React Bull* 1999; 18: 6–7. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9906.pdf (accessed 25/07/08)
2. Ioulios P, *et al.* The spectrum of cutaneous reactions associated with calcium antagonists: a review of the literature and the possible etiopathogenic mechanisms. *Dermatol Online J* 2003; 9: 6. Available at: http://dermatology.cdlib.org/95/reviews/calcium/ioulios.html (accessed 23/01/09)

PAROTITIS. Acute swelling of the parotid glands occurred in a patient after sublingual administration of nifedipine.[1]

1. Bosch X, *et al.* Nifedipine-induced parotitis. *Lancet* 1986; ii: 467.

Effects on the neuromuscular system. Severe muscle cramps have been reported in a few patients taking nifedipine;[1,2] in one patient[2] the cramps were associated with widespread paraesthesia. Severe rhabdomyolysis developed in a patient with a transplanted kidney who was receiving an intravenous infusion of nifedipine.[3] The patient recovered rapidly once the infusion was stopped. There has also been a report[4] of myopathy, myalgia, and arthralgia associated with amlodipine, and of arthralgia in a patient[5] receiving diltiazem.

1. Keidar S, *et al.* Muscle cramps during treatment with nifedipine. *BMJ* 1982; 285: 1241–2.
2. Macdonald JB. Muscle cramps during treatment with nifedipine. *BMJ* 1982; 285: 1744.
3. Horn S, *et al.* Severe rhabdomyolysis in a kidney-transplant recipient receiving intravenous nifedipine. *Lancet* 1995; 346: 848–9.
4. Phillips BB, Muller BA. Severe neuromuscular complications possibly associated with amlodipine. *Ann Pharmacother* 1998; 32: 1165–7.
5. Smith KM. Arthralgia associated with calcium-channel blockers. *Am J Health-Syst Pharm* 2000; 57: 55–7.

Effects on the oesophagus. Calcium-channel blockers decrease lower oesophageal sphincter pressure and have been used in oesophageal motility disorders (see p. 1449.2), but a retrospective cohort study[1] found that

calcium-channel blockers may also precipitate or exacerbate gastro-oesophageal reflux disease.

1. Hughes J, *et al.* Do calcium antagonists contribute to gastro-oesophageal reflux disease and concomitant noncardiac chest pain? *Br J Clin Pharmacol* 2007; 64: 83–9.

Effects on the peripheral circulation. An erythromelalgia-like eruption occurred in a patient 8 weeks after starting therapy with nifedipine. Symptoms included severe burning pain and swelling in the feet and lower legs, which were fiery red, tender, and warm to the touch. Symptoms resolved in 2 days when nifedipine was stopped.[1] Similar effects have been reported in other patients on nifedipine.[2-4] Erythromelalgia has also been reported with nicardipine.[5] This type of erythromelalgia may be termed secondary erythermalgia.[6]

1. Fisher JR, *et al.* Nifedipine and erythromelalgia. *Ann Intern Med* 1983; 98: 671–2.
2. Grunwald Z. Painful edema, erythematous rash, and burning sensation due to nifedipine. *Drug Intell Clin Pharm* 1982; 16: 492.
3. Brodmerkel GJ. Nifedipine and erythromelalgia. *Ann Intern Med* 1983; 99: 415.
4. Sunahara JF, *et al.* Possible erythromelalgia-like syndrome associated with nifedipine in a patient with Raynaud's phenomenon. *Ann Pharmacother* 1996; 30: 484–6.
5. Levesque H, *et al.* Erythromelalgia induced by nicardipine (inverse Raynaud's phenomenon?) *BMJ* 1989; 298: 1252–3.
6. Drenth JPH, Michiels JJ. Three types of erythromelalgia. *BMJ* 1990; 301: 454–5.

Effects on the respiratory system. Reversible acute pulmonary oedema (with pleural effusion[1]) has been reported in patients receiving *nifedipine*[1-4] or *nicardipine*.[5] Nifedipine has also been reported to exacerbate impaired tissue oxygenation in patients with cor pulmonale secondary to obstructive airways disease.[6]

For a report of exacerbation of laryngeal oedema, see under Hypersensitivity, below.

1. Chaouat A, *et al.* Pulmonary oedema and pleural effusion in two patients with primary pulmonary hypertension treated with calcium channel blockers. *Heart* 1996; 75: 383.
2. Gillmer DJ, Kark P. Pulmonary oedema precipitated by nifedipine. *BMJ* 1980; 280: 1420–1.
3. Aderka D, Pinkhas J. Pulmonary oedema precipitated by nifedipine. *BMJ* 1984; 289: 1272.
4. Abbas OM, *et al.* Acute pulmonary edema during tocolytic therapy with nifedipine. *Am J Obstet Gynecol* 2006; 195: e3–e4.
5. Vaast P, *et al.* Acute pulmonary oedema during nicardipine therapy for premature labour: report of five cases. *Eur J Obstet Gynecol Reprod Biol* 2004; 113: 98–9.
6. Kalra L, Bone MF. Nifedipine and impaired oxygenation in patients with chronic bronchitis and cor pulmonale. *Lancet* 1989; i: 1135–6.

Effects on the skin and nails. The commonest skin reactions to nifedipine have been rash, pruritus, urticaria, alopecia, and exfoliative dermatitis;[1] there have been a few reports of erythema multiforme and the Stevens-Johnson syndrome.[1] Erythema multiforme occurred in a patient after substitution of amlodipine for nifedipine[2] and cross-sensitivity, manifest as a pruritic maculopapular rash, has been reported between amlodipine and diltiazem.[3] Generalised pruritus has been reported with amlodipine.[4] Other skin reactions that have been reported with nifedipine include severe photosensitivity reactions,[5] nonthrombocytopenic purpuric rashes,[6] and telangiectasias,[7] including photodistributed telangiectasias,[8] and pemphigoid nodularis.[9] Telangiectasias have also been reported with amlodipine[10,11] and felodipine.[12] Lichen planus[13] and hyperpigmentation[14] have also occurred with amlodipine. Nail and periungual pigmentation developed[15] in a 75-year-old man 18 months after starting amlodipine; it was much improved 2 years after the drug was stopped.

For reference to erythromelalgia, see under Effects on the Peripheral Circulation, above.

1. Stern R, Khalsa JH. Cutaneous adverse reactions associated with calcium channel blockers. *Arch Intern Med* 1989; 149: 829–32.
2. Bewley AP, *et al.* Erythema multiforme following substitution of amlodipine for nifedipine. *BMJ* 1993; 307: 241.
3. Baker BA, Cacchione JG. Dermatologic cross-sensitivity between diltiazem and amlodipine. *Ann Pharmacother* 1994; 28: 118–19.
4. Orme S, *et al.* Generalised pruritus associated with amlodipine. *BMJ* 1997; 315: 463.
5. Thomas SE, Wood ML. Photosensitivity reactions associated with nifedipine. *BMJ* 1986; 292: 992.
6. Oren R, *et al.* Nifedipine-induced nonthrombocytopenic purpura. *DICP Ann Pharmacother* 1989; 23: 88.
7. Tsele E, Chu AC. Nifedipine and telangiectasias. *Lancet* 1992; 339: 365–6.
8. Collins P, Ferguson J. Photodistributed nifedipine-induced facial telangiectasia. *Br J Dermatol* 1993; 129: 630–3.
9. Ameen M, *et al.* Pemphigoid nodularis associated with nifedipine. *Br J Dermatol* 2000; 142: 575–7.
10. Basarab T, *et al.* Calcium antagonist-induced photo-exposed telangiectasia. *Br J Dermatol* 1997; 136: 974–5.
11. Grabczynska SA, Cowley N. Amlodipine induced-photosensitivity presenting as telangiectasia. *Br J Dermatol* 2000; 142: 1255–6.
12. Al-Nisimi F, Lyon C. Felodipine-induced eruptive telangiectasia following mastectomy and radiotherapy. *Br J Dermatol* 2010; 162: 210–11.
13. Swale VJ, McGregor JM. Amlodipine-associated lichen planus. *Br J Dermatol* 2001; 144: 920–1.
14. Erbagci Z. Amlodipine associated hyperpigmentation. *Saudi Med J* 2004; 25: 103–5.
15. Sladden MJ, *et al.* Longitudinal melanonychia and pseudo-Hutchinson sign associated with amlodipine. *Br J Dermatol* 2005; 153: 219–20.

Effects on taste. Distortion of taste and smell has been reported in 2 patients taking nifedipine,[1] but a large survey involving 922 patients receiving nifedipine and 343 taking captopril did not show any association of taste disturbances with nifedipine.[2] Sudden loss of taste has also been reported[3] in a patient who had been taking amlodipine for several years; the sense of taste returned when amlodipine was stopped, but taste loss recurred on rechallenge.

1. Levenson JL, Kennedy K. Dysomia, dysgeusia, and nifedipine. *Ann Intern Med* 1985; 102: 135–6.
2. Coulter DM. Eye pain with nifedipine and disturbance of taste with captopril: a mutually controlled study showing a method of postmarketing surveillance. *BMJ* 1988; 296: 1086–8.
3. Sadasivam B, Jhaj R. Dysgeusia with amlodipine—a case report. *Br J Clin Pharmacol* 2007; 63: 253.

Extrapyramidal disorders. Extrapyramidal effects have been seen with calcium-channel blockers of all chemical classes, although most reports seem to concern the phenylalkylamine, verapamil, rather than the dihydropyridines or diltiazem. **Parkinsonism** has been reported in patients taking amlodipine,[1,2] diltiazem,[3] and verapamil.[4,5] Parkinsonism is also a recognised effect of flunarizine and cinnarizine, which have calcium-channel blocking properties (see under Flunarizine, p. 630.1). However, for the suggestion that some dihydropyridines may reduce the risk of developing Parkinson's disease, see under Uses and Administration, p. 1449.2.

Other movement disorders seen with calcium-channel blockers include **akathisia** with diltiazem,[6,7] **dystonia** with verapamil,[8] **myoclonic dystonia** with verapamil[9] and nifedipine,[10] and **myoclonus** with verapamil.[11,12]

1. Sempere AP, *et al.* Parkinsonism induced by amlodipine. *Mov Disord* 1995; 10: 115–16.
2. Teive HA, *et al.* Parkinsonian syndrome induced by amlodipine: case report. *Mov Disord* 2002; 17: 833–5.
3. Dick RS, Baroid SS. Diltiazem-induced parkinsonism. *Am J Med* 1989; 87: 95–6.
4. García-Albea E, *et al.* Parkinsonism unmasked by verapamil. *Clin Neuropharmacol* 1993; 16: 263–5.
5. Padrell MD, *et al.* Verapamil-induced parkinsonism. *Am J Med* 1995; 99: 436.
6. Jacobs MB. Diltiazem and akathisia. *Ann Intern Med* 1983; 99: 794–5.
7. Brink DD. Diltiazem and hyperactivity. *Ann Intern Med* 1984; 100: 459–60.
8. Pina MA, *et al.* Verapamil and acute dystonia. *J Clin Pharm Ther* 1998; 23: 79–80.
9. Hicks CB, Abraham K. Verapamil and myoclonic dystonia. *Ann Intern Med* 1985; 103: 154.
10. de Medina A, *et al.* Nifedipine and myoclonic dystonia. *Ann Intern Med* 1986; 104: 125.
11. Maiteb M, Daoud AS. Myoclonic seizure following intravenous verapamil injection: case report and review of the literature. *Ann Trop Paediatr* 2001; 21: 271–2.
12. Vadlamudi L, Wijdicks EFM. Multifocal myoclonus due to verapamil overdose. *Neurology* 2002; 58: 984.

Gynaecomastia. Unilateral gynaecomastia developed in 3 men 4, 6, and 26 weeks after starting nifedipine therapy.[1] Gynaecomastia has also been reported[2] in 2 patients receiving amlodipine while on haemodialysis; symptoms resolved on stopping the drug.

1. Clyne CAC. Unilateral gynaecomastia and nifedipine. *BMJ* 1986; 292: 380.
2. Komine N, *et al.* Amlodipine-induced gynecomastia in two patients on long-term hemodialysis therapy. *Clin Exp Nephrol* 2003; 7: 85–6.

Haemorrhage. See Effects on the Blood, p. 1450.3.

Hypersensitivity. *Nifedipine* is associated with various hypersensitivity reactions including rashes (above) and effects on the liver (p. 1451.3).

Nifedipine, given sublingually, exacerbated laryngeal swelling that developed in a woman after the use of isosorbide dinitrate spray.[1] *Amlodipine* has also been associated with angioedema.[2]

1. Silfvast T, *et al.* Laryngeal oedema after isosorbide dinitrate spray and sublingual nifedipine. *BMJ* 1995; 311: 232.
2. Southward J, *et al.* Probable amlodipine-induced angioedema. *Ann Pharmacother* 2009; 43: 772–6.

Oedema. Oedema of the feet and ankles is a common adverse effect of nifedipine and other dihydropyridine calcium-channel blockers. It occurs typically 2 or more weeks after starting treatment and is caused by pre-capillary arteriolar dilatation rather than fluid retention.[1] Evidence from a study in 10 diabetic subjects beginning nifedipine therapy, 5 of whom developed ankle oedema, suggested that nifedipine abolished the reflex vasoconstriction produced when the feet are below the level of the heart which is believed to prevent excessive fluid filtration into the tissues.[2]

The oedema may respond to simple measures such as elevation of the feet or to a reduction in dosage but if it persists the calcium-channel blocker should be withdrawn.[1]

Generalised oedema[3] and facial and upper extremity oedema[4] have been reported in patients taking amlodipine, but in both cases symptoms resolved on withdrawal of the drug.

For the view that second-generation lipophilic dihydropyridines may be less prone to cause oedema than earlier drugs such as amlodipine or nifedipine see Tolerability, under Lercanidipine, p. 1419.3.

1. Maclean D, MacConnachie AM. Selective side-effects: peripheral oedema with dihydropyridine calcium antagonists. *Prescribers' J* 1991; 31: 4–6.
2. Williams SA, *et al.* Dependent oedema and attenuation of postural vasoconstriction associated with nifedipine therapy for hypertension in diabetic patients. *Eur J Clin Pharmacol* 1989; 37: 333–5.
3. Şener D, *et al.* Anasarca edema with amlodipine treatment. *Ann Pharmacother* 2005; 39: 761–3.
4. Ganeshalingham A, Wong W. Amlodipine-induced bilateral upper extremity edema. *Ann Pharmacother* 2007; 41: 1536–8.

Treatment of Adverse Effects

Toxicity in calcium-channel blocker overdose may potentially be very severe. Activated charcoal may be given orally to adults or children who present within 1 hour of ingesting a potentially toxic overdose of a calcium-channel blocker, although later use has been suggested for those who have ingested modified-release preparations. Alternatively, gastric lavage may be considered in adults.

Supportive and symptomatic care should be given. Hypotension may respond to placing the patient in the supine position with the feet raised; plasma expanders may be given, although cardiac overload should be avoided. Atropine should be given for symptomatic bradycardia, although cardiac pacing may be more effective if there is evidence of AV conduction delay. Isoprenaline has also been used but may exacerbate hypotension by reducing systemic vascular resistance.

Intravenous calcium should be given to those with significant features of poisoning. A typical dose is up to 6.8 mmol of calcium given by slow intravenous injection over 5 minutes, repeated as required every 10 to 20 minutes up to a maximum of 4 doses. Alternatively, up to about 6.8 mmol per hour of calcium may be given by intravenous infusion. 6.8 mmol of calcium is provided by about 10 mL of calcium chloride 10%, or about 30 mL of calcium gluconate 10%.

In severe cases an insulin and glucose infusion may improve myocardial contractility and systemic perfusion. A lipid infusion may be helpful for unresponsive cardiotoxicity due to lipophilic calcium-channel blockers. Unresponsive hypotension may require use of an adrenoceptor agonist such as noradrenaline or dopamine. Glucagon has also been used to correct myocardial depression and hypotension.

Dialysis is not useful for nifedipine as it is highly protein bound. Plasmapheresis may be beneficial.

Overdosage. Although severe toxicity is more likely in overdosage with non-dihydropyridines such as verapamil or diltiazem, treatment of overdosage is similar for all calcium-channel blockers.[1-4] Management is mainly supportive (see Treatment of Adverse Effects, above). Alternative suggestions to standard therapy have included lampridine[5] as a specific antagonist, and amrinone[1] as an inotrope. Successful use of vasopressin[6] or terlipressin[7] has been reported in patients with resistant hypotension; plasma exchange has also been tried[8] successfully. There is some evidence[9,10] that high-dose insulin (with glucose if required to prevent hypoglycaemia) may be of benefit, particularly in patients with acidosis, and its safety has been shown.[11]

Most reports of overdosage have been with verapamil (see p. 1524.2). The following are some individual reports for nifedipine:

- Hypotension, tachycardia, and flushing, followed by hypokalaemia, were seen in a patient who took nifedipine 600 mg as modified-release tablets together with an overdose of paracetamol, but there was no evidence of heart block.[12] The patient was given calcium gluconate intravenously and subsequently activated charcoal and lactulose. Absorption of nifedipine was essentially complete 10 hours after ingestion. Potassium chloride was given orally to treat hypokalaemia and acetylcysteine was used to manage the paracetamol poisoning.
- Third-degree AV block, progressing to asystole, developed in a 14-month-old child who ingested about 800 mg of nifedipine.[13] During cardiopulmonary resuscitation a total of 700 mg of calcium chloride was given, together with atropine, adrenaline, and sodium bicarbonate. The stomach was subsequently emptied by gastric lavage and activated charcoal given. The child remained tachycardic and hypotensive, with evidence of pulmonary oedema and hyperglycaemia, and was given intravenous electrolytes and dopamine infusions and assisted ventilation and treatment to control tonic-clonic seizures. She eventually made an apparently complete recovery apart from a moderate speech delay.

1. Salhanick SD, Shannon MW. Management of calcium channel antagonist overdose. *Drug Safety* 2003; 26: 65–79.
2. DeWitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity. *Toxicol Rev* 2004; 23: 223–38.

3. Olson KR, *et al.* Calcium channel blocker ingestion: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol* 2005; 43: 797–822.
4. Shepherd G. Treatment of poisoning caused by beta-adrenergic and calcium-channel blockers. *Am J Health-Syst Pharm* 2006; 63: 1828–35.
5. Stevens JJWM, Ghosh S. Overdose of calcium channel blockers. *BMJ* 1994; 309: 193.
6. Kanagarajan K, *et al.* The use of vasopressin in the setting of recalcitrant hypotension due to calcium channel blocker overdose. *Clin Toxicol* 2007; 45: 56–9.
7. Leone M, *et al.* Terlipressin: a new therapeutic for calcium-channel blockers overdose. *J Crit Care* 2005; 20: 114–15.
8. Ezidiegwu C, *et al.* A case report on the role of plasma exchange in the management of a massive amlodipine besylate intoxication. *Ther Apher Dial* 2008; 12: 180–4.
9. Mégarbane B, *et al.* The role of insulin and glucose (hyperinsulinaemia/euglycaemia) therapy in acute calcium channel antagonist and beta-blocker poisoning. *Toxicol Rev* 2004; 23: 215–22.
10. Shepherd G, Klein-Schwartz W. High-dose insulin therapy for calcium-channel blocker overdose. *Ann Pharmacother* 2005; 39: 923–30.
11. Greene SL, *et al.* Relative safety of hyperinsulinaemia/euglycaemia therapy in the management of calcium channel blocker overdose: a prospective observational study. *Intensive Care Med* 2007; 33: 2019–24.
12. Ferner RE, *et al.* Pharmacokinetics and toxic effects of nifedipine in massive overdose. *Hum Exp Toxicol* 1990; 9: 309–11.
13. Wells TG, *et al.* Nifedipine poisoning in a child. *Pediatrics* 1990; 86: 91–4.

Precautions

Nifedipine should be used with caution in patients with hypotension, in patients whose cardiac reserve is poor, and in those with heart failure since deterioration of heart failure has been noted. Nifedipine should not be used in cardiogenic shock, in patients who have suffered a myocardial infarction in the previous 2 to 4 weeks, or in acute unstable angina. Nifedipine should not be used to treat an anginal attack in chronic stable angina, nor should it be used for the acute reduction of blood pressure in adults, though it may be used for this purpose in children (see p. 1447.3). In patients with severe aortic stenosis nifedipine may increase the risk of developing heart failure. Sudden withdrawal of nifedipine might be associated with an exacerbation of angina. The dose may need to be reduced in patients with hepatic impairment.

Nifedipine should be stopped in patients who have ischaemic pain after use.

Nifedipine is reported to be teratogenic in *animals* and may inhibit labour, but it has been used in hypertension in pregnancy (see Hypertension, under Uses and Administration, p. 1448.3).

Breast feeding. Nifedipine is distributed into breast milk[1,2] but the amount present is probably too small to be harmful. There have been no reports of any clinical effects in breast-fed infants whose mothers were receiving nifedipine and the last available guidance from the American Academy of Pediatrics therefore considered[3] that it was usually compatible with breast feeding.

1. Ehrenkranz RA, *et al.* Nifedipine transfer into human milk. *J Pediatr* 1989; 114: 478–80.
2. Penny WJ, Lewis MJ. Nifedipine is excreted in human milk. *Eur J Clin Pharmacol* 1989; 36: 427–8.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Cardiac surgery. For the suggestion that dihydropyridine calcium-channel blockers may increase perioperative mortality in patients undergoing aortic aneurysm surgery see Effects on Mortality, under Adverse Effects, p. 1450.2.

Diabetes mellitus. Nifedipine's effect on insulin and glucose responses (see Effects on Carbohydrate Metabolism under Adverse Effects, p. 1451.1) may require antidiabetic therapy to be adjusted. Also some studies have suggested that nifedipine can worsen proteinuria and renal dysfunction in diabetic patients with some degree of renal insufficiency,[1,2] but other studies, (see Kidney Disorders under Uses and Administration, p. 1449.1), have suggested that nifedipine may have a beneficial effect on proteinuria.

Some studies have suggested that patients with diabetes mellitus[3,4] or impaired glucose metabolism[5] may be more susceptible to adverse cardiovascular effects of calcium-channel blockers. The calcium-channel blockers used in these studies were the dihydropyridines nisoldipine, amlodipine, and isradipine (long-acting or intermediate-acting calcium-channel blockers). However, two of the studies[3,4] compared the calcium-channel blocker with an ACE inhibitor and it has been suggested that ACE inhibitors may be particularly beneficial in these patients rather than calcium-channel blockers being particularly harmful.[6] Improved cardiovascular outcomes were seen from adding a long-acting nifedipine formulation to therapy in another study in patients with type 2 diabetes.[7]

1. Mimran A, *et al.* Contrasting effects of captopril and nifedipine in normotensive patients with incipient diabetic nephropathy. *J Hypertens* 1988; 6: 919–23.
2. Demarie BK, Bakris GL. Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; 113: 987–8.
3. Estacio RO, *et al.* The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998; 338: 645–52. Correction. *ibid.*; 339: 1339.
4. Tatti P, *et al.* Outcome results of the fosinopril versus amlodipine cardiovascular events randomized trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998; 21: 597–603.
5. Byington RP, *et al.* Isradipine, raised glycosylated haemoglobin, and risk of cardiovascular events. *Lancet* 1997; 350: 1075–6.
6. Poulter NR. Calcium channel blockers and cardiovascular risk in diabetes. *Lancet* 1998; 351: 1809–10.
7. Elliott HL, *et al.* Improving blood pressure control in patients with diabetes mellitus and high cardiovascular risk. *Int J Hypertens* 2011; 2010: 490769.

Interference with diagnostic tests. Calcium-channel blockers reduce the plasma aldosterone:renin ratio by increasing renin production and reducing plasma aldosterone concentrations; consequently, primary hyperaldosteronism has been misdiagnosed as essential hypertension in patients taking calcium-channel blockers.[1] A diagnostic ratio was seen in each patient within two weeks of stopping the calcium-channel blocker.

Nifedipine may give falsely elevated spectrophotometric values of urinary vanillylmandelic acid; HPLC estimations are unaffected.

1. Grasko JM, *et al.* Delayed diagnosis of primary hyperaldosteronism. *BMJ* 2010; 340: 1358.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nifedipine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Withdrawal. Sudden withdrawal of nifedipine might be associated with an exacerbation of angina.

For a report of life-threatening coronary vasospasm occurring after withdrawal of nifedipine before a revascularisation procedure, see under Effects on the Heart, in Diltiazem, p. 1360.3.

Interactions

Nifedipine may enhance the antihypertensive effects of other antihypertensive drugs such as beta blockers although the combination is generally well toierated. Enhanced antihypertensive effects may also be seen if used with drugs such as aldesleukin and antipsychotics that cause hypotension. Nifedipine may modify insulin and glucose responses (see Effects on Carbohydrate Metabolism, p. 1451.1) and therefore diabetic patients may need to adjust their antidiabetic treatment when receiving nifedipine. Nifedipine is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4, and interactions may occur with other drugs, such as quinidine, sharing the same metabolic pathway, and with enzyme inducers, such as carbamazepine, phenytoin, and rifampicin, and enzyme inhibitors, such as cimetidine, erythromycin, and HIV-protease inhibitors.

Alcohol. A study involving 10 healthy subjects showed that the area under the concentration-time profile for nifedipine 20 mg was increased by 54% when taken orally with alcohol, and maximum pulse rate was achieved more rapidly, which was in line with *animal* and *in-vitro* studies suggesting that the metabolism of nifedipine is inhibited by alcohol.[1]

1. Qureshi S, *et al.* Nifedipine-alcohol interaction. *JAMA* 1990; 264: 1660–1.

Antiarrhythmics. Nifedipine and *quinidine* probably have a common metabolic pathway in the liver and might be expected to interact if given concurrently. In one study,[1] quinidine appeared to inhibit nifedipine metabolism resulting in increased serum concentrations of nifedipine; quinidine concentrations were unchanged. However, conflicting effects on serum-quinidine concentrations have been reported, see p. 1483.2.

1. Bowles SK, *et al.* Evaluation of the pharmacokinetic and pharmacodynamic interaction between quinidine and nifedipine. *J Clin Pharmacol* 1993; 33: 727–31.

Antibacterials. The macrolide antibacterials are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may inhibit the metabolism of calcium-channel blockers. Two days after *clarithromycin* was started,[1] vasodilatory shock and heart block occurred in a 77-year-old man whose antihypertensive medication included nifedipine. Clarithromycin was continued and when his condition improved nifedipine was reintroduced at half the previous dose; his blood pressure was stable on discharge. A population-based, nested, case crossover study[2] of elderly patients who were receiving calcium-channel blockers found that of 7100 who were admitted to hospital for the treatment of hypotension, 176 had been taking a macrolide antibacterial. Analysis indicated that the greatest risk for developing hypotension was with *erythromycin*, followed by clarithromycin, while use of *azithromycin* was not associated with an increased risk.

1. Gerónimo-Pardo M, *et al.* Clarithromycin–nifedipine interaction as possible cause of vasodilatory shock. *Ann Pharmacother* 2005; 39: 538–42.
2. Wright AJ, *et al.* The risk of hypotension following co-prescription of macrolide antibiotics and calcium-channel blockers. *CMAJ* 2011; 183: 303–7.

Antidiabetics. See Diabetes Mellitus under Precautions (above) and Effects on Carbohydrate Metabolism under Adverse Effects, p. 1451.1.

Antiepileptics. The effects of dihydropyridine calcium-channel blockers may be reduced by enzyme-inducing antiepileptics such as *carbamazepine, phenobarbital,* and *phenytoin.*[1-4] In contrast, *sodium valproate* has been reported to increase plasma-nimodipine concentrations.[3]

For reports of an interaction between dihydropyridines and *phenytoin* resulting in raised serum-phenytoin concentration, see p. 544.2.

1. Capewell S, *et al.* Reduced felodipine bioavailability in patients taking anticonvulsants. *Lancet* 1988; ii: 480–2.
2. Schellens JHM, *et al.* Influence of enzyme induction and inhibition on the oxidation of nifedipine, sparteine, mephenytoin and antipyrine in humans as assessed by a "cocktail" study design. *J Pharmacol Exp Ther* 1989; 249: 638–45.
3. Tartara A, *et al.* Differential effects of valproic acid and enzyme-inducing anticonvulsants on nimodipine pharmacokinetics in epileptic patients. *Br J Clin Pharmacol* 1991; 32: 335–40.
4. Yasui-Furukori N, Tateishi T. Carbamazepine decreases antihypertensive effect of nilvadipine. *J Clin Pharmacol* 2002; 42: 100–103.

Antifungals. Azole antifungals inhibit the cytochrome P450 enzyme system and may therefore interfere with metabolism of calcium-channel blockers. Two women who had been taking felodipine for about a year developed peripheral oedema a few days after starting treatment with *itraconazole*.[1] Plasma-felodipine concentrations were measured in one of the women before and during a subsequent course of itraconazole and increased considerably when the two drugs were used together. A similar interaction occurred when itraconazole therapy was started in a patient already taking nifedipine.[2] Potentiation of the effects of nifedipine by *fluconazole* has also been reported.[3]

1. Neuvonen PJ, Suhonen R. Itraconazole interacts with felodipine. *J Am Acad Dermatol* 1995; 33: 134–5.
2. Tailor SAN, *et al.* Peripheral edema due to nifedipine-itraconazole interaction: a case report. *Arch Dermatol* 1996; 132: 350–2.
3. Kremens B, *et al.* Loss of blood pressure control on withdrawal of fluconazole during nifedipine therapy. *Br J Clin Pharmacol* 1999; 47: 707–8.

Antihistamines. Severe angina developed in a patient stabilised on nifedipine who took *terfenadine* 60 mg for seasonal allergy. The pain resolved within an hour or two.[1]

1. Falkenberg HM. Possible interaction report. *Can Pharm J* 1988; 121: 294.

Antineoplastics. For reports of increased *vincristine* toxicity in children also taking itraconazole and nifedipine see Antifungals, under Interactions of Vincristine, p. 884.1. The development of gallstones in a 76-year-old man receiving nifedipine and *imatinib* was thought[1] to result from imatinib interfering with nifedipine metabolism via the cytochrome P450 isoenzyme CYP3A4.

1. Breccia M, *et al.* Can nifedipine and estrogen interaction with imatinib be responsible for gallbladder stone development? *Eur J Haematol* 2005; 75: 89–90.

Antivirals. The HIV-protease inhibitors are known to inhibit the cytochrome P450 isoenzyme CYP3A4 and may therefore interfere with the metabolism of calcium-channel blockers. A woman stable on felodipine developed oedema[1] in both legs when she was given *nelfinavir* after a needle-stick injury. The oedema resolved on withdrawal of felodipine, and was attributed to inhibition of felodipine metabolism. A man[2] taking nifedipine for hypertension developed symptomatic orthostatic hypotension and heart block when HAART including nelfinavir was started. Symptoms improved when nelfinavir was stopped; they occurred on rechallenge, and again when the HAART was altered to include *ritonavir-boosted indinavir.* A study[3] in healthy subjects found that ritonavir-boosted indinavir increased exposure to both amlodipine and diltiazem.

1. Izzedine H, *et al.* Nelfinavir and felodipine: a cytochrome P450 3A4-mediated drug interaction. *Clin Pharmacol Ther* 2004; 75: 362–3.
2. Rossi DR, *et al.* Symptomatic orthostasis with extended-release nifedipine and protease inhibitors. *Pharmacotherapy* 2002; 22: 1312–16.
3. Glesby MJ, *et al.* Pharmacokinetic interactions between indinavir plus ritonavir and calcium channel blockers. *Clin Pharmacol Ther* 2005; 78: 143–53.

Beta blockers. Although nifedipine is often used with beta blockers without untoward effects, heart failure has been reported in a few patients with angina who were given nifedipine and a beta blocker.[1,2] Severe hypotension has been reported in 1 of 15 angina patients given nifedipine and *atenolol*;[3] withdrawal of the beta blocker precipitated severe unstable angina in this patient. Severe hypotension in a patient was attributed to the use of nifedipine with

propranolol, and was thought to have contributed to fatal myocardial infarction.[4]

1. Anastassiades CJ. Nifedipine and beta-blocker drugs. *BMJ* 1980; **281:** 1251–2.
2. Robson RH, Vishwanath MC. Nifedipine and beta-blockade as a cause of cardiac failure. *BMJ* 1982; **284:** 104.
3. Opie LH, White DA. Adverse interaction between nifedipine and β-blockade. *BMJ* 1980; **281:** 1462.
4. Staffurth JS, Emery P. Adverse interaction between nifedipine and beta-blockade. *BMJ* 1981; **282:** 225.

Calcium-channel blockers. Plasma concentrations of nifedipine were increased in a study in 6 healthy subjects when pretreated with *diltiazem*; the elimination half-life of nifedipine was prolonged from 2.54 hours to 3.40 hours after pretreatment with diltiazem 30 mg daily and to 3.47 hours after 90 mg daily. The effect was probably due to reduced hepatic metabolism of nifedipine.[1] Nifedipine and diltiazem are reported to be metabolised by the same hepatic enzyme and, conversely, pretreatment with nifedipine has resulted in increased concentrations of diltiazem.[2] Paralytic ileus was thought[3] to result from elevated nifedipine concentrations in a 62-year-old man when diltiazem was added to his therapy.

1. Tateishi T, *et al.* Dose dependent effect of diltiazem on the pharmacokinetics of nifedipine. *J Clin Pharmacol* 1989; **29:** 994–7.
2. Tateishi T, *et al.* The effect of nifedipine on the pharmacokinetics and dynamics of diltiazem: the preliminary study in normal volunteers. *J Clin Pharmacol* 1993; **33:** 738–40.
3. Harada T, *et al.* Paralytic ileus induced by the combined use of nifedipine and diltiazem in the treatment of vasospastic angina. *Cardiology* 2002; **97:** 113–14.

Digoxin. For the effect of nifedipine and other dihydropyridine calcium-channel blockers on digoxin, see p. 1357.2.

Grapefruit juice. Grapefruit juice inhibits the cytochrome P450 isoenzyme CYP3A4, particularly in the intestinal wall, and markedly increases the bioavailability of oral calcium-channel blockers;[1-3] calcium-channel blockers given intravenously appear to be unaffected.[4] The interaction may be less significant with calcium-channel blockers such as amlodipine that have a higher bioavailability,[5] but most calcium-channel blockers should not be taken orally at the same time as grapefruit juice.[6] A stereoselective effect has also been reported.[7]

1. Bailey DG, *et al.* Interaction of citrus juices with felodipine and nifedipine. *Lancet* 1991; **337:** 268–9.
2. Bailey DG, *et al.* Effect of grapefruit juice and naringin on nisoldipine pharmacokinetics. *Clin Pharmacol Ther* 1993; **54:** 589–94.
3. Lundahl J, *et al.* Relationship between time of intake of grapefruit juice and its effect on pharmacokinetics and pharmacodynamics of felodipine in healthy subjects. *Eur J Clin Pharmacol* 1995; **49:** 61–7.
4. Rashid TJ, *et al.* Factors affecting the absolute bioavailability of nifedipine. *Br J Clin Pharmacol* 1995; **40:** 51–8.
5. Vincent J, *et al.* Lack of effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of amlodipine. *Br J Clin Pharmacol* 2000; **50:** 455–63.
6. CSM/MCA. Drug interactions with grapefruit juice. *Current Problems* 1997; **23:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015623&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)
7. Uno T, *et al.* Effect of grapefruit juice on the disposition of manidipine enantiomers in healthy subjects. *Br J Clin Pharmacol* 2006; **61:** 533–7.

Histamine H_2-antagonists. Pharmacokinetic studies have indicated that use of nifedipine with *cimetidine* can increase the bioavailability of nifedipine.[1-4] An increase in the area under the plasma concentration-time curve of between 77 and 92% has been reported.[2,3] Potentiation of the hypotensive effect of nifedipine by cimetidine was also shown in 7 hypertensive patients.[1] The mechanism of the interaction was thought to be due to inhibition of the cytochrome P450 system by cimetidine and thus inhibition of the metabolism of nifedipine.

Ranitidine was found to have little effect on the pharmacokinetics of nifedipine, although there was an increase in the bioavailability of nifedipine during use of ranitidine.[5] *Famotidine* has been reported not to interact with nifedipine.[6]

1. Kirch W, *et al.* Einfluss von Cimetidin und Ranitidin auf Pharmakokinetik und antihypertensiven Effekt von Nifedipin. *Dtsch Med Wochenschr* 1983; **108:** 1757–61.
2. Renwick AG, *et al.* Factors affecting the pharmacokinetics of nifedipine. *Eur J Clin Pharmacol* 1987; **32:** 351–5.
3. Smith SR, *et al.* Ranitidine and cimetidine: drug interactions with single dose and steady-state nifedipine administration. *Br J Clin Pharmacol* 1987; **23:** 311–15.
4. Schwartz JB, *et al.* Effect of cimetidine or ranitidine administration on nifedipine pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 1988; **43:** 673–80.
5. Kirch W, *et al.* Ranitidine increases bioavailability of nifedipine. *Clin Pharmacol Ther* 1985; **37:** 204.
6. Kirch W, *et al.* Negative effects of famotidine on cardiac performance assessed by noninvasive hemodynamic measurements. *Gastroenterology* 1989; **96:** 1388–92.

Immunosuppressants. Flushing, paraesthesias, and rashes were reported in 2 patients given nifedipine 40 mg daily while taking *ciclosporin* for psoriasis.[1] A study in 8 psoriatic patients indicated that giving nifedipine with ciclosporin resulted in reduced recovery of the principal metabolite of nifedipine, presumably because ciclosporin reduced nifedipine metabolism through competition for the cytochrome P450 metabolising enzymes.

For reference to the effects of calcium-channel blockers on ciclosporin concentrations in blood, see p. 1957.3. For the possible protective effect of nifedipine against ciclosporin-induced nephrotoxicity, see Transplantation under Uses and Administration, p. 1450.2.

For the effect of nifedipine on *tacrolimus*, see p. 1978.2.

1. McFadden JP, *et al.* Cyclosporin decreases nifedipine metabolism. *BMJ* 1989; **299:** 1224.

Magnesium salts. Profound hypotension has been reported in 2 women in whom a single oral dose of nifedipine 10 mg was added to treatment with magnesium sulfate infusion for pre-eclampsia; both women were also receiving methyldopa.[1] Neuromuscular blockade has been reported in 2 women after use of nifedipine with intravenous magnesium sulfate. In one woman given nifedipine as a tocolytic, symptoms of neuromuscular blockade occurred immediately on injection of magnesium sulfate and resolved within 25 minutes of stopping the injection.[2] In another woman who was receiving a magnesium sulfate infusion for pre-eclampsia, symptoms developed 30 minutes after the second of 2 doses of nifedipine had been given and improved after receiving calcium gluconate injection.[3] However, a chart review[4] of women given intravenous magnesium sulfate with nifedipine for pre-eclampsia found no increase in serious magnesium-related adverse effects compared with women who received magnesium sulfate with either another antihypertensive or no antihypertensive.

1. Waisman GD, *et al.* Magnesium plus nifedipine: potentiation of hypotensive effect in pre-eclampsia? *Am J Obstet Gynecol* 1988; **159:** 308–9.
2. Snyder SW, Cardwell MS. Neuromuscular blockade with magnesium sulfate and nifedipine. *Am J Obstet Gynecol* 1989; **161:** 35–6.
3. Ben-Ami M, *et al.* The combination of magnesium sulphate and nifedipine: a cause of neuromuscular blockade. *Br J Obstet Gynaecol* 1994; **101:** 262–3.
4. Magee LA, *et al.* Therapy with both magnesium sulfate and nifedipine does not increase the risk of serious magnesium-related maternal side effects in women with preeclampsia. *Am J Obstet Gynecol* 2005; **193:** 153–63.

Melatonin. Melatonin may cause a reduction in blood pressure and might be expected to have additive effects if given with antihypertensives. However, in a study[1] in hypertensive patients taking nifedipine, giving melatonin led to an increase in both blood pressure and heart rate.

1. Lusardi P, *et al.* Cardiovascular effects of melatonin in hypertensive patients well controlled by nifedipine: a 24-hour study. *Br J Clin Pharmacol* 2000; **49:** 423–7.

Tobacco. In a study of the effects of cigarette smoking and the treatment of angina with nifedipine, propranolol, or atenolol, smoking was shown to have direct and adverse effects on the heart and to interfere with the efficacy of all 3 anti-anginal drugs, with nifedipine being the most affected.[1]

1. Deanfield J, *et al.* Cigarette smoking and the treatment of angina with propranolol, atenolol, and nifedipine. *N Engl J Med* 1984; **310:** 951–4.

Xanthines. For the effect of nifedipine on *theophylline*, see Calcium-channel Blockers, p. 1235.3.

Pharmacokinetics

Nifedipine is rapidly and almost completely absorbed from the gastrointestinal tract, but undergoes extensive hepatic first-pass metabolism. Bioavailability of oral liquid-filled capsules is between 45 and 56%, but is lower for longer-acting formulations. Peak blood concentrations are reported to occur 30 to 60 minutes after oral doses of liquid-filled capsules.

Nifedipine is about 92 to 98% bound to plasma proteins. It is distributed into breast milk. It is extensively oxidised in the liver via the cytochrome P450 isoenzyme CYP3A4, and 80 to 95% of a dose is excreted in the urine, and the remainder in the faeces, almost entirely as inactive metabolites. The half-life is about 2 hours after intravenous doses or oral liquid-filled capsules. Hepatic impairment considerably reduces the clearance of nifedipine (see below), whereas renal impairment has little effect on its pharmacokinetics.

Reviews.

1. Sorkin EM, *et al.* Nifedipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy, in ischaemic heart disease, hypertension and related cardiovascular disorders. *Drugs* 1985; **30:** 182–274.
2. Kelly JG, O'Malley K. Clinical pharmacokinetics of calcium antagonists: an update. *Clin Pharmacokinet* 1992; **22:** 416–33.

Absorption. Studies have indicated that the absorption of nifedipine may be affected by food; the results appear to vary depending upon the preparation used. Decreased peak plasma concentrations[1] and a delay in achieving them[1,2] have been reported with certain preparations when given after a meal; conversely, food has caused an increase in bioavailability[3] and plasma concentrations[3,4] with some preparations, while the pharmacokinetics of others appear to be minimally affected by food.[2,4,5] It has been suggested that traditional measures of bioequivalence may fail to reflect differences in the absorption and distribution characteristics of different nifedipine modified-release formulations.[6-8]

1. Hirasawa K, *et al.* Effect of food ingestion on nifedipine absorption and haemodynamic response. *Eur J Clin Pharmacol* 1985; **28:** 105–7.
2. Schug BS, *et al.* The effect of food on the pharmacokinetics of nifedipine in two slow release formulations: pronounced lag-time after a high fat breakfast. *Br J Clin Pharmacol* 2002; **53:** 582–8.
3. Ueno K, *et al.* Effect of food on nifedipine sustained-release preparation. *DICP Ann Pharmacother* 1989; **23:** 662–5.
4. Wonnemann M, *et al.* Significant food interactions observed with a nifedipine modified-release formulation marketed in the European Union. *Int J Clin Pharmacol Ther* 2006; **44:** 38–48.
5. Ueno K, *et al.* Effect of a light breakfast on the bioavailability of sustained-release nifedipine. *DICP Ann Pharmacother* 1991; **25:** 317–19.
6. Endrenyi L, Tothfalusi L. Do regulatory bioequivalence requirements adequately reflect the therapeutic equivalence of modified-release drug products? *J Pharm Pharm Sci* 2010; **13:** 107–13.
7. Pollak PT. Therapeutically relevant blood pressure differences with two nifedipine (60 mg) osmotic delivery systems of differing design: three case reports. *Int J Clin Pharmacol Ther* 2010; **48:** 400–4.
8. Woodcock BG. Critical questions concerning nifedipine extended release formulations. *Int J Clin Pharmacol Ther* 2010; **48:** 355.

Hepatic impairment. The pharmacokinetics of nifedipine were found to be considerably altered in 7 patients with liver cirrhosis.[1] Systemic plasma clearance was substantially reduced and the elimination half-life was considerably longer than in healthy subjects. In addition, systemic availability of oral nifedipine was much higher in patients with cirrhosis and was complete in 3 patients with surgical portacaval shunt. Patients with liver cirrhosis seemed to be more sensitive to the effects of nifedipine on diastolic blood pressure and heart rate, and this could be explained by the higher free drug concentrations seen. It was concluded that lower doses of nifedipine may be required in patients with liver cirrhosis, and the patient's response should be closely monitored.

1. Kleinbloesem CH, *et al.* Nifedipine: kinetics and hemodynamic effects in patients with liver cirrhosis after intravenous and oral administration. *Clin Pharmacol Ther* 1986; **40:** 21–8.

Interindividual variation. A Dutch study in 53 healthy subjects found a bimodal distribution of plasma concentrations of nifedipine after a single oral dose; it was proposed that the higher plasma concentrations in 17% of subjects represented a slow metaboliser phenotype, with the majority of the population being fast metabolisers.[1] Although further studies[2,3] in European populations have not confirmed these results, a study in 12 Mexican healthy subjects supported the concept of polymorphic metabolism, with 5 fast and 7 slow metabolisers, a much higher proportion of slow metabolisers than in the European studies.[4] Studies have also reported a markedly increased area under the concentration-time curve in those from South Asia,[5,6] Mexico,[7] and Nigeria[8] compared with Caucasians. The difference did not appear to be due to diet.[5,6] The initial dose of nifedipine might need to be lower in these ethnic groups. Another population study[9] found that clearance was slower in blacks compared with whites, and in men compared with women; alcohol ingestion and smoking both also reduced nifedipine clearance.

1. Kleinbloesem CH, *et al.* Variability in nifedipine pharmacokinetics and dynamics: a new oxidation polymorphism in man. *Biochem Pharmacol* 1984; **33:** 3721–4.
2. Renwick AG, *et al.* The pharmacokinetics of oral nifedipine—a population study. *Br J Clin Pharmacol* 1988; **25:** 701–8.
3. Lobo J, *et al.* The intra- and inter-subject variability of nifedipine pharmacokinetics in young volunteers. *Eur J Clin Pharmacol* 1986; **30:** 57–60.
4. Hoyo-Vadillo C, *et al.* Pharmacokinetics of nifedipine slow release tablet in Mexican subjects: further evidence for an oxidation polymorphism. *J Clin Pharmacol* 1989; **29:** 816–20.
5. Ahsan CH, *et al.* Ethnic differences in the pharmacokinetics of oral nifedipine. *Br J Clin Pharmacol* 1991; **31:** 399–403.
6. Ahsan CH, *et al.* The influences of dose and ethnic origins on the pharmacokinetics of nifedipine. *Clin Pharmacol Ther* 1993; **54:** 329–38.
7. Castañeda-Hernández G, *et al.* Interethnic variability in nifedipine disposition: reduced systemic plasma clearance in Mexican subjects. *Br J Clin Pharmacol* 1996; **41:** 433–4.
8. Sowunmi A, *et al.* Ethnic differences in nifedipine kinetics: comparisons between Nigerians, Caucasians and South Asians. *Br J Clin Pharmacol* 1995; **40:** 489–93.
9. Krecic-Shepard ME, *et al.* Race and sex influence clearance of nifedipine: results of a population study. *Clin Pharmacol Ther* 2000; **68:** 130–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Adalat; Nifed Sol; Nifedel; *Austral.*: Adalat; Addos; Adefin; Nifecard†; Nifehexal; Nyefax; Nypine†; *Austria*: Adalat; Buconif; Fedip; Nifebene; Nifehexal; Ospocard; *Belg.*: Adalat; Hypan; *Braz.*: Adalat; Cardalin; Dilaflux; Dilavax†; Dipinal; Neo Fedipina; Nifadil; Nifedax; Nifedicard†; Nioxil; Normopres; Oxcord; Prodopina†; *Canad.*: Adalat; Apo-Nifed; Nu-Nifed; *Chile*: Adalat; Cardicon; Coronovo; Nipress; Sulotil; *China*: Adalat (拜新同); Ai Di Qing (爱地清); De Gao Ning (得高宁); Jiu Bao Ka Di (久保卡迪); Jiubaopine (久保平); Li Huan (利焕); Na Xin Tong (纳欣同); Nifuda (伲福达); Xin Ran (欣然); Yuan Fu (源孚); *Cz.*: Adalat†; Cordipin; Corinfar†; Nifecard; *Denm.*: Adalat; Hexadilat; *Fin.*: Adalat;

Nifangin; *Fr.*: Adalate; Chronadalate; *Ger.*: Adalat; Aprical; Cisday†; Corinfar; Jutadilat†; Nife†; Nifeclair†; Nifecor†; Nifehexal†; Nifelat†; Nifical†; Pidilat†; *Gr.*: Adalat; Antiblut; Citidipine; Coracten; Flecor-N; Ftelile; Glopir; Macorel; Nefelid; Nifedicor; Nifedipat; Nucul; Nydral; Orix; Reanimat; Viscard; *Hong Kong*: Adalat; Coracten; Cordipin; Nadipinia; Nifecard; Nifelat; Vidalat†; *Hung.*: Adalat; Cordaflex; Corinfar; Nifecard†; *India*: Adalat; Angiblock; Calbloc; Calcigard; Calnif; Cardipin; Cardules; Depicor; Depin; Myogard; N-Dip; Needin; NF; Nicardia; Nifcard; Nifedine; Nifelat; Niferil; Novacard; *Indon.*: Adalat; Calcianta; Carvas; Cordalat; Coronipin; Farmalat; Fedipin†; Ficor; Nifedin; Vasdalat; Xepalat; *Irl.*: Adalat; Cardilate†; Nifed; *Israel*: Nifedilong; Osmo-Adalat; Pressolat; *Ital.*: Adalat; Amarkor; Citilat; Coral; Euxat; Fenidina; Nifedicor; Nifesal; Nipin; *Jpn*: Adalat; *Malaysia*: Adalat; Adifen; Calcigard; Fenamon; Nifecip; Nifelat; *Mex.*: Adalat; Anhiten-A; Atenses; Cordilat; Corogal†; Corotrend†; Fusepina†; Gelprim; Linam; Nifar; Nifedigel; Nifedipres; Nifezzard; Nifser; Noviken; Pidef; *Neth.*: Adalat; Nifret†; *Norw.*: Adalat; *NZ*: Adalat; Adefin; Nyefax; *Philipp.*: Adalat; Calcibloc; Calcigard†; Cardicap†; Darat; Hartigard; Heblopin; Hypertent†; Nelapine; Nifestad; Normadil†; Odipin; Tensibloc†; *Pol.*: Adalat†; Cordafen†; Cordipin†; *Port.*: Adalat; Angipina; Meborilan; *Rus.*: Adalat (Адалат); Calcigard (Кальцигард); Carin-Fer (Карин-Фер); Cordafen (Кордафен); Cordaflex (Кордафлекс); Cordipin (Кордипин); Corinfar (Коринфар); Depin-E (Депин-Е); Fenamon (Фенамон)†; Nicardia (Никардия); Nifecard (Нифекард); Nifelat (Нифелат); Osmo-Adalat (Осмо-Адалат); Phenihidin (Фенигидин); *S.Afr.*: Adalat; Adco-Vascard; Cardifen; Cipalat; Fedaloc; Macorel; Nifedalat; *Singapore*: Adalat; Apo-Nifed; Beadalet; Calcigard; Cordipin; Depin-E; Fenamon†; Nifecard; Nifedi-Denk; Nifelat; Nipin; Servidipine†; Stada Uno; Vasdalat; *Spain*: Adalat; Pertensal†; *Swed.*: Adalat; *Switz.*: Adalat; Cardipin; Corotrend; Ecodipine; Nifedicor†; *Thai.*: Adalat; Adipine; Calcigard; Coracten†; Depin-E; Fenamon†; Nelapine; Nicardia; Nifecard†; Nifedi-Denk; Nifelat; Nyefax†; Stada Uno†; *Turk.*: Adalat; Kardilat; Nidicard; Nidilat; *UAE*: Cardiopine; *UK*: Adalat; Adipine; Calchan; Cardilate MR†; Coracten; Fortipine; Hypolar Retard; Nifedipress; Nifopress†; Slofedipine; Tensipine; Valni; *Ukr.*: Adalat (Адалат); Cordipin (Кордипин); Corinfar (Коринфар); Farmadipin (Фармадипин); Nifecard (Нифекард); Osmo-Adalat (Осмо-Адалат); *USA*: Adalat; Afeditab; Nifediac; Nifedical; Procardia; *Venez.*: Adalat; Conducil; Nifal; Tensomax; Tensopin.

Multi-ingredient Preparations. *Austria*: Beta-Adalat; Nif-Ten; *Belg.*: Tenif; *Braz.*: Nifelat; Orosprevent; *Canad.*: Adalat XL Plus; *Fin.*: Nif-Ten†; *Fr.*: Beta-Adalate; Tenordate; *Ger.*: AteNif beta†; Belnif; Bresben†; Nif-Ten; Nifatenol†; Sali-Adalat; Tredalat; *Hong Kong*: Nif-Ten; *India*: Beta-Nicardia; Beta-Nifedipine; Betanif; Betatrop; Cardules Plus; Depten; Nifetolol; Nilol; Presolar; Tenofed; *Indon.*: Nif-Ten; *Irl.*: Beta-Adalat; Nif-Ten; *Ital.*: Antrolin; Nif-Ten; *Mex.*: Plenacor; *Philipp.*: Nif-Ten†; *Singapore*: Beta Nicardia; Nif-Ten; Nifetex; *Switz.*: Beta-Adalat; Nif-Ten; *UK*: Beta-Adalat; Tenif; *Ukr.*: Tonorma (Тонорма).

Pharmacopoeial Preparations

BP 2014: Nifedipine Capsules; Prolonged-release Nifedipine Capsules; Prolonged-release Nifedipine Tablets;

USP 36: Nifedipine Capsules; Nifedipine Extended-release Tablets.

Nifekalant Hydrochloride *(rINNM)*

Hidrocloruro de nifekalant; MS-551; Nifékalant, Chlorhydrate de; Nifekalant, hidrocloruro de; Nifekalanti Hydrochloridum; Нифекаланта Гидрохлорид.

6-[(2-(2-Hydroxyethyl)[3-(*p*-nitrophenyl)propyl]amino]ethyl) amino]-1,3-dimethyluracil hydrochloride.

$C_{19}H_{27}N_5O_5$,HCl=441.9

CAS — 130636-43-0 (nifekalant); 130656-51-8 (nifekalant hydrochloride).

Profile

Nifekalant is a class III antiarrhythmic (p. 1243.1) used intravenously as the hydrochloride in the management of life-threatening ventricular arrhythmias (p. 1266.1).

References.

1. Katoh T, *et al.* Emergency treatment with nifekalant, a novel class III anti-arrhythmic agent, for life-threatening refractory ventricular tachyarrhythmias: post-marketing special investigation. *Circ J* 2005; 69: 1237–43.
2. Yusu S, *et al.* Effects of intravenous nifekalant as a lifesaving drug for severe ventricular tachyarrhythmias complicating acute coronary syndrome. *Circ J* 2009; 73: 2021–8.
3. Shiga T, *et al.* Refractory VT/VF, Prospective Evaluation to Differentiate Lidocaine Efficacy from Nifekalant (RELIEF) Study Investigators. Nifekalant versus lidocaine for in-hospital shock-resistant ventricular fibrillation or tachycardia. *Resuscitation* 2010; 81: 47–52.

Effects on the heart. A woman who had been receiving intravenous nifekalant continuously for 10 months was found[1] to have a round mass in the right atrium. This was resected and shown to be a fibrin thrombus containing a large amount of nifekalant in the form of needle crystals.

1. Okamura H, *et al.* Crystals in the heart. *Heart* 2004; 90: 1106.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Shinbit.

Nilvadipine *(USAN, rINN)*

CL-287389; FK-235; Nilvadipidiini; Nilvadipidin; Nilvadipidinum; Nilvadipin; Nilvadipino; Nilvadipinum; Nivadipine; SKF-102362; Нильвадипин.

5-Isopropyl 3-methyl 2-cyano-1,4-dihydro-6-methyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate.

$C_{19}H_{19}N_3O_6$=385.4

CAS — 75530-68-6.

ATC — C08CA10.

ATC Vet — QC08CA10.

UNII — 0214FUT37I.

Pharmacopoeias. In *Jpn*.

Profile

Nilvadipine is a dihydropyridine calcium-channel blocker with general properties similar to those of nifedipine (p. 1447.2). It is used in the management of hypertension (p. 1251.1). Nilvadipine is given orally, usually as a modified-release preparation, in a dose of up to 16 mg daily.

References.

1. Brogden RN, McTavish D. Nilvadipine: a review of its pharmacodynamic and pharmacokinetic properties, therapeutic use in hypertension and potential in cerebrovascular disease and angina. *Drugs Aging* 1995; 6: 150–71. Correction. *ibid.*; 7: 116.
2. Koseki N, *et al.* A placebo-controlled 3-year study of a calcium blocker on visual field and ocular circulation in glaucoma with low-normal pressure. *Ophthalmology* 2008; 115: 2049–57.
3. Nakazawa M, *et al.* Effect of nilvadipine on central visual field in retinitis pigmentosa: a 30-month clinical trial. *Ophthalmologica* 2011; 225: 120–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Tensan; *Cz.*: Escor†; *Fin.*: Escor; *Ger.*: Escor; Nivadil; *Gr.*: Peroma; *Irl.*: Nivadil; *Jpn*: Nivadil; *Port.*: Nivadil; *Turk.*: Nilvadis.

Nimodipine *(BAN, USAN, rINN)*

Bay-e-9736; Nimodipiini; Nimodipin; Nimodipina; Nimodipinas; Nimodipino; Nimodipinum; Nimódypina; Нимодипин.

Isopropyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate.

$C_{21}H_{26}N_2O_7$=418.4

CAS — 66085-59-4.

ATC — C08CA06.

ATC Vet — QC08CA06.

UNII — 57WA9QZ5WH.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Nimodipine). A light yellow or yellow crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in ethyl acetate. Exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Solutions should be prepared in the dark or under light of wavelength greater than 420 nm, immediately before use. Protect from light.

USP 36: (Nimodipine). A light yellow or yellow crystalline powder, affected by light. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in ethyl acetate. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Licensed product information states that solutions of nimodipine are incompatible with some plastics, including PVC, and that the only plastics suitable for use are polyethylene and polypropylene. Nimodipine solution must not be added to an infusion bag or bottle, or be mixed with other drugs.

Uses and Administration

Nimodipine is a dihydropyridine calcium-channel blocker that has the general properties of nifedipine (p. 1447.2), but acts particularly on cerebral blood vessels. It is used in cerebrovascular disorders (see below), particularly in the prevention and treatment of ischaemic neurological deficits after aneurysmal subarachnoid haemorrhage.

To reduce the incidence and severity of ischaemic neurological deficit after aneurysmal haemorrhage nimodipine is given orally in a dose of 60 mg every 4 hours. Treatment should begin within 4 days of onset of haemorrhage and should continue for 21 days. In patients with hepatic impairment the dose may be reduced (see below) and blood pressure should be closely monitored.

If cerebral ischaemia occurs or has already occurred, neurological deficit may be treated by intravenous infusion of an appropriate formulation of nimodipine. It should be given via a bypass into a running intravenous infusion into a central vein. The initial dose should be nimodipine 1 mg/hour for 2 hours, increased (provided that no severe decrease in blood pressure occurs) to 2 mg/hour. The starting dose should be reduced to 500 micrograms/hour, or even lower if necessary, in patients weighing less than 70 kg and in those with unstable blood pressure; a similar reduction in dosage has been suggested in hepatic impairment, and blood pressure should be closely monitored. Treatment should be started as soon as possible and continued for at least 5 and no more than 14 days; if the patient has already received oral nimodipine, the total duration of nimodipine use should not exceed 21 days.

For doses in children, see below.

Administration in children. The *BNFC* recommends that children aged from 1 month may be given nimodipine orally for the **prevention** of vasospasm after subarachnoid haemorrhage in a dose of 0.9 to 1.2 mg/kg (up to a maximum of 60 mg) six times daily; treatment should start within 4 days of haemorrhage and be continued for 21 days.

For the **treatment** of haemorrhage once cerebral ischaemia has already occurred, it suggests that nimodipine may be given by intravenous infusion under specialist advice. The dose in those from 1 month to 12 years of age is 15 micrograms/kg per hour initially (to a maximum of 500 micrograms/hour), or half this rate if blood pressure is unstable. After 2 hours, provided there is no severe decrease in blood pressure, the rate may be increased up to 30 micrograms/kg per hour (maximum 2 mg/hour) and treatment continued for at least 5 but no more than 14 days. Doses in older children are similar to those in adults.

Administration in hepatic impairment. The clearance of nimodipine is reduced in patients with cirrhosis, and blood pressure should be closely monitored in such patients. US licensed product information recommends that the oral dose of nimodipine should be halved to 30 mg every 4 hours in patients with hepatic cirrhosis. Some manufacturers have also suggested a reduction in the initial intravenous dose to 500 micrograms or less per hour.

Cerebrovascular disorders. Nimodipine is used orally and intravenously in the prevention and treatment of ischaemic neurological deficits caused by arterial vasospasm after aneurysmal *subarachnoid haemorrhage* (see Stroke, p. 1269.2), although the evidence for benefit after intravenous use is limited.[1] Intrathecal[2] and intra-arterial[3] administration have also been proposed. Nimodipine has also been used for traumatic subarachnoid haemorrhage,[4] but results have been mixed,[5,6] and UK licensed product information recommends against such use. In addition to dilating cerebral blood vessels and improving cerebral blood flow, nimodipine may also prevent or reverse ischaemic damage to the brain by limiting transcellular calcium influx. These effects have led to the investigation of nimodipine in other conditions associated with *cerebral ischaemia*.[7] Studies[8,9] of nimodipine given orally after ischaemic stroke have produced conflicting results. A meta-analysis[10] of controlled studies suggested that nimodipine is beneficial if given within 12 hours of stroke onset but a further study[11] failed to confirm this. In a controlled study[12] of 155 patients suffering a cardiac arrest, nimodipine was given by intravenous infusion for 24 hours. Nimodipine had no effect on overall survival, although it did improve survival of patients in whom advanced life support was delayed for more than 10 minutes after arrest, suggesting a possible beneficial effect on anoxic-ischaemic brain injury.

Nimodipine has also been tried in *dementia* (p. 388.1). Two multicentre studies[13] involving a total of 755 patients with dementia of vascular or degenerative origin given nimodipine for up to 6 months reported improvements in cognitive function and disability, and a systematic review[14] concluded that nimodipine could be of some benefit in patients with various forms of dementia.

1. Dorhout Mees S, *et al.* Calcium antagonists for aneurysmal subarachnoid haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 12/03/08).
2. Hänggi D, *et al.* Feasibility and safety of intrathecal nimodipine on posthaemorrhagic cerebral vasospasm refractory to medical and endovascular therapy. *Clin Neurol Neurosurg* 2008; 110: 784–90.
3. Wolf S, *et al.* Continuous selective intraarterial infusion of nimodipine for therapy of refractory cerebral vasospasm. *Neurocrit Care* 2010; 12: 346–51.
4. Harders A, *et al.* Traumatic subarachnoid hemorrhage and its treatment with nimodipine. *J Neurosurg* 1996; 85: 82–9.
5. Langham J, *et al.* Calcium channel blockers for acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 12/03/08).
6. Vergouwen MDI, *et al.* Effect of nimodipine on outcome in patients with traumatic subarachnoid haemorrhage: a systematic review. *Lancet Neurol* 2006; 5: 1029–32.

7. Tomassoni D, *et al.* Nimodipine and its use in cerebrovascular disease: evidence from recent preclinical and controlled clinical studies. *Clin Exp Hypertens* 2008; 30: 744–66.
8. Gelmers HJ, *et al.* A controlled trial of nimodipine in acute ischemic stroke. *N Engl J Med* 1988; 318: 203–7.
9. Trust Study Group. Randomised, double-blind, placebo-controlled trial of nimodipine in acute stroke. *Lancet* 1990; 336: 1205–9.
10. Mohr JP, *et al.* Meta-analysis of oral nimodipine trials in acute ischemic stroke. *Cerebrovasc Dis* 1994; 4: 197–203.
11. Horn J, *et al.* Very Early Nimodipine Use in Stroke (VENUS): a randomized, double-blind, placebo-controlled trial. *Stroke* 2001; 32: 461–5.
12. Roine RO, *et al.* Nimodipine after resuscitation from out-of-hospital ventricular fibrillation: a placebo-controlled, double-blind, randomized trial. *JAMA* 1990; 264: 3171–7.
13. Pametti L, *et al.* Nimodipine Study Group. Mental deterioration in old age: results of two multicenter, clinical trials with nimodipine. *Clin Ther* 1993; 15: 394–406.
14. Birks J, López-Arrieta J. Nimodipine for primary degenerative, mixed and vascular dementia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 12/07/05).

Migraine and cluster headache. For reference to the use of calcium-channel blockers, including nimodipine, in the management of migraine and cluster headache, see under Nifedipine, p. 1449.1.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2).

Nimodipine should be used with caution in patients with cerebral oedema or severely raised intracranial pressure.

Effects on the heart. Marked bradycardia developed in a patient with acute ischaemic stroke during treatment with nimodipine and was suspected to be related to the drug therapy.[1] Severe myocardial depression occurred[2] in another patient given intravenous nimodipine after an aneurysmal subarachnoid haemorrhage. The authors advised dose-reduction or withholding of nimodipine until the myocardium recovered from the acute insult caused by subarachnoid haemorrhage.

1. Fagan SC, Nacci N. Nimodipine and bradycardia in acute stroke—drug or disease? *DICP Ann Pharmacother* 1991; 25: 247–9.
2. Subramani K, Ghrew M. Severe myocardial depression following intravenous nimodipine for aneurysmal subarachnoid haemorrhage. *Intensive Care Med* 2004; 30: 1498–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nimodipine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Pharmacokinetics

Nimodipine is rapidly absorbed from the gastrointestinal tract after oral doses but undergoes extensive first-pass metabolism in the liver. The oral bioavailability is reported to be about 13%. Peak plasma concentrations occur within 1 hour of ingestion. Nimodipine is more than 95% bound to plasma proteins. It crosses the blood-brain barrier, but concentrations in CSF are lower than those in plasma. Nimodipine is extensively metabolised in the liver via the cytochrome P450 isoenzyme CYP3A4. It is excreted in faeces via the bile, and in urine, almost entirely as metabolites. The terminal elimination half-life is reported to be about 9 hours but the initial decline in plasma concentration is much more rapid, equivalent to a half-life of 1 to 2 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: AC Vascular; Acival; Ampina†; Aniduv; Cebrofort; Dunaden; Eugerial; Explaner; Finaclen; Macobal; Nimo-Somazina; Nimodilat; Nimotop; Nivas; Tenocard; *Austral.*: Nimotop; *Austria*: Nimotop; *Belg.*: Nimotop; *Braz.*: Eugerial; Neuron; Nimobal; Nimopax; Nimotop; Noodipina; Oxigen; Vasodipina; *Canad.*: Nimotop; *Chile*: Grifonimod; Nimotop; Regental; *China*: Bao Yi Tian; Bu Rui Xi (布瑞喜); En Tong (恩通); Erping (尔平); Hai Meng Hui (海盟惠); JiLi (济立); Ni Da Er (尼达尔); Nilisu (尼立苏); Nimotop (尼膜同); Ping Da Er (平达尔); Xing You Fu (星尤复); Yi Fu Lin (易夫林); Yi Fu Zheng (一夫正); You Ni Xin (尤尼欣); Yuan Gan (元甘); Yun Di En (云迪恩); *Cz.*: Dilceren; Nimotop; *Denm.*: Nimotop; *Fin.*: Nimotop; *Fr.*: Nimotop; *Ger.*: Nimotop; *Gr.*: Arfine; Aurodipine; Befimat; Curban; Figozant; Genovox; Myodipine; Naborel; Nelbinex; Nimodil; Nimotop; Nimovac-V; Nortolan; Rosital; Stigmicarpin; Thrionipen; Vastripine; Zirem ex; *Hong Kong*: Nimotop; *Hung.*: Nimotop; *India*: Modipin; Nimocard; Nimocer; Nimodec; Nimodip; Nimotide; Vasotop; *Indon.*: Ceremax; Nimotop; *Irl.*: Nimotop; *Israel*: Nimotop; *Ital.*: Iskidrop; Nimobrain; Nimotop; Periplum; *Malaysia*: Nimotop; *Mex.*: Eugerial†; Imolans†; Kenzolol; Nimotop; Vacer; *Neth.*: Nimotop; *Norw.*: Nimotop; *NZ*: Nimotop; *Philipp.*: Nimotop; *Pol.*: Nimotop; *Port.*: Brainox; Genogris†; Modibloq; Modina; Nimotop; Niton; Sobrepina; Trinalion; *Rus.*: Nemotan (Немотан)†; Nimopine (Нимопин); Nimotop (Нимотоп); *S.Afr.*: Nimotop; *Singapore*: Nimotop; *Spain*: Admon†; Brainal; Calnit†; Kenesil; Modus; Nimotop; Remontal†; *Swed.*: Nimotop; *Switz.*: Nimotop; *Thai.*: Nimotop; *Turk.*: Nimotop; *UK*: Nimotop; *Ukr.*: Nimodiphexal (НимодиГЕКСАЛ)†; Nimotop (Нимотоп); *USA*: Nimotop†; Nymalize; *Venez.*: Nemodine; Nimotop; Tropocer.

Multi-ingredient Preparations. *Arg.*: Idenimo; Idesole Plus; Nemocebral Plus; Nimodilat Plus; Nimoreagin; Nivas Plus.

Pharmacopoeial Preparations
BP 2014: Nimodipine Infusion; Nimodipine Tablets.

Nisoldipine *(BAN, USAN, rINN)*

Bay-k-5552; Nisoldipiini; Nisoldipin; Nisoldipina; Nisoldipino; Nisoldipinum; Низольдипин.

Isobutyl methyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl) pyridine-3,5-dicarboxylate.

$C_{20}H_{24}N_2O_6$=388.4

CAS — 63675-72-9.

ATC — C08CA07.

ATC Vet — QC08CA07.

UNII — 4I8HAB65SZ.

Uses and Administration

Nisoldipine is a dihydropyridine calcium-channel blocker with actions and uses similar to those of nifedipine (p. 1447.2). It is used in the management of hypertension (p. 1251.1) and angina pectoris (p. 1254.3). Nisoldipine is given orally. Both immediate- and modified-release preparations are available, and doses vary between preparations. Immediate-release preparations are typically given in an initial dose of 5 or 10 mg twice daily, increased if necessary at intervals of no less than 1 week to a maximum of 20 mg twice daily. Similar daily doses may be given as modified-release tablets, which are taken once daily. Alternatively, in the USA, modified-release tablets are indicated for hypertension in an initial dose of 17 mg once daily, adjusted according to response by increments of 8.5 mg at intervals of at least 1 week. The usual maintenance dose is 17 to 34 mg once daily. This preparation should be taken on an empty stomach, at least 1 hour before, or 2 hours after a meal.

Lower initial doses and cautious titration are required in the elderly and in hepatic impairment—see below.

Reviews.

1. Mitchell J, *et al.* Nisoldipine: a new dihydropyridine calcium-channel blocker. *J Clin Pharmacol* 1993; 33: 46–52.
2. Plosker GL, Faulds D. Nisoldipine coat-core: a review of its pharmacology and therapeutic efficacy in hypertension. *Drugs* 1996; 52: 232–53.
3. Langtry HD, Spencer CM. Nisoldipine coat-core: a review of its pharmacodynamic and pharmacokinetic properties and clinical efficacy in the management of ischaemic heart disease. *Drugs* 1997; 53: 867–84.
4. White WB. Pharmacologic agents in the management of hypertension—nisoldipine coat-core. *J Clin Hypertens (Greenwich)* 2007; 9: 259–66.

Administration in hepatic impairment. Licensed product information for nisoldipine recommends that immediate-release preparations are given to the elderly and those with hepatic impairment in a reduced initial oral dose of 5 or 10 mg once daily. In the USA, a modified-release preparation may be given in a reduced initial oral dose of 8.5 mg once daily. Doses should be titrated with caution.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Pharmacokinetics

Nisoldipine is well absorbed from the gastrointestinal tract after oral doses but undergoes rapid and extensive first-pass metabolism in the gut wall and liver and bioavailability has been reported to be only about 4 to 8%. About 60 to 80% of an oral dose is excreted in the urine and the remainder in the faeces, mainly as metabolites. The terminal elimination half-life is about 7 to 12 hours. Nisoldipine is more than 99% bound to plasma proteins.

A study[1] in 11 patients given oral nisoldipine 10 mg once or twice daily indicated that the pharmacokinetics of nisoldipine could best be described by an open 2-compartment model. Peak plasma concentrations occurred 1 hour after a single oral dose, and varied greatly between the patients. The mean plasma elimination half-life was 11.4 hours after a single dose and 14.0 hours after repeated dosing, which was longer than had been previously reported, perhaps reflecting the greater sensitivity of the assay.

In another study oral, but not intravenous, nisoldipine increased liver blood flow in 10 healthy subjects and thus affected its own systemic availability.[2] Variations in liver blood flow may account for the interindividual variation in the pharmacokinetics of nisoldipine.

1. Ottosson A-M, *et al.* Analysis and pharmacokinetics of nisoldipine in hypertensive patients. *Curr Ther Res* 1989; 45: 347–58.
2. van Harten J, *et al.* Variability in the pharmacokinetics of nisoldipine as caused by differences in liver blood flow response. *J Clin Pharmacol* 1989; 29: 714–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Syscor; *Belg.*: Sular; Syscor; *Braz.*: Syscor; *Chile*: Nivast; *China*: Bo Ping (博平); Di Yi Xin (蒂益欣); Ji Ni Le Er (吉尼乐尔); Ke Di (可谛); Mo Tai; Ni Er Xin (尼尔欣); Ruidi (锐地); Xin Nuo Jin (欣诺金); Xin Xue Ping (欣雪平); Yi Li (易立); You De Ning (优得宁); *Fin.*: Syscor; *Ger.*: Baymycard; *Gr.*: Syscor; *Hung.*: Baymycard; *Ital.*: Syscor; *NZ*: Syscor; *Spain*: Sular; Syscor; *Turk.*: Syscor; *UK*: Syscor†; *USA*: Sular.

Nitrendipine *(BAN, USAN, rINN)*

Bay-e-5009; Nitrendipiini; Nitrendipin; Nitrendipina; Nitrendipinas; Nitrendipino; Nitrendipinum; Нитрендипин.

Ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate.

$C_{18}H_{20}N_2O_6$=360.4

CAS — 39562-70-4.

ATC — C08CA08.

ATC Vet — QC08CA08.

UNII — 9B627AW319.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8: (Nitrendipine). A yellow crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in dehydrated alcohol and in methyl alcohol; freely soluble in ethyl acetate. Exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Solutions should be prepared in the dark or under light of wavelength greater than 420 nm, immediately before use. Protect from light.

Uses and Administration

Nitrendipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p. 1447.2). It is given orally in the treatment of hypertension (p. 1251.1).

The usual dose is 20 mg daily as a single dose or as 2 divided doses. The dose may be increased to 20 mg twice daily if necessary for the control of resistant hypertension. In the elderly, an initial dose of 10 mg daily should be used. The dose should also be reduced in hepatic impairment (see below).

Reviews.

1. Santiago TM, Lopez LM. Nitrendipine: a new dihydropyridine calcium-channel antagonist for the treatment of hypertension. *DICP Ann Pharmacother* 1990; 24: 167–75.

Administration in hepatic impairment. The initial oral dose of nitrendipine should be reduced to 5 to 10 mg once daily in patients with hepatic impairment.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1450.2).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p. 1453.2).

Pharmacokinetics

Nitrendipine is reported to be well absorbed after oral doses but undergoes extensive first-pass metabolism; the absolute oral bioavailability is reported to range from about 10 to 30%, depending in part on the dosage form. Peak plasma concentrations occur within 1 to 3 hours. Nitrendipine is about 98% bound to plasma proteins. It is extensively metabolised in the liver and is excreted as inactive metabolites in the urine and faeces, with less than 0.1% as unchanged drug. Although early studies reported a terminal elimination half-life of about 2 to 4 hours, later studies, using more sensitive assay procedures, have recorded values between about 10 and 22 hours. The half-life is prolonged in patients with hepatic impairment.

References.
1. Soons PA, Breimer DD. Stereoselective pharmacokinetics of oral and intravenous nitrendipine in healthy male subjects. *Br J Clin Pharmacol* 1991; 32: 11–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Nirapel; Nitrendil; *Austria*: Baypress; *Belg.*: Baypress; *Braz.*: Caltren; Nitrencord; *Chile*: Cardiazem; Grifonitren; Tensofar†; *China*: Shu Mai Te (舒麦特); *Cz.*: Baypress; Lusopress; Nitrepress; Nitresan; Unipres; *Denm.*: Baypress; *Fr.*: Baypress; Nidrel; *Ger.*: Bayotensin; Jutapress†; Nitre-Puren†; Nitregamma; Nitren Lich; Nitrendidoc†; Nitrensal; Nitrepress†; *Gr.*: Arianit; Aroselin; Baypress; Crivion; G-Press; Issopres; Lanocardique; Leonitren; Lisba; Lostradyl; Midonat; Nelconil; Nifecard; Nitrendilat; Nivitron; Pallohyman; Potional; Pressodipin; Spidox; Tepanil; Thriffin; Ufocard; Zulexen; *Hong Kong*: Baypress†; *Hung.*: Baypress; Unipres; *India*: Nitrepin; *Ital.*: Baypress; *Jpn*: Baylotensin; *Neth.*: Baypress; *Port.*: Farnitran†; Hiperdipina; *Spain*: Baypresol; Gericin; Niprina†; Sub Tensin; Sub-Tensin; Tensogradal; Vastensium†; *Switz.*: Baypress; *Thai.*: Baypress; Ditrenil; Miniten; *Turk.*: Baypress; *Venez.*: Baypress; Nitrendil.

Multi-ingredient Preparations. *Austria*: Cenipres; *Ger.*: Eneas; *Gr.*: Eneas; Enit; *India*: Cardif Beta†; *Port.*: Eneas; Enit; *Spain*: Eneas; Enit; Vipres; *Turk.*: Eneas; Enit; *Ukr.*: Eneas (Энеас).

Nitric Oxide *(USAN)*

Azote, monoxyde d'; Azoto oksidas; Azotu(II) tlenek; Kväveoxid; Mononitrogen Monoxide; Monóxido de nitrógeno; Nitrogen Monoxide; Nitrogenii Oxidum; Nitrogénmonoxid; OHM-11771; Oxid dusnatý; Óxido nítrico; Stickstoffmonoxid; Typpioksidi; Оксид Азота.

NO=30.01

CAS — 10102-43-9.

ATC — R07AX01.

ATC Vet — QR07AX01.

UNII — 31C4KY9ESH.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Nitric Oxide). A colourless gas that turns brown when exposed to air. At 20 degrees and at a pressure of 101 kPa, 1 volume dissolves in about 21 volumes of water. Store compressed at a pressure not exceeding 2.5 MPa measured at 15 degrees in suitable containers.

Uses and Administration

Nitric oxide is an endogenous chemical messenger that acts mainly by stimulating guanylate cyclase in smooth muscle to cause vasodilatation. It is also involved in platelet aggregation, neurotransmission, and the immune system, and possesses antimicrobial, antitumour, and antiviral activity.

Endogenous nitric oxide is now recognised to be the same substance as endothelium-derived relaxing factor (EDRF). It is synthesised from L-arginine by the enzyme, nitric oxide synthase, of which three isoforms have been identified. Constitutive isoforms occur in endothelial cells (such as in vascular endothelium, platelets, and the heart) and neuronal cells (in some central and peripheral neurones). Small amounts of nitric oxide are regularly produced by these systems. In contrast, an inducible isoform producing larger amounts of nitric oxide is expressed only after activation by external stimuli such as infection or inflammation. This inducible nitric oxide synthase may be expressed in many cells, including macrophages and cells in vascular smooth muscle, the heart, gastrointestinal tract, and liver.

Inhaled nitric oxide is a highly selective pulmonary vasodilator. It is used in the management of term and near-term neonates with hypoxic respiratory failure associated with pulmonary hypertension. It is also used as a diagnostic tool to test acute vasoreactivity in patients with pulmonary hypertension of various aetiologies, and is being studied in other bronchopulmonary disorders and in different age groups.

In the management of hypoxic respiratory failure in neonates, nitric oxide is given by inhalation in a usual concentration of 20 ppm. Doses have been titrated above and below this concentration but due to the risk of methaemoglobinaemia, doses above 20 ppm are not generally recommended. The concentration should be reduced gradually before stopping treatment.

General reviews.
1. Hart CM. Nitric oxide in adult lung disease. *Chest* 1999; 115: 1407–17.
2. Vallance P, Chan N. Endothelial function and nitric oxide: clinical relevance. *Heart* 2001; 85: 342–50.
3. Ichinose F, *et al.* Inhaled nitric oxide: a selective pulmonary vasodilator: current uses and therapeutic potential. *Circulation* 2004; 109: 3106–11.
4. Griffiths MJD, Evans TW. Inhaled nitric oxide therapy in adults. *N Engl J Med* 2005; 353: 2683–95.
5. Creagh-Brown BC, *et al.* Bench-to-bedside review: inhaled nitric oxide therapy in adults. *Crit Care* 2009; 13: 221. Available at: http://ccforum.com/content/pdf/cc7734.pdf (accessed 10/03/10)

Respiratory disorders. Inhaled nitric oxide is a potent and highly selective pulmonary vasodilator used in the management of persistent pulmonary hypertension of the newborn (below) and other conditions leading to hypoxic respiratory failure in neonates.

Nitric oxide has also been tried in acute respiratory distress syndrome (below), severe acute respiratory syndrome,[1] respiratory failure,[2] acute severe asthma,[3] pulmonary arterial hypertension[4,5] including that in pregnancy,[6,7] and in pulmonary hypertension associated with a wide range of conditions including chronic obstructive pulmonary disease,[8] heart failure,[9] post-cardiac surgery,[10-13] heart or lung transplantation,[14-16] and high-altitude disorders.[17]

1. Chen L, *et al.* Inhalation of nitric oxide in the treatment of severe acute respiratory syndrome: a rescue trial in Beijing. *Clin Infect Dis* 2004; 39: 1531–5.
2. Dobyns EL, *et al.* Multicenter randomized controlled trial of the effects of inhaled nitric oxide therapy on gas exchange in children with acute hypoxemic respiratory failure. *J Pediatr* 1999; 134: 406–12.
3. Nakagawa TA, *et al.* Life-threatening status asthmaticus treated with inhaled nitric oxide. *J Pediatr* 2000; 137: 119–22.
4. Kinsella JP, *et al.* Selective and sustained pulmonary vasodilation with inhalational nitric oxide therapy in a child with idiopathic pulmonary hypertension. *J Pediatr* 1993; 122: 803–6.
5. Goldman AP, *et al.* Is it time to consider domiciliary nitric oxide? *Lancet* 1995; 345: 199–200.
6. Lam GK, *et al.* Inhaled nitric oxide for primary pulmonary hypertension in pregnancy. *Obstet Gynecol* 2001; 98: 895–8.
7. Decoene C, *et al.* Use of inhaled nitric oxide for emergency Cesarean section in a woman with unexpected primary pulmonary hypertension. *Can J Anaesth* 2001; 48: 584–7.
8. Vonbank K, *et al.* Controlled prospective randomised trial on the effects on pulmonary haemodynamics of the ambulatory long term use of nitric oxide and oxygen in patients with severe COPD. *Thorax* 2003; 58: 289–93.
9. Matsumoto A, *et al.* Inhaled nitric oxide and exercise capacity in congestive heart failure. *Lancet* 1997; 349: 999–1000. Correction. *ibid.*: 350: 818.
10. Haydar A, *et al.* Inhaled nitric oxide for postoperative pulmonary hypertension in patients with congenital heart defects. *Lancet* 1992; 340: 1545.
11. Miller OI, *et al.* Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. *Lancet* 2000; 356: 1464–9.
12. Journois D, *et al.* Effects of inhaled nitric oxide administration on early postoperative mortality in patients operated for correction of atrioventricular canal defects. *Chest* 2005; 128: 3537–44.
13. Bizzarro M, Gross I. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 27/10/09).
14. Rea RS, *et al.* Role of inhaled nitric oxide in adult heart or lung transplant recipients. *Ann Pharmacother* 2005; 39: 913–17.
15. Botha P, *et al.* Inhaled nitric oxide for modulation of ischemia-reperfusion injury in lung transplantation. *J Heart Lung Transplant* 2007; 26: 1199–1205.
16. Yerebakan C, *et al.* Effects of inhaled nitric oxide following lung transplantation. *J Card Surg* 2009; 24: 269–74.
17. Scherrer U, *et al.* Inhaled nitric oxide for high-altitude pulmonary edema. *N Engl J Med* 1996; 334: 624–9.

ACUTE RESPIRATORY DISTRESS SYNDROME. Although inhalation of nitric oxide has been reported to improve oxygenation in patients with acute respiratory distress syndrome (p. 1599.3), meta-analyses[1,2] have failed to confirm any significant mortality benefit, and there is some evidence[2] that nitric oxide increases the risk of renal dysfunction.

1. Afshari A, *et al.* Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults. Available in The Cochrane Database of Systematic Reviews; Issue 7. Chichester: John Wiley; 2010 (accessed 02/08/10).
2. Adhikari NKJ, *et al.* Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. Abridged version: *BMJ* 2007; 334: 779–82. Full version: http://www.bmj.com/cgi/reprint/334/7597/779 (accessed 31/07/08)

RESPIRATORY DISORDERS IN NEONATES. Inhaled nitric oxide is used in the management of hypoxic respiratory failure in term and near-term neonates.[1-3] It has also been studied in premature neonates.[4,5]

Most studies have been in neonates with persistent pulmonary hypertension of the newborn (p. 1278.2), although varying definitions have been used. A systematic review[6] of controlled studies in term and near-term neonates with hypoxic respiratory failure found that oxygenation was improved with inhaled nitric oxide, with a reduction in the need for extracorporeal membrane oxygenation, but no effect on mortality has been shown. A randomised study[7] also found no mortality benefit when nitric oxide was started early in the disease process, although progression was slowed. Neonates with congenital diaphragmatic hernia (CDH), however, have not been shown to benefit,[8,9] and nitric oxide is not recommended in such patients,[6] although the optimal treatment of this condition is controversial; one study[10] suggested that inhaled nitric oxide may have a role in patients with CDH who develop late pulmonary hypertension. Another study[11] suggested that the improvement in oxygenation may not be sustained, and that neonates with pulmonary hypoplasia and dysplasia are less sensitive to nitric oxide.

The dose of nitric oxide found to be effective in most studies has been from 20 to 80 ppm. However, since nitric oxide is associated with dose-related toxicity, lower doses (1 to 2 ppm) have also been studied. One study[12] found no significant difference between high and low doses, but another study[13] found that low doses did not improve oxygenation and diminished the response to subsequent higher doses.

Inhaled nitric oxide has also been reported to improve oxygenation in premature neonates with hypoxic respiratory failure, but its use is not yet established.[14,15] A study[16] in premature infants with respiratory distress syndrome suggested that the incidence of chronic lung disease and death was reduced by nitric oxide, and an open study[17] in very premature infants who had already developed chronic lung disease also found an improvement in oxygenation with nitric oxide therapy. However, a systematic review[18] found that use of rescue nitric oxide therapy in severely ill infants was ineffective, and that late use to prevent chronic lung disease also had no effect. There was some evidence that early routine use in mildly sick infants might improve outcomes, but further studies were needed to identify those infants who were most likely to benefit.

There have been concerns that use of inhaled nitric oxide might adversely affect neurodevelopmental outcome more than conventional therapy particularly in premature infants, but follow-up studies have reported mixed results. Studies in term and near-term infants,[19-21] and in premature infants,[22] have found that use of nitric oxide has no effect on neurodevelopment, but there have also been reports of poor neurodevelopmental outcome[23] and of improved outcome,[24,25] and a review[26] of studies in preterm infants followed up after 4 to 5 years suggested that inhaled nitric oxide may confer neurodevelopmental protection; however, differences in study design make comparisons between studies difficult, and the effect on neurodevelopment remains to be confirmed.

1. American Academy of Pediatrics Committee on Fetus and Newborn. Use of inhaled nitric oxide. *Pediatrics* 2000; 106: 344–5.
2. Kinsella JP. Inhaled nitric oxide in the term newborn. *Early Hum Dev* 2008; 84: 709–16.
3. Soll RF. Inhaled nitric oxide in the neonate. *J Perinatol* 2009; 29 (suppl 2): S63–S67.
4. Miller SS, Rhine WD. Inhaled nitric oxide in the treatment of preterm infants. *Early Hum Dev* 2008; 84: 703–7.
5. Arul N, Konduri GG. Inhaled nitric oxide for preterm neonates. *Clin Perinatol* 2009; 36: 43–61.
6. Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 04/06/08).
7. Konduri GG, *et al.* A randomized trial of early versus standard inhaled nitric oxide therapy in term and near-term newborn infants with hypoxic respiratory failure. *Pediatrics* 2004; 113: 559–64.
8. Clark RH, *et al.* Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. *N Engl J Med* 2000; 342: 469–74.
9. The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. *Pediatrics* 1997; 99: 838–45.
10. Kinsella JP, *et al.* Noninvasive delivery of inhaled nitric oxide therapy for late pulmonary hypertension in newborn infants with congenital diaphragmatic hernia. *J Pediatr* 2003; 142: 397–401.
11. Goldman AP, *et al.* Four patterns of response to inhaled nitric oxide for persistent pulmonary hypertension of the newborn. *Pediatrics* 1996; 98: 706–13.
12. Finer NN, *et al.* Randomized, prospective study of low-dose versus high-dose inhaled nitric oxide in the neonate with hypoxic respiratory failure. *Pediatrics* 2001; 108: 949–55.
13. Cornfield DN, *et al.* Randomized, controlled trial of low-dose inhaled nitric oxide in the treatment of term and near-term infants with respiratory failure and pulmonary hypertension. *Pediatrics* 1999; 104: 1089–94.
14. Subhedar N, Dewhurst C. Is nitric oxide effective in preterm infants? *Arch Dis Child Fetal Neonatal Ed* 2007; 92: F337–F341.
15. Kinsella JP, Abman SH. Inhaled nitric oxide in the premature newborn. *J Pediatr* 2007; 151: 10–15.
16. Schreiber MD, *et al.* Inhaled nitric oxide in premature infants with the respiratory distress syndrome. *N Engl J Med* 2003; 349: 2099–2107.
17. Clark PL, *et al.* Safety and efficacy of nitric oxide in chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 2002; 86: F41–F45.
18. Barrington KJ, Finer NN. Inhaled nitric oxide for respiratory failure in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 04/06/08).
19. Rosenberg AA, *et al.* Longitudinal follow-up of a cohort of newborn infants treated with inhaled nitric oxide for persistent pulmonary hypertension. *J Pediatr* 1997; 131: 70–5.
20. The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in term and near-term infants: neurodevelopmental follow-up of the Neonatal Inhaled Nitric Oxide Study Group (NINOS). *J Pediatr* 2000; 136: 611–17.
21. Konduri GG, *et al.* Neonatal Inhaled Nitric Oxide Study Group. Early inhaled nitric oxide therapy for term and near-term newborn infants with hypoxic respiratory failure: neurodevelopmental follow-up. *J Pediatr* 2007; 150: 235–40.
22. Hintz SR, *et al.* NICHD Neonatal Research Network. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. *J Pediatr* 2007; 151: 16–22.
23. Cheung P-Y, *et al.* The outcome of very low birth weight neonates (≤1500g) rescued by inhaled nitric oxide: neurodevelopment in early childhood. *J Pediatr* 1998; 133: 735–9.
24. Mestan KKL, *et al.* Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. *N Engl J Med* 2005; 353: 23–32.
25. Tanaka Y, *et al.* Inhaled nitric oxide therapy decreases the risk of cerebral palsy in preterm infants with persistent pulmonary hypertension of the newborn. *Pediatrics* 2007; 119: 1159–64.
26. Marks JD, Schreiber MD. Inhaled nitric oxide and neuroprotection in preterm infants. *Clin Perinatol* 2008; 35: 793–807.

Sickle-cell disease. Sickle-cell crisis due to vaso-occlusion is an acute complication of sickle-cell disease (p. 1123.2), requiring hospitalisation, with the use of large volumes of intravenous fluids for dehydration, and analgesia including opioids for pain. Concentrations of nitric oxide metab-

olites and L-arginine have been found to be low in vaso-occlusive crisis and a study[1] in paediatric patients showed that inhaled nitric oxide may be of benefit.

1. Weiner DL, *et al.* Preliminary assessment of inhaled nitric oxide for acute vaso-occlusive crisis in pediatric patients with sickle cell disease. *JAMA* 2003; 289: 1136–42.

Adverse Effects

Inhaled nitric oxide may lead to the development of methaemoglobinaemia, particularly at higher doses. Although it is a selective pulmonary vasodilator, systemic hypotension may occur. Abrupt withdrawal of therapy may lead to a deterioration in oxygenation and the development of rebound pulmonary hypertension.

Nitrogen dioxide produced when nitric oxide combines with oxygen can cause acute lung injury; high concentrations of inhaled nitric oxide are directly irritant to the lungs.

A potential complication of inhaled nitric oxide is methaemoglobinaemia but this is probably related to the dose; the risk does not appear to be increased during low-dose (20 ppm) therapy.[1] Another possible adverse event is an increased risk of bleeding due to inhibition of platelet aggregation.[2-5] Rebound pulmonary hypertension[6] and deterioration in oxygenation[7,8] have been reported in some children after stopping nitric oxide therapy. Severe systemic hypotension has also been reported[9] after starting therapy in a neonate with severe left ventricular dysfunction. Pulmonary oedema has been associated with the use of nitric oxide in 2 patients with CREST syndrome, a form of systemic sclerosis.[10] Motor neurone disease in a patient with alcoholism has been partly attributed[11] to the use of nitric oxide for pulmonary hypertension.

1. Kinsella JP, Abman SH. Methaemoglobin during nitric oxide therapy with high-frequency ventilation. *Lancet* 1993; 342: 615.
2. Högman M, *et al.* Bleeding time prolongation and NO inhalation. *Lancet* 1993; 341: 1664–5.
3. Joannidis M, *et al.* Inhaled nitric oxide. *Lancet* 1996; 348: 1448–9.
4. Cheung P-Y, *et al.* Inhaled nitric oxide and inhibition of platelet aggregation in critically ill neonates. *Lancet* 1998; 351: 1181–2.
5. George TN, *et al.* The effect of inhaled nitric oxide therapy on bleeding time and platelet aggregation in neonates. *J Pediatr* 1998; 132: 731–4.
6. Miller OI, *et al.* Rebound pulmonary hypertension on withdrawal from inhaled nitric oxide. *Lancet* 1995; 346: 51–2.
7. Aly H, *et al.* Weaning strategy with inhaled nitric oxide treatment in persistent pulmonary hypertension of the newborn. *Arch Dis Child Fetal Neonatal Ed* 1997; 76: F118–F122.
8. Davidson D, *et al.* Safety of withdrawing inhaled nitric oxide therapy in persistent pulmonary hypertension of the newborn. *Pediatrics* 1999; 104: 231–6.
9. Henrichsen T, *et al.* Inhaled nitric oxide can cause severe systemic hypotension. *J Pediatr* 1996; 129: 183.
10. Preston IR, *et al.* Pulmonary edema caused by inhaled nitric oxide therapy in two patients with pulmonary hypertension associated with the CREST syndrome. *Chest* 2002; 121: 656–9.
11. Tsai GE, Gastfriend DR. Nitric oxide-induced motor neuron disease in a patient with alcoholism. *N Engl J Med* 1995; 332: 1036.

Precautions

Patients given inhaled nitric oxide should be monitored for methaemoglobinaemia and oxygenation. Inhaled nitric oxide and nitrogen dioxide levels should also be monitored. Treatment should not be stopped abruptly since rebound pulmonary hypertension and deterioration in oxygenation may occur. Caution is required in patients with pre-existing left ventricular dysfunction, as symptoms of heart failure, including pulmonary oedema, may occur.

The exposure of workers to nitric oxide and nitrogen dioxide should be limited.

References.

1. CSM/MCA. Inhaled nitric oxide. *Current Problems* 1996; 22: 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015620&RevisionSelectionMethod=LatestReleased (accessed 02/06/08)
2. Cuthbertson BH, *et al.* Use of inhaled nitric oxide in British intensive therapy units. *Br J Anaesth* 1997; 78: 696–700.
3. Phillips ML, *et al.* Assessment of medical personnel exposure to nitrogen oxides during inhaled nitric oxide treatment of neonatal and pediatric patients. *Pediatrics* 1999; 104: 1095–1100.

Pharmacokinetics

Nitric oxide is absorbed systemically after inhalation but is rapidly inactivated by reaction with haemoglobin to form methaemoglobin and nitrate; it has a half-life of only a few seconds. It is excreted mainly in the urine as nitrate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Noxap; VasoKINOX; *Canad.*: INOmax; *Cz.*: INOmax; Noxap; *Denm.*: INOmax; *Fin.*: Pulmonox; *Fr.*: INOmax; Noxap; *Ger.*: INOmax; *Gr.*: INOmax; *Irl.*: INOmax; *Ital.*: INOmax; *Neth.*: INOmax; Neophyr; Noxap; *Pol.*: INOmax; *Port.*: INOmax; *Spain*: INOmax; Noxap; VasoKINOX; *Swed.*: INOmax; *Switz.*: INOmax; *USA*: INOmax.

Noradrenaline (BAN) ⊗

Levarterenol; Noradrenalini; Noradrenalin; Noradrenalina; Noradrenalinum; Norepinefriini; Norépinéfrin; Norepinefrina; Norepinephrine (BAN); Norepinephrine (rINN); Norépinéphrine; Norepinephrinum; Norepirenamine; Норэпинефрин.

(*R*)-2-Amino-1-(3,4-dihydroxyphenyl)ethanol.

$C_8H_{11}NO_3$=169.2.

CAS — 51-41-2.

ATC — C01CA03.

ATC Vet — QC01CA03.

UNII — X4W3ENH1CV.

Pharmacopoeias. *Jpn* includes the racemic form.

Noradrenaline Acid Tartrate (BANM) ⊗

Arterenol Acid Tartrate; *l*-Arterenol Bitartrate; Bitartrato de noradrenalina; Bitartrato de norepinefrina; Levarterenol Acid Tartrate; Levarterenol Bitartrate; Levarterenoli Bitartras; Noradrenalinitartraatti; Noradrenaline Bitartrate; Noradrenaline Tartrate; Noradrénaline, tartrate de; Noradrenalini tartras; Noradrenalino tartratas; Noradrenalintartarát; Noradrenalintartrat; Norepinefrin tartarát monohydrát; Norepinefrina, bitartrato de; Norepinefryny wodorowinian; Norepinephrine Acid Tartrate (BANM); *l*-Norepinephrine Bitartrate; Norepinephrine Bitartrate (rINNM); Norepinephrine Bitartrate (USAN); Norépinéphrine, Bitartrate de; Norepinephrini Bitartras; Norepinephrini Tartras Monohydricus; Norepinephrintartrat/Noradrenalintartrat; Tartrato ácido de norepinefrina; Норэпинефрина битартрат.

$C_8H_{11}NO_3.C_4H_6O_6.H_2O$=337.3

CAS — 51-40-1 (anhydrous noradrenaline acid tartrate); 69815-49-2 (noradrenaline acid tartrate monohydrate).

ATC — C01CA03.

ATC Vet — QC01CA03.

UNII — ZW81GF4088 (anhydrous noradrenaline acid tartrate); IFY5PE3ZRW (noradrenaline acid tartrate monohydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Noradrenaline Tartrate; Noradrenaline Acid Tartrate BP 2014; Norepinephrine Acid Tartrate BP 2014). A white or almost white crystalline powder. Freely soluble in water; slightly soluble in alcohol. Store in airtight containers, or preferably, in a sealed tube under vacuum or an inert gas. Protect from light.

USP 36: (Norepinephrine Bitartrate). A white or faintly grey, odourless, crystalline powder. It slowly darkens on exposure to air and light. Soluble 1 in 2.5 of water and 1 in 300 of alcohol; practically insoluble in chloroform and in ether. Its solutions in water have a pH of about 3.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Noradrenaline acid tartrate is strongly acidic in solution, and would be expected to be incompatible with drugs having an alkaline pH. Licensed product information in the UK states that solutions are reportedly incompatible with alkalis and oxidising agents, barbiturates, chlorphenamine, chlorothiazide, nitrofurantoin, novobiocin, phenytoin, sodium bicarbonate, sodium iodide, and streptomycin. Incompatibility with insulin has also been reported.[1]

1. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; 53: 1048–51.

Noradrenaline Hydrochloride (BANM) ⊗

Hidrocloruro de noradrenalina; Hidrocloruro de norepinefrina; Noradrenaliinihydrokloridi; Noradrénaline, chlorhydrate de; Noradrenalin-hidroklorid; Noradrénalinhydroklorid; Noradrenalini hydrochloridum; Noradrenalino hidrochloridas; Norepinefrin hydrochlorid; Norepinefrina, hidrocloruro de; Norépinéphrine, Chlorhydrate de; Norepinephrine Hydrochloride (rINNM); Norepinephrine Hydrochloride (BANM); Norepinephrinhydrochlorid/Noradrenalinhydrochlorid; Norepinephrini Hydrochloridum; Норэпинефрина Гидрохлорид.

$C_8H_{11}NO_3.HCl$=205.6

CAS — 329-56-6.

ATC — C01CA03.

ATC Vet — QC01CA03.

UNII — 4W6461XR05.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Noradrenaline Hydrochloride; Norepinephrine Hydrochloride BP 2014). A white or brownish-white, crystalline powder. It becomes coloured on exposure to air and light. Very soluble in water; slightly soluble in alcohol. A 2% solution in water has a pH of 3.5 to 4.5. Store in airtight containers, or preferably, in a sealed tube under vacuum or an inert gas. Protect from light.

Uses and Administration

Noradrenaline is a direct-acting catecholamine sympathomimetic (p. 1507.3) with pronounced effects on alpha-adrenergic receptors; it also stimulates beta$_1$ receptors but has little effect on beta$_2$ receptors. It is the major neurotransmitter in postganglionic adrenergic neurones, and is stored in granules in the nerve axons. Some is also present in the adrenal medulla and is released with adrenaline.

The major effects of noradrenaline relate to its alpha-agonist properties. It causes peripheral vasoconstriction, leading to an increase in systolic and diastolic blood pressure, which is accompanied by reflex slowing of the heart rate. Blood flow is reduced in the kidneys, liver, skin, and usually skeletal muscle. Noradrenaline causes the pregnant uterus to contract; high doses liberate glucose from the liver and have other hormonal effects similar to those of adrenaline. Beta-stimulant effects of noradrenaline have a positive inotropic action on the heart, but there is little bronchodilator effect. It produces little stimulation of the CNS.

Noradrenaline is used for the emergency restoration of blood pressure in acute hypotensive states such as shock (p. 1279.3). It has also been used in the management of cardiac arrest. Noradrenaline has been used in local anaesthesia to diminish the absorption and localise the effect of the local anaesthetic (see Uses and Administration, p. 1980.1) but adrenaline is now preferred (see also Dental Use under Adverse Effects, below). Locally applied solutions have been used to control bleeding in upper gastrointestinal haemorrhage and similar disorders.

In **acute hypotensive states**, noradrenaline is used as the acid tartrate, or occasionally as the hydrochloride, but doses are expressed in terms of the base; noradrenaline acid tartrate 2 micrograms or noradrenaline hydrochloride 1.2 micrograms are equivalent to about 1 microgram of noradrenaline. It is given by intravenous infusion of a solution containing the equivalent of 4 micrograms of the base per mL in glucose 5%, or sodium chloride 0.9% and glucose 5%. To avoid tissue necrosis the infusion should be given through a central venous catheter or into a large vein high up in a limb, preferably the arm. Some sources have suggested that addition of phentolamine 5 to 10 mg/litre to the infusion may prevent dermal necrosis without affecting the vasopressor action. The infusion is usually given initially at a rate of 2 to 3 mL/minute (8 to 12 micrograms/minute) and adjusted according to the blood pressure response. Blood pressure is initially recorded every 2 minutes and the rate of infusion continuously monitored. The infusion must not be stopped suddenly but should be gradually withdrawn to avoid disastrous falls in blood pressure. The average maintenance dose is 0.5 to 1 mL/minute (2 to 4 micrograms/minute), but there is a wide variation and higher doses may be required. The concentration of the infusion may be altered according to clinical needs. Alternatively a solution containing the equivalent of 40 micrograms of the base per mL may be given at an initial rate of 0.16 to 0.33 mL/minute via a central venous catheter, using a syringe pump or drip counter.

For doses in children, see below.

Administration in children. In the treatment of acute hypotension, the *BNFC* suggests that neonates, infants, and children may be given noradrenaline by intravenous infusion at a dose (expressed in terms of the base) of 20 to 100 nanograms/kg per minute, adjusted according to response to a maximum of 1 microgram/kg per minute.

Adverse Effects

As for Sympathomimetics, p. 1508.2. Noradrenaline is an extremely potent peripheral vasoconstrictor and its adverse effects include hypertension (possibly associated with reflex bradycardia), headache, and peripheral ischaemia, which may be severe enough to result in gangrene of the extremities. Extravasation may lead to severe phlebitis and sloughing.

Dental use. Severe headache,[1,2] including fatal cerebral haemorrhage,[1,3] has been reported after the use of lidocaine with noradrenaline 1 in 25 000 for dental anaesthesia. It was suggested[1-3] that preparations containing noradrenaline 1 in 25 000 should not be used, and that a concentration of 1 in 80 000 was to be preferred. However, in the UK the *Dental Practitioners' Formulary*[4] (issued in 2002) stated that noradrenaline should not be used as a vasoconstrictor in local anaesthetic solutions since it presented no advantage over adrenaline and carried additional hazard.

1. Boakes AJ, *et al.* Adverse reactions to local anaesthetic/vasoconstrictor preparations: a study of the cardiovascular responses to Xylestesin and Hostacain-with-Noradrenaline. *Br Dent J* 1972; 133: 137–40.
2. van der Bijl P, Victor AM. Adverse reactions associated with norepinephrine in dental local anesthesia. *Anesth Prog* 1992; 39: 87–9.

3. Okada Y, *et al.* Fatal subarachnoid haemorrhage associated with dental local anaesthesia. *Aust Dent J* 1989; 34: 323–5.
4. *Dental Practitioners' Formulary.* 2002–2004. London: British Dental Association, British Medical Association, and the Royal Pharmaceutical Society of Great Britain; 2002. D6.

Treatment of Adverse Effects

As for Sympathomimetics, p. 1508.3. If extravasation occurs, infiltration with phentolamine (see p. 1469.1) as soon as possible, and certainly within 12 hours, may relieve pain and prevent tissue necrosis.

Precautions

As for Sympathomimetics, p. 1508.3. Noradrenaline has mainly alpha-agonist properties and must be avoided in the presence of hypertension; blood pressure and infusion rate must be monitored frequently. Noradrenaline-induced cardiac arrhythmias are more likely in patients with hypoxia or hypercapnia.

Noradrenaline is a severe tissue irritant and only very dilute solutions should be used. It should be infused centrally or into a large vein if possible, and care should be taken to avoid extravasation.

Noradrenaline may reduce placental perfusion throughout pregnancy and some consider that it and similar vasoconstrictor sympathomimetics are best avoided; also in late pregnancy noradrenaline provokes uterine contractions which can result in fetal asphyxia.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies noradrenaline as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Sympathomimetics, p. 1508.3. Severe hypertension may occur if noradrenaline is given to patients taking tricyclic antidepressants since tricyclics block the uptake of noradrenaline into nerve endings.

Pharmacokinetics

Like adrenaline (p. 1295.1), noradrenaline is inactive when given orally, and it is rapidly inactivated in the body by similar processes. When given intravenously it is extensively metabolised and only small amounts are excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fioritina; ***Austral.***: Levophed; ***Belg.***: Levophed; Norepine; ***Braz.***: Levophed; ***Canad.***: Levophed; ***Chile***: Adine; ***Ger.***: Arterenol; ***Gr.***: Levophed†; Noradren; ***Hong Kong***: Levophed; ***India***: Adrenor; Adronis; Epinor; Nodresol; Nor-S; Norad; Noradria; Noralin; Norepirin; ***Indon.***: Levophed; N-Epi; Raivas; Vascon; ***Irl.***: Levophed†; ***Israel***: Levophed; ***Malaysia***: Cardiamed; Levophed; ***Mex.***: Pridam; ***NZ***: Levophed; ***Philipp.***: Inotrop; Levofin; Levophed; Norepin; Norphed; ***Pol.***: Levonor; ***Singapore***: Levophed; ***Spain***: Norages; ***Thai.***: Levophed; N-Epi; Norpin; ***USA***: Levophed.

Used as an adjunct in:. *Austria*: Scandonest; ***Braz.***: Xylestesin; Xylocaina; ***Fr.***: Biodicaine†; Pressicaine N†; Scandicaine; Xylonor; Ziacaine; ***Gr.***: Lidocosil; Narcodon; Neo-Lidocaton; Scandonest; Xylestesin-S Special; Xylestesin; Xylonor Noradrenaline; ***Israel***: Xylonor Noradrenaline; ***Ital.***: Lident Adrenor; Xylonor; ***Port.***: Scandonest; Xilonibsa; ***S.Afr.***: Xylotox; ***Spain***: Xylonor Especial; ***Switz.***: Scandonest.

Pharmacopoeial Preparations

BP 2014: Noradrenaline Injection;
USP 36: Norepinephrine Bitartrate Injection; Propoxycaine and Procaine Hydrochlorides and Norepinephrine Bitartrate Injection.

Norfenefrine Hydrochloride *(rINNM)* ⊗

Hidrocloruro de norfenefrina; Norfenefrin Hidroklorür; Norfenefrina, hidrocloruro de; Norfénéfrine, Chlorhydrate de; Norfenefrini Hydrochloridum; Norphenylephrine Hydrochloride; *m*-Norsynephrine Hydrochloride; WV-569; Норфенефрина гидрохлорид.

2-Amino-1-(3-hydroxyphenyl)ethanol hydrochloride

$C_8H_{11}NO_2$,HCl=189.6

CAS — 536-21-0 (norfenefrine); 15308-34-6 (norfenefrine hydrochloride).

ATC — C01CA05.

ATC Vet — QC01CA05.

UNII — 1FCN9TAU6R.

NOTE. *m*-Octopamine has been used as a synonym for norfenefrine. Care should be taken to avoid confusion with octopamine, which is the *p*-isomer.

Profile

Norfenefrine is a sympathomimetic (p. 1507.3) with mainly alpha-adrenergic activity. It has been used as the hydrochloride for its vasopressor effect in the treatment of hypotensive states (p. 1277.2) in a usual oral dose of 15 mg three times daily of norfenefrine hydrochloride. Norfenefrine hydrochloride has also been given by injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Novadral†; ***Mex.***: AS Cor; ***Switz.***: Novadral†; ***Turk.***: Novadral.

Multi-ingredient Preparations. ***Switz.***: Ortho-Maren retard†.

Olmesartan Medoxomil

(BAN, USAN, rINN)

CS-866; Olmésartan Médoxomil; Olmesartán medoxomilo; Olmesartanum Medoxomilum; RNH-6270 (olmesartan); Ольмезартан Медоксомил.

(5-Methyl-2-oxo-1,3-dioxol-4-yl) methyl ester of 4-(1-Hydroxy-1-methylethyl)-2-propyl-1-{[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl}-1*H*-imidazole-5-carboxylic acid.

$C_{29}H_{30}N_6O_6$=558.6

CAS — 144689-24-7 (olmesartan); 144689-63-4 (olmesartan medoxomil).

ATC — C09CA08.

ATC Vet — QC09CA08.

UNII — 6M97XTV3HD.

NOTE. The name olmesartan has been applied to both the base and to the medoxomil ester.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Olmesartan Medoxomil). A white or almost white, crystalline powder. Practically insoluble in water and in heptane; slightly soluble in alcohol.

USP 36: (Olmesartan Medoxomil). A white to off-white crystalline powder. Practically insoluble in water; sparingly soluble in methyl alcohol. Store at a temperature below 25 degrees. Protect from moisture.

Uses and Administration

Olmesartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p. 1422.2). It is used in the management of hypertension (p. 1251.1).

Olmesartan is given orally as the ester prodrug olmesartan medoxomil. After a dose the hypotensive effect lasts for 24 hours. Most of the hypotensive effect is apparent within 2 weeks after starting therapy and is maximal within about 8 weeks.

In hypertension, olmesartan medoxomil is given in a usual dose of 20 mg once daily, although in the UK an initial dose of 10 mg once daily is recommended. The dose may be increased to 40 mg once daily if required.

For doses in children, see below.

For doses in hepatic or renal impairment, see below.

References.

1. Mire DE, *et al.* A review of the structural and functional features of olmesartan medoxomil, an angiotensin receptor blocker. *J Cardiovasc Pharmacol* 2005; 46: 585–93.
2. Takai S, Miyazaki M. Effect of olmesartan medoxomil on atherosclerosis: clinical implications of the emerging evidence. *Am J Cardiovasc Drugs* 2006; 6: 363–6.
3. Smith DH. Dose-response characteristics of olmesartan medoxomil and other angiotensin receptor antagonists. *Am J Cardiovasc Drugs* 2007; 7: 347–56.
4. Zannad F, Fay R. Blood pressure-lowering efficacy of olmesartan relative to other angiotensin II receptor antagonists: an overview of randomized controlled studies. *Pundam Clin Pharmacol* 2007; 21: 181–90.
5. Scott LJ, McCormack PL. Olmesartan medoxomil: a review of its use in the management of hypertension. *Drugs* 2008; 68: 1239–72.
6. Punzi HA. Efficacy and safety of olmesartan medoxomil alone and in combination with hydrochlorothiazide. *Expert Rev Cardiovasc Ther* 2009; 7: 229–39.
7. Redon J, Fabia MJ. Efficacy in angiotensin receptor blockade: a comparative review of data with olmesartan. *J Renin Angiotensin Aldosterone Syst* 2009; 10: 147–56.
8. Destro M, *et al.* Olmesartan medoxomil: recent clinical and experimental acquisitions. *Expert Opin Drug Metab Toxicol* 2009; 5: 1149–57.
9. Hirohata A, *et al.* Impact of olmesartan on progression of coronary atherosclerosis: a serial volumetric intravascular ultrasound analysis from the OLIVUS (impact of OLmesartan on progression of coronary atherosclerosis: evaluation by intravascular ultrasound) trial. *J Am Coll Cardiol* 2010; 55: 976–82.
10. Barrios V, Escobar C. Beating the clock: reducing cardiovascular risk by rapid blood pressure reduction with olmesartan. *Expert Opin Pharmacother* 2010; 11: 1549–58.

Administration in children. In the USA, children aged from 6 to 16 years of age may be given olmesartan medoxomil for **hypertension** in recommended initial oral doses of 10 mg once daily in those weighing under 35 kg, or 20 mg once daily in those weighing 35 kg and over. Doses may be doubled once if necessary after 2 weeks. For those who cannot swallow tablets, US licensed product information (*Benicar, Daiichi Sankyo*) provides instructions for making an extemporaneous liquid preparation.

Administration in hepatic or renal impairment. Olmesartan is excreted in both urine and bile and raised plasma concentrations have been noted in patients with renal or hepatic impairment.

- In patients with *renal impairment*, licensed product information in the UK does not recommend the use of olmesartan in severe impairment (creatinine clearance (CC) below 20 mL/minute) since experience is limited, and the maximum dose in mild to moderate impairment (CC 20 to 60 mL/minute) is 20 mg once daily.
- Similarly, in patients with *hepatic impairment*, licensed product information in the UK does not recommend the use of olmesartan in severe impairment since there is no experience. Those with moderate hepatic impairment should be given an initial dose of 10 mg once daily and the maximum dose is 20 mg once daily.

Migraine. For reference to the use of angiotensin II receptor antagonists, including olmesartan, in the prophylaxis of migraine, see under Losartan, p. 1423.3.

Adverse Effects and Precautions

As for Losartan Potassium, p. 1424.1.

Interactions

As for Losartan Potassium, p. 1424.3.

Pharmacokinetics

Olmesartan medoxomil is an ester prodrug that is hydrolysed during absorption from the gastrointestinal tract to the active form olmesartan. The absolute bioavailability is about 26%. Peak plasma concentrations of olmesartan occur about 1 to 2 hours after oral doses. Olmesartan is at least 99% bound to plasma proteins. It is excreted in the urine and the bile as olmesartan; about 35 to 50% of the absorbed dose is excreted in the urine and the remainder in the bile. The terminal elimination half-life is between 10 and 15 hours.

References.

1. Yoshihara K, *et al.* Population pharmacokinetics of olmesartan following oral administration of its prodrug, olmesartan medoxomil: in healthy volunteers and hypertensive patients. *Clin Pharmacokinet* 2005; 44: 1329–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Olmec; Olmetec; Tensonit; ***Austral.***: Olmetec; ***Austria***: Mencord; Olmetec; ***Belg.***: Belsar; Olmetec; ***Braz.***: Benicar; Olmetec; ***Canad.***: Olmetec; ***Chile***: Cardioplus; Olmetec; ***China***: Lan Sha (兰沙); Olmetec (傲坦); ***Cz.***: Olmetec; Sarten; ***Denm.***: Benetor; Olkingo; Olkreso; Olmetec; ***Fin.***: Benetor; Olmetec; ***Fr.***: Alteis; Olmetec; ***Ger.***: Olmetec Votum; ***Gr.***: Olartan; Olmetec; ***Hong Kong***: Olmetec; ***India***: Olmat; Olmax; Olmecip; Olmefast; Olmesar; Olmetor; Olmezest; Olmighty; Olmy; Olsar; Oukat; ***Indon.***: Olmetec; ***Irl.***: Benetor; Omesar; ***Israel***: Olmetec†; ***Ital.***: Olmetec; Olpress; Plaunac; ***Jpn***: Olmetec; ***Malaysia***: Olmetec; ***Mex.***: Almetec; ***Neth.***: Olmetec; ***Norw.***: Olmetec; ***Philipp.***: Alzor; Olmetec; Olmezar; ***Pol.***: Olimestra; ***Port.***: Olmetec; Olsar; ***Rus.***: Cardosal (Кардосал); ***Singapore***: Olmetec; ***Spain***: Ixia; Olmetec; Openvas; ***Switz.***: Olmetec; Votum; ***Thai.***: Olmetec; ***Turk.***: Hipersar; Olmetec; Olmysar; Terminate; ***UK***: Olmetec; ***Ukr.***: Cardosal (Кардосал); ***USA***: Benicar; ***Venez.***: Benicar; Olmetec.

Multi-ingredient Preparations. *Arg.*: Olmetec D; ***Austral.***: Olmetec Plus; Sevikar; ***Austria***: Amelior; Mencord Plus; Olmetec Plus; Sevikar; ***Belg.***: Belsar Plus; Forzaten HCT; Forzaten; Olmetec Plus; Sevikar; ***Braz.***: Benicar HCT; Olmetec HCT; ***Canad.***: Olmetec Plus; ***Chile***: Cardioplus AM; Cardioplus D; Olmetec Plus; ***China***: Olmetec Plus (复傲坦); ***Cz.***: Olmetec Plus H; Sarten Plus H; Sintonyn; ***Denm.***: Alea; Benetor Comp; Olmetec Plus; Sevikar; ***Fin.***: Benetor Comp; Olmetec Plus; Sevikar; ***Fr.***: Alteisduo; Axeler; CoOlmetec; Sevikar; ***Ger.***: Olmetec Plus; Sevikar HCT; Sevikar; Vocado HCT; Vocado; Votum Plus; ***Gr.***: Olartan Plus; Olmetec Plus; Orizal; Sevikar; ***Hong Kong***: Azoren; Olmetec Plus; ***India***: Hybreed-H; Olmat-AM; Olmat-AMH; Olmat-H; Olmax-H; Olmefast-H; Olmesar-A; Olmesar-H; Olmetor-H; Olmezest-H; Olmighty-H; Olsar-A; Olsar-H; Olsar-M; Oukat-H; ***Irl.***: Benetor Plus; Konverge Plus; Konverge; Omesar Plus; Sevikar Plus; Sevikar; ***Ital.***: Olmegan; Olprezide; Plaunazide; ***Malaysia***: Olmetec Plus; ***Mex.***: Almetec-Co; ***Neth.***: Belfor HCT; Belfor; Capenon HCT; Capenon; Olmetec HCTZ; Sevikar HCT; Sevikar; ***Norw.***: Olmetec Comp; Sevikar; ***Philipp.***: Alzor CCB; Alzor HCT; Normetec; Olmetec Plus; ***Port.***: Olmetec Plus; Olsar Plus; Sevikar; Zolnor; ***Singapore***: Azoren; Olmetec Plus; ***Spain***: Balzak Plus; Balzak; Capenon HCT; Capenon; Ixia Plus; Olmetec Plus; Openvas Plus; Sevikar HCT; Sevikar; ***Switz.***: Olmetec Plus; Sevikar HCT; Sevikar; Vascord; Votum Plus; ***Thai.***: Normetec; Olmetec Plus; ***Turk.***: Hipersar Plus; Olmetec Plus; Olmysar

Plus; *UK*: Olmetec Plus; Sevikar HCT; *Ukr.*: Cardosal Plus (Кардосал Плюс); *USA*: Azor; Benicar HCT.

Olprinone Hydrochloride *(rINNM)*

E-1020; Hidrocloruro de olprinona; Loprinone Hydrochloride; Olprinona, hidrocloruro de; Olprinone, Chlorhydrate d'; Olprinoni Hydrochloridum; Ольпринона Гидрохлорид.
1,2-Dihydro-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-2-oxonicotinonitrile hydrochloride.
$C_{14}H_{10}N_4O.HCl$=286.7
CAS — 106730-54-5 (olprinone); 119615-63-3 (olprinone hydrochloride).
UNII — F188658J56.

Profile

Olprinone is a phosphodiesterase type 3 inhibitor with positive inotropic and vasodilator activity, used in acute heart failure (p. 1262.3). It is given intravenously as the hydrochloride in an initial dose of 10 micrograms/kg given over 5 minutes, followed by a continuous infusion at a rate of 100 to 400 nanograms/kg per minute, according to response.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Coretec.

Omapatrilat *(BAN, USAN, rINN)*

BMS-186716-01; BMS-186716; Omapatrilate; Omapatrilato; Omapatrilatum; Омапатрилат.
(4*S*,7*S*,10a*S*)-Octahydro-4-[(*S*)-α-mercaptohydrocinnamamido]-5-oxo-7*H*-pyrido[2,1-*b*][1,3]thiazepine-7-carboxylic acid.
$C_{19}H_{24}N_2O_4S_2$=408.5
CAS — 167305-00-2.
UNII — 36NU90E7T.

NOTE. The name Vanlev has been used as a trade mark for omapatrilat.

Profile

Omapatrilat is a vasopeptidase inhibitor. It inhibits both angiotensin-converting enzyme and neutral endopeptidase and is under investigation in the management of hypertension and heart failure. However, its use may be limited by severe angioedema.

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Omega-3 Fatty Acids

Acidos grasos omega 3; Ômega-3 Жирные Кислоты.
ATC — C10AX06.
ATC Vet — QC10AX06.
UNII — 71M78END5S.

Docosahexaenoic Acid

Cervonic Acid; DHA; Doconexent (rINN); Doconexent; Doconexento; Doconexentum; Доконексент.
(*all-Z*)-Docosahexa-4,7,10,13,16,19-enoic acid.
$C_{22}H_{32}O_2$=328.5
CAS — 6217-54-5; 25167-62-8.
UNII — ZAD9OKH9JC.

NOTE. DHA is also used as a synonym for dihydroxyacetone (p. 1700.1).

Docosahexaenoic Acid Ethyl Ester

Cervonic Acid Ethyl Ester; Doconexent d'Ethyle; Doconexent Ethyl (rINNM); Doconexento de etilo; Ethyl Docosahexaenoate; Ethylum Doconexentum; Этил Доконексент.
$C_{24}H_{36}O_2$=356.6
CAS — 81926-94-5 (all-Z); 84494-72-4.
UNII — 7PO7G8PA8M.

Eicosapentaenoic Acid

Acidum Eicosapentaenoicum; Eikosapentaeenihappo; Eikosapentaensyra; EPA; Icosapent (rINN); Icosapento; Icosapentum; Timnodonic Acid; Икозапент.
(*all-Z*)-Eicosapenta-5,8,11,14,17-enoic acid.
$C_{20}H_{30}O_2$=302.5
CAS — 10417-94-4 (all-z); 1553-41-9.
UNII — AAN7QOV9EA.

NOTE. EPA is also used as a synonym for pheneturide.

Eicosapentaenoic Acid Ethyl Ester

AMR-101; Ethyl Eicosapentaenoate; Ethyl-EPA; Ethyl Icosapentate; Ethyl-eicosapentaenoic acid; Ethylum Icosapentum; Icosapent d'Ethyle; Icosapent Ethyl (USAN); Icosapent Ethyl (rINNM); Icosapento de etilo; LAX-101; Timnodonic Acid Ethyl Ester; Этил Икозапент.
Ethyl (5*Z*,8*Z*,11*Z*,14*Z*,17*Z*)-icosa-5,8,11,14,17-pentaenoate.
$C_{22}H_{34}O_2$=330.5
CAS — 73310-10-8 (all-Z); 86227-47-6 (all-Z); 84494-70-2.
UNII — 6GC8A4PAYH.

NOTE. The name Miraxion has been used as a trade mark for eicosapentaenoic acid ethyl ester.

Pharmacopoeias. In *Jpn*.

Linolenic Acid

ALA; Alpha-linolenic Acid; Kwas linolenowy; α-Linolenic Acid; Линоленовая Кислота.
(*all-Z*)-9,12,15-Octadecatrienoic acid.
$C_{18}H_{30}O_2$=278.4
CAS — 463-40-1.
UNII — 0RBV727H71.

NOTE. Do not confuse with γ-linolenic acid (Gamolenic Acid, p. 2509.2)

Omega-3-acid Ethyl Esters *(USAN)*

Ethylestery omega-3-kyselin; K-85; Omega-3 Acidorum Esteri Ethylici; Omega-3 Acidorum Esteri Ettylici; Omega-3 rūgščių etilo esteriai; Omega-3-sav-etilészterek; Омега-3-кислоты Этиловых Эфиров.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Omega-3-Acid Ethyl Esters 60). A mixture of ethyl esters of omega-3 acids. They are obtained by transesterification of the body oil of fish species coming from families such as Engraulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae, and Scombridae or from animals of the class Cephalopoda. The acids consist of alpha-linolenic acid, moroctic acid, eicosatetraenoic acid, eicosapentaenoic acid (timnodonic acid), heneicosapentaenoic acid, clupanodonic acid, and docosahexaenoic acid (cervonic acid). The total amount of omega-3 acid ethyl esters, eicosapentaenoic acid ethyl esters, and docosahexaenoic acid ethyl esters should be stated on the label. For a total omega-3 acid ethyl ester content of 55%, the amount of eicosapentaenoic acid ethyl esters and docosahexaenoic acid ethyl esters together is not less than 50% and the content of eicosapentaenoic acid ethyl esters is not less than 40%; for a total omega-3 acid ethyl ester content of 60%, the amount of eicosapentaenoic acid ethyl esters and docosahexaenoic acid ethyl esters together is not less than 50% and the content of docosahexaenoic acid ethyl esters is not less than 40%; and for a total omega-3 acid ethyl ester content of 65%, the amount of eicosapentaenoic acid ethyl esters and docosahexaenoic acid ethyl esters together is not less than 50%, the content of eicosapentaenoic acid ethyl esters is not less than 25%, and the content of docosahexaenoic acid ethyl esters is not less than 20%. Antoxidants may be added.

A light yellow liquid with a slight fish-like odour. Practically insoluble in water; very soluble in acetone, in alcohol, in heptane, and in methyl alcohol. Store in airtight containers under inert gas. Protect from light.

Ph. Eur. 8: (Omega-3-Acid Ethyl Esters 90). A mixture of ethyl esters of omega-3 acids. They are obtained by transesterification of the body oil of fish species coming from families such as Engraulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae, and Scombridae or from animals of the class Cephalopoda. The acids consist of alpha-linolenic acid, moroctic acid, eicosatetraenoic acid, eicosapentaenoic acid (timnodonic acid), heneicosapentaenoic acid, clupanodonic acid, and docosahexaenoic acid (cervonic acid). The total amount of omega-3 acid ethyl esters is not less than 90%, and that of both eicosapentaenoic acid ethyl esters and docosahexaenoic acid ethyl esters together is not less than 80%; the content of eicosapentaenoic acid ethyl esters is not less than 40% and of docosahexaenoic acid ethyl esters is not less than 34%. Antoxidants may be added.

A light yellow liquid. Practically insoluble in water; very soluble in acetone, in alcohol, in heptane, and in methyl alcohol. Store in airtight containers under inert gas. Protect from light.

USP 36: (Omega-3 Acids Ethyl Esters). They are obtained by transesterification of the body oil obtained from fish of families such as Engraulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae, and Scombridae and subsequent purification processes including urea fractionation followed by molecular distillation. The content of eicosapentaenoic acid ethyl ester plus the content of docosahexaenoic acid ethyl ester is not less than 800 mg/g and not more than 880 mg/g, with not less than 430 mg/g and not more than 495 mg/g of eicosapentaenoic acid ethyl ester and not less than 347 mg/g and not more than 403 mg/g of docosahexaenoic acid ethyl ester. Tocopherol may be added as an antoxidant. Store in airtight containers under an atmosphere of nitrogen at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Omega-3 Marine Triglycerides

Deniz Kaynaklı Omega-3 Trigliseridler; Poisson (huile de) riche en acides oméga-3 (fish oil, rich in omega-3-acids); Saumon d'élevage, hulle de (salmon oil, farmed); Triglicéridos marinos omega 3; Омега-3 Триглицериды Морского Происхождения.
UNII — D87YGH4Z0Q.

NOTE. Omega-3 Marine Triglycerides (BAN) is a mixture of triglycerides of fatty acids from marine fish containing the equivalent of about 18% of eicosapentaenoic acid and 12% of docosahexaenoic acid. The content of triglycerides is not the same as that in Omega-3-Marine Triglycerides BP.

Pharmacopoeias. *Eur.* (see p. vii) includes Omega-3-Acid Triglycerides, Fish Oil, Rich in Omega-3-Acids, and Salmon Oil, Farmed. *US* includes Fish Oil containing Omega-3 Acids and Omega-3 Acid Triglycerides.

Ph. Eur. 8: (Omega-3-Acid Triglycerides; Omega-3 Acidorum Triglycerida; Omega-3-Marine Triglycerides). A mixture of mono-, di-, and triesters of omega-3 acids with glycerol, containing mainly triesters. They are obtained by esterification of concentrated and purified omega-3 acids with glycerol or by transesterification of the omega-3 acid ethyl esters with glycerol. The omega-3 acids are from the body oil of fish species coming from families such as Engraulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae, and Scombridae or from animals of the class Cephalopoda. The acids consist of alpha-linolenic acid, moroctic acid, eicosatetraenoic acid, eicosapentaenoic acid (timnodonic acid), heneicosapentaenoic acid, clupanodonic acid, and docosahexaenoic acid (cervonic acid). The total amount of omega-3 acids expressed as triglycerides is not less than 60% and that of both eicosapentaenoic acid and docosahexaenoic acid together, expressed as triglycerides, is not less than 45%. Antoxidants may be added.

A pale yellow liquid. Practically insoluble in water; slightly soluble in dehydrated alcohol; very soluble in acetone and in heptane. Store in well-filled, airtight containers under inert gas. Protect from light.

Ph. Eur. 8: (Fish Oil, Rich in Omega-3-Acids; Piscis Oleum Omega-3 Acidis Abundans). The purified, winterised, and deodorised fatty oil obtained from fish of the families Engraulidae, Carangidae, Clupeidae, Osmeridae, Scombridae (except the genera *Thunnus* and *Sarda*), and Ammodytidae (type I) or from the genera *Thunnus* and *Sarda* within the family Scombridae (type II). The acids consist of alpha-linolenic acid, moroctic acid, eicosatetraenoic acid, eicosapentaenoic acid (timnodonic acid), heneicosapentaenoic acid, clupanodonic acid, and docosahexaenoic acid (cervonic acid). The minimum content, expressed as triglycerides, is eicosapentaenoic acid 13% (type I) or 4 to 8% (type II), docosahexaenoic acid 9% (type I) or 20% (type II), and total omega-3 acids 28% (type I and II). Antoxidants may be added.

A pale yellow liquid. Practically insoluble in water; slightly soluble in dehydrated alcohol; very soluble in acetone and in heptane. Store in well-filled, airtight containers under inert gas. Protect from light.

Ph. Eur. 8: (Salmon Oil, Farmed; Salmonis Domestici Oleum). The purified fatty oil obtained from fresh farmed *Salmo salar*. The positional distribution (β(2)-acyl) is 60 to 70% for docosahexaenoic acid (cervonic acid), 25 to 35% for eicosapentaenoic acid (timnodonic acid), and 40 to 55% for moroctic acid. The sum of the contents of eicosapentaenoic acid and docosahexaenoic acid, expressed as triglycerides, is 10.0 to 28.0%. Antoxidants may be added. A pale pink liquid. Practically insoluble in water; slightly soluble in dehydrated alcohol; very soluble in acetone and in heptane. Store in well-filled airtight containers under an inert gas. Protect from light.

USP 36: (Fish Oil containing Omega-3 Acids). The purified, winterised, and deodorised fatty oil obtained from fish of the families Engraulidae, Carangidae, Clupeidae, Osmeridae, Scombroidae, and Ammodytidae. The acids consist of alpha-linolenic acid, moroctic acid, eicosatetraenoic acid, eicosapentaenoic acid (EPA), heneicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid (DHA). It contains not less than 28% (w/w) of total omega-3 acids (expressed as free acids) consisting of not less than 13% of EPA and not less than 9% of DHA. Antoxidants may be added. A pale yellow liquid. Practically insoluble in water; slightly soluble in anhydrous alcohol; very soluble in acetone and in heptane. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. It may be stored under vacuum or under an inert gas. Protect from light.

USP 36: (Omega-3 Acid Triglycerides). A mixture of mono-, di-, and triesters of omega-3 acids with glycerol containing mainly triesters. They are obtained by esterification of concentrated and purified omega-3 acids with glycerol or by transesterification of the omega-3 acid ethyl esters with glycol. The omega-3 acids are from the body oil of fish of the families Engraulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae, and Scombridae. The acids consist of alpha-linolenic acid, moroctic acid, eicosatetraenoic acid, eicosapentaenoic acid, heneicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid. It contains not less than 58% of total omega-3 acids (expressed as triglycerides). Antoxidants may be added. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light. It may be stored under a vacuum or under an inert gas.

Uses and Administration

Omega-3 fatty acids are long-chain polyunsaturated fatty acids containing 18 to 22 carbon atoms and a varying number of double bonds, the first of which is in the n-3 position. They are essential fatty acids and must be obtained from the diet. They have an important role as eicosanoid precursors and as components of cell membranes; in humans, they compete with arachidonic acid (p. 2446.1), an omega-6 fatty acid precursor. Their actions in humans include a hypolipidaemic action (especially a reduction in plasma triglycerides), an anti-inflammatory action, and an antiplatelet effect. The main dietary omega-3 fatty acids are eicosapentaenoic acid and docosahexaenoic acid and are derived from marine fish; other omega-3 fatty acids found in fish oils (defined in terms of number of carbon atoms and number of double bonds) include linolenic acid, moroctic acid (C18:4), eicosatetraenoic acid (C20:4), heneicosapentaenoic acid (C21:5), and clupanodonic acid (C22:5). Linolenic acid is also found in some plant sources and is converted to a limited extent in the body to eicosapentaenoic acid and docosahexaenoic acid.

Fish oils and purified omega-3 fatty acid preparations are used in patients with severe hypertriglyceridaemia (see Hyperlipidaemias, p. 1248.1) and for secondary prevention after myocardial infarction (see Cardiovascular Disorders below). They are also marketed as dietary supplements, and are used in preparations for parenteral nutrition.

The preparations available vary widely in purity and omega-3 fatty acid content, usually expressed in terms of eicosapentaenoic acid and docosahexaenoic acid; the fatty acids may be present as triglycerides or as ethyl esters. Typical oral doses of fish oil for the treatment of hypertriglyceridaemia are 5 g twice daily of a preparation containing 17% eicosapentaenoic acid and 11.5% docosahexaenoic acid, or 2 to 4 g daily of a preparation containing 46% eicosapentaenoic acid and 38% docosahexaenoic acid. For the secondary prevention of myocardial infarction, 1 g daily of a preparation containing 46% eicosapentaenoic acid and 38% docosahexaenoic acid may be given. Eicosapentaenoic acid ethyl ester may also be used alone in the treatment of hyperlipidaemia, and to improve the symptoms associated with arteriosclerosis obliterans.

Linolenic acid and its esters, such as ethyl linolenate, have been included in mixtures known as 'essential fatty acids' (see Uses of Gamolenic Acid, p. 2509.2).

Action. Interest in omega-3 fatty acids arose from observations that populations with a diet rich in marine fish oils generally have a low incidence of cardiovascular disease, while the incidence of asthma, psoriasis, and autoimmune diseases appears to be lower among Eskimos (Inuit) than in populations consuming a typical western diet (although the incidence of haemorrhagic stroke and epilepsy may be higher). Increased omega-3 fatty acid intake has been suggested to underlie these differences, and fish oil and other omega-3 preparations have therefore been promoted as dietary supplements, with benefit suggested for many conditions.

The beneficial health effects of omega-3 fatty acids have been attributed to their effects on eicosanoid balance, lipid metabolism, and cell membranes. Essential fatty acids of both the omega-3 and omega-6 series have an important role as components of cell membranes and as precursors of eicosanoids (prostaglandins, leukotrienes, and thromboxanes). Eicosanoids derived from omega-3 fatty acids generally have anti-inflammatory, antithrombotic, antiarrhythmic, and vasodilator effects, while those derived from omega-6 fatty acids tend to be pro-inflammatory and prothrombotic. Since omega-3 and omega-6 fatty acids compete for the same enzymatic pathways, increasing the intake of omega-3 fatty acids promotes the formation of anti-inflammatory and antithrombotic eicosanoids, and may have beneficial effects. Production of inflammatory cytokines such as interleukins and tumour necrosis factor alpha may also be affected.

For further information on the actions of omega-3 fatty acids in cardiovascular disorders, inflammatory and autoimmune disorders, malignant neoplasms, and neurological and psychiatric disorders, see below and p. 1462.1.

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Cardiovascular disorders. Omega-3 fatty acids have several actions that are potentially beneficial for patients at risk of cardiovascular disease.[1-6] They have a hypolipidaemic effect due to inhibition of very-low-density lipoprotein (VLDL) synthesis in the liver, and this particularly reduces triglyceride concentrations.[7] Heart rate may be reduced,[8] and they may also have an antiarrhythmic effect,[9] possibly due to a direct action on myocardial cells, although evidence is conflicting.[9] Omega-3 fatty acids may also reduce blood pressure in hypertensive patients,[10] as well as increasing erythrocyte deformability and decreasing blood viscosity. They appear to stabilise atherosclerotic plaques,[11] and may reduce progression of atherosclerosis[12] and of restenosis after percutaneous coronary intervention.[13]

Despite these benefits, the role of dietary or supplementary omega-3 fatty acids for cardiovascular risk reduction (p. 1246.1) remains controversial. Epidemiological studies have suggested that increased dietary fish intake is associated with a reduced risk of fatal coronary events,[14] and possibly also ischaemic stroke,[15,16] and there is also evidence for benefit with omega-3 fatty acid supplements, particularly for secondary prevention.[1-4,17] In the GISSI-Prevenzione study,[18] long-term use of omega-3 fatty acid supplements reduced the risk of fatal cardiovascular events in a large group of Italian post-infarction patients studied for 3.5 years,[18] while the JELIS investigators[19] reported a reduction in primary and secondary cardiovascular events in Japanese patients with hypercholesterolaemia. However, a systematic review[20] found no clear benefit from omega-3 fatty acids, whether dietary or supplemental, in people with or without cardiac risk factors.

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Inflammatory and auto-immune disorders. Omega-3 fatty acids have effects on several immunological and inflammatory mediators[1,2] and have been tried in several inflammatory and auto-immune disorders. Beneficial effects have been reported in rheumatoid arthritis[3] (p. 13.2), and an evidence-based report[4] by the Arthritis Research Campaign considered it to be safe with good evidence for improvement in symptoms in this condition, although there were insufficient data for its use in osteoarthritis. Benefit has also been reported in glomerular kidney disease[5-7] (p. 1604.3), but results in kidney transplantation (p. 1939.2) have been mixed, and systematic reviews[8,9] suggest no significant effect on rejection episodes or graft survival. Some studies have shown benefit in psoriasis (p. 1688.1), both with oral[10,11] and with intravenous dosage,[12,13] but other studies found neither the oral[14] nor the topical[15] route to be effective. Variable benefit has been seen in inflammatory bowel disease[16] (p. 1811.3) although this may relate to the different formulations used. However, systematic reviews have found omega-3 fatty acids to be ineffective in Crohn's disease[17] and ulcerative colitis.[18] Fish oils have also been tried in lung disorders, although systematic reviews have found little evidence of benefit in asthma;[19,20] however, limited benefit has been reported in cystic fibrosis,[21] with one study[22] reporting that fish oil supplementation reduced the need for antibacterial treatment.

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Malignant neoplasms. There is some evidence that the incidence of cancer may be lower in populations with a high fish intake, and *animal* studies have suggested that omega-3 fatty acids may slow the progression of some cancers.[1] However, studies of omega-3 fatty acid intake and

cancer incidence in humans have given conflicting results, and systematic reviews[2,3] have found no evidence of a beneficial effect. It has also been suggested that omega-3 fatty acids might be beneficial in patients with cancer cachexia, but a randomised study[4] found that eicosapentaenoic acid supplementation was less effective than megestrol acetate, and a systematic review[5] found insufficient evidence to establish whether eicosapentaenoic acid was more effective than placebo.

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Neurological and psychiatric disorders. Omega-3 fatty acids concentrate in neuronal membranes and appear to have an important role in brain development and function. Supplementation during pregnancy and in infants has been investigated. There is little evidence that maternal supplements improve neonatal outcomes,[1] but there may be a benefit on growth and neurodevelopment in preterm infants given milk formulas supplemented with both omega-3 and omega-6 fatty acids.[2-5] In older children with phenylketonuria treated with dietary restriction, omega-3 fatty acid supplements may improve motor skills.[6]

Omega-3 fatty acids have also been tried in the treatment of neurological and psychiatric disorders.[7,8] There appears to be a link between deficient fatty acid intake and mood disorders,[9] and there is reasonable evidence to support the use of omega-3 fatty acids as adjuncts in the treatment of depression, including possible benefit in the depressive symptoms of bipolar disorder, but further studies are needed to confirm this.[10-13] Benefit has been shown in schizophrenia, but results have been mixed and the role of omega-3 fatty acids is not established.[14] Some positive results have been reported in hyperactivity and in autism, but further studies are needed.[15,16] Omega-3 fatty acids have also been tried in dementia, but there is not yet sufficient evidence[17,18] to recommend them for prevention.

Eicosapentaenoic acid ethyl ester has been tried in Huntington's disease. An early study suggested improvements in motor function,[19] but this was not borne out in a later study,[20] which found no difference in measures of function, cognition, or global impression when compared with placebo.

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3. Clandinin MT, *et al.* Growth and development of preterm infants fed infant formulas containing docosahexaenoic acid and arachidonic acid. *J Pediatr* 2005; 146: 461–8.
4. Henriksen C, *et al.* Improved cognitive development among preterm infants attributable to early supplementation of human milk with docosahexaenoic acid and arachidonic acid. *Pediatrics* 2008; 121: 1137–45.
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16. Bent S, *et al.* Omega-3 fatty acids for autistic spectrum disorder: a systematic review. *J Autism Dev Disord* 2009; 39: 1145–54.
17. Lim WS, *et al.* Omega 3 fatty acid for the prevention of dementia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 30/05/08).
18. Cederholm T, Palmblad J. Are omega-3 fatty acids options for prevention and treatment of cognitive decline and dementia? *Curr Opin Clin Nutr Metab Care* 2010; 13: 150–5.
19. Puri BK, *et al.* Ethyl-EPA in Huntington disease: a double-blind, randomized, placebo-controlled trial. *Neurology* 2005; 65: 286–92.
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Adverse Effects and Precautions

The most common adverse effects of omega-3 fatty acid preparations are gastrointestinal disturbances, particularly at high doses, including nausea, eructation, vomiting, abdominal distension, diarrhoea, and constipation. There have been rare reports of acne and eczema. Moderate increases in hepatic transaminases have been reported in patients with hypertriglyceridaemia.

Preparations vary widely in concentration and purity. Some preparations contain significant amounts of vitamins A and D and long-term use could cause toxicity. There is a theoretical possibility of vitamin E deficiency with long-term use, although many preparations contain vitamin E as an antoxidant. Concern has been expressed over the high calorific value and cholesterol content of some preparations.

Omega-3 fatty acids have antithrombotic activity and should be given with caution to patients with haemorrhagic disorders or to those receiving anticoagulants or other drugs affecting coagulation. Hepatic function should be monitored in patients with hepatic impairment, particularly if receiving high doses. Caution may also be required in asthmatic patients sensitive to aspirin since omega-3 fatty acids may affect prostaglandin synthesis (see also Inflammatory and Auto-immune Disorders, p. 1461.3, for studies of fish oils in the management of asthma).

Reviews.
1. Bays HE. Safety considerations with omega-3 fatty acid therapy. *Am J Cardiol* 2007; 99 (suppl): 35C–43C.

Effects on the blood. Omega-3 fatty acids have antithrombotic effects and may increase bleeding. In a study[1] in adolescents with familial hypercholesterolaemia, epistaxis occurred in 8 of 11 patients treated with a fish oil supplement; prolonged bleeding time was noted in 3 patients. There have also been case reports of INR elevation and haematoma in patients taking fish oil preparations with antithrombotics (see Lipid Regulating Drugs under Interactions of Warfarin, p. 1534.3), although controlled studies have failed to show an effect.

1. Clarke JTR, *et al.* Increased incidence of epistaxis in adolescents with familial hypercholesterolemia treated with fish oil. *J Pediatr* 1990; 116: 139–41.

Effects on glucose metabolism. Although a deterioration in glycaemic control has been reported in diabetic patients taking omega-3 fatty acids and fish oil preparations, a meta-analysis[1] of studies in type 1 and type 2 diabetics, and a systematic review[2] of controlled studies in type 2 diabetics, both concluded that fish oils effectively lowered triglycerides without a deleterious effect on glycaemic control.

1. Friedberg CE, *et al.* Fish oil and glycemic control in diabetes: a meta-analysis. *Diabetes Care* 1998; 21: 494–500.
2. Hartweg J, *et al.* Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 30/05/08).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: OMG 3; Regulip; ***Austral.***: Fishaphos†; Kids Fruity Fishies; Maxepa; Omacor; ***Austria***: Omacor; Omegaven; ***Belg.***: Omacor; ***Braz.***: Corabion HC; Votag; ***Canad.***: Flex†; Focus 425†; ***Chile***: DHA Kids; DHA Mathern; Dr Einst Gold; Dr Einstein Mama: Epasan Omega 3; Eykosacol; Omega-3; Omegaven; Prenamin; ***China***: Omegaven (无文); ***Cz.***: FolGravid; Omacor; Omegaven; ***Denm.***: Omegaven; ***Fr.***: Maxepa†; Molval; OM3†; Omacor; Omegabiane; Omegaven; Psoriacalm; Triglistab; Ysomega; ***Ger.***: Ameu; Eicosan; Eicosapen; Lipiscor; Omacor; Omegaven; Zodin; ***Gr.***: Farlipid; Maxepa; Omacor; Zodin; ***Hong Kong***: Lipomega; Omegaven; Smartfish†; ***Hung.***: Eskimo-3; Omacor; Omegaven; ***India***: Maxepa; Mega-Omega; Natolac; Omegaven; ***Indon.***: Astacor; Champs DHA; Prolacta with DHA for Baby; Prolacta with DHA for Mother; ***Irl.***: Maxepa†; Omacor; ***Israel***: Alsepa Focus; Alsepa Super; Alsepa; Omacor; Omegaven; Tri-Omega Extra EPA; ***Ital.***: Almic; Esapent; Eskim; Fish Factor; Maxepa; Omegaven; Seacor; Triolip; Triomar; ***Jpn***: Emeradole; Epadel; Lotriga; Solmiran; ***Malaysia***: Caprovid; Champs DHA; Mepa†; Quest Gamma EPA Plus; ***Mex.***: Biomega; Colega-3†; Presomega; Omegavite; ***Neth.***: Omacor; Omegaven; ***Norw.***: Omacor; ***NZ***: Omegaven; ***Philipp.***: Fisol†; Omacor; Omega Gold; Zymechol; ***Pol.***: BioCardine†; Omacor; Omega-3; Omegaven; Trienyl†; ***Port.***: Omacor; Omegaven; Zodin; ***Rus.***: Omacor (Омакор); Omegaven (Омегавен); ***Singapore***: Champs DHA†; ***Spain***: Omacor; ***Swed.***: Omegaven; Pikasol; ***Switz.***: Biorganic Omega-3; Eicosapen; Epacaps; Omegaven; ***Thai.***: Omacor; ***Turk.***: Efa; Marincap; Omega III; Omegaven; Somon; ***UK***: DocOmega; Maxepa; Omacor; Omegaven; Prestylon; Pure Omega; Teromeg; ***Ukr.***: Omacor (Омакор); Omegaven (Омегавен); ***USA***: Cardi-Omega 3; Cholestin; Lovasa; Lovaza; Maxepa; Promega; Sea-Omega; SuperEPA; Vascepa; ***Venez.***: Epax; Fizoil; Marina; Maxepa; Ometrix.

Multi-ingredient Preparations. *Arg.*: Cellasene Gold; Cellasene†; Epasterol; Ocuvite Omega3; Omeganorm†; Percutalia; ***Austral.***: Arthri Plus†; Arthriforte†; Arthro-Eze; Bonlutin; CardiWell Omega Q10; Conceive Well Gold; EFA Compound; Hypol Cherry; Lutein-Vision Advanced; Maxepa Evening Primrose Oil; NA Neurocard; Once Daily Mens Multi; PM Bright Kids; PM Eye Tonic; PM IQShield; PM Kids Intelligent; PM Procare; Pregnancy & Breast-Feeding Gold; Pregnancy & Breastfeeding Formula; SMOFlipid; Teen Multi; TotalCare†; Zellulean with Escin†; ***Austria***: Lipidem; SMOFlipid; Sulgan 99; ***Belg.***: Lipoplus; ***Braz.***: Borag; Glavit†; Votag O6; ***Canad.***: Balance†; Bionagre plus E†; Herbalifeline†; ***Chile***: A-Colest TG; Celltech; Infor; Naticare; Tonopron Plus; ***Cz.***: Lipoplus; NuTRIflex Omega; SMOFKabiven; SMOFlipid: ***Denm.***: Lipidem; SMOFKabiven; SMOFlipid; ***Fin.***: Lipoplus; SMOFKabiven; SMOFlipid; ***Fr.***: Alphalarm; Androlistica; Base; Bi-Osteo; Cardilane; Corvitec; Derm; Difravision; Diomega; Dioptec; DNV; Donaclim; Donalis; Effadiane relipidantes; Elteans; Feminabiane Conception; Gestarelle S; Gynefam; Kotor Articulations; Lero Pervulane; Lero; Lipidem; Liporegul; Macula; Memozan; Menolistica; Mix-Alpha 3; Natallence; Naturophta Macula; Neurovitol; Nutriarm; Nutrof Total; OM3flex†; OM3junior†; OM3memory†; Omegacoeur; Optibiol; Photoderm; Phyltalzeal; Phytalgic; Phytophanere†; PreserVision; Reanutriflex Omega; Regederm; Reti-Nat†; Rhu; Selomega; Serenite Grossesse; SMOFKabiven; SMOFlipid; Solaire; Sun Vue; Synaptiv; Trioptec; Visioprev; Vitalux Plus; ***Ger.***: Lipidem; NuTRIflex Omega; SMOFKabiven; SMOFlipid; ***Gr.***: Atroil; Dynapen-3; Emfrastop; Epadoc; Lipemia; Lipoplus; Loitroi; Mega-Tria; Pazeril; Prolipid; Salmon Oil†; SMOFKabiven; SMOFlipid; ***Hong Kong***: Biomega-3†; Cardiozen; Doctor's Choice Omega 3; Eye Q; Mumomega; PM Eye Tonic†; SMOFlipid; ***Hung.***: Epasel; Epavir; Memolife; SMOFlipid; ***India***: Alphamix-BT; Alphamix; Aqua-E; Bio-10; Bree-C; Cadvion; Catalyst; Celadrin; Coq Forte; Doravit Forte; Ducat Plus; E-Cod Omega; Efalife; Ega; Eldervit-ZC; Elmega-3; Enduranz; Enew; Eriz; Evion Forte; Evox; Exerge; FDH; Fol-DHA; Fol-G2; Fol-Thrive; Folsafe; Folwise; Gissicor; Gissistat; Glace-X; Hartivit; I-Zen; Jivak; Kefive Plus; Maxigard; Maxoflam; Maxolic; Mega-3; Megagin; Megalip; Megaminvit; Megasoft-E; Meskina; MMO3; Mobix; Moisturex-AF; Momvita; Multivite Vision; Multivite-FM Omega; Natrolip; O-NE; Oiz; Olevon; Omegachek; Omegic; Winofit; ***Indon.***: Afomix; Anabion Plus DHA; Asedas; Baliin Q10; Bio-Curlam; Biolysin Smart; Biostrum; Brainvit; Calcidol; Calcimega; Caloma Plus; Calostrum; Cerebrofort AA+DHA; Cerebrofort Gold; Co-Q-10; Curbexon; Curfos; Curmunos; Curvit CL; Dhavit; Flexasur; Folamil Genio; Grafola DHA; Gravimin DHA; Igastrum Plus; Imustrum; Inlacta DHA; Intrum Plus; Kolivit; Kuminta; Lysmin Plus; Maxitrin†; Mulsanol; Natavit; Nufagrabion-GM; Nulacta Plus; Nulacta; Obiplus; Osmetin 3; Pharmaton Matruelle; Prenatal DHA; Prenatin-DF; Procalma; Probelic; Prokids; Promavit; Scott's Cod Liver Oil; Seltifort Gold; Seltifort Kids; Solvita Baby; Truvit; Vidoran Smart Plus; Vidoran Smart Plus; Vitaplex; Vitazym; Vitro-Mega; ***Irl.***: Lipidem; MorDHA†; MorEPA†; SMOFKabiven; SMOFlipid; ***Israel***: Alsepa 9 Months; SMOFKabiven; SMOFlipid; Tri-Omega Super; Triomar; ***Ital.***: Astar; Chiton; Derman-Oil; Dermana Crema; Dermana Pasta; DHA; Ditrevit K; Ditrevit; Eicovis; Elageno OS; Esterol; Euretin; Eutears; Fitogenase; Fotrec DHA; Gammaplus; LCP; Lipidem; Lipoacid Combi; Natalben; Osvit; Phototrop; SMOFlipid; Trofinerv Antiox; Trofinerv; Venoton; ***Malaysia***: Adult Citrex Multivitamin + Ginseng + Omega 3; Bio-Enhanced Fish Oil Plus; BiOmega†; Celadrin†; DHA Plus; Eurobio Bio-Vizmax; Flexasur; Junior Citrex; Neuro-Plus; Pharmaton†; Provas; Tocovid Emulsion Plus; Tocovid Suprabio with DHA; ***Mex.***: Pharmaton Matruelle; ***Mon.***: Conceptio; ***Neth.***: Lipoplus; SMOFKabiven; SMOFlipid; ***Norw.***: Lipidem; NuTRIflex Omega; SMOFKabiven; SMOFlipid; ***NZ***: Efalex; Efamarine; Efamax†; Efanatal; ***Philipp.***: Complectia†; Dreamvite; Megavit; Memory Plus; Neurosmart; Nutri-Aid; OB Smart SG; Omegabloc Omnimune; Pharmaton; Polynerv-E with lecithin; Premium Memori Plus; Trilipid; ***Pol.***: SMOFKabiven; SMOFlipid; ***Port.***: Ever-Fit Dermo; Fortal Vision; Lipoacid Combi; Lipoplus; Rilastil Anti-Oxidante; SMOFKabiven; SMOFlipid; ***Rus.***: Lipoplus (Липоплюс); SMOFlipid (СМОФлипид); ***Singapore***: Androlistica; Arterodiet†; Belvea Pregnancy & Breastfeeding Formula; Biomega†; Cardio Cocktail; CardioCare; Dhaxtra; Eye Q Equazent†; EyeMax; Gissicor; Manhae; Mum-2-B; Mumomega Equazent†; NataBoost; Natal Care; Obimin Plus; Ocuvite Adult 50+; Optibiol; Seven Seas JointCare High Strength; Seven Seas JointCare Max; Seven Seas JointCare; Seven Seas Pulse High Strength Triomega; VitaEPA Plus; VitaEPA; ***Spain***: Lipoplus; NuTRIflex Omega; SMOFKabiven; SMOFlipid; ***Swed.***: Efalex; Efanatal†; Lipoplus; SMOFKabiven; SMOFlipid; ***Switz.***: Lipoplus; SmofKabiven; SMOFlipid; Sulgan N; Vitafissan N; ***Thai.***: Gilomax; Lipidem; SMOFlipid; ***Turk.***: SMOFlipid; ***UK***: Chol-Aid; Efalex; Efamarine; Efanatal; Fishogar; GlucOsamax; Lacrima; Lipidem; NuTRIflex Omega; Pregnacare Plus; ProBrain; SMOFlipid; Super Antioxidant Plus; ***Ukr.***: Bodimarin (Бодимарин); Doppelherz Aktiv Omega-3 Clean Vessels (Доппельгерц Актив Омега-3 Чистые Сосуды); Femibion 400 (Фемибион 400); Ocuvite Complete (Окювайт Комплит); Optix Forte (Оптикс Форте); Perfectil Plus (Перфектил Плюс); Reytoil (Рейтоил); Smart Omega (Смарт Омега); SMOFlipid (СМОФлипид); Vitrum Cardio Omega-3 (Витрум Кардио Омега-3); ***USA***: Active OB; Animi-3 with Vitamin D; Animi-3; Brainstrong Prenatal Multivitamin plus DHA; Cardio Omega Benefits with Vitamin D-3; Citracal Prenatal + DHA; CitraNatal Harmony; Complete Prenatal Multivitamin/ Prenatal DHA Combo Pack; Dry Eye Omega Benefits with Vitamin D-3; Duet DHA; Extra-Virt Plus DHA; Flex Omega Benefits with Vitamin D-3; Hemenatal OB + DHA; Infanate Balance; Macnatal CN DHA;

Marine Lipid Concentrate; Natalvirt CA; Natalvirt DHA; Nestabs ABC; Nestabs DHA; Nexa Plus; Nexa Select; OB Complete; Omega Essentials with Vitamin D-3; Optinate Omega-3; PNV OB+DHA; PNV-DHA; PR Natal; Prena 1 Plus with Quatrefolic; Prena1 with Quatrefolic; Prenaissance DHA; Prenaissance Harmony DHA; Prenaissance Promise; Prenaissance; Prenatal 1; Prenate Essential; Prenate Mini; PreNexa; PreQue 10; Preservision Eye Vitamin; ProtectNatal; Reaphirm Plant Source DHA; Select-OB + DHA; Stuart One; Stuart prenatal + DHA; Tandem DHA; TheraNatal Complete; TL-Assure ONE†; TL-Assure†; TriCare Prenatal Compleat; Triveen-PRx RNF; Triveen-Ten; Ultimate OB DHA; V-Natal DHA; Virt-Bal DHA; Virt-PN DHA; Virt-PNV-DHA; Virt-Select; Vitafol-One; Vitafol-Plus; Vitafol-Ultra; VitaMedMD One Rx; VitaMedMD Plus Rx; VP-CH-PNV; VP-Heme One; *Venez.*: Eidoca; Maternavit; Optibiol; Piscis 3; Provax.

Pharmacopoeial Preparations

USP 36: Fish Oil containing Omega-3 Acids Capsules; Fish Oil containing Omega-3 Acids Delayed-release Capsules; Omega-3-Acid Ethyl Esters Capsules.

Orbofiban Acetate *(USAN, rINNM)*

Acetato de orbofibán; CS-511; Orbofiban, Acétate d'; Orbofibani Acetas; Orbofibán, acetato de; SC-57099-8; Орбофибана Ацетат.

*N*²-[[(3*S*)-1-(*p*-Amidinophenyl)-2-oxo-3-pyrrolidinyl]carbamoyl]-β-alanine ethyl ester monoacetate quadrantihydrate.

$C_{17}H_{23}N_5O_4.C_2H_4O_2.¼H_2O$=426.0

CAS — 163250-90-6 (orbofiban); 165800-05-5 (orbofiban acetate).

UNII — UP77J8QOVX.

Profile

Orbofiban is a glycoprotein IIb/IIIa-receptor antagonist. It has been investigated as an oral antiplatelet drug in unstable angina and myocardial infarction but has been associated with an increase in mortality.

References.

1. Cannon CP, *et al.* Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. *Circulation* 2000; **102:** 149–56.

Ouabain

Acocantherin; G-Strophanthin; Ouabaïni; Ouabain oktahydrát; Ouabaina; Ouabainas; Ouabaine; Ouabainum; Ouabainum Octahydricum; Strophanthin-G; Strophanthinum; Strophanthoside-G; Uabaina; Ubaina.

3β-(α-L-Rhamnopyranosyloxy)-1β,5,11α,14,19-pentahydroxy-5β,14β-card-20(22)-enolide octahydrate.

$C_{29}H_{44}O_{12}.8H_2O$=728.8

CAS — 630-60-4 (anhydrous ouabain); 11018-89-6 (ouabain octahydrate).

ATC — C01AC01.

ATC Vet — QC01AC01.

UNII — 5ACL011P69.

Pharmacopoeias. In *Eur.* (see p. vii) and *Viet.*

Ph. Eur. 8: (Ouabain). Colourless crystals or white or almost white, crystalline powder. Sparingly soluble in water and in dehydrated alcohol; practically insoluble in ethyl acetate. Protect from light.

Profile

Ouabain is a cardiac glycoside with positive inotropic activity that is obtained from the seeds of *Strophanthus gratus* or from the wood of *Acokanthera schimperi* or *A. ouabaio* (Apocynaceae). It has general properties similar to those of digoxin (p. 1353.3) and may be used in the treatment of heart failure (p. 1262.3). Ouabain is given orally in a dose of up to 24 mg daily; it has also been given intravenously.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Strodival†.

Oxedrine *(BAN)*

Oksedriini; Oxedrin; Oxedrina; Oxedrinum; Sinefrina; Sympaethaminum; *p*-Synephrine; Synephrine; Окседрин.

(*RS*)-1-(4-Hydroxyphenyl)-2-(methylamino)ethanol.

$C_9H_{13}NO_2$=167.2

CAS — 94-07-5.

ATC — C01CA08; S01GA06.

ATC Vet — QC01CA08; QS01FB90; QS01GA06.

UNII — PEG5DP7434.

NOTE. Synephrine and *p*-synephrine have been used as synonyms for oxedrine. Care should be taken to avoid confusion with *m*-synephrine, which is phenylephrine (p. 1672.2).

Oxedrine Hydrochloride *(BANM)*

Sinefrina, hidrocloruro de; Synephrine Hydrochloride; Окседрина Гидрохлорид.

$C_9H_{13}NO_2.HCl$=203.7

ATC — C01CA08; S01GA06.

ATC Vet — QC01CA08; QS01GA06.

UNII — ENSD1IH09S.

Oxedrine Tartrate *(BANM)*

Aetaphen. Tartrat; Aethaphenum Tartaricum; Oksedriinitartraatti; Oxedrini Tartras; Oxedrintartrat; Oxyphenylmethylaminoethanol Tartrate; Sinefrina Tartrato; Sinefrina, tartrato de; Synephrine Tartrate; Окседрина Тартрат.

$(C_9H_{13}NO_2)_2.C_4H_6O_6$=484.5

CAS — 16589-24-5 (oxedrine tartrate); 67-04-9 (±oxedrine tartrate).

ATC — C01CA08; S01GA06.

ATC Vet — QC01CA08; QS01GA06.

UNII — 9I99I5995J.

Profile

Oxedrine is a sympathomimetic (p. 1507.3) that has been given as the tartrate in the treatment of hypotensive states in oral doses of about 100 to 150 mg three times daily; it has also been given by subcutaneous, intramuscular, or intravenous injection.

Oxedrine tartrate has been used in eye drops as an ocular decongestant. The hydrochloride has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Sympatol†; *Hong Kong*: Ocuton†; *Hung.*: Sympathomim; *Ital.*: Sympatol†; *Switz.*: Sympalept†.

Multi-ingredient Preparations. *Fr.*: Dacryoboraline†; Polyfra†; Sedacollyre†; Uvicol†.

Oxilofrine Hydrochloride *(rINNM)* ⊗

Hidrocloruro de oxilofrina; *p*-Hydroxyephedrine Hydrochloride; Methylsynephrine Hydrochloride; Oxilofrina, hidrocloruro de; Oxilofrine, Chlorhydrate d'; Oxilofrini Hydrochloridum; Oxyephedrine Hydrochloride; Оксилофрина Гидрохлорид.

erythro-*p*-Hydroxy-α-[1-(methylamino)ethyl]benzyl alcohol hydrochloride.

$C_{10}H_{15}NO_2.HCl$=217.7

CAS — 942-51-8.

UNII — 3O9694M5EO.

Profile

Oxilofrine is a sympathomimetic (p. 1507.3) related to ephedrine (p. 1663.1). It has been used orally as the hydrochloride in the treatment of hypotensive states. It has also been used in antitussive preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Carnigen†; *Ger.*: Carnigen†.

Multi-ingredient Preparations. *Canad.*: Cophylac.

Oxprenolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Ba-39089; Hidrocloruro de oxiprenolol; Hidrocloruro de oxprenolol; Oksprenolol Hidroklorür; Oksprenololihydrokloridi; Oksprenololio hidrochloridas; Oksprenololu chlorowodorek; Oxprénolol, Chlorhydrate d'; Oxprenolol, hidrocloruro de; Oxprenolol hydrochlorid; Oxprenolol-hidroklorid; Oxprenololhydrochlorid; Oxprenololhydroklorid; Oxprenolol Hydrochloridum; Oxyprenolol Hydrochloride; Оксипренолола Гидрохлорид.

1-(*o*-Allyloxyphenoxy)-3-isopropylaminopropan-2-ol hydrochloride.

$C_{15}H_{23}NO_3.HCl$=301.8

CAS — 6452-71-7 (oxprenolol); 6452-73-9 (oxprenolol hydrochloride).

ATC — C07AA02.

ATC Vet — QC07AA02.

UNII — F4XSI7SNIU.

NOTE. Compounded preparations of oxprenolol hydrochloride may be represented by the following names:

- Co-prenozide *(BAN)*—oxprenolol hydrochloride 640 parts and cyclopenthiazide 1 part (w/w).

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US. Chin.* includes the base.

Ph. Eur. 8: (Oxprenolol Hydrochloride). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. A 10% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 36: (Oxprenolol Hydrochloride). A white crystalline powder. Freely soluble in water, in alcohol, and in chloroform; sparingly soluble in acetone; practically insoluble in ether. A 10% solution in water has a pH of 4.0 to 6.0.

Uses and Administration

Oxprenolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to possess intrinsic sympathomimetic and membrane-stabilising activity.

Oxprenolol is given orally as the hydrochloride in the management of hypertension (p. 1251.1), angina pectoris (p. 1254.3), and cardiac arrhythmias (p. 1266.1). It is also used in anxiety disorders (p. 1028.1).

In **hypertension** oxprenolol hydrochloride is given in a usual dose of 80 to 160 mg daily in two or three divided doses. The dose may be increased at weekly or fortnightly intervals until a satisfactory response is achieved. The usual maximum dose is 320 mg daily although up to 480 mg daily has been given.

The usual dose for **angina pectoris** is 80 to 160 mg daily in two or three divided doses with a usual maximum of 320 mg daily.

For **cardiac arrhythmias** a dose of 40 mg daily to not more than 240 mg daily in two or three divided doses may be used.

To relieve **anxiety** in stressful situations oxprenolol hydrochloride is given in usual doses of 40 to 80 mg daily, either as a single dose or in two divided doses.

Modified-release preparations allowing once daily dosing are also available.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Breast feeding. Oxprenolol is distributed into breast milk but the amount likely to be ingested by an infant is small (see under Pharmacokinetics, below). No adverse effects have been seen in breast-fed infants whose mothers were given oxprenolol and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. [Retired May 2010] Correction. *Ibid:* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Hypersensitivity. Oxprenolol-induced drug fever has been reported[1] in a patient and was confirmed by a challenge test.

1. Hasegawa K, *et al.* Drug fever due to oxprenolol. *BMJ* 1980; **281:** 27–8.

Overdosage. Rhabdomyolysis with myoglobinuria has been reported[1] as a complication of severe overdosage with oxprenolol.

1. Schofield PM, *et al.* Recovery after severe oxprenolol overdose complicated by rhabdomyolysis. *Hum Toxicol* 1985; **4:** 57–60.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Oxprenolol is well absorbed from the gastrointestinal tract, but is subject to first-pass metabolism resulting in variable bioavailability (20 to 70%). Peak plasma concentrations occur about 1 or 2 hours after a dose. Oxprenolol is about 80% bound to plasma proteins. It crosses the placenta and is distributed into breast milk. It is moderately lipid-soluble and crosses the blood-brain barrier. Oxprenolol is metabolised in the liver and almost entirely excreted in the urine. An elimination half-life of 1 to 2 hours has been reported.

Pregnancy and breast feeding. The placental transfer of oxprenolol and its passage into breast milk was studied[1] in 32 pregnant women given a preparation containing oxprenolol and dihydralazine (*Trasipressol*). At delivery the mean maternal plasma concentration was 0.386 nanomoles/mL compared with 0.071 and 0.081 nanomoles/mL in plasma from the umbilical artery and vein respectively.

Oxprenolol plasma concentrations in the newborn ranged from 0 to 0.186 nanomoles/mL during the first 24 hours of life. The concentrations of oxprenolol in breast milk 3 to 6 days after delivery ranged from 0 to 1.342 nanomoles/mL, and the milk to plasma concentration ratio was 0.45:1. Based on the highest milk concentration seen it was calculated that a breast-fed infant could receive, at a maximum, a daily dose at least 60 times less than an average adult daily dose (240 mg daily) for hypertension. In another study[2] in 12 women given oxprenolol, mean milk to plasma concentration ratios were 0.21:1 to 0.43:1, depending on dose.

1. Sioufi A, *et al.* Oxprenolol placental transfer, plasma concentrations in newborns and passage into breast milk. *Br J Clin Pharmacol* 1984; 18: 453–6.
2. Fidler J, *et al.* Excretion of oxprenolol and timolol in breast milk. *Br J Obstet Gynaecol* 1983; 90: 961–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Corbeton; *Canad.*: Trasicor†; *Fr.*: Trasicor†; *Ger.*: Trasicor†; *Gr.*: Drisoftaline; Trasicor; Vrachor; Zetonium; *Hong Kong*: Corbeton†; *Neth.*: Trasicor†; *Spain*: Trasicor†; *Switz.*: Slow-Trasicor†; Trasicor†; *Turk.*: Trasicor†; *UK*: Slow-Trasicor; Trasicor.

Multi-ingredient Preparations. *Fr.*: Trasitensine†; *Gr.*: Trasitensin; *Ital.*: Trasitensin; *Spain*: Trasitensin; *Switz.*: Slow-Trasitensine; *UK*: Trasidrex†.

Pharmacopoeial Preparations
BP 2014: Oxprenolol Tablets;
USP 36: Oxprenolol Hydrochloride Extended-release Tablets; Oxprenolol Hydrochloride Tablets.

Oxyfedrine Hydrochloride *(BANM, rINNM)*

D-563; Hidrocloruro de oxifedrina; Oxifedrina, hidrocloruro de; Oxifedrini Chloridum; Oxyfédrine, Chlorhydrate d'; Oxyfedrini Hydrochloridum; Оксифедрина Гидрохлорид.
L-3-(β-Hydroxy-α-methylphenethylamino)-3′-methoxypropiophenone hydrochloride.
$C_{19}H_{23}NO_3.HCl$=349.9
CAS — 15687-41-9 (oxyfedrine); 16777-42-7 (oxyfedrine hydrochloride).
ATC — C01DX03.
ATC Vet — QC01DX03.
UNII — 63CF9XK7DA.

Profile

Oxyfedrine hydrochloride has vasodilator properties and has been used in angina pectoris, and myocardial infarction. It is metabolised to phenylpropanolamine (p. 1674.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Ildamen; *Philipp.*: Ildamen; *Port.*: Ildamen.

Pamabrom *(USAN)*

Pamabromo.
2-Amino-2-methylpropan-1-ol 8-bromotheophyllinate.
$C_4H_{11}NO.C_7H_7BrN_4O_2$=348.2
CAS — 606-04-2.
UNII — UA8U0KJM72.

Pharmacopoeias. In *US*.

Profile

Pamabrom is a weak diuretic that has been used, with analgesics and antihistamines, for symptomatic relief of the premenstrual syndrome.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Diurex; *USA*: Maximum Strength Aqua-Ban.

Multi-ingredient Preparations. *Arg.*: Everfem; *Canad.*: Extra Strength Multi-Symptom PMS Relief; Midol PMS; Multi-Symptom PMS Relief; Painaid PMF; Pamprin; Relievol PMS; Tylenol Menstrual; *Chile*: Dolo-Esan Periodo Menstrual; Kitadol Periodo Menstrual; Minfaden; Panagesic Periodo Menstrual; Predual; Sentual Periodo; Tapsin Periodo Menstrual; Tapsin Periodo Premenstrual; *China*: Ai Jia (艾佳); *Malaysia*: Panadol Menstrual; *Mex.*: Femsedin Kutz; *Rus.*: Pemizol (Фемизол); *Singapore*: Panadol Menstrual; *USA*: Lurline PMS; Midol Pre-Menstrual Syndrome; Midol Teen Formula; Painaid PMF Premenstrual Formula; Pamprin; Premsyn PMS; Womens Tylenol Multi-Symptom Menstrual Relief.

Pamiteplase *(rINN)*

Pamiteplasa; Pamitéplase; Pamiteplasum; YM-866; Памитеплаза.
275-L-Glutamic acid-(1–91)-(174–527)-plasminogen activator (human tissue-type protein moiety).
CAS — 151912-42-4.
UNII — KVX79QFV4W.

Profile

Pamiteplase is a thrombolytic related to alteplase (p. 1296.3) that has been used in acute myocardial infarction. It has been investigated in ischaemic stroke.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Solinase†.

Pantethine

Panteteina; Pantetina; Пантетин.
(*R*)-*NN*′-[Dithiobis(ethyleneiminocarbonylethylene)]bis(2,4-dihydroxy-3,3-dimethylbutyramide).
$C_{22}H_{42}N_4O_8S_2$=554.7
CAS — 16816-67-4.
ATC — A11HA32.
ATC Vet — QA11HA32.
UNII — 7K81IL792L.

NOTE. The names Dermorizin, Palfadin, Panholeata, Panpyotin, Parutox, and Youtetine have been used as trade marks for pantethine.

Pharmacopoeias. In *Jpn*.

Profile

Pantethine, a derivative of pantothenic acid (p. 2085.2), is a component of coenzyme A. It is used as a lipid regulating drug in the treatment of hyperlipidaemias (p. 1248.1). The usual oral dose is 0.6 to 1.2 g daily in divided doses.

Pantethine is also used as a nutritional supplement.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Pantetina; *Jpn*: Pantosin.

Parnaparin Sodium *(BAN, rINN)*

OP-21-23; Parnapariininatrium; Parnaparin-Natrium; Parnaparin sodná sůl; Parnaparin Sodyum; Parnaparina sódica; Parnaparine Sodique; Parnaparinnatrium; Parnaparinnátrium; Parnaparino natrio druska; Parnaparinum natricum; Парнапарин Натрий.
CAS — 9041-08-1.
ATC — B01AB07.
ATC Vet — QB01AB07.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Parnaparin Sodium). It is prepared by hydrogen peroxide and cupric salt depolymerisation of heparin obtained from the intestinal mucosa of pigs and cattle. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 2-*N*,6-*O*-disulfo-D-glucosamine structure at the reducing end of their chain. The mass-average molecular mass ranges between 4000 and 6000, with a characteristic value of about 5000. The mass percentage of chains lower than 3000 is not more than 30%. The degree of sulfation is 2.0 to 2.6 per disaccharide unit. Potency is not less than 75 units and not more than 110 units of anti-factor Xa activity per mg with reference to the dried substance, and the ratio of anti-factor Xa activity to anti-factor IIa (antithrombin) activity is between 1.5 and 3.0.

Profile

Parnaparin sodium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant activity used in the prevention of postoperative venous thromboembolism (p. 1274.1); it has also been used in other thromboembolic disorders. For general surgical procedures it is given by subcutaneous injection in a dose of 3200 units 2 hours before the procedure, followed by 3200 units once daily for 7 days or until the patient is fully ambulant. For higher risk or orthopaedic patients a dose of 4250 units is given 12 hours before the procedure, followed by 4250 units 12 hours postoperatively and then once daily for 10 days.

For treatment of thromboembolism a dose of 6400 units is given by subcutaneous injection twice daily for 7 to 10 days. This may be followed by a once-daily subcutaneous injection of 4250, 6400, or 8500 units for a further 10 to 20 days.

References.

1. Prampton JR, Paulds D. Parnaparin: a review of its pharmacology, and clinical application in the prevention and treatment of thromboembolic and other vascular disorders. *Drugs* 1994; 47: 652–76.
2. McKeage K, Keating GM. Parnaparin: a review of its use in the management of venous thromboembolism, chronic venous disease and other vascular disorders. *Drugs* 2008; 68: 105–22.

Inflammatory bowel disease. Oral parnaparin, formulated for colonic release, has been investigated[1,2] in the management of patients with mild to moderate ulcerative colitis (p. 1811.3). See also under Low-molecular-weight Heparins, p. 1426.2.

1. Pastorelli L, *et al.* Oral, colonic-release low-molecular-weight heparin: an initial open study of Parnaparin-MMX for the treatment of mild-to-moderate left-sided ulcerative colitis. *Aliment Pharmacol Ther* 2008; 28: 581–8.
2. Celasco G, *et al.* Clinical trial: oral colon-release parnaparin sodium tablets (CB-01-05 MMX) for active left-sided ulcerative colitis. *Aliment Pharmacol Ther* 2010; 31: 375–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Fluxum (希非全); *Cz.*: Fluxum; *Gr.*: Thromboparin; Tromboparin; *Hung.*: Fluxum; *India*: Fluxum; *Indon.*: Fluxum; *Ital.*: Fluxum; Zoltar; *Mex.*: Fluxum; *Pol.*: Fluxum†; *Port.*: Fluxum; Tromboparin; *Turk.*: Fluxum; *Venez.*: Tromboparin.

Penbutolol Sulfate *(BANM, USAN, rINNM)* ⊗

Hoe-39-893d; Hoe-893d; Levopenbutolol Sulfate; Penbutolol Hemisulfate; Penbutolol sulfát; Penbutolol, Sulfate de; Penbutolol, sulfato de; Penbutolol Sulphate; Penbutololi sulfas; Penbutololio sulfatas; Penbutololisulfaatti; Penbutololsulfat; Penbutolol-szulfát; Sulfato de penbutolol; Пенбутолола Сульфат.
(*S*)-1-*tert*-Butylamino-3-(2-cyclopentylphenoxy)propan-2-ol hemisulfate.
$(C_{18}H_{29}NO_2)_2.H_2SO_4$=680.9
CAS — 38363-40-5 (penbutolol); 38363-32-5 (penbutolol sulfate).
ATC — C07AA23.
ATC Vet — QC07AA23.
UNII — US71433228.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Penbutolol Sulfate). A white or almost white, crystalline powder. Slightly soluble in water; practically insoluble in cyclohexane; soluble in methyl alcohol. Protect from light.

USP 36: (Penbutolol Sulfate). A white to off-white, crystalline powder. Soluble in water and in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Penbutolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to possess some intrinsic sympathomimetic activity but lacks membrane-stabilising properties.

Penbutolol is used as the sulfate in the management of hypertension (p. 1251.1). It may also be used in cardiac disorders such as angina pectoris (p. 1254.3).

In **hypertension** penbutolol sulfate is given in an initial oral dose of 20 mg daily; the dose may be increased if necessary to 40 to 80 mg daily. Maximum antihypertensive efficacy is reported to occur within 2 weeks in patients given a dose of 20 mg daily but about 4 weeks may be required for maximum effect in patients given 10 mg daily.

Penbutolol sulfate has also been used in similar doses in cardiac disorders such as **angina**.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Penbutolol is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 3 hours after a dose. Penbutolol is 80 to 98% bound to plasma proteins. It has a high lipid solubility. It is extensively metabolised in the liver by hydroxylation and glucuronidation, the metabolites being excreted in the urine with only small amounts of unchanged penbutolol. A plasma elimination half-life of about 20 hours has been reported.

Renal impairment. Glucuronidation was considered more prominent than hydroxylation in the metabolism of

penbutolol and its activity was not altered in patients with renal impairment.[1]

1. Bernard N, *et al.* Pharmacokinetics of penbutolol and its metabolites in renal insufficiency. *Eur J Clin Pharmacol* 1985; 29: 215–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Betapressin; *USA*: Levatol.

Multi-ingredient Preparations. *Ger.*: Betarelix; Betasemid.

Pharmacopoeial Preparations
USP 36: Penbutolol Sulfate Tablets.

Pentaerithrityl Tetranitrate *(BAN, rINN)*

Erynite; Nitropentaerythrol; Nitropenthrite; Pentaérithrityle, Tétranitrate de; Pentaerithrityli Tetranitras; Pentaeritritilio tetranitratas; Pentaeritritilo, tetranitrato de; Pentaeritritol Tetranitrat; Pentaeritrit-tetranitrát; Pentaerithrityltetranitrat; Pentaeritrityylitetranitraatti; Pentaerythritol Tetranitrate; Pentaerythritolum Tetranitricum; Pentaerythrityl Tetranitrate; Pentaérythrityle, tétranitrate de; Pentaerythrityli Tetranitras; Pentaerythrityl-tetranitrát; Pentaerytrityltetranitrat; Pentaerytrityylitetranitraatti; Pentaerytrytylu tetraazotan; Pentanitrol; PETN; Tetranitrato de pentaeritritilo; Tetranitrato de pentaeritritol; Пентаэритритила Тетранитрат.

2,2-Bis(hydroxymethyl)propane-1,3-diol tetranitrate.

$C_5H_8N_4O_{12}$=316.1

CAS — 78-11-5.

ATC — C01DA05.

ATC Vet — QC01DA05.

UNII — 10L39TRG1Z.

NOTE. The synonym PETN has been applied to both niceritrol and pentaerithrityl tetranitrate.

Pharmacopoeias. *Chin.* and *Eur.* (see p. vii) include as diluted pentaerithrityl tetranitrate.

Ph. Eur. 8: (Pentaerithrityl Tetranitrate, Diluted). A mixture of pentaerithrityl tetranitrate with lactose monohydrate or mannitol. Its solubility depends on the diluent and its concentration. Protect from light and heat.

Undiluted pentaerithrityl tetranitrate is a white or slightly yellowish powder. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone.

Handling. Undiluted pentaerithrityl tetranitrate can be exploded by percussion or excessive heat.

Profile

Pentaerithrityl tetranitrate is a vasodilator with general properties similar to those of glyceryl trinitrate (p. 1393.3) but its duration of action is more prolonged.

It is used in angina pectoris (p. 1254.3) in typical oral doses of 50 mg two or three times daily before food, although higher doses have been given. An oral modified-release preparation, given in a dose of 80 mg twice daily, is available in some countries.

Pentaerithrityl trinitrate, an active metabolite of pentaerithrityl tetranitrate, has also been used clinically under the name pentrinitrol.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Pentalong; *Ger.*: Nirason N†; Pentalong†; *Hung.*: Nitropenton†; *India*: Peritrate; *Ital.*: Peritrate; *Pol.*: Galpent; *Rus.*: Erynit (Эринит); *Thai.*: Peritrate; *Turk.*: Danitrin†.

Multi-ingredient Preparations. *Chile*: Cardiosedantol; *Pol.*: Pentaerythritol Compositum; *Turk.*: Danitrin Fort.

Pentosan Polysulfate Sodium

(BAN, USAN, rINN)

Natrii pentosani polysulfas; Natrii Pentosani Polysulfas; Natriumpentosaanipolysulfaatti; Natriumpentosanpolysulfat; Pentosan Polysulphate Sodium; Pentosane Polysulfate Sodique; Pentosano polisulfato de sodio; PZ-68; Sodium Pentosan Polysulphate; Sodium Xylanpolysulphate; SP-54; Натрия Пентозана Полисульфат.

CAS — 37319-17-8; 116001-96-8.

ATC — C05BA04.

ATC Vet — QC05BA04.

UNII — 914032762Y.

Description. Pentosan polysulfate sodium is a mixture of linear polymers of β-1→4-linked xylose, usually sulfated at the 2- and 3-positions and occasionally (about 1 in every 4 residues) substituted at the 2-position with 4-*O*-methyl-α-D-glucuronic acid 2,3-*O*-sulfate. The average molecular weight lies between 4000 and 6000 with a total molecular weight range of 1000 to 40 000.

Uses and Administration

Pentosan polysulfate sodium is a heparinoid with anticoagulant and fibrinolytic properties; it may also have hypolipidaemic and anti-inflammatory effects. It has been used in thromboembolic disorders, although its anticoagulant effect is less than that of heparin. It is also used in the management of interstitial cystitis (see below) and has been tried in several other conditions, including variant Creutzfeldt-Jakob disease (see below). Pentosan polysulfate sodium has been used orally, parenterally, and topically. It has also been used in veterinary medicine.

In the management of interstitial cystitis, pentosan polysulfate sodium is given orally in a dose of 100 mg three times daily.

Cystitis. Pentosan polysulfate sodium has been used orally in inflammatory conditions of the bladder, including interstitial cystitis (p. 2348.1) and is thought to act by enhancing the protective effect of mucins at the bladder surface.[1] Studies have differed concerning its efficacy in the treatment of interstitial cystitis and an analysis[2] of controlled studies concluded that pentosan polysulfate sodium was more effective than placebo in treating pain, urgency, and frequency, but that the difference was small. Any benefit is usually apparent within 3 to 6 months and only occurs in a minority of patients.[3] Pentosan polysulfate sodium was reported[4] to have minimal long-term efficacy in a group of patients with severe or refractory interstitial cystitis.

A combination of oral and intravesical treatment with the drug has been tried in some patients.[5]

Pentosan polysulfate sodium has also been reported[6-8] to be useful in the control of radiation-induced haemorrhagic cystitis (p. 2347.3).

1. Anderson VR, Perry CM. Pentosan polysulfate: a review of its use in the relief of bladder pain or discomfort in interstitial cystitis. *Drugs* 2006; 66: 821–35.
2. Hwang P, *et al.* Efficacy of pentosan polysulfate in the treatment of interstitial cystitis: a meta-analysis. *Urology* 1997; 50: 39–43.
3. Anonymous. Pentosan for interstitial cystitis. *Med Lett Drugs Ther* 1997; 39: 56.
4. Jepsen JV, *et al.* Long-term experience with pentosanpolysulfate in interstitial cystitis. *Urology* 1998; 51: 381–7.
5. Davis EL, *et al.* Safety and efficacy of the use of intravesical and oral pentosan polysulfate sodium for interstitial cystitis: a randomized double-blind clinical trial. *J Urol (Baltimore)* 2008; 179: 177–85.
6. Parsons CL. Successful management of radiation cystitis with sodium pentosanpolysulfate. *J Urol (Baltimore)* 1986; 136: 813–14.
7. Hampson SJ, Woodhouse CRJ. Sodium pentosanpolysulphate in the management of haemorrhagic cystitis: experience with 14 patients. *Eur Urol* 1994; 25: 40–2.
8. Sandhu SS, *et al.* The management of haemorrhagic cystitis with sodium pentosan polysulphate. *BJU Int* 2004; 94: 845–7.

Prostatitis. Pentosan polysulfate sodium is one of several drugs that have been tried in the management of prostatitis (p. 2350.2). An improvement in symptoms was reported[1] in an uncontrolled study of oral pentosan polysulfate sodium in men with chronic prostatitis/chronic pelvic pain syndrome. A randomised study[2] using pentosan polysulfate sodium 300 mg three times daily found that symptoms were moderately or markedly improved at the end of the 16-week treatment period in more members of the active treatment group than in the group given placebo.

1. Nickel JC, *et al.* Pentosan polysulfate therapy for chronic nonbacterial prostatitis (chronic pelvic pain syndrome category IIIA): a prospective multicenter clinical trial. *Urology* 2000; 56: 413–17.
2. Nickel JC, *et al.* Pentosan polysulfate sodium therapy for men with chronic pelvic pain syndrome: a multicenter, randomized, placebo controlled study. *J Urol (Baltimore)* 2005; 173: 1252–5.

Variant Creutzfeldt-Jakob disease. Variant Creutzfeldt-Jakob disease (vCJD) is a transmissible spongiform encephalopathy believed to be caused by infection of the nervous system with prions. Pentosan polysulfate sodium has been tried in small numbers of patients with vCJD, although there is little published research data. In 2003 the UK Department of Health[1] took advice from the CJD Therapy Advisory Group and the CSM; both groups considered that there was insufficient information on which to base prescribing regimens, and further work was needed.

1. UK DoH. Use of pentosan polysulphate in the treatment of, or prevention of, vCJD. Available at: http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/Publichealth/Communicablediseases/CJD/CJDgeneralInformation/DH_4031039 (accessed 03/08/10)

Adverse Effects and Precautions

As for Heparin, p. 1398.3. Gastrointestinal disturbances may also occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Elmiron; *Austria*: Polyanion†; *Canad.*: Elmiron; *Fr.*: Hemoclar; *Ger.*: Fibrezym; *Hong Kong*: Elmiron; *Hung.*: SP 54; *Ital.*: Fibrase; *Malaysia*: SP 54; *Port.*: Fibrocide; *S.Afr.*: Tavan-SP 54; *Spain*: Thrombocid; *Ukr.*: Thrombocid (Тромбоцид); *USA*: Elmiron.

Multi-ingredient Preparations. *Austria*: Thrombocid; *Cz.*: Thrombocid; *Ger.*: Thrombocid; Thrombocid; *Hong Kong*: Anso; Thrombocid; *Port.*: Thrombocid; Thrombocid; *Spain*: Anso.

Pentoxifylline *(BAN, USAN, rINN)*

8L-191; Okspentifilin; Oxpentifillina; Oxpentifylline; Pentoksifilin; Pentoksifilinas; Pentoksifyllliin; Pentoxifillina; Pentoxifillin; Pentoxifylin; Pentoxifyllin; Pentoxifyllinum; Пентоксифиллин.

3,7-Dimethyl-1-(5-oxohexyl)xanthine.

$C_{19}H_{18}N_4O_3$=278.3

CAS — 6493-05-6.

ATC — C04AD03.

ATC Vet — QC04AD03.

UNII — SD6QCT3TSU.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Pentoxifylline). A white or almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 36: (Pentoxifylline). A white to almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in chloroform and in methyl alcohol; slightly soluble in ether.

Uses and Administration

Pentoxifylline is a xanthine derivative used in the treatment of peripheral vascular disorders (p. 1272.3). Although often classified as a vasodilator, its primary action seems to be a reduction in blood viscosity, probably by effects on erythrocyte deformability and platelet adhesion and aggregation. It is reported to increase blood flow to ischaemic tissues and improve tissue oxygenation in patients with peripheral vascular disease and to increase oxygen tension in the cerebral cortex and in the cerebrospinal fluid; it has been used in cerebrovascular disorders. Pentoxifylline also inhibits production of the cytokine TNFα, and this property is under investigation in several diseases (see below).

In the treatment of peripheral vascular disease the usual oral dose is 400 mg three times daily in a modified-release formulation; this may be reduced to 400 mg twice daily for maintenance or if adverse effects are troublesome. Doses should be taken with meals to reduce gastrointestinal disturbances. In severe hepatic or renal impairment, doses may need to be reduced (see below). Beneficial effects may not be evident until after 2 to 8 weeks of treatment. Pentoxifylline may also be given parenterally.

General references.

1. Ward A, Clissold SP. Pentoxifylline: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. *Drugs* 1987; 34: 50–97.
2. Samlaska CP, Winfield EA. Pentoxifylline. *J Am Acad Dermatol* 1994; 30: 603–21.

Administration in hepatic and renal impairment. The elimination half-life of pentoxifylline and its metabolites is significantly prolonged in patients with hepatic cirrhosis,[1] and some metabolites have a prolonged half-life in renal impairment.[2] UK licensed product information states that in patients with severely impaired hepatic function the dose of pentoxifylline may need to be reduced, while accumulation may occur in patients with severe renal impairment (creatinine clearance less than 30 mL/minute) who receive more than 400 mg once or twice daily.

References.

1. Ramos A, *et al.* Pharmacokinetics of intravenous and oral pentoxifylline in healthy volunteers and in cirrhotic patients. *Clin Pharmacol Ther* 1990; 47: 354–9.
2. Paap CM, *et al.* Multiple-dose pharmacokinetics of pentoxifylline and its metabolites during renal insufficiency. *Ann Pharmacother* 1996; 30: 724–9.

Inhibition of TNFα. Pentoxifylline inhibits production of TNFα, a cytokine that is implicated in the pathogenesis of many diseases, and investigative work with pentoxifylline is being, or has been, carried out in many such disorders. Studies have been performed in patients with alcoholic hepatitis,[1-3] cardiomyopathy,[4] cerebral malaria[5,6] diabetic nephropathy,[7,8] and retinopathy,[9] endometriosis,[10] leishmaniasis,[11,12] leprosy,[13,14] membranous nephropathy,[15] radiation-induced damage,[16-19] severe sepsis or septic shock,[20] recurrent aphthous stomatitis,[21-23] and various vasculitic syndromes, including Behçet's syndrome.[24] Pen-

toxifylline has also been tried for improving graft survival in kidney transplantation.[25,26] For mention of a possible benefit in sarcoidosis, see p. 1612.2. Although promising results have been reported in some of these studies, the place of pentoxifylline in the overall management of these disorders remains to be established.

1. Akriviadis E, *et al.* Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; 119: 1637–48.
2. De BK, *et al.* Pentoxifylline versus prednisolone for severe alcoholic hepatitis: a randomized controlled trial. *World J Gastroenterol* 2009; 15: 1613–19.
3. Whitfield K, *et al.* Pentoxifylline for alcoholic hepatitis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 14/06/10).
4. Skudicky D, *et al.* Beneficial effects of pentoxifylline in patients with idiopathic dilated cardiomyopathy treated with angiotensin-converting enzyme inhibitors and carvedilol: results of a randomized study. *Circulation* 2001; 103: 1083–8.
5. Di Perri, *et al.* Pentoxifylline as a supportive agent in the treatment of cerebral malaria in children. *J Infect Dis* 1995; 171: 1317–22.
6. Looareesuwan S, *et al.* Pentoxifylline as an ancillary treatment for severe falciparum malaria in Thailand. *Am J Trop Med Hyg* 1998; 58: 348–53.
7. Navarro JF, *et al.* Urinary protein excretion and serum tumor necrosis factor in diabetic patients with advanced renal failure: effects of pentoxifylline administration. *Am J Kidney Dis* 1999; 33: 458–63.
8. McCormick BB, *et al.* The effect of pentoxifylline on proteinuria in diabetic kidney disease: a meta-analysis. *Am J Kidney Dis* 2008; 52: 454–63.
9. Lopes de Jesus CC, *et al.* Pentoxifylline for diabetic retinopathy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 21/10/09).
10. Lv D, *et al.* Pentoxifylline versus medical therapies for subfertile women with endometriosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 10/09/09).
11. Lessa HA, *et al.* Successful treatment of refractory mucosal leishmaniasis with pentoxifylline plus antimony. *Am J Trop Med Hyg* 2001; 65: 87–9.
12. Machado PRL, *et al.* Oral pentoxifylline combined with pentavalent antimony: a randomized trial for mucosal leishmaniasis. *Clin Infect Dis* 2007; 44: 788–93.
13. Nery JAC, *et al.* The use of pentoxifylline in the treatment of type 2 reactional episodes in leprosy. *Indian J Lepr* 2000; 72: 457–67.
14. Dawiah ZM, *et al.* A phase 2 open trial of pentoxifylline for the treatment of leprosy reactions. *Int J Lepr Other Mycobact Dis* 2002; 70: 38–43.
15. Ducloux D, *et al.* Use of pentoxifylline in membranous nephropathy. *Lancet* 2001; 357: 1672–3.
16. Okunieff P, *et al.* Pentoxifylline in the treatment of radiation-induced fibrosis. *J Clin Oncol* 2004; 22: 2207–13.
17. Chiao TB, Lee AJ. Role of pentoxifylline and vitamin E in attenuation of radiation-induced fibrosis. *Ann Pharmacother* 2005; 39: 516–22.
18. Delanian S, *et al.* Kinetics of response to long-term treatment combining pentoxifylline and tocopherol in patients with superficial radiation-induced fibrosis. *J Clin Oncol* 2005; 23: 8570–9.
19. Misirlioglu CH, *et al.* Pentoxifylline and alpha-tocopherol in prevention of radiation-induced lung toxicity in patients with lung cancer. *Med Oncol* 2007; 24: 308–11.
20. Staubach K-H, *et al.* Effect of pentoxifylline in severe sepsis: results of a randomized, double-blind, placebo-controlled study. *Arch Surg* 1998; 133: 94–100.
21. Pizarro A, *et al.* Treatment of recurrent aphthous stomatitis with pentoxifylline. *Br J Dermatol* 1995; 133: 659–60.
22. Chandrasekhar J, *et al.* Oxypentifylline in the management of recurrent aphthous oral ulcers: an open clinical trial. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; 87: 564–7.
23. Thornhill MH, *et al.* A randomized, double-blind, placebo-controlled trial of pentoxifylline for the treatment of recurrent aphthous stomatitis. *Arch Dermatol* 2007; 143: 463–70.
24. Hisamatsu T, *et al.* Combination therapy including pentoxifylline for entero-Behçet's disease. *Bull Tokyo Dent Coll* 2001; 42: 169–76.
25. Noel C, *et al.* Immunomodulatory effect of pentoxifylline during human allograft rejection: involvement of tumor necrosis factor α and adhesion molecules. *Transplantation* 2000; 69: 1102–7.
26. Shu K-H, *et al.* Effect of pentoxifylline on graft function of renal transplant recipients complicated with chronic allograft nephropathy. *Clin Nephrol* 2007; 67: 157–63.

Venous leg ulcers. A systematic review[1] of pentoxifylline used in the treatment of venous leg ulcers (p. 1690.1) concluded that it was an effective adjunct to compression bandaging, and may be effective alone.

1. Jull AB, *et al.* Pentoxifylline for treating venous leg ulcers. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 08/05/08).

Adverse Effects

Pentoxifylline can cause nausea, gastrointestinal disturbances, dizziness, and headache. Flushing, angina, palpitations, cardiac arrhythmias, and hypersensitivity reactions, including urticaria, rash, and anaphylactic reactions, may also occur. Bleeding events have been reported rarely, usually in association with bleeding risk factors.

Overdosage with pentoxifylline may be associated with fever, faintness, flushing, hypotension, drowsiness, agitation, and seizures.

Haemorrhage. Three major bleeding episodes including 2 fatal cerebral haemorrhages were reported in a group of patients taking pentoxifylline 400 mg three times daily with acenocoumarol for intermittent claudication.[1] Gastrointestinal bleeding occurred in a 67-year-old patient with a history of duodenal ulcer after a single dose of pentoxifylline for optic neuropathy.[2]

1. APIC Study Group. Acenocoumarol and pentoxifylline in intermittent claudication: a controlled clinical study. *Angiology* 1989; 40: 237–48.
2. Oren R, *et al.* Pentoxifylline-induced gastrointestinal bleeding. *DICP Ann Pharmacother* 1991; 25: 315–16.

Overdosage. A 22-year-old woman who took pentoxifylline 4 to 6 g with suicidal intent developed severe bradycardia and first- and second-degree AV block; other effects included nausea, vomiting, abdominal cramps, hypokalaemia, excitation, and insomnia.[1] She recovered after intensive supportive and symptomatic therapy.

1. Sznajder LJ, *et al.* First and second degree atrioventricular block in oxpentifylline overdose. *BMJ* 1984; 288: 26.

Precautions

Pentoxifylline should be avoided in cerebral haemorrhage, extensive retinal haemorrhage, severe cardiac arrhythmias, and acute myocardial infarction. It should be used with caution in patients with ischaemic heart disease or hypotension. The dose of pentoxifylline may need to be reduced in patients with hepatic or renal impairment (see under Uses and Administration, p. 1465.3).

Interactions

Pentoxifylline may potentiate the effect of antihypertensives. High parenteral doses of pentoxifylline may enhance the action of insulin and oral hypoglycaemics in diabetic patients. Pentoxifylline should not be given with ketorolac as there is reported to be an increased risk of bleeding and/or prolongation of the prothrombin time. There may also be an increased risk of bleeding during use with meloxicam. Serum levels of theophylline may be raised by pentoxifylline.

Cimetidine. A pharmacokinetic study in healthy subjects reported increased average steady-state plasma concentrations of pentoxifylline when given with cimetidine. The clinical relevance of the interaction was not known, but adverse effects such as headache, nausea, and vomiting were reported more often with the combination than with pentoxifylline alone.[1]

1. Mauro VF, *et al.* Alteration of pentoxifylline pharmacokinetics by cimetidine. *J Clin Pharmacol* 1988; 28: 649–54.

Pharmacokinetics

Pentoxifylline is readily absorbed from the gastrointestinal tract but undergoes first-pass hepatic metabolism. Some metabolites are active. The apparent plasma half-life of pentoxifylline is reported to be 0.4 to 0.8 hours; that of the metabolites varies from 1.0 to 1.6 hours. In 24 hours most of a dose is excreted in the urine, mainly as metabolites, and less than 4% is recovered in the faeces. Elimination of pentoxifylline is decreased in elderly patients and patients with hepatic disease. Pentoxifylline and its metabolites are distributed into breast milk.

References.
1. Beermann B, *et al.* Kinetics of intravenous and oral pentoxifylline in healthy subjects. *Clin Pharmacol Ther* 1985; 37: 25–8.
2. Witter FR, Smith RV. The excretion of pentoxifylline and its metabolites into human breast milk. *Am J Obstet Gynecol* 1985; 151: 1094–7.
3. Smith RV, *et al.* Pharmacokinetics of orally administered pentoxifylline in humans. *J Pharm Sci* 1986; 75: 47–52.
4. Ramos A, *et al.* Pharmacokinetics of intravenous and oral pentoxifylline in healthy volunteers and in cirrhotic patients. *Clin Pharmacol Ther* 1990; 47: 354–9.
5. Paap CM, *et al.* Multiple-dose pharmacokinetics of pentoxifylline and its metabolites during renal insufficiency. *Ann Pharmacother* 1996; 30: 724–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dospan Pento; Pentolab; Previscan; Tamixol; Trental; *Austral.*: Trental; *Austria*: Haemodyn†; Pentohexal; Pentomer; Pentoxi; Pentoximed†; Trental; Vasonit; *Belg.*: Torental; *Braz.*: Arteron; Pentalox; Pentox; Pentoxin; Pentral; Pentrat; Peripan†; Prodoxifilina†; Trentafilina; Trental; Trentofil; Vascer; *Canad.*: Trental; *Chile*: Trental; *China*: An Ruo Ning (安若宁); Ao Le Ni (澳乐尼); Ao Nuo Hong (奥诺红); Aotong (奥酮); Bo Shu Te (博舒特); Chang Long Lei (长龙雷); DanKe (丹可); De Bao Xing (德宝星); De Luo Wei (德洛威); Dian Ke Shu (点可舒); Fei Ke Wei Kang (菲克维康); Fu Shu (福枢); Gan Feng (甘风); Jia Li Bo (嘉立博); Ka Kai (卡开); Ni Fu Ping (尼扶平); Pan Duo Xi Lai (潘多喜莱); Pan Ke Fu Lin (潘可福林); Pentomer (瑞潘通); Qi Ming (奇铭); Qiquan (奇全); Run Xin Shu (润心舒); Shu An Ling (舒安灵); Shu Pu Luo (舒芙罗); Shuang Ke (双可); Tai Tong (太通); Tian Cun (天存); Tian Mai (天脉); Wei You (维友); Xi Shu Tong (喜舒同); Xiang Di (祥迪); Xin Ke Duo Na (欣可多那); Xinfu (辛弗); YiShu (益枢); *Cz.*: Agapurin; Pentilin†; Pentomer; Trental; Vasonit; *Denm.*: Elorgan; Trental; *Fin.*: Artal†; Pentoxin; Trental; *Fr.*: Pentoflux; Torental†; *Ger.*: Agapurin†; Claudicat; Pento-Puren†; Pentohexal†; Pentox†; Ralofekt†; Rentylin; Trental; *Gr.*: Razylfin; Tarontal; *Hong Kong*: Pentong†; Trenlin; Trental; *Hung.*: Chinotal; Pentoxyl-EP; Trental; *India*: Flexital; Kinetal; Trental; *Indon.*: Erytral†; Lentrin; Pentoxifillene†; Platof; Reotal; Tarontal; Tioxad; Trenat; Trenfyl; Trental; Trentox; Trenxy; *Irl.*: Trental†; *Israel*: Oxopurin; Trental; *Ital.*: Behrifil; Trental; *Malaysia*: Trenlin; Trental; *Mex.*: Artelife; Eurotofi; Fixoten; Kentadin; Pensiral; Peridane; Profiben; Sinsufyva; Sufisal; Tecxifil; Trental; Vantoxyl; Vasofyl; Vaxolem†; Xinsol†; Xipen; *Neth.*: Trental; *Norw.*: Trental; *NZ*: Trental; *Philipp.*: C-Vex; Pentox; Pentoxal; Toxipen; Trental; *Pol.*: Agapurin; Apo-Pentox; Dartelin†; Pentilin†; Pentohexal; Polfilin; Trental; *Port.*: Claudicat; Trental; *Rus.*: Agapurin (Агапурин); Flexital (Флекситал); Mellinorm (Мелинорм)†; Pentilin (Пентилин); Trenpental (Трепентал); Trental (Трентал 400); Vasonit (Вазонит); *S.Afr.*: Trental†; *Singapore*: Trenlin; Trental; *Spain*: Elorgan; Hemovas; Nelorpin; Retimax†; *Switz.*: Pentoxi; Trental†; *Thai.*: Agapurin†; Cerator; Ceretal; Elastab†; Flexital; Penlol†; Pentiline; Sipental; Trental; Trepal; *Turk.*: Hemopene; Penfixteva; Pentox; Trental; Trentilin; Vasoplan; *UK*: Neotren†; Pentofin†; Trental; *Ukr.*: Latren (Латрен); Trental (Трентал); *USA*: Trental; *Venez.*: Agapurin; Trental.

Multi-ingredient Preparations. *Arg.*: Ikatral Periferico.

Pharmacopoeial Preparations
USP 36: Pentoxifylline Extended-Release Tablets; Pentoxifylline Oral Suspension.

Perhexiline Maleate *(BANM, USAN, rINNM)*

Maleato de perhexilina; Perhexilina, maleato de; Perhexiline, Maléate de; Perhexilini Maleas; WSM-3978G; Пергексиллина Малеат.

2-(2,2-Dicyclohexylethyl)piperidine hydrogen maleate.

$C_{19}H_{35}N,C_4H_4O_4$=393.6

CAS — 6621-47-2 (perhexiline); 6724-53-4 (perhexiline maleate).

ATC — C08EX02.

ATC Vet — QC08EX02.

UNII — K7V8Y90G0H.

Profile

Perhexiline maleate may be used in the long-term management of severe angina pectoris (p. 1254.3) in patients who have not responded to other anti-anginal drugs. Its mode of action is complex.

The usual initial oral dose is 100 mg daily, subsequently either increased or decreased, as necessary, at intervals of 2 to 4 weeks; it is generally recommended not to give more than 300 mg daily although doses of 400 mg daily have been necessary in some patients. The maintenance of plasma-perhexiline concentrations between 150 and 600 nanograms/mL has been recommended.

Perhexiline occasionally produces severe adverse effects including peripheral neuropathy affecting all four limbs with associated papilloedema, severe and occasionally fatal hepatotoxicity, and metabolic abnormalities with marked weight loss, hypertriglyceridaemia, and profound hypoglycaemia. It is contra-indicated in patients with hepatic or renal impairment. Perhexiline should be used with caution in diabetic patients. Hepatic metabolism of perhexiline is mediated by the cytochrome P450 isoenzyme CYP2D6. Therefore caution is advised if perhexiline is used with other drugs that inhibit or are metabolised by this enzyme, and perhexiline toxicity has been reported with SSRIs such as fluoxetine or paroxetine.

References.
1. Killalea SM, Krum H. Systematic review of the efficacy and safety of perhexiline in the treatment of ischemic heart disease. *Am J Cardiovasc Drugs* 2001; 1: 193–204.
2. Ashrafian H, *et al.* Perhexiline. *Cardiovasc Drug Rev* 2007; 25: 76–97.
3. Phan TT, *et al.* Multi-centre experience on the use of perhexiline in chronic heart failure and refractory angina: old drug, new hope. *Eur J Heart Fail* 2009; 11: 881–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Pexsig; *NZ*: Pexsig.

Perindopril *(BAN, USAN, rINN)*

McN-A-2833; Perindopriili; Périndopril; Perindoprilum; S-9490; Периндоприл.

(2*S*,3a*S*,7a*S*)-1-[*N*-[(*S*)-1-Ethoxycarbonylbutyl]-L-alanyl]perhydroindole-2-carboxylic acid.

$C_{19}H_{32}N_2O_5$=368.5

CAS — 82834-16-0.

ATC — C09AA04.

ATC Vet — QC09AA04.

UNII — Y5GMK36KGY.

Perindopril Arginine *(BANM, rINNM)*

Perindopril arginina; Périndopril Arginine; Perindoprilum Argininum; Периндоприл Аргинин.

CAS — 612548-45-5.

ATC — C09AA04.

ATC Vet — QC09AA04.

UNII — TFT5IM1KGB.

Perindopril Erbumine (BANM, USAN, rINNM)

Butylamini Perindoprilum; Butylamin-perindopril; Erbumina de perindopril; McN-A-2833-109; Perindopriili-*tert*-butyyliamiini; Perindopril, erbumina de; Périndopril, Erbumine de; Perindopril Terbutalamin; Perindopril *tert*-Butylamine; Périndopril tert-butylamine; Perindopril-erbumin; Perindoprili Erbuminum; Perindopril-*tert*-butylamin; Perindoprilum Erbuminum; Peryndopryl z tert-butyloamina; S-9490-3; tert-Butylamini perindoprilum; *tert*-Butilamino perindoprilis; Tert-Butylamini Perindoprilum; Периндоприла Эрбумин.

$C_{19}H_{32}N_2O_5C_4H_{11}N$=441.6

CAS — 107133-36-8.

ATC — C09AA04.

ATC Vet — QC09AA04.

UNII — 1964X464OJ.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Perindopril *tert*-Butylamine; Perindopril Erbumine BP 2014). A white or almost white, slightly hygroscopic, crystalline powder. It exhibits polymorphism. Freely soluble in water and in alcohol; soluble or sparingly soluble in dichloromethane. Store in airtight containers.

Uses and Administration

Perindopril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1) and heart failure (p. 1262.3). It is also used to reduce the risk of cardiovascular events in patients with stable ischaemic heart disease (see Cardiovascular Risk Reduction, p. 1246.1).

Perindopril is converted in the body into its active metabolite perindoprilat. ACE inhibition is reported to occur within 1 hour of a dose, to be at a maximum at about 4 to 8 hours, and to be maintained for 24 hours. Perindopril is given orally as the erbumine or arginine salts; 5 mg of perindopril arginine is equivalent to about 4 mg of perindopril erbumine.

In the treatment of **hypertension** perindopril is given in an initial dose of 4 mg of the erbumine or 5 mg of the arginine salt once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. However, licensed product information for perindopril recommends that doses should be taken in the morning, before food. Hypotension is particularly likely in patients with renovascular hypertension, volume depletion, heart failure, or severe hypertension and in such patients the initial dose may be halved to 2 or 2.5 mg respectively once daily. Patients taking diuretics should have the diuretic withdrawn 2 or 3 days before perindopril is started and resumed later if required; if this is not possible, the initial dose may be halved similarly. The same lower initial dose may also be used in the elderly. The dose of perindopril may be increased after 1 month according to response to a maximum of 8 mg of the erbumine or 10 mg of the arginine salt daily. In the USA a maximum dose of 16 mg of perindopril erbumine daily is allowed in uncomplicated hypertension.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision. Perindopril is given in an initial dose of 2 mg of the erbumine or 2.5 mg of the arginine salt once daily in the morning, increased after at least 2 weeks to a usual maintenance dose of 4 mg or 5 mg respectively once daily.

In the management of patients with **ischaemic heart disease** perindopril is given in an initial dose of 4 mg (erbumine) or 5 mg (arginine) once daily for 2 weeks, then titrated up to a maintenance dose of 8 or 10 mg respectively once daily if tolerated. Elderly patients should be started on 2 or 2.5 mg once daily for the first week.

Dosage should be reduced in patients with impaired renal function (see below).

References.

1. Todd PA, Fitton A. Perindopril: a review of its pharmacological properties and therapeutic use in cardiovascular disorders. *Drugs* 1991; 42: 90–114.
2. Doyle AE, ed. Angiotensin-converting enzyme (ACE) inhibition: benefits beyond blood pressure control. *Am J Med* 1992; 92 (suppl 4B): 1S–107S.
3. Hurst M, Jarvis B. Perindopril: an updated review of its use in hypertension. *Drugs* 2001; 61 867–96.
4. Simpson D, *et al.* Perindopril: in congestive heart failure. *Drugs* 2002; 62: 1367–77.
5. Curran MP, *et al.* Perindopril: a review of its use in patients with or at risk of developing coronary artery disease. *Drugs* 2006; 66: 235–55.
6. Telejko B. Perindopril arginine: benefits of a new salt of the ACE inhibitor perindopril. *Curr Med Res Opin* 2007; 23: 953–60.
7. Snyman JR, Wessels F. Perindopril: do randomised, controlled trials support an ACE inhibitor class effect? A meta-analysis of clinical trials. *Cardiovasc J Afr* 2009; 20: 127–34.

Administration in renal impairment. The dose of perindopril should be reduced in patients with renal impairment. UK licensed product information recommends the following doses:

- creatinine clearance (CC) between 30 and 60 mL/minute: 2 mg of the erbumine or 2.5 mg of the arginine salt daily
- CC between 15 and 30 mL/minute: 2 mg (erbumine) or 2.5 mg (arginine) on alternate days
- CC less than 15 mL/minute: 2 mg (erbumine) or 2.5 mg (arginine) on dialysis days.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

In a postmarketing surveillance study[1] of 47 351 patients receiving perindopril for hypertension, no unexpected adverse effects were reported and serious reactions were rare; 1587 (6.3%) women and 782 (3.5%) men withdrew from therapy due to adverse effects.

Although a study[2] of perindopril use in patients with stable chronic heart failure reported no significant first-dose hypotension, there has been a case report[3] of ischaemic stroke, possibly associated with hypotension, after a single dose of perindopril in a patient with post-infarction heart failure. Standard precautions as for other ACE inhibitors (p. 1287.2) should be followed when starting perindopril therapy.

1. Speirs C, *et al.* Perindopril postmarketing surveillance: a 12 month study in 47 351 hypertensive patients. *Br J Clin Pharmacol* 1998; 46: 63–70.
2. MacFadyen RJ, *et al.* Differences in first dose response to angiotensin converting enzyme inhibition in congestive heart failure: a placebo controlled study. *Br Heart J* 1991; 66: 206–11.
3. Bagger JP. Adverse event with first-dose perindopril in congestive heart failure. *Lancet* 1997; 349: 1671–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies perindopril as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Perindopril acts as a prodrug of the diacid perindoprilat, its active form. After oral doses perindopril is rapidly absorbed with a bioavailability of about 65 to 75%. It is extensively metabolised, mainly in the liver, to perindoprilat and inactive metabolites including glucuronides. The presence of food is reported to reduce the conversion of perindopril to perindoprilat. Peak plasma concentrations of perindoprilat occur 3 to 4 hours after an oral dose of perindopril. Perindoprilat is about 10 to 20% bound to plasma proteins. Perindopril is excreted mainly in the urine, as unchanged drug, as perindoprilat, and as other metabolites. The elimination of perindoprilat is biphasic with a distribution half-life of about 5 hours and an elimination half-life of 25 to 30 hours or longer, the latter half-life probably representing strong binding to angiotensin-converting enzyme. The excretion of perindoprilat is decreased in renal impairment. Both perindopril and perindoprilat are removed by dialysis.

References.

1. Lecocq B, *et al.* Influence of food on the pharmacokinetics of perindopril and the time course of angiotensin-converting enzyme inhibition in serum. *Clin Pharmacol Ther* 1990; 47: 397–402.
2. Verpooten GA, *et al.* Single dose pharmacokinetics of perindopril and its metabolites in hypertensive patients with various degrees of renal insufficiency. *Br J Clin Pharmacol* 1991; 32: 187–92.
3. Sennesael J, *et al.* The pharmacokinetics of perindopril and its effects on serum angiotensin converting enzyme activity in hypertensive patients with chronic renal failure. *Br J Clin Pharmacol* 1992; 33: 93–9.
4. Thiollet M, *et al.* The pharmacokinetics of perindopril in patients with liver cirrhosis. *Br J Clin Pharmacol* 1992; 33: 326–8.
5. Guérin A, *et al.* The effect of haemodialysis on the pharmacokinetics of perindoprilat after long-term perindopril. *Eur J Clin Pharmacol* 1993; 44: 183–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Coverene; *Austral.*: Coversyl; Indopril; Perindo; *Austria*: Coversum; *Belg.*: Coversyl; Perindocyl; *Braz.*: Coversyl; Pericor; *Canad.*: Coversyl; *Chile*: Coversyl; *China*: Acertil (雅施达); *Cz.*: Apo-Perindo; Cordesyl†; Covedaspen†; Covemarin†; Covemedal†; Covepet†; Coverdosyn†; Coverdyne†; Coverex; Coversidin†; Coversyspes†; Covethanar†; Domanion; Gleperil; Pamonova; Perinalon; Pinbarix; Prenessa; Prestarium Neo; Prestarium; Prexanil†; Pricoron; Valperal; Vidotin; *Denm.*: Asyntilsan†; Coversyl Arginine; Coversyl Novum; Mariper; Percarnil; Perineva; Prenessa†; Prestarium; Prillana; Rinder; Tanipril†; *Fin.*: Acertil; Coveram; Coversyl; *Fr.*: Coversyl; *Ger.*: Coversum; *Gr.*: Coversyl; *Hong Kong*: Acertil; Provinace; *Hung.*: Armix; Coverex; Levenor; Perindan†; Perineva; Prenessa; Ranbapril; Vidotin; *India*: Coversyl; Eviper; Perigard; *Indon.*: Bioprexum; Prexum†; *Irl.*: Coversyl; Pendrex; Percarnil; Perisom; Prindace; Prindex; Rinoprex; Tevaryl†; *Ital.*: Coversyl; Procaptan; Romapal; *Jpn*: Coversyl; *Malaysia*: Covapril; Coversyl; Covinace; Perigard; Perinace; Provinace; *Mex.*: Coversyl; *Neth.*: Coversyl; Permetor†; Prilanil†; *NZ*: Coversyl; *Philipp.*: Coversyl; Hypergo; Novaril; Perigard; *Pol.*: Apo-Perindox; Coverex†; Irpax; Lextril; Perindoran; Prenessa; Prestarium; Stopress; Vidotin; *Port.*: Coversyl; Ostion†; Prexum†; Ripax; Tensoliber; *Rus.*: Arentopres (Аренторпес); Coverex (Коверекс); Gypernik (Гиперник); Parnavel (Парнавел); Perineva (Перинева); Perinpress (Перинпресс); Prenessa (Пренесса); Prestarium (Престариум); *S.Afr.*: Acesyl; Acti-Prex; Bindace; Ciplasyl; Coversyl; Pearinda; Prexum; Vectoryl; *Singapore*: Coversyl; Perinace; *Spain*: Coversyl; *Swed.*: Coversyl Novum; *Switz.*: Coversum; *Thai.*: Coversyl; Covrix; *Turk.*: Coversyl; Serperil; *UK*: Coversyl; *Ukr.*: Prenesa (Пренеса); Prestarium (Престариум); *USA*: Aceon; *Venez.*: Coversyl.

Multi-ingredient Preparations. *Arg.*: Bipreterax†; Preterax; *Austral.*: Coveram; Coversyl Plus; Doprilamide; Perindo Combi; Reaptan; *Austria*: Preterax; *Belg.*: Bi Preterax†; Coperindo; Coveram; Coversyl Plus; Preterax; *Braz.*: Coversyl Plus; *Canad.*: Coversyl Plus; Preterax†; *China*: Biprel (百普乐); *Cz.*: Coverex Combi; Noliprel; Noliterax; Pamocombi; Parateraх; Perinpa; Prenewel; Prestance; Prestarium Combi; Prestarium Neo Combi; *Denm.*: Coprenessa; Coprindomid†; Coversical; Coversyl Arginine Plus; Coversyl Comp Novum; Domanion Comp†; Parateraх; Tertensif kombi; *Fin.*: Acertil Comp; Coprenessa; Coversyl Comp; Noliterax; Reaptan; Teraxans; *Fr.*: Bipreterax; Coveram; Parateraх; Preterax; *Ger.*: Bipreterax; Coversum Combi†; Preterax; *Gr.*: Coveram; Pediur; Preterax; *Hong Kong*: Acertil Plus; Predonium; *Hung.*: Armix Komb; Armix Prekomb; Co-Perineva; Co-Prenessa; Covercard; Coverex Komb; Coverex Prekomb†; Pretanix Komb; *India*: Adpace; Coversyl Plus; Coversyl-AM; Eviper-D; Perigard-D; Perigard-DF; *Indon.*: Bioprexum Plus; Coveram; *Irl.*: Acerycal; Bipreterax; Coversyl Plus; Pendrex Plus; Preterax; Prindavam; Reaptan; Teraxans; *Ital.*: Coverlam; Prelectal; Preterax; Reaptan; *Malaysia*: Coveram; Coversyl Plus; *Mex.*: Preterax; *Neth.*: Comaranil; Coveram; Coversyl Plus; Noliterax; Predonium†; Preterax; Preterian; *NZ*: Coversyl Plus; Predonium; *Philipp.*: Bi-Preterax; Coveram; Coversyl Plus; Preterax; *Pol.*: Co-Prenessa; Co-Prestarium; Noliprel; Prestarium Plus†; Tertensif Bi-Kombi; Tertensif Kombi; *Port.*: Bi Predonium; Bi Preterax; Coveram; Imprex; Mixanval; Predonium; Preterax; Prilpa; Tecazo; *Rus.*: Noliprel (Нолипрел); Noliprel A (Нолипрел А); Prestance (Престанс); *S. Afr.*: Acesyl Co; Bipreterax†; Coversyl Plus; Pearinda Plus; Preterax; Prexum Plus; Vectoryl Plus; *Singapore*: Coveram; Coversyl Plus; Preterax†; *Spain*: Bipreterax; Preterax; *Switz.*: Coveram; Coversum Combi; Preterax†; *Thai.*: Coveram; Coversyl Plus; *Turk.*: Bipreterax; Calversum; Coversyl Plus; Perivel Plus; Preterax; Serperil Plus; *UK*: Coversyl Plus; *Ukr.*: Bi-Prestarium (Би-Престариум); Co-Prenesa (Ко-Пренеса); Noliprel (Нолипрел); Prestarium Combi (Престариум Комби); *Venez.*: Bipreterax; Preterax.

Pharmacopoeial Preparations

BP 2014: Perindopril Erbumine Tablets.

Phenindione (BAN, rINN)

Fenindion; Fenindiona; Fenindione; Fenindioni; Phénindione; Phenindionum; Phenylindanedione; Phenylinium; Фениндион.

2-Phenylindan-1,3-dione.

$C_{15}H_{10}O_2$=222.2

CAS — 83-12-5.

ATC — B01AA02.

ATC Vet — QB01AA02.

UNII — 5M7Y6274ZE.

Pharmacopoeias. In *Br.* and *Fr.*

BP 2014: (Phenindione). Soft, odourless or almost odourless, white or creamy-white crystals. Very slightly soluble in water; slightly soluble in alcohol and in ether; freely soluble in chloroform. Solutions are yellow to red.

Uses and Administration

Phenindione is an oral indanedione anticoagulant with actions similar to those of warfarin (p. 1527.2). It is given in the management of thromboembolic disorders (p. 1273.2), but because of its higher incidence of severe adverse effects is now rarely used.

The usual initial dose of phenindione is 200 mg on the first day, 100 mg on the second day, and then usual maintenance doses of 50 to 150 mg daily according to coagulation tests.

Adverse Effects and Treatment

As for Warfarin Sodium, p. 1528.2. However, phenindione and the other indanediones are generally more toxic than warfarin with hypersensitivity reactions involving many organs and sometimes resulting in death. Some of the reactions include rashes and exfoliative dermatitis, pyrexia, diarrhoea, vomiting, sore throat, liver and kidney damage, myocarditis, agranulocytosis, leucopenia, eosinophilia, and a leukaemoid syndrome.

Phenindione may discolour the urine pink or orange and this is independent of any haematuria.

Effects on the gastrointestinal tract. There have been cases of paralytic ileus, one fatal, associated with phenindione.[1,2]

1. Menon IS. Phenindione and paralytic ileus. *Lancet* 1966; i: 1421–2.
2. Nash AG. Phenindione and paralytic ileus. *Lancet* 1966; ii: 51–2.

Precautions

As for Warfarin Sodium, p. 1529.2.

Phenindione is not recommended in pregnancy.

Breast feeding. Phenindione is distributed into breast milk, with reported concentrations[1] of 1 to 5 micrograms/mL after a single dose of 50 or 75 mg. A woman given phenindione 50 mg each morning and 50 and 25 mg on alternate nights breast fed her infant son,[2] who required a herniotomy at 5 weeks. After surgery he had an enormous scrotal haematoma with oozing from the wound and was found to have extended prothrombin and partial thromboplastin times. Last available guidance from the American Academy of Pediatrics therefore considered[3] that phenindione should be given with caution to breast-feeding mothers.

1. Goguel M, *et al.* Thérapeutique anticoagulante et allaitement: etude du passage de la phényl-2-dioxo, 1,3 indane dans le lait maternel. *Rev Fr Gynecol Obstet* 1970; 65: 409–12.
2. Eckstein HB, Jack B. Breast-feeding and anticoagulant therapy. *Lancet* 1970; i: 672–3.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *Ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Interactions

The interactions associated with oral anticoagulants are described in detail under warfarin (p. 1529.3). Specific references to interactions involving phenindione can be found there under the headings for the following drug groups: antibacterials; antifungals; antiplatelets; anxiolytic sedatives; gastrointestinal drugs; lipid regulating drugs; and sex hormones.

Pharmacokinetics

Phenindione is completely absorbed from the gastrointestinal tract, with peak plasma levels attained after 1 to 3 hours and a half-life of 5 to 6 hours. It crosses the placenta and is distributed into breast milk. Metabolites of phenindione excreted in the urine are responsible for any discoloration that may occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Dindevan; *Gr.*: Solu-thrombine; *India*: Dindevan; *Rus.*: Phenylin (Фенилин).

Pharmacopoeial Preparations
BP 2014: Phenindione Tablets.

Phenoxybenzamine Hydrochloride *(BANM, rINNM)*

Fenoksybenzaminy chlorowodorek; Fenoxibenzamina, hidrocloruro de; Hidrocloruro de fenoxibenzamina; Phénoxybenzamine, Chlorhydrate de; Phenoxybenzamini Hydrochloridum; SKF-688A; Феноксибензамина Гидрохлорид.

Benzyl(2-chloroethyl)(1-methyl-2-phenoxyethyl)amine hydrochloride.

$C_{18}H_{22}ClNO,HCl$=340.3

CAS — 59-96-1 (phenoxybenzamine); 63-92-3 (phenoxybenzamine hydrochloride).

ATC — C04AX02.

ATC Vet — QC04AX02.

UNII — X1IEG24OHL.

Pharmacopoeias. In *Br.*, *Chin.*, and *US.*

BP 2014: (Phenoxybenzamine Hydrochloride). A white or almost white, odourless or almost odourless, crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in chloroform.

Uses and Administration

Phenoxybenzamine is a powerful alpha-adrenoceptor blocker (p. 1243.1) with a prolonged duration of action; it binds covalently to alpha receptors in smooth muscle to produce an irreversible ('non-competitive') blockade. A single large dose of phenoxybenzamine can cause alpha-adrenoceptor blockade for 3 days or longer.

Phenoxybenzamine is used in the management of phaeochromocytoma (p. 1278.1). It has also been employed in severe shock (p. 1279.3) and in the treatment of urinary retention (p. 2349.2).

Phenoxybenzamine is used as the hydrochloride. It is given orally or by intravenous infusion as a dilute solution.

In **phaeochromocytoma** it is used to control the hypertension associated with excessive catecholamine release during the pre-operative period and in patients whose tumours are inoperable. A beta blocker may also be given to control tachycardia, but not before alpha blockade has completely suppressed the pressor effects of the phaeochromocytoma. The usual initial oral dose of phenoxybenzamine hydrochloride is 10 mg once or twice daily, increased gradually, according to the patient's response, to a usual dose of 1 to 2 mg/kg daily in 2 divided doses. It may be given intravenously for operative cover in patients with phaeochromocytoma in a daily dose of 1 mg/kg in 200 mL of sodium chloride 0.9% infused over at least 2 hours. A similar intravenous dose in 200 to 500 mL of sodium chloride 0.9% has been given in the management of severe **shock**.

For **urinary retention** due to neurogenic bladder an oral dose of 10 mg twice daily has been given.

Adverse Effects and Treatment

The adverse effects of phenoxybenzamine are mainly due to its alpha-adrenoceptor blocking activity. They include orthostatic hypotension and dizziness, reflex tachycardia, nasal congestion, and miosis. Inhibition of ejaculation may occur. These effects may be minimised by using a low initial dose, and may diminish with continued use, but the hypotensive effect can be exaggerated by exercise, heat, a large meal, or alcohol ingestion. Other adverse effects include dry mouth, decreased sweating, drowsiness, fatigue, and confusion. Gastrointestinal effects are usually slight. When phenoxybenzamine is given intravenously, idiosyncratic profound hypotension can occur within a few minutes of starting the infusion. Convulsions have been reported after rapid intravenous infusion of phenoxybenzamine.

Severe hypotension may occur in overdose and treatment includes support of the circulation by postural measures and parenteral fluid volume replacement. Sympathomimetics are considered to be of little value, and adrenaline is contra-indicated since it also stimulates beta receptors causing increased hypotension and tachycardia. Sources differ as to the value of noradrenaline in overcoming alpha-receptor blockade.

Phenoxybenzamine has been shown to be mutagenic *in vitro* tests and carcinogenic in *rodents*. There have been case reports of carcinoma in patients given long-term treatment with phenoxybenzamine for bladder dysfunction; US licensed product information therefore advises against long-term use.

Precautions

Phenoxybenzamine should be given with care to patients with heart failure, ischaemic heart disease, cerebrovascular disease, or renal impairment, and should be avoided if a fall in blood pressure would be dangerous. Phenoxybenzamine may aggravate the symptoms of respiratory infections.

When given intravenously, phenoxybenzamine hydrochloride should always be diluted and given by infusion. Intravenous fluids must always be given beforehand to ensure an adequate circulating blood volume and to prevent a precipitous fall in blood pressure. Care should be taken to avoid extravasation. Contamination of the skin should also be avoided since contact sensitisation may occur.

Interactions

Since phenoxybenzamine only blocks alpha receptors, leaving the beta receptors unopposed, use with drugs such as adrenaline that also stimulate beta receptors may enhance the cardiac-accelerating and hypotensive action of phenoxybenzamine.

Pharmacokinetics

Phenoxybenzamine is incompletely and variably absorbed from the gastrointestinal tract. After oral dosage the onset of action is gradual over several hours; the maximum effect is attained in about 1 hour after an intravenous dose. The duration of action is usually 3 or 4 days and is thought to depend on the rate of synthesis of new alpha receptors after irreversible covalent bonding to existing alpha receptors by a reactive intermediate of phenoxybenzamine. The plasma half-life after intravenous dosage is about 24 hours. Phenoxybenzamine is metabolised in the liver and excreted in the urine and bile, but small amounts remain in the body for several days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Dibenyline†; *Austria*: Dibenzyran; *Ger.*: Dibenzyran; *Gr.*: Dibenyline; Dibenzyran; *Hong Kong*: Dibeline†; Dibenyline; *India*: Biophenox; Fenoben; Fenoxene; *Israel*: Dibenyline; *NZ*: Dibenyline; *S.Afr.*: Dibenyline†; *UK*: Dibenyline; *USA*: Dibenzyline.

Pharmacopoeial Preparations
BP 2014: Phenoxybenzamine Capsules;
USP 36: Phenoxybenzamine Hydrochloride Capsules.

Phenprocoumon *(BAN, USAN, rINN)*

Femprocumona; Fenprocomón; Fenprocumon; Fenprokumon; Fenprokumoni; Phenprocoumone; Phenprocoumonum; Phenylpropylhydroxycoumarin; Фенпрокумон.

4-Hydroxy-3-(1-phenylpropyl)coumarin.

$C_{18}H_{16}O_3$=280.3

CAS — 435-97-2.

ATC — B01AA04.

ATC Vet — QB01AA04.

UNII — Q08SIO485D.

Uses and Administration

Phenprocoumon is an oral coumarin anticoagulant with actions similar to those of warfarin (p. 1527.2). It is used in the management of thromboembolic disorders (p. 1273.2). Initial doses are up to 9 mg on the first day followed by 6 mg on the second day. Maintenance doses are usually from 1.5 to 6 mg daily, depending on the response.

Adverse Effects, Treatment, and Precautions

As for Warfarin Sodium, p. 1528.2.

Effects on the liver. A woman who had twice previously developed jaundice while taking phenprocoumon developed jaundice and parenchymal liver damage when, after some years, phenprocoumon was again given.[1] Other cases of phenprocoumon-associated liver damage have been reported.[2-4]

1. den Boer W, Loeliger EA. Phenprocoumon-induced jaundice. *Lancet* 1976; i: 912.
2. Slagboom G, Loeliger EA. Coumarin-associated hepatitis: report of two cases. *Arch Intern Med* 1980; 140: 1028–9.
3. Cordes A, *et al.* Phenprocoumon-induziertes Leberversagen. *Dtsch Med Wochenschr* 2003; 128: 1884–6.
4. Bulang T, *et al.* Akutes Leberversagen durch Phenprocoumon–drei Fallberichte. *Z Gastroenterol* 2004; 42: 1055–8.

Interactions

The interactions associated with oral anticoagulants are discussed in detail under warfarin (p. 1529.3). Specific references to interactions involving phenprocoumon can be found there under the headings for the following drug groups: analgesics; antiarrhythmics; antidepressants; antidiabetics; antigout drugs; antineoplastics; gastrointestinal drugs; lipid regulating drugs; and sex hormones.

Pharmacokinetics

Phenprocoumon is readily absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Metabolism is mediated partly by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism. The half-life is around 6 days. It is excreted in the urine and faeces as conjugated hydroxy metabolites and parent compound. Phenprocoumon is given as a racemic mixture; the *S*-isomer is more potent. The stereo-isomers have different pharmacokinetics.

References.

1. Husted S, Andreasen F. Individual variation in the response to phenprocoumon. *Eur J Clin Pharmacol* 1977; 11: 351–8.
2. Toon S, *et al.* Metabolic fate of phenprocoumon in humans. *J Pharm Sci* 1985; 74: 1037–40.
3. Ufer M. Comparative pharmacokinetics of vitamin K antagonists: warfarin, phenprocoumon and acenocoumarol. *Clin Pharmacokinet* 2005; 44: 1227–46.
4. Werner D, *et al.* Pharmacogenetic characteristics of patients with complicated phenprocoumon dosing. *Eur J Clin Pharmacol* 2009; 65: 783–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Marcoumar; *Belg.*: Marcoumar; *Braz.*: Marcoumar; *Denm.*: Marcoumar; *Ger.*: Falithrom†; Marcumar; marcuphen; Phenpro; Phenprogamma; *Neth.*: Marcoumar; *Switz.*: Marcoumar.

Phentolamine Mesilate *(BANM, rINNM)*

Fentolamiinimesilaatti; Fentolamin mesylát; Fentolamina, mesilato de; Fentolaminmesilat; Fentolamin-mezilát; Fento-

lamino mesilatas; Mesilato de fentolamina; Phentolamine Mésilate de; Phentolamine Mesylate; Phentolamine Methanesulphonate; Phentolamini Mesilas; Phentolaminmesilat; Фентоламина Мезилат.

3-[*N*-(2-Imidazolin-2-ylmethyl)-*p*-toluidino]phenol methanesulphonate.

$C_{17}H_{19}N_3O,CH_4SO_3$=377.5

CAS — 50-60-2 (phentolamine); 73-05-2 (phentolamine hydrochloride); 65-28-1 (phentolamine mesilate).

ATC — C04AB01; V03AB36.

ATC Vet — QC04AB01; QG04BE05.

UNII — Y7543E5K9T.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Phentolamine Mesilate). A white or almost white, slightly hygroscopic, crystalline powder. Freely soluble in water and in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Phentolamine Mesylate). A white or off-white, odourless crystalline powder. Soluble 1 in 1 of water, 1 in 4 of alcohol, and 1 in 700 of chloroform. Its solutions in water have a pH of about 5 and slowly deteriorate. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Phentolamine is an alpha-adrenoceptor blocker (p. 1243.1) which also has a direct action on vascular smooth muscle. It produces vasodilatation, an increase in cardiac output, and has a positive inotropic effect, but is reported to have little effect on the blood pressure of patients with essential hypertension. The alpha-receptor blocking action is reversible ('competitive') and non-selective, and the duration of effect is relatively short.

Phentolamine is given in the management of hypertensive crises, particularly those due to excessive catecholamine release associated with surgery for phaeochromocytoma (p. 1278.1). It has been used for the differential diagnosis of phaeochromocytoma, but has largely been superseded by estimations of catecholamines in blood and urine.

Phentolamine is also used to prevent or treat dermal necrosis and sloughing associated with the intravenous infusion or extravasation of noradrenaline, and to reverse soft-tissue anaesthesia associated with intra-oral submucosal injection of local anaesthetic preparations containing vasoconstrictors (below). It has been used in the treatment of erectile dysfunction (p. 2348.2).

Phentolamine is given by injection as the mesilate.

In patients with hypertensive crises during surgery for **phaeochromocytoma**, a dose of 2 to 5 mg of phentolamine mesilate is given intravenously and repeated if necessary; blood pressure should be monitored. The intramuscular route may be used pre-operatively and for diagnostic procedures.

For prevention of **dermal necrosis** during intravenous infusion of noradrenaline, 10 mg of phentolamine mesilate is added to each litre of solution containing noradrenaline. For treatment of extravasation of noradrenaline, 5 to 10 mg of phentolamine mesilate in 10 mL of sodium chloride 0.9% is injected into the affected area.

For **reversal of soft-tissue anaesthesia** in the mouth, phentolamine mesilate is given using the same location and technique as for the local anaesthetic. The dose depends on the amount of local anaesthetic used and ranges from 200 to 800 micrograms.

For **erectile dysfunction**, phentolamine mesilate is given by injection into the corpora cavernosa of the penis. It is usually given with papaverine, but a preparation containing phentolamine with aviptadil (vasoactive intestinal peptide) may also be used. Phentolamine has also been tried orally.

For doses in children, see below.

Administration in children. In the treatment of hypertensive crises during surgery for **phaeochromocytoma**, children may be given phentolamine mesilate intravenously (or intramuscularly when used pre-operatively) in a dose of 1 mg. Alternatively, doses of 50 to 100 micrograms/kg or 3 mg/m^2 have been suggested. The dose may be repeated if necessary.

For **reversal of soft-tissue anaesthesia** in the mouth, phentolamine mesilate is given to children aged 6 years and over and weighing 15 to 30 kg in a dose of up to 200 micrograms. The dose depends on the amount of local anaesthetic used, and should be given using the same location and technique as for the local anaesthetic.

Hyperhidrosis. Hyperhidrosis (p. 1685.1) is usually treated with topical aluminium salts or topical antimuscarinics, but intradermal botulinum A toxin or procedures such as endoscopic transthoracic sympathectomy may be needed in severe cases. Phentolamine has been tried as an alternative. Improvement in symptoms has been reported[1] in 2 patients with generalised hyperhidrosis given 100 mg of phentolamine mesilate by intravenous infusion over 6 hours. Improvement lasted for 2 to 3 months and the infusion was repeated, in 1 patient several times.

1. McCleane G. The use of intravenous phentolamine mesilate in the treatment of hyperhidrosis. *Br J Dermatol* 2002; 146: 533–4.

Pain. Sympathetic nerve block (p. 1981.3) is used in some pain syndromes and usually involves injection of local anaesthetics. Phentolamine has been used as an alternative and beneficial results have been reported in pain associated with chronic pancreatitis,[1] pancreatic and other visceral cancers,[2,3] and chronic gastroparesis.[4]

Complete resolution of pain has also been reported in 2 patients with cutaneous leiomyomata given oral doxazosin.[5]

1. McCleane GJ. Phentolamine abolishes the pain of chronic pancreatitis. *Br J Hosp Med* 1996; 55: 521.
2. McCleane GJ. Intravenous phentolamine mesylate alleviates the pain of pancreatic carcinoma. *Pain* 1997; 73: 263–4.
3. Yasukawa M, *et al.* Intravenous phentolamine infusion alleviates the pain of abdominal visceral cancer, including pancreatic carcinoma. *J Anesth* 2007; 21: 420–3.
4. Phillips WJ, *et al.* Relief of acute pain in chronic idiopathic gastroparesis with intravenous phentolamine. *Ann Pharmacother* 2006; 40: 2032–6.
5. Batchelor RJ, *et al.* Successful treatment of pain in two patients with cutaneous leiomyomata with the oral alpha-1 adrenoceptor antagonist, doxazosin. *Br J Dermatol* 2004; 150: 775–6.

Reversal of local anaesthesia. During dental procedures, local anaesthetics are often given with vasoconstrictor sympathomimetics such as adrenaline or noradrenaline to improve the depth and duration of anaesthesia (see Infiltration Anaesthesia, p. 1981.2), but prolonged oral anaesthesia may be a problem after the procedure. Phentolamine, injected intra-orally, reverses the effects of the vasoconstrictor and accelerates systemic absorption of the local anaesthetic,[1] and has been shown to reduce the time to return of normal sensation.[2] The procedure also appears to be safe and effective in children between 4 and 11 years of age.[3]

1. Moore PA, *et al.* Pharmacokinetics of lidocaine with epinephrine following local anesthesia reversal with phentolamine mesylate. *Anesth Prog* 2008; 55: 40–8.
2. Laviola M, *et al.* Randomized study of phentolamine mesylate for reversal of local anesthesia. *J Dent Res* 2008; 87: 635–9.
3. Tavares M, *et al.* Soft Tissue Anesthesia Reversal Group. Reversal of soft-tissue local anesthesia with phentolamine mesylate in pediatric patients. *J Am Dent Assoc* 2008; 139: 1095–1104. Correction. *ibid.*: 1312.

Adverse Effects and Treatment

The adverse effects of phentolamine are primarily due to its alpha-adrenoceptor blocking activity and include orthostatic hypotension and tachycardia. Myocardial infarction and cerebrovascular spasm or occlusion have been reported occasionally, usually in association with marked hypotension; flushing, sweating, and feelings of apprehension may accompany hypotensive episodes. Anginal pain and arrhythmias have been reported rarely. Nausea, vomiting, and diarrhoea may also occur. Other adverse effects include weakness, dizziness, flushing, and nasal congestion. Hypoglycaemia has been reported after overdosage.

Severe hypotension may occur in overdosage although phentolamine has a short duration of action. Treatment may include support of the circulation by postural measures and parenteral fluid volume replacement. Noradrenaline may be given cautiously to overcome alpha-adrenoceptor blockade. Adrenaline is contra-indicated since it also stimulates beta receptors causing increased hypotension and tachycardia.

When injected into the corpus cavernosum of the penis phentolamine has been associated with local pain; induration and fibrosis may occur with repeated use. Priapism has occurred.

Precautions

Phentolamine should not generally be given to patients with angina pectoris or other evidence of ischaemic heart disease. Care should be taken in patients with peptic ulcer disease, which may be exacerbated.

Interactions

Since phentolamine only blocks alpha receptors, use with drugs such as adrenaline may lead to severe hypotension and tachycardia due to unopposed beta-adrenoceptor stimulation.

Pharmacokinetics

After intravenous dosage, the half-life of phentolamine has been reported to be 19 minutes. It is extensively metabolised and about 13% of an intravenous dose is excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Regitina; *Austral.*: Regitine; *Belg.*: Regitine†; *Braz.*: Herivyl; Vigamed; *Canad.*: Rogitine; *China*: AnTing (安赋); He Li Ke (赫立可); He Xin (和欣); Mei Zhen (美珍); Pu Ding Yang (普丁阳); QiWei (启惟); Regitine (利其丁); Zhi Li (至力); *Gr.*: Regitine; *Hong Kong*: Regitine†; *Hung.*: Regitine†; *India*: Fentanor; *Israel*: Regitine; *Neth.*: Regitine; *NZ*: Invicorp; Regitine; *Singapore*: Rogitine; *Switz.*: Regitine; *UK*: Rogitine†; *USA*: OraVerse.

Multi-ingredient Preparations. *Austria*: Androskat; *Denm.*: Invicorp; *Neth.*: Androskat; *USA*: Tri-Mix.

Pharmacopoeial Preparations
BP 2014: Phentolamine Injection;
USP 36: Phentolamine Mesylate for Injection.

Pholedrine Sulfate *(BANM, rINNM)* ⊗

Foledrina, sulfato de; Isodrine Sulphate; Pholédrine, Sulfate de; Pholedrine Sulphate; Pholedrini Sulfas; Sulfato de foledrina; Sympropaminum (pholedrine); Фоледрина Сульфат.

4-(2-Methylaminopropyl)phenol sulfate.

$(C_{10}H_{15}NO)_2,H_2SO_4$=428.5

CAS — 370-14-9 (pholedrine); 6114-26-7 (pholedrine sulfate).

UNII — WB6LNL73BR.

Profile

Pholedrine is a sympathomimetic (p. 1507.3) used in the treatment of hypotensive states. It has been given orally as the sulfate, often in combination with other drugs, and has also been included in preparations promoted for vascular disorders. Pholedrine eye drops have been used as an alternative to hydroxyamfetamine (p. 2529.3) in the diagnosis of Horner's syndrome.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Switz.*: Ortho-Maren retard†.

Picotamide *(BANM)*

G-137; Picotamida; Picotamide, monohydrate de; Picotamidmonohidrát; Picotamidum Monohydricum; Pikotamid monohydrát; Pikotamidimonohydraatti; Pikotamidmonohydrat; Pikotamido monohidratas.

4-Methoxy-*N*,*N*′-bis(3-pyridinylmethyl)-1,3-benzenedicarboxamide monohydrate.

$C_{21}H_{20}N_4O_3,H_2O$=394.4

CAS — 32828-81-2 (anhydrous picotamide); 80530-63-8 (picotamide monohydrate).

ATC — B01AC03.

ATC Vet — QB01AC03.

UNII — 654G2VCI4Q.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Picotamide Monohydrate). A white or almost white, polymorphic, crystalline powder. Slightly soluble in water; soluble in dehydrated alcohol and in dichloromethane; dissolves in dilute mineral acids.

Profile

Picotamide is a thromboxane synthase inhibitor and thromboxane receptor antagonist with antiplatelet activity. It is given orally in thromboembolic disorders (p. 1273.2) in initial doses of 900 to 1200 mg daily in divided doses, reducing to a maintenance dose of 300 to 600 mg daily.

Reviews.

1. Celestini A, Violi F. A review of picotamide in the reduction of cardiovascular events in diabetic patients. *Vasc Health Risk Manag* 2007; 3: 93–8.

ACE inhibitor-induced cough. Cough is a recognised adverse effect of ACE inhibitors (see p. 1285.3). Picotamide led to the disappearance of cough in 8 of 9 patients taking enalapril for hypertension,[1] suggesting that thromboxanes were involved in the aetiology of ACE inhibitor-induced cough.

1. Malini PL, *et al.* Thromboxane antagonism and cough induced by angiotensin-converting-enzyme inhibitor. *Lancet* 1997; 350: 15–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Plactidil.

Pilsicainide Hydrochloride *(rINNM)*

DU-6552; Hidrocloruro de pilsicainida; Pilsicainida; hidrocloruro de; Pilsicainide, Chlorhydrate de; Pilsicainidi Hydrochloridum; Pilzicainide Hydrochloride; SUN-1165; Пильсикаинида Гидрохлорид.

Tetrahydro-1*H*-pyrrolizine-7a(5*H*)-aceto-2',6'-xylidide hydrochloride.

$C_{17}H_{24}N_2O.HCl$=308.8

CAS — 88069-67-4 (pilsicainide); 88069-49-2 (pilsicainide hydrochloride).

UNII — 03C8I9296V.

Profile

Pilsicainide hydrochloride is an antiarrhythmic with class Ic activity (p. 1243.1). It has been given orally in typical doses of 150 mg daily in three divided doses, or intravenously in a dose of 0.75 to 1 mg/kg, in the treatment of tachyarrhythmias.

References.

1. Takabatake T, *et al.* Pharmacokinetics of SUN 1165, a new antiarrhythmic agent, in renal dysfunction. *Eur J Clin Pharmacol* 1991; 40: 411–14.
2. Okishige K, *et al.* Pilsicainide for conversion and maintenance of sinus rhythm in chronic atrial fibrillation: a placebo-controlled, multicenter study. *Am Heart J* 2000; 140: 437–44.
3. Kumagai K, *et al.* Single oral administration of pilsicainide versus infusion of disopyramide for termination of paroxysmal atrial fibrillation: a multicenter trial. *Pacing Clin Electrophysiol* 2000; 23: 1880–2.
4. Ogawa R, *et al.* Population pharmacokinetic and pharmacodynamic analysis of a class IC antiarrhythmic, pilsicainide, in patients with cardiac arrhythmias. *J Clin Pharmacol* 2006; 46: 59–68.
5. Kumagai K, *et al.* Pilsicainide for atrial fibrillation. *Drugs* 2006; 66: 2067–73.
6. Plosker GL. Pilsicainide. *Drugs* 2010; 70: 455–67.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Alisrythm; Pilsinic; Rizmsat; Rizumcote; Sunrythm; Tatsupilljin.

Pimobendan *(BAN, USAN, rINN)*

Pimobendaani; Pimobendán; Pimobendanas; Pimobendane; Pimobendanum; UDCG-115; Пимобендан.

4,5-Dihydro-6-[2-(*p*-methoxyphenyl)-5-benzimidazolyl]-5-methyl-3(2*H*)-pyridazinone.

$C_{19}H_{18}N_4O_2$=334.4

CAS — 74150-27-9; 118428-36-7.

ATC Vet — QC01CE90.

UNII — 34AP3BBP9T.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Pimobendan). A white or slightly yellowish, hygroscopic powder. Practically insoluble in water; slightly soluble in acetone and in methyl alcohol; freely soluble in dimethylformamide. Store in airtight containers.

Profile

Pimobendan is a phosphodiesterase type 3 inhibitor with calcium-sensitising properties. It has positive inotropic and vasodilator activity and is used as an adjunct to standard therapy in the management of heart failure (p. 1262.3). It is given in a usual oral dose of 1.25 to 2.5 mg twice daily after food, adjusted according to age and response.

Studies with other inotropic phosphodiesterase inhibitors have shown that their prolonged oral use can lead to an increased mortality rate.

Pimobendan is also used in veterinary medicine.

References.

1. Przechera M, *et al.* Pharmacokinetic profile and tolerability of pimobendan in patients with terminal renal insufficiency. *Eur J Clin Pharmacol* 1991; 40: 107–11.
2. The Pimobendan in Congestive Heart Failure (PICO) Investigators. Effect of pimobendan on exercise capacity in patients with heart failure: main results from the Pimobendan in Congestive Heart Failure (PICO) trial. *Heart* 1996; 76: 223–31.
3. Yoshikawa T, *et al.* Effectiveness of carvedilol alone versus carvedilol + pimobendan for severe congestive heart failure. *Am J Cardiol* 2000; 85: 1495–7.
4. The EPOCH Study Group. Effects of pimobendan on adverse cardiac events and physical activities in patients with mild to moderate chronic heart failure: the effects of pimobendan on chronic heart failure study (EPOCH study). *Circ J* 2002; 66: 149–57.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Acardi.

Pindolol *(BAN, USAN, rINN)* ⊗

LB-46; Pindololi; Pindololis; Pindololum; Prindolol; Prinodolol; Пиндолол.

1-(Indol-4-yloxy)-3-isopropylaminopropan-2-ol.

$C_{14}H_{20}N_2O_2$=248.3

CAS — 13523-86-9.

ATC — C07AA03.

ATC Vet — QC07AA03.

UNII — BJ4HF6IU1D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Pindolol). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in methyl alcohol; dissolves in dilute mineral acids. Protect from light.

USP 36: (Pindolol). A white to off-white, crystalline powder with a faint odour. Practically insoluble in water; very slightly soluble in chloroform; slightly soluble in methyl alcohol. Protect from light.

Uses and Administration

Pindolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to have intrinsic sympathomimetic activity but little membrane-stabilising activity.

Pindolol is used in the management of hypertension (p. 1251.1), angina pectoris (p. 1254.3), cardiac arrhythmias (p. 1266.1), and other cardiovascular disorders. It is also used in glaucoma (p. 1999.1). For investigation of its value in psychiatric disorders, see below.

In **hypertension** pindolol is usually given initially in an oral dosage of 5 mg two or three times daily, or 15 mg once daily, subsequently increased according to response. The usual maintenance dose is 15 to 30 mg once daily, but up to 45 mg daily, as a single dose or in divided doses, may be required. Additional benefit is rarely obtained from doses higher than 45 mg daily, although doses up to 60 mg daily have been given.

The usual oral dose for **angina pectoris** is 2.5 to 5 mg up to three times daily; however, doses of up to 40 mg daily have been used.

Eye drops containing pindolol 1% are used in the management of **glaucoma**.

Pindolol has also been given intravenously in the management of cardiac arrhythmias.

Psychiatric disorders. In addition to its beta-blocking properties, pindolol is also a partial agonist at serotonin 5-HT_1-receptors and has been used to augment the effects of SSRIs in patients with depression (p. 398.1).[1,2] Results have been conflicting,[3] but a meta-analysis[4] found that the time to response was shorter in patients given pindolol with an SSRI, although there was no effect on long-term outcomes. Small studies have also reported positive effects with pindolol augmentation of SSRIs in obsessive-compulsive disorder[5] (p. 1028.2) and in panic disorder[6] (p. 1029.1), although no effect was seen in social phobia.[7] Another study[8] found that pindolol augmentation of antipsychotic therapy reduced aggression in patients with schizophrenia (p. 1031.3).

1. Portella MJ, *et al.* Pindolol augmentation enhances response outcomes in first depressive episodes. *Eur Neuropsychopharmacol* 2009; 19: 516–19.
2. Whale R, *et al.* Pindolol augmentation of serotonin reuptake inhibitors for the treatment of depressive disorder: a systematic review. *J Psychopharmacol* 2010; 24: 513–20.
3. Segrave R, Nathan PJ. Pindolol augmentation of selective serotonin reuptake inhibitors: accounting for the variability of results of placebo-controlled double-blind studies in patients with major depression. *Hum Psychopharmacol* 2005; 20: 163–74.
4. Ballesteros J, Callado LF. Effectiveness of pindolol plus serotonin uptake inhibitors in depression: a meta-analysis of early and late outcomes from randomised controlled trials. *J Affect Disord* 2004; 79: 137–47.
5. Dannon PN, *et al.* Pindolol augmentation in treatment-resistant obsessive compulsive disorder: a double-blind placebo controlled trial. *Eur Neuropsychopharmacol* 2000; 10: 165–9.
6. Hirschmann S, *et al.* Pindolol augmentation in patients with treatment-resistant panic disorder: a double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2000; 20: 556–9.
7. Stein MB, *et al.* Pindolol potentiation of paroxetine for generalized social phobia: a double-blind, placebo-controlled, crossover study. *Am J Psychiatry* 2001; 158: 1725–7.
8. Caspi N, *et al.* Pindolol augmentation in aggressive schizophrenic patients: a double-blind crossover randomized study. *Int Clin Psychopharmacol* 2001; 16: 111–5.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Effects on lipid metabolism. Beta blockers can affect plasma-lipid concentrations, although this may be less of a problem with those that have intrinsic sympathomimetic activity. For reference to the lack of effect of pindolol, see p. 1320.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies piridolol as probably not porphyrinogenic it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Tremor. Fine tremor in the extremities of 5 patients during pindolol therapy was considered to have been due to its partial agonist activity.[1]

1. Hod H, *et al.* Pindolol-induced tremor. *Postgrad Med J* 1980; 56: 346–7.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Pindolol is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 2 hours after an oral dose. It has a bioavailability of about 87%. About 40 to 60% is reported to be bound to plasma proteins. It is moderately lipid-soluble. Pindolol crosses the placenta and is distributed into breast milk. It is only partially metabolised in the liver and is excreted in the urine both unchanged and in the form of metabolites. A plasma elimination half-life of 3 to 4 hours has been reported in healthy adults. The half-life may be prolonged in elderly hypertensive patients and in patients with renal or hepatic impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Barbloc; Visken; *Austria*: Visken; *Belg.*: Visken; *Braz.*: Visken; *Canad.*: Apo-Pindol; Novo-Pindol†; Nu-Pindol; Visken; *Denm.*: Hexapindol; Visken; *Fin.*: Pinloc; Visken; *Fr.*: Visken; *Ger.*: Glauco-Stullnt†; Visken†; *Gr.*: Dranolis; Treparasen; Visken; *Hong Kong*: Barbloc†; Visken; *Hung.*: Visken; *India*: Visken; *Irl.*: Visken†; *Israel*: Pinden†; *Ital.*: Visken; *Mex.*: Visken; *Neth.*: Viskeen; *NZ*: Pindol†; *Philipp.*: Pyndale; Visken; *Pol.*: Visken; *Rus.*: Visken (Вискен); *Swed.*: Visken; *Switz.*: Viskene; *Turk.*: Visken; *UK*: Visken; *USA*: Visken.

Multi-ingredient Preparations. *Belg.*: Viskaldix; *Braz.*: Viskaldix; *Canad.*: Viskazide; *Chile*: Viskaldix; *Fr.*: Viskaldix; *Ger.*: Viskaldix†; *Gr.*: Viskaldix; *Hung.*: Viskaldix; *Irl.*: Viskaldix†; *Malaysia*: Viskaldix; *Neth.*: Viskaldix†; *Philipp.*: Viskaldix; *Rus.*: Viskaldix (Вискалдикс); *Switz.*: Viskaldix; *UK*: Viskaldix.

Pharmacopoeial Preparations
BP 2014: Pindolol Tablets;
USP 36: Pindolol Tablets.

Piretanide *(BAN, USAN, rINN)* ⊗

Hoe-118; Piretanid; Piretanida; Piretanidas; Pirétanide; Piretanidi; Piretanidum; S73-4118; Пиретанид.

4-Phenoxy-3-(pyrrolidin-1-yl)-5-sulphamoylbenzoic acid.

$C_{17}H_{18}N_2O_5S$=362.5

CAS — 55837-27-9.

ATC — C03CA03.

ATC Vet — QC03CA03.

UNII — DQ6KK6GV93.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Piretanide). A yellowish-white to yellowish powder. It exhibits polymorphism. Very slightly soluble in water; sparingly soluble in dehydrated alcohol. Protect from light.

Uses and Administration

Piretanide is a loop diuretic with actions and uses similar to those of furosemide (p. 1387.1). It is used for oedema, including that associated with heart failure (p. 1262.3), in oral doses of 3 to 6 mg daily. In the treatment of hypertension (p. 1251.1) it is given in a usual oral dose of 6 to 12 mg daily. The sodium salt is given by injection.

References.

1. Clissold SP, Brogden RN. Piretanide: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1985; 29: 489–530.

Adverse Effects

As for Furosemide, p. 1388.3. Muscle cramps have been reported after high doses of piretanide.

Precautions

Piretanide's precautions and contra-indications, which are dependent on its effects on fluid and electrolyte balance, are similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1406.1). Patients with impaired micturition or prostatic hyperplasia may develop retention of urine with piretanide.

Interactions

As for Furosemide, p. 1389.3.

Pharmacokinetics

Piretanide has been reported to be almost completely absorbed after oral doses. It is extensively bound to plasma proteins, and is reported to have a half-life of about 1 hour after an oral dose.

References.
1. Beermann B, Grind M. Clinical pharmacokinetics of some newer diuretics. *Clin Pharmacokinet* 1987; 13: 254–66.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Arelix; *Fr.*: Eurelix; *Ger.*: Arelix†; *Gr.*: Timonor; *Irl.*: Arelix; *Ital.*: Tauliz; *Mex.*: Diural; *S. Afr.*: Arelix; *Spain*: Perbilen; *Switz.*: Arelix.

Multi-ingredient Preparations. *Ger.*: Arelix ACE†; Betarelix; Ramitanid†; *Irl.*: Trialix; *Ital.*: Prilace; *Switz.*: Trialix.

Pirmenol Hydrochloride *(USAN, rINNM)*

CI-845; CL-845; Hidrocloruro de pirmenol; Pirmenol, Chlorhydrate de; Pirmenol, hidrocloruro de; Pirmenoli Hydrochloridum; Пирменола Гидрохлорид.

(±)-*cis*-2,6-Dimethyl-α-phenyl-α-2-pyridyl-1-piperidinebutanol hydrochloride.

$C_{22}H_{30}N_2O,HCl$=375.0

CAS — 68252-19-7 (pirmenol); 61477-94-9 (pirmenol hydrochloride).

UNII — JA79OMG4QT.

Profile

Pirmenol hydrochloride is an antiarrhythmic with class Ia activity (p. 1243.1).

References.
1. Hampton EM, *et al.* Initial and long-term outpatient experience with pirmenol for control of ventricular arrhythmias. *Eur J Clin Pharmacol* 1986; 31: 15–22.
2. Stringer KA, *et al.* Enhanced pirmenol elimination by rifampin. *J Clin Pharmacol* 1988; 28: 1094–7.
3. Janiczek N, *et al.* Pharmacokinetics of pirmenol enantiomers and pharmacodynamics of pirmenol racemate in patients with premature ventricular contractions. *J Clin Pharmacol* 1997; 37: 502–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Pimenol.

Pitavastatin *(rINN)*

Itavastatin; Nisvastatin; NK-104; Pitavastatina; Pitavastatine; Pitavastatinum; Питавастатин.

(3*R*,5*S*,6*E*)-7-[2-Cyclopropyl-4-(*p*-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoic acid.

$C_{25}H_{24}FNO_4$=421.5

CAS — 147511-69-1.

ATC — C10AA08.

ATC Vet — QC10AA08.

UNII — M5681Q5F9P.

Pitavastatin Calcium *(rINNM)*

Calcii Pitavastatinum; Itavastatin Calcium; Nisvastatin Calcium; NKS-104; Pitavastatina calcica; Pitavastatine Calcique; Кальций Питавастатин.

$(C_{25}H_{24}FNO_4)_2Ca$=883.0

CAS — 147526-32-7.

UNII — IYD54XEG3W.

Uses and Administration

Pitavastatin, a hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with similar properties to simvastatin (p. 1489.2). It is used as the calcium salt in the treatment of hyperlipidaemias in an oral dose equivalent to 1 to 4 mg of pitavastatin once daily. If given with erythromycin or rifampicin, both of which increase pitavastatin exposure, a maximum dose of pitavastatin of 1 mg or 2 mg respectively should not be exceeded.

Reduced doses should be given in renal impairment (see below).

References.
1. Hayashi T, *et al.* Pitavastatin: efficacy and safety in intensive lipid lowering. *Expert Opin Pharmacother* 2007; 8: 2315–27.
2. Koshiyama H, *et al.* Effects of pitavastatin on lipid profiles and high-sensitivity CRP in Japanese subjects with hypercholesterolemia: Kansai Investigation of Statin for Hyperlipidemic Intervention in Metabolism and Endocrinology (KISHIMEN) Investigators. *J Atheroscler Thromb* 2008; 15: 345–50.
3. Teramoto T, *et al.* Effects of pitavastatin (LIVALO Tablet) on high density lipoprotein cholesterol (HDL-C) in hypercholesterolemia. *J Atheroscler Thromb* 2009; 16: 654–61.
4. Wensel TM, *et al.* Pitavastatin: a new HMG-CoA reductase inhibitor. *Ann Pharmacother* 2010; 44: 507–14.
5. Sansanayudh N, *et al.* Comparative efficacy and safety of low-dose pitavastatin versus atorvastatin in patients with hypercholesterolemia. *Ann Pharmacother* 2010; 44: 415–23.
6. Teramoto T, *et al.* New evidence on pitavastatin: efficacy and safety in clinical studies. *Expert Opin Pharmacother* 2010; 11: 817–28.

Administration in renal impairment. Patients with moderate renal impairment (creatinine clearance [CC] 30 to 60 mL/min) and those on haemodialysis may be given pitavastatin in an initial oral dose of 1 mg once daily, and a maximum dose of 2 mg once daily. Pitavastatin should not be used in those with severe renal impairment (CC less than 30 mL/min) unless on haemodialysis.

Adverse Effects and Precautions

As for Simvastatin, p. 1492.1 and p. 1494.1, respectively.

Interactions

The interactions of statins with other drugs are described under simvastatin (p. 1494.2). Pitavastatin is only marginally metabolised by the cytochrome P450 isoenzyme CYP2C9 and may not have the same interactions with CYP3A4 inhibitors as simvastatin. However, ciclosporin significantly increases pitavastatin exposure and the combination should be avoided. On theoretical grounds, use with ritonavir-boosted lopinavir is also contra-indicated. Rifampicin and erythromycin also increase pitavastatin exposure; if such combinations must be used, lower doses of pitavastatin should be used (see Uses and Administration, above).

Pharmacokinetics

Peak plasma concentrations of pitavastatin are reached about 1 hour after an oral dose, with an absolute bioavailability of about 51%. Pitavastatin is more than 99% bound to plasma proteins. It is marginally metabolised by the cytochrome P450 isoenzyme CYP2C9 and to a lesser extent by CYP2C8, but the main route of metabolism is by glucuronidation to a lactone metabolite. The majority of a dose is excreted in faeces with only about 15% in urine. The mean plasma elimination half-life of pitavastatin is 12 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Livalo (力清之); *Fr.*: Trolise; *India*: Flovas; *Irl.*: Alipza; Livazo; *Jpn*: Livalo; *Neth.*: Livazo; Vezepra; *Spain*: Alipza; Livazo; *Thai.*: Livalo; *Ukr.*: Livazo (Ливазо); *USA*: Livalo.

Plant Stanols and Sterols

Phytosterols; Станолы и Стерины из Растений.

Phytosterol

Fitosterolis; Fitoszterin; Fytosterol; Fytosteroli; Phytosterin; Phytostérol; Phytosterolum; Фитостерол; Фитостерин.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Phytosterol). A natural mixture of sterols obtained from plants of the genera *Hypoxis*, *Pinus*, and *Picea*. It contains not less than 70% β-sitosterol, calculated with reference to the dried substance. A white or almost white powder. Practically insoluble in water; soluble in tetrahydrofuran; sparingly soluble in ethyl acetate. Store in airtight containers. Protect from light.

Sitostanol

Dihydro-β-sitosterol; Fucostanol; β-Sitostanol; Stigmastanol; Ситостанол.

(3β,5α)-Stigmastan-3-ol.

$C_{29}H_{52}O$=416.7

CAS — 83-45-4.

UNII — C2NJ9WO6O7.

Sitosterol

β-Sitosterin; β-Sitosteriha; β-Sitosterol; Ситостерол; Ситостерин.

(3β)-Stigmast-5-en-3-ol.

$C_{29}H_{50}O$=414.7

CAS — 83-46-5.

UNII — S347WMO6M4.

Profile

Stanols and sterols occur naturally in plants and are chemically related to cholesterol. The term phytosterol is used to describe both unsaturated plant sterols and their saturated (hydrogenated) counterparts, plant stanols (phytostanols). Sitosterol, campesterol, and stigmasterol are the commonest phytosterols; their respective stanols are found in lower amounts naturally, but can be produced by hydrogenation of sterols.

Dietary phytosterols have a cholesterol-lowering action; they reduce cholesterol absorption from the intestine and may also have other mechanisms. Sitosterol has been used as a lipid regulating drug, and both sterol and stanol esters (formed by esterification with unsaturated fatty acids) have been incorporated into margarines and other food products for use in the dietary management of hypercholesterolaemia. Sitosterol, sitostanol, and other phytosterols, are also used in nutritional supplements.

Sitosterol is also used in benign prostatic hyperplasia (p. 2347.1), although its mechanism of action is not clear. It is given orally in usual initial doses of 20 mg three times daily.

There have been reports of bleeding complications associated with supplements containing phytosterols.

References.
1. Wilt T, *et al.* Beta-sitosterols for benign prostatic hyperplasia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 24/06/05).
2. Law M. Plant sterol and stanol margarines and health. *BMJ* 2000; 320: 861–4.
3. Lichtenstein AH, Deckelbaum RJ. Stanol/sterol ester-containing foods and blood cholesterol levels: a statement for healthcare professionals from the Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association. *Circulation* 2001; 103: 1177–9. Also available at: http://circ.ahajournals.org/cgi/reprint/103/8/1177.pdf (accessed 01/06/08)
4. Katan MB, *et al.* Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. *Mayo Clin Proc* 2003; 78: 965–78.
5. Health Canada. Sterol and sterolin-containing products: hematologic adverse reactions. *Can Adverse React News* 2004; 14 (2): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n2-eng.pdf (accessed 19/08/08)
6. Miettinen TA, Gylling H. Plant stanol and sterol esters in prevention of cardiovascular diseases: a review. *Int J Clin Pharmacol Ther* 2006; 44: 247–50.
7. Devaraj S, Jialal I. The role of dietary supplementation with plant sterols and stanols in the prevention of cardiovascular disease. *Nutr Rev* 2006; 64: 348–54.
8. Moruisi KG, *et al.* Phytosterols/stanols lower cholesterol concentrations in familial hypercholesterolemic subjects: a systematic review with meta-analysis. *J Am Coll Nutr* 2006; 25: 41–8.
9. Naruszewicz M, Kozlowska-Wojciechowska M. Plant sterols beyond low-density lipoprotein-cholesterol. *Br J Nutr* 2007; 98: 454–5.
10. Weingärtner O, *et al.* Pflanzliche Sterole als Nahrungsmittelzusätze zur Prävention kardiovaskulärer Erkrankungen. *Dtsch Med Wochenschr* 2008; 133: 1201–4.
11. Weingärtner O, *et al.* Controversial role of plant sterol esters in the management of hypercholesterolaemia. *Eur Heart J* 2009; 30: 404–9.
12. Talati R, *et al.* The comparative efficacy of plant sterols and stanols on serum lipids: a systematic review and meta-analysis. *J Am Diet Assoc* 2010; 110: 719–26.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fitoadapt; Prostacur; *Austria*: Harzol; *Chile*: A-Colest; *Ger.*: Azuprostat†; Harzol; Sitosterin; Triastonal†; *Indon.*: Cholbalance; *Pol.*: Prostalizyna; Prosterol; *Thai.*: Mebo; *UAE*: Mebo.

Multi-ingredient Preparations. *Austral.*: Cholesterol Health; *Chile*: Rebakol; *Fr.*: Acyprost; Bakol; Prostaform; *Hong Kong*: Basikol; Physiogel; *Hung.*: Shilajit; *Ital.*: Sametrix; *Malaysia*: O'Yes; *Philipp.*: Trilipid; *Rus.*: Herbion Urtica (Гербион Уртика); *Singapore*: Basikol; Bios Life; Centrum Cardio; ES-TriGUARD; *UK*: Kolestop; Lestrin; *Ukr.*: Vitrum Cardio (Вітрум Кардіо); *USA*: Animi-3 with Vitamin D; Better Cholesterol; Cholesterol Support; MacuTrition; Prostate Support; Super Beta Prostate.

Plasminogen *(BAN)*

Plasminógeno; Плазминоген.

CAS — 9001-91-6.

Profile

Plasminogen is the specific substance derived from plasma which, when activated to plasmin, has the property of lysing fibrinogen, fibrin, and some other proteins. Its role in the control of haemostasis is described further on p. 1124.3. Plasminogen has been investigated as a thrombolytic and has been used with other blood products in wound-sealant preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Tissucol Duo Quick†; Tissucol†; *Belg.*: Tissucol Duo; Tissucol Kit; *Canad.*: Tisseel; *Cz.*: Tissucol; *Denm.*: Tisseel Duo Quick; *Fin.*: Tisseel Duo Quick; *Fr.*: Tissucol; *Ger.*: Tissucol Duo S; Tissucol-Kit; *Hong Kong*: Tisseel; *Hung.*: Tissucol-Kit; *Israel*: Tisseel†; *Rus.*: Tissucol Kit (Тиссукол Кит); *Spain*: Tissucol Duo; *Swed.*: Tisseel Duo Quick; *Switz.*: Tissucol Duo S†; Tissucol†; *UK*: Tisseel.

Policosanol

Поликосанол.
CAS — 142583-61-7.
ATC — C10AX08.
ATC Vet — QC10AX08.

Octacosanol

Cluytyl Alcohol; Montanyl Alcohol; Octacosyl Alcohol; Октакосанол.
1-Octacosanol.
$C_{28}H_{58}O$=410.8
CAS — 557-61-9.
UNII — 8112215OVK.

Profile

Policosanol is a mixture of higher primary aliphatic alcohols (fatty alcohols) derived from plant waxes such as sugar cane wax; it is also found in beeswax and in wheat-germ oil (p. 2647.1). The main component is octacosanol. Policosanol appears to have cholesterol-lowering properties and has been used in the treatment of hypercholesterolaemias, although its benefit has been disputed. Both policosanol and octacosanol are used in nutritional supplements.

References.
1. Gouni-Berthold I, Berthold HK. Policosanol: clinical pharmacology and therapeutic significance of a new lipid-lowering agent. *Am Heart J* 2002; 143: 356–65.
2. Pepping J. Policosanol. *Am J Health-Syst Pharm* 2003; 60: 1112–5.
3. Berthold HK, *et al.* Effect of policosanol on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia: a randomized controlled trial. *JAMA* 2006; 295: 2262–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lipex; *Austral.*: Policor; *Chile*: PPG; *China*: PPG (呗呗嘿); *India*: Cosanol; *Indon.*: Polikos†; *Mex.*: Mercol†; *S.Afr.*: Phytocor.

Multi-ingredient Preparations. *India*: Cardistim; Enduranz; Megalip; Natrolip; *Ital.*: Ad$_3$; Artedin; Berart; Colesterase; Esterol Plus; Novostatin; Plusvit; *Singapore*: Bios Life; *UK*: Chol-Aid; Octacosanol; *USA*: Otic Edge†.

Polythiazide *(BAN, USAN, rINN)* ⊗

NSC-108161; P-2525; Politiazida; Polythiazidum; Polytiatsidi; Polytiazid; Политиазид.
6-Chloro-3,4-dihydro-2-methyl-3-(2,2,2-trifluoroethylthiomethyl)-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.
$C_{11}H_{13}ClF_3N_3O_4S_3$=439.9
CAS — 346-18-9.
ATC — C03AA05.
ATC Vet — QC03AA05.
UNII — 36780APV5N.

Pharmacopoeias. In *Br.*

BP 2014: (Polythiazide). A white or almost white, crystalline powder with an alliaceous odour. Practically insoluble in water and in chloroform; sparingly soluble in alcohol.

Profile

Polythiazide is a thiazide diuretic with actions and uses similar to those of hydrochlorothiazide (p. 1403.2). It has been given orally for hypertension, and for oedema, including that associated with heart failure.

Pharmacokinetics. Polythiazide is fairly readily absorbed from the gastrointestinal tract. Diuresis begins within about 2 hours of an oral dose, and lasts for 24 to 48 hours. The estimated plasma elimination half-life is about 26 hours. More than 80% may be bound to plasma proteins. It is excreted mainly in the urine as unchanged polythiazide and metabolites.

References.
1. Hobbs DC, Twomey TM. Kinetics of polythiazide. *Clin Pharmacol Ther* 1978; 23: 241–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Gr.*: Renese R.

Pharmacopoeial Preparations
BP 2014: Polythiazide Tablets.

Potassium Canrenoate *(BANM, rINN)* ⊗

Aldadiene Potassium; Canrénoate de Potassium; Canrenoate Potassium (USAN); Canrenoato de potasio; Kalii Canrenoas; Kaliumkanrenoaatti; Kaliumkanrenoat; MF-465a; SC-14266; Калия канреноат.
Potassium 17-hydroxy-3-oxo-17α-pregna-4,6-diene-21-carboxylate.
$C_{22}H_{29}KO_4$=396.6
CAS — 4138-96-9 (canrenoic acid); 2181-04-6 (potassium canrenoate).
ATC — C03DA02.
ATC Vet — QC03DA02.
UNII — M671F9NLEA.

Pharmacopoeias. In *Jpn.*

Uses and Administration

Potassium canrenoate is a potassium-sparing diuretic with actions and uses similar to those of spironolactone (p. 1500.1), but only about 0.7 times its potency. Canrenone (p. 1331.1) is a metabolite common to both drugs, but its contribution to the pharmacological action is unclear. Potassium canrenoate is used in the treatment of refractory oedema associated with heart failure (p. 1262.3) or hepatic disease when an injectable aldosterone antagonist is required. It may be given in doses of 200 to 400 mg daily, increasing to 800 mg daily in exceptional cases; it is given by slow intravenous injection over a period of 2 to 3 minutes for each 200 mg or by intravenous infusion in glucose 5% or sodium chloride 0.9%.

For doses in children, see below.

Administration in children. Although potassium canrenoate is unlicensed in the UK for children, the *BNFC* suggests that it may be given to neonates, infants, and children for short-term diuresis in heart failure, oedema, and ascites. The intravenous dose, given by injection (over at least 3 minutes) or infusion, is 1 to 2 mg/kg (maximum 200 mg) twice daily.

Adverse Effects and Precautions

As for Spironolactone, p. 1501.2. Irritation or pain may occur at the site of injection.

Effects on endocrine function. A lower incidence of gynaecomastia has been reported in patients with hepatic cirrhosis and ascites during use of potassium canrenoate than with equivalent doses of spironolactone,[1] and spironolactone-induced gynaecomastia disappeared when spironolactone was replaced by potassium canrenoate in a patient with hyperaldosteronism.[2] This suggests that metabolites other than canrenone (a common metabolite of both canrenoate and spironolactone thought to be responsible for their activity) or possibly spironolactone itself may be responsible for the anti-androgenic effects of spironolactone.[3,4]

1. Bellati G, Idéo G. Gynaecomastia after spironolactone and potassium canrenoate. *Lancet* 1986; i: 626.
2. Dupont A. Disappearance of spironolactone-induced gynaecomastia during treatment with potassium canrenoate. *Lancet* 1985; ii: 731.
3. Gardiner P. Spironolactone and potassium canrenoate metabolism. *Lancet* 1985; ii: 1432.
4. Overdiek JWPM, Merkus FWHM. Spironolactone metabolism and gynaecomastia. *Lancet* 1986; i: 1103.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies potassium canrenoate as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Spironolactone, p. 1502.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Aldactone; *Belg.*: Canrenol; Soldactone; *Cz.*: Aldactone; *Fr.*: Soludactone; *Ger.*: Aldactone; *Ital.*: Diurek; Kanrenol; Luvion; *Neth.*: Soldactone; *Pol.*: Aldactone; *Switz.*: Soldactone.

Multi-ingredient Preparations. *Ital.*: Kadiur.

Prajmalium Bitartrate *(BAN, rINN)*

Bitartrato de prajmalio; GT-1012; NPAB; Prajmalii Bitartras; Prajmaline Bitartrate; Prajmalio, bitartrato de; Prajmallum, Bitartrate de; Праймалия битартрат.
N-Propylajmalinium hydrogen tartrate.
$C_{23}H_{33}N_2O_2.C_4H_5O_6$=518.6
CAS — 35080-11-6 (prajmalium); 2589-47-1 (prajmalium bitartrate).
ATC — C01BA08.
ATC Vet — QC01BA08.
UNII — H671L9190Z.

Uses and Administration

Prajmalium is a class I antiarrhythmic (p. 1243.1) and is the *N*-propyl derivative of ajmaline (p. 1295.2). It is given orally as the bitartrate in the management of supraventricular and ventricular arrhythmias (p. 1266.1) in initial doses of 60 to 80 mg daily. Maintenance doses of 20 to 40 mg daily in divided doses are used.

Adverse Effects and Precautions

As for Ajmaline, p. 1295.2.

Effects on the liver. Cholestatic jaundice associated with pruritus, chills, and eosinophilia[1] was attributed to an allergic reaction to prajmalium bitartrate in a patient 20 days after the start of treatment.

1. Rutmensch HH, *et al.* Cholestatic jaundice: an immune response to prajmalium bitartrate. *Postgrad Med J* 1980; 56: 738–41.

Effects on mental state. Confusion and disorientation occurred[1] on 2 occasions in a 67-year-old man given prajmalium bitartrate 100 mg daily for the control of tachycardia; the confusion rapidly disappeared when prajmalium was withdrawn.

1. Lessing JB, Copperman U. Severe cerebral confusion produced by prajmalium bitartrate. *BMJ* 1977; 2: 675.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Neo-Gilurytmal; *Cz.*: Neo-Gilurytmal; *Ger.*: Neo-Gilurytmal; *Hung.*: Neo-Gilurytmal; *Indon.*: Neo-Gilurytmal.

Multi-ingredient Preparations. *Spain*: Cresophene.

Prasugrel Hydrochloride

(BANM, USAN, rINNM)

LY-640315; Prasugrel, Chlorhydrate de; Prasugrel, hidrocloruro de; Prasugrelі Hydrochloridum; Празугрела гидрохлорид.
5-[(1*RS*)-2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate hydrochloride.
$C_{20}H_{20}FNO_3S,HCl$=409.9
CAS — 389574-19-0.
ATC — B01AC22.
ATC Vet — QB01AC22.
UNII — G89JQ59I13.

Uses and Administration

Prasugrel hydrochloride is a thienopyridine antiplatelet drug with similar properties to clopidogrel (p. 1342.3). It is given, with aspirin, for the prevention of atherothrombotic events in patients with acute coronary syndromes, including unstable angina (p. 1254.3) and myocardial infarction (p. 1257.1) who are undergoing percutaneous coronary interventions (see Reperfusion and Revascularisation Procedures, p. 1259.2).

Prasugrel is given orally as the hydrochloride, but doses are expressed in terms of the base; 5.5 mg of prasugrel hydrochloride is equal to about 5 mg of base. Treatment should be started with a loading dose of 60 mg and then continued at a dose of 10 mg once daily for up to 12 months. Patients weighing under 60 kg and those aged 75 years and older should be given a maintenance dose of 5 mg, although use in those aged 75 years and older is not generally recommended due to the increased risk of bleeding.

References.
1. Wiviott SD, *et al.* Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine $P2Y_{12}$ antagonist, with clopidogrel in percutaneous coronary intervention: results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 trial. *Circulation* 2005; 111: 3366–73.
2. Jakubowski JA, *et al.* A multiple dose study of prasugrel (CS-747), a novel thienopyridine $P2Y_{12}$ inhibitor, compared with clopidogrel in healthy humans. *Br J Clin Pharmacol* 2006; 63: 421–30.
3. Brandt JT, *et al.* A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J* 2007; 153: 66.
4. Wiviott SD, *et al.* TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; 357: 2001–15.
5. Wiviott SD, *et al.* PRINCIPLE-TIMI 44 Investigators. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and

Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation* 2007; 116: 2923–32.
6. Antman EM, *et al.* Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRIal to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. *J Am Coll Cardiol* 2008; 51: 2028–33.
7. Montalescot G, *et al.* TRITON-TIMI 38 Investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet* 2009; 373: 723–31.
8. Reinhart KM, *et al.* Prasugrel: a critical comparison with clopidogrel. *Pharmacotherapy* 2009; 29: 1441–51.
9. Duggan ST, Keating GM. Prasugrel: a review of its use in patients with acute coronary syndromes undergoing percutaneous coronary intervention. *Drugs* 2009; 69: 1707–26.
10. Scott DM, *et al.* P2Y12 inhibitors in cardiovascular disease: focus on prasugrel. *Ann Pharmacother* 2009; 43: 64–76.
11. Mousa SA, *et al.* Antiplatelet therapy prasugrel: a novel platelet ADP P2Y12 receptor antagonist. *Clin Appl Thromb Hemost* 2010; 16: 170–6.

Adverse Effects and Precautions

As for Ticlopidine, p. 1512.2. The incidence of blood dyscrasias is lower with prasugrel and routine blood counts are not required.

Consideration should be given to stopping prasugrel at least 7 days before elective surgery.

Interactions

Prasugrel should be used with caution in patients receiving other drugs that increase the risk of bleeding, including anticoagulants, other antiplatelet drugs, and NSAIDs. Clinically significant interactions associated with cytochrome P450 isoenzymes have not been reported; however, prasugrel is a weak inhibitor of CYP2B6 and might affect drugs with a narrow therapeutic window metabolised by this isoenzyme, such as cyclophosphamide and efavirenz.

Pharmacokinetics

Prasugrel is a prodrug. It is rapidly absorbed after oral doses and undergoes hydrolysis in the intestine before being metabolised by several cytochrome P450 isoenzymes to the active metabolite. Peak plasma concentrations of the active metabolite occur in about 30 minutes. Binding of the active metabolite to human serum albumin is about 98%. The active metabolite is further metabolised to 2 inactive compounds which are excreted in the urine and faeces; about 68% of a dose is excreted in urine and about 27% in faeces. The elimination half-life of the active metabolite is about 7.4 hours.

References.
1. Wrishko RE, *et al.* Population pharmacokinetic analyses to evaluate the influence of intrinsic and extrinsic factors on exposure of prasugrel active metabolite in TRITON-TIMI 38. *J Clin Pharmacol* 2009; 49: 984–98.
2. Mega JL, *et al.* Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. *Circulation* 2009; 119: 2553–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Effient; Nefagrel; Procardia; Trocal; *Austral.*: Effient; *Austria*: Efient; *Belg.*: Efient; *Braz.*: Effient; *Canad.*: Effient; *Cz.*: Efient; *Denm.*: Efient; *Fr.*: Efient; *Ger.*: Efient; *Gr.*: Efient; *Hong Kong*: Effient; *Irl.*: Efient; *Israel*: Effient; *Malaysia*: Effient; *Neth.*: Efient; *Norw.*: Efient; *NZ*: Effient; *Philipp.*: Effient; *Pol.*: Efient; *Port.*: Efient; *Singapore*: Effient; *Spain*: Efient; *Swed.*: Efient; *Switz.*: Efient; *UK*: Efient; *USA*: Effient.

Pravastatin Sodium

(BANM, USAN, rINNM)

CS-514; Eptastatin Sodium; 3β-Hydroxycompactin Sodium; Natrii Pravastatinum; Pravastatininatrium; Pravastatin-Natrium; Pravastatin sodná sůl; Pravastatina sódica; Pravastatine sodique; Pravastatinnatrium; Pravastatino natrio druska; Pravastatinum Natricum; Pravasztatin-nátrium; SQ-31000; Натрий Правастатин.

Sodium (3*R*,5*R*)-7-[(1*S*,2*S*,6*S*,8*S*,8a*R*)-1,2,6,7,8,8a-hexahydro-6-hydroxy-2-methyl-8-[(*S*)-2-methylbutyryloxy]-1-naphthyl]-3,5-dihydroxyheptanoate.

$C_{23}H_{35}O_7Na$=446.5

CAS — 81093-37-0 (pravastatin); 81131-70-6 (pravastatin sodium).

ATC — C10AA03.

ATC Vet — QC10AA03.

UNII — 3M8608UQ61.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Pravastatin Sodium). A white to yellowish-white, hygroscopic, powder or crystalline powder. Freely soluble in water and in methyl alcohol; soluble in dehydrated alcohol. A 5% solution in water has a pH of 7.2 to 9.0. Store in airtight containers.

USP 36: (Pravastatin Sodium). A white to yellowish white hygroscopic powder. Freely soluble in water and in methyl alcohol; soluble in dehydrated alcohol; practically insoluble in acetonitrile and in chloroform. Store in airtight containers.

Uses and Administration

Pravastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p. 1489.3).

Pravastatin is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the treatment of hyperlipidaemias (p. 1248.1), including hypercholesterolaemias, combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias), hypertriglyceridaemia (type IV), dysbetalipoproteinaemia (type III), and post-transplantation hyperlipidaemia. It is also used for cardiovascular risk reduction (p. 1246.1), including primary prophylaxis in hypercholesterolaemic patients, and secondary prophylaxis, including prevention of stroke, in patients with clinically-evident ischaemic heart disease.

Pravastatin is given orally as the sodium salt; the usual dose is 10 to 40 mg of pravastatin sodium once daily at bedtime. The dose may be adjusted, according to response, at intervals of not less than 4 weeks. UK licensed product information states that the maximum dose is 40 mg once daily, but US licensed product information allows a maximum of 80 mg once daily in patients with hypercholesterolaemia. Low initial doses are recommended in patients with hepatic or renal impairment (see below).

In patients also taking *ciclosporin*, UK licensed product information recommends an initial dose of 20 mg once daily, but US licensed product information states an initial dose of 10 mg; dose increases should be made with caution.

For the use of pravastatin in children and adolescents, see below.

General reviews.
1. McTavish D, Sorkin EM. Pravastatin: a review of its pharmacological properties and therapeutic potential in hypercholesterolaemia. *Drugs* 1991; 42: 65–89.
2. Haria M, McTavish D. Pravastatin: a reappraisal of its pharmacological properties and clinical effectiveness in the management of coronary heart disease. *Drugs* 1997; 53: 299–336.
3. Bang LM, Goa KL. Pravastatin: a review of its use in elderly patients. *Drugs Aging* 2003; 20: 1061–82.
4. del Sol AI, Nanayakkara PW. Pravastatin: an evidence-based statin? *Expert Opin Drug Metab Toxicol* 2008; 4: 821–5.

Administration in children. In children with heterozygous familial hypercholesterolaemia, pravastatin sodium is licensed in doses of 10 to 20 mg once daily in those aged 8 to 13 years and 10 to 40 mg once daily in those aged 14 to 18 years. Short-term studies have suggested that pravastatin effectively reduces cholesterol and is safe in children with familial hypercholesterolaemia[1] and in children taking immunosuppressants after heart transplant,[2] although plasma concentrations may be higher in the latter group. A randomised controlled study[3] and a prospective study[4] have also found that pravastatin is effective and well tolerated in familial hypercholesterolaemia, and there is some evidence[3] that carotid intima media thickness (a marker of atherosclerosis) may be reduced.

1. Hedman M, *et al.* Pharmacokinetics and pharmacodynamics of pravastatin in children with familial hypercholesterolemia. *Clin Pharmacol Ther* 2003; 74: 175–85.
2. Hedman M, *et al.* Pharmacokinetics and pharmacodynamics of pravastatin in pediatric and adolescent cardiac transplant recipients on a regimen of triple immunosuppression. *Clin Pharmacol Ther* 2004; 75: 101–109.
3. Wiegman A, *et al.* Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 2004; 292: 331–7.
4. Hedman M, *et al.* Efficacy and safety of pravastatin in children and adolescents with heterozygous familial hypercholesterolemia: a prospective clinical follow-up study. *J Clin Endocrinol Metab* 2005; 90: 1942–52.

Administration in hepatic or renal impairment. Patients with moderate or severe renal or significant hepatic impairment should be given pravastatin sodium in an initial dose of 10 mg daily, and the dose should be increased with caution.

Adverse Effects and Precautions

As for Simvastatin, p. 1492.1 and p. 1494.1, respectively.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pravastatin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions of statins with other drugs are described under simvastatin (p. 1494.2). Pravastatin is not significantly metabolised by the cytochrome P450 enzyme system and does not have the same interactions with enzyme inhibitors as simvastatin, although caution has been advised when such combinations are used. Increased plasma-pravastatin concentrations have been reported in some patients receiving ciclosporin and low doses should be used (see Uses and Administration, above).

Pharmacokinetics

Pravastatin is rapidly but incompletely absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver, its primary site of action. The absolute bioavailability of pravastatin is 17%. About 50% of the circulating drug is bound to plasma proteins. The plasma elimination half-life of pravastatin is 1.5 to 2 hours. About 70% of an oral dose of pravastatin is excreted in the faeces, as unabsorbed drug and via the bile, and about 20% is excreted in the urine.

General reviews.
1. Quion JAV, Jones PH. Clinical pharmacokinetics of pravastatin. *Clin Pharmacokinet* 1994; 27: 94–103.
2. Hatanaka T. Clinical pharmacokinetics of pravastatin: mechanisms of pharmacokinetic events. *Clin Pharmacokinet* 2000; 39: 397–412.
3. Neuvonen PJ, *et al.* Pharmacokinetic comparison of the potential over-the-counter statins simvastatin, lovastatin, fluvastatin and pravastatin. *Clin Pharmacokinet* 2008; 47: 463–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Pravacol; *Austral.*: Cholstat; Lipostat; Lipracholt; Pravachol; Pravastat; Vastoran†; *Austria*: Panchol; *Belg.*: Prareduct; Pravasine; *Braz.*: Mevalotin; Pravacol; *Canad.*: Pravachol; *Chile*: Pravacol; *China*: Fu Li Ta Zhi (富利他之); Fu Ta Ning (福他宁); Mevalotin (美百乐镇); Pravachol; Pu Hui Zhi (浦惠普); *Cz.*: Vitastat; *Denm.*: Pravachol†; *Fin.*: Pravachol†; *Fr.*: Elisor; Vasten; *Ger.*: Mevalotin†; Prava-Q†; Pravabeta†; Pravagamma†; PravaLich†; Pravalip†; Pravasin; *Gr.*: Analipin; Antisterin; Asto-Chol; Cholipravin; Cosivatin; Defantum; Liplow; Lipoprav; Maxudin; Ostiron; Pan-lipol; Pravachol; Pravadium; Pravafact; Pravahelp; Pravalen; Pravalip; Pravalong; Pravanox; Pravaxis; Pravedol; Pravin; Pravostin; Privast; Sosmin; Vastil; Zoter; Zyon; *Hong Kong*: Pravachol†; *Hung.*: Nikron; Prastin†; Pravastar†; *India*: Pravator; *Indon.*: Cholespar; Gravastin; Koleskol; Mevachol; Novales; Pravachol†; Pravinat; *Irl.*: Bellprav†; Beneprav; ByStat; Cholstat†; Lipaprav; Lipostat; Lipovas; Pravalo†; Pravamel; Pravat; Pravitin; *Israel*: Pravalip; *Ital.*: Aplactin; Langiprav; Prasterol; Pravaselect; Sanaprav; Selectin; Setac; Vasticor; *Jpn*: Mevalotin; *Malaysia*: Pratin; Pravachol; Pravid; *Mex.*: Accogard; Astin; Brakhor; Celuterol; Colpradin; Emival†; Kenstatin; Kenvastin; Lexet; Loretsin; Mavitina; Novina; Paver; Piflaxan; Prascolend†; Prasiver; Pravacol; Striacol; Tissulest; Tratinal; Tridanil-H; Valprastin; Vaprasil; Varlex; Vastoran; Xipral; *Neth.*: Lipratif; Pratiflip; Pravandrea; Selektine; Statifil; Vastatifix; *Norw.*: Pravachol; *NZ*: Cholvastin; Lipostat†; Pravachol; *Philipp.*: Lipostat†; Pravaz; Stanidine†; *Pol.*: Apo-Prava†; Pravator; *Port.*: Lipra; Pravacol; Pritanol; Sanaprav; *S.Afr.*: Colite; Novales; Pixeta; Pixeta; Pranalip†; Prava; Pravacor; Pravacor; *Singapore*: Pravachol; *Spain*: Bristacol; Lipemol; Liplat; Minuscol; Prareduct; Pritadol; *Swed.*: Pravachol†; *Switz.*: Mevalotin; Pravalotin; Pravasta eco†; Pravastax; Pravatine; Selipran; *Thai.*: Mevalotin; *Turk.*: Pravachol; Praxal; *UK*: Lipostat; *USA*: Pravachol; *Venez.*: Mevalotin; Pravacol.

Multi-ingredient Preparations. *Canad.*: PravASA†; *Cz.*: Pravafenix; *Fr.*: Pravadual; *Indon.*: Novosta; *Irl.*: Pravafenix.

Pharmacopoeial Preparations
BP 2014: Pravastatin Tablets;
USP 36: Pravastatin Sodium Tablets.

Prazosin Hydrochloride

(BANM, USAN, rINNM)

CP-12299-1; Furazosin Hydrochloride; Hidrocloruro de prazosina; Pratsosilinihydrokloridi; Prazosin Hydroklorür; Prazosina, hidrocloruro de; Prazosine, Chlorhydrate de; Prazosinhydrochlorid; Prazosin-hydrochlorid; Prazosinhydroklorid; Prazosini Hydrochloridum; Prazozin-hidroklorid; Prazozino hidrochloridas; Празозина гидрохлорид.

2-[4-(2-Furoyl)piperazin-1-yl]-6,7-dimethoxyquinazolin-4-ylamine hydrochloride.

$C_{19}H_{21}N_5O_4$,HCl=419.9

CAS — 19216-56-9 (prazosin); 19237-84-4 (prazosin hydrochloride).

ATC — C02CA01.

ATC Vet — QC02CA01.

UNII — X0Z7645890.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Prazosin Hydrochloride). A white or almost white powder. Very slightly soluble in water; slightly soluble in alcohol and in methyl alcohol; practically insoluble in acetone. Protect from light.

USP 36: (Prazosin Hydrochloride). A white to tan powder. Slightly soluble in water, in dimethylacetamide, in

dimethylformamide, and in methyl alcohol; very slightly soluble in alcohol; practically insoluble in acetone and in chloroform. Store in airtight containers. Protect from light.

Uses and Administration

Prazosin is an alpha blocker (p. 1243.1) that acts by selective blockade of alpha$_1$-adrenoceptors. It is used in the management of hypertension (p. 1251.1), in Raynaud's syndrome (see Peripheral Vascular Disease, below), and to relieve symptoms of urinary obstruction in benign prostatic hyperplasia (p. 2347.1). It has also been used in heart failure (p. 1262.3).

Prazosin produces peripheral dilatation of both arterioles and veins and reduction of peripheral resistance, usually without reflex tachycardia. It reduces both standing and supine blood pressure with a greater effect on the diastolic pressure. It is reported to have no effect on renal blood flow or glomerular filtration rate, and has little effect on cardiac output in hypertensive patients. In patients with heart failure, prazosin reduces both preload and afterload and produces an improvement in cardiac output, although tolerance may develop. In benign prostatic hyperplasia, prazosin may relieve the symptoms of urinary obstruction by reducing smooth muscle tone in the prostate and bladder neck.

Prazosin is given orally as the hydrochloride, but doses are usually expressed in terms of the base. Prazosin hydrochloride 1.1 mg is equivalent to about 1 mg of prazosin. After oral dosage the hypotensive effect is seen within 2 to 4 hours and persists for several hours. Full effects are seen after 4 to 6 weeks.

A low starting dose is given in the evening to lessen the risk of collapse which may occur in some patients after the first dose (see Adverse Effects, below). Doses may need to be reduced in the elderly and in patients with hepatic or renal impairment.

In **hypertension**, the usual initial dose in the UK is 500 micrograms two or three times daily for 3 to 7 days; if tolerated the dose may then be increased to 1 mg two or three times daily for a further 3 to 7 days, and thereafter gradually increased, according to the patient's response, to a usual maximum of 20 mg daily in divided doses. In the US the recommended starting dose is 1 mg two or three times daily and up to 40 mg daily in divided doses has been given; however, the usual maintenance dose is between 6 and 15 mg daily. Smaller doses may be required in patients also taking other antihypertensives. Modified-release preparations may allow once daily dosing.

In **Raynaud's syndrome** and in **benign prostatic hyperplasia** an initial dose of 500 micrograms twice daily may be given, increasing to a maintenance dose not exceeding 2 mg twice daily.

In **heart failure**, treatment has been started with 500 micrograms two to four times daily and increased gradually according to response; the usual maintenance dose has been 4 to 20 mg daily.

Alcohol dependence. Prazosin has been investigated in the maintenance of abstinence (p. 1735.1) in patients with alcohol dependence.[1]

1. Simpson TL, *et al.* A pilot trial of the alpha-1 adrenergic antagonist, prazosin, for alcohol dependence. *Alcohol Clin Exp Res* 2009; 33: 255–63.

Erectile dysfunction. Prazosin has been given transurethrally with alprostadil[1] in the management of erectile dysfunction (p. 2348.2). However, alpha blockers have also been reported to cause erectile dysfunction (see Effects on Sexual Function, below).

1. Peterson CA, *et al.* Erectile response to transurethral alprostadil, prazosin and alprostadil-prazosin combinations. *J Urol (Baltimore)* 1998; 159: 1523–8.

Familial Mediterranean fever. Attacks of familial Mediterranean fever (p. 605.1) are usually treated with prophylactic colchicine, but its use may be limited by adverse effects. A Japanese man who had suffered from attacks for 16 years was treated[1] with prazosin 3 mg daily. There were no further attacks for more than a year after starting treatment, but stopping prazosin resulted in a recurrence.

1. Kataoka H, *et al.* Treating familial Mediterranean fever with prazosin hydrochloride. *Ann Intern Med* 1998; 129: 424–5.

Muscle cramp. Skeletal muscle cramp may occur during haemodialysis, possibly due to activation of the sympathetic nervous system. Prazosin was reported[1] to reduce the incidence of cramp in 4 of 5 patients with frequent haemodialysis-associated muscle cramp. However, the increased incidence of hypotension reported might limit its use for this indication.

1. Sidhom OA, *et al.* Low-dose prazosin in patients with muscle cramps during hemodialysis. *Clin Pharmacol Ther* 1994; 56: 445–51.

Peripheral vascular disease. Alpha blockers, including prazosin, may be used in the management of Raynaud's syndrome (see Vasospastic Arterial Disorders, p. 1275.3). Studies of the benefits of prazosin have produced varying results. A short-term reduction in number and duration of attacks was reported in 5 of 7 patients given prazosin 2 mg daily but only 1 patient had complete relief from attacks and few could tolerate doses higher than 6 mg daily.[1] Improvements were not maintained during continued treatment for 2 months. Others[2,3] have reported benefit from prazosin 1 mg two or three times daily in the majority of patients, with one study suggesting greater benefit in Raynaud's disease (the primary, idiopathic form) than in secondary Raynaud's syndrome.[2] In a subsequent study, higher doses of prazosin (2 or 4 mg three times daily) were no more effective than 1 mg three times daily, and were associated with a significantly greater incidence of adverse effects.[4] A systematic review[5] concluded that prazosin was modestly effective in the treatment of Raynaud's syndrome secondary to scleroderma.

1. Nielsen SL, *et al.* Prazosin treatment of primary Raynaud's phenomenon. *Eur J Clin Pharmacol* 1983; 24: 421–3.
2. Allegra C, *et al.* Pharmacological treatment of Raynaud's phenomenon: a new therapeutic approach. *Curr Ther Res* 1986; 40: 303–11.
3. Wollersheim H, *et al.* Double-blind, placebo-controlled study of prazosin in Raynaud's phenomenon. *Clin Pharmacol Ther* 1986; 40: 219–25.
4. Wollersheim R, Thien T. Dose-response study of prazosin in Raynaud's phenomenon: clinical effectiveness versus side effects. *J Clin Pharmacol* 1988; 28: 1089–93.
5. Harding SE, *et al.* Prazosin for Raynaud's phenomenon in progressive systemic sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 24/06/05).

Post-traumatic stress disorder. Post-traumatic stress disorder (PTSD—p. 1029.2) is usually treated with psychotherapy or drugs such as SSRIs. Increased alpha$_1$-adrenergic receptor activity may be a contributory factor, and several studies have reported that treatment with prazosin improves nightmares and sleep disturbances in patients with this condition.[1-3] A reduction in nightmares occurred in 5 patients taking part in a small 6-week open-label study;[4] doses ranged from 1 mg at night to 2 mg night and morning. A similar improvement was found in a retrospective study[5] of combat veterans with chronic treatment-resistant symptoms, where doses of prazosin were increased gradually from 1 mg at night up to a maximum daily dose of 20 mg if required, and in a placebo-controlled study[6] in similar patients given doses of up to 15 mg at night. Another small study[7] and a case report[8] have also reported benefit; doses varied from 1 mg at night to 10 mg daily in 2 divided doses. A cohort study involving retrospective review of 62 patients with PTSD treated with prazosin and 175 given quetiapine found that short-term benefits with the 2 drugs were comparable;[9] however, prazosin was better tolerated and patients were less likely to stop therapy, so long-term efficacy was therefore greater in this group.

1. Dierks MR, *et al.* Prazosin treatment of nightmares related to posttraumatic stress disorder. *Ann Pharmacother* 2007; 41: 1013–17.
2. Taylor HR, *et al.* Prazosin for treatment of nightmares related to posttraumatic stress disorder. *Am J Health-Syst Pharm* 2008; 65: 716–22.
3. Miller LJ. Prazosin for the treatment of posttraumatic stress disorder sleep disturbances. *Pharmacotherapy* 2008; 28: 656–66.
4. Taylor F, Raskind MA. The α_1-adrenergic antagonist prazosin improves sleep and nightmares in civilian trauma posttraumatic stress disorder. *J Clin Psychopharmacol* 2002; 22: 82–5.
5. Raskind MA, *et al.* Prazosin reduces nightmares in combat veterans with posttraumatic stress disorder. *J Clin Psychiatry* 2002; 63: 565–8.
6. Raskind MA, *et al.* A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biol Psychiatry* 2007; 61: 928–34.
7. Raskind MA, *et al.* Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *Am J Psychiatry* 2003; 160: 371–3.
8. Griffith LJ. Case report: use of prazosin for treatment of posttraumatic stress disorder. *Am Fam Physician* 2005; 72: 758, 761.
9. Byers MG, *et al.* Prazosin versus quetiapine for nighttime posttraumatic stress disorder symptoms in veterans: an assessment of long-term comparative effectiveness and safety. *J Clin Psychopharmacol* 2010; 30: 225–9.

Renal calculi. For the potential use of alpha blockers to aid the passage of renal calculi, see under Uses of Tamsulosin Hydrochloride, p. 2369.2.

Scorpion stings. Stings from the Indian red scorpion (*Mesobuthus tamulus*) are potentially fatal. The scorpion venom is a potent sympathetic stimulator resulting in high circulating catecholamines, hypertension, arrhythmias, pulmonary oedema, and circulatory failure. The efficacy of antivenom is questionable and treatment for cardiotoxicity is supportive (see p. 2418.1). Prazosin, given orally, appears to be beneficial and has been suggested[1,2] as first-line treatment, except in cases of severe pulmonary oedema. Prazosin has also been used in other countries to treat stings by dangerous scorpion species.[3-5]

1. Bawaskar HS, Bawaskar PH. Scorpion envenoming and the cardiovascular system. *Trop Doct* 1997; 27: 6–9.
2. Bawaskar HS, Bawaskar PH. Utility of scorpion antivenin vs prazosin in the management of severe Mesobuthus tamulus (Indian red scorpion) envenoming at rural setting. *J Assoc Physicians India* 2007; 55: 14–21.
3. Koseoglu Z, Koseoglu A. Use of prazosin in the treatment of scorpion envenomation. *Am J Ther* 2006; 13: 285–7.
4. Al-Asmari AK, *et al.* Role of prazosin on cardiovascular manifestations and pulmonary edema following severe scorpion stings in Saudi Arabia. *Saudi Med J* 2008; 29: 299–302.
5. Peker E, *et al.* Prazosin treatment in the management of scorpion envenomation. *Hum Exp Toxicol* 2010; 29: 231–3.

Adverse Effects

Prazosin hydrochloride can cause orthostatic hypotension which may be severe and produce syncope after the initial dose; it may be preceded by tachycardia. This reaction can be avoided by starting treatment with a low dose, preferably at night (see Uses and Administration, above). The hypotensive effects may be exaggerated by exercise, heat, or alcohol ingestion.

The more common adverse effects include dizziness, drowsiness, headache, lack of energy, nausea, and palpitations, and may diminish with continued prazosin therapy or with a reduction in dosage. Other adverse effects include oedema, chest pain, dyspnoea, constipation, diarrhoea, vomiting, depression and nervousness, sleep disturbances, vertigo, hallucinations, paraesthesia, nasal congestion, epistaxis, dry mouth, urinary frequency and incontinence, reddened sclera, blurred vision, tinnitus, abnormal liver enzyme values, pancreatitis, arthralgia, alopecia, lichen planus, skin rashes, pruritus, and diaphoresis. Impotence and priapism have also been reported.

General reviews.

1. Carruthers SG. Adverse effects of α_1-adrenergic blocking drugs. *Drug Safety* 1994; 11: 12–20.

Effects on the cardiovascular system. Orthostatic hypotension, preceded by tachycardia and sometimes producing syncope, is an established adverse effect of the initial dose of prazosin. Sinus bradycardia was associated with prazosin in a patient who had light headedness after each daily dose.[1]

Chest pain is a known adverse effect of prazosin, but in a report[2] of acute intermittent left-sided chest pain in a patient being treated with the drug for post-traumatic stress disorder there was no evidence of hypotension or significant abnormalities of heart function, suggesting the symptom was non-specific.

1. Ball J. Symptomatic sinus bradycardia due to prazosin. *Lancet* 1994; 343: 121.
2. Nuzhat SS, Osser DN. Chest pain in a young patient treated with prazosin for PTSD. *Am J Psychiatry* 2009; 166: 618–19.

Effects on the gastrointestinal tract. Faecal incontinence in a 52-year-old man receiving prazosin was exacerbated by haemorrhoidectomy and appeared to be due to diminished resting anal tone, presumably because of smooth muscle relaxation secondary to alpha-adrenoceptor blockade.[1] Symptoms ceased almost immediately on stopping the drug.

1. Holmes SAV, *et al.* Faecal incontinence resulting from α_1-adrenoceptor blockade. *Lancet* 1990; 336: 685–6.

Effects on mental function. Psychiatric symptoms including confusion, paranoia, and hallucinations developed in 3 patients associated with prazosin treatment.[1] Two of the patients had chronic renal failure and the other had mild renal impairment. Abnormal behaviour and dissociative symptoms were reported in another patient[2] given prazosin for post-traumatic stress disorder. Acute psychosis has also been reported with doxazosin.[3]

1. Chin DKF, *et al.* Neuropsychiatric complications related to use of prazosin in patients with renal failure. *BMJ* 1986; 293: 1347.
2. Reardon CL, Factor RM. Bizarre behavior in a patient treated with prazosin for PTSD. *Am J Psychiatry* 2008; 165: 774–9.
3. Evans M, *et al.* Drug induced psychosis with doxazosin. *BMJ* 1997; 314: 1869.

Effects on sexual function. Alpha blockers have complex effects on male sexual function[1] and both priapism and erectile dysfunction have been reported. They promote erection by blocking alpha$_1$-adrenoceptors in the penis, and have been tried in erectile dysfunction (see under Uses and Administration, above), but the reduction in blood pressure they also cause may impair erectile function, leading to impotence. Alpha blockers may also have adverse effects on ejaculation, although this is less clear.

1. van Dijk MM, *et al.* Effects of α_1-adrenoceptor antagonists on male sexual function. *Drugs* 2006; 66: 287–301.

Hypersensitivity. Urticaria and angioedema in a 70-year-old woman were attributed to prazosin.[1]

1. Ruzicka T, Ring J. Hypersensitivity to prazosin. *Lancet* 1983; i: 473–4.

Lupus erythematosus. One study has reported the formation of antinuclear antibodies in patients receiving prazosin,[1] but this is not in agreement with other reports,[2,3] and commentators consider the association unproven.[4] There is no evidence of the development of lupus erythematosus.[1]

1. Marshall AJ, *et al.* Positive antinuclear factor tests with prazosin. *BMJ* 1979; 1: 165–6.
2. Wilson JD, *et al.* Antinuclear factor in patients on prazosin. *BMJ* 1979; 1: 553–4.
3. Mellkild A, Gaarder PI. Does prazosin induce formation of antinuclear factor? *BMJ* 1979; 1: 620–1.
4. Kristensen BØ. Does prazosin induce formation of antinuclear factor? *BMJ* 1979; 1: 621.

Urinary incontinence. There have been reports of urinary incontinence developing in patients receiving prazosin. Analysis[1] of 56 cases reported to the Australian Adverse Drug Reactions Advisory Committee indicated that typically symptoms appeared within 1 or 2 days of the start of therapy and persisted until the drug was withdrawn or the dose reduced. Both stress and urge incontinence occurred, sometimes in the same patient. Of the 56 patients, 51 were women and most were elderly. In a study[2] in women attending a hypertension clinic urinary incontinence was reported in 40.8% of 49 women receiving alpha blockers (prazosin, terazosin, or doxazosin) and in 16.3% of controls. Incontinence might be due to a reduction in urethral pressure induced by alpha-adrenoceptor blockade.

Interestingly, faecal incontinence has also been reported with prazosin—see Effects on the Gastrointestinal Tract, p. 1474.3.

1. Mathew TH, *et al.* Urinary incontinence secondary to prazosin. *Med J Aust* 1988; 148: 305–6.
2. Marshall HJ, Beevers DG. α-Adrenoceptor blocking drugs and female urinary incontinence: prevalence and reversibility. *Br J Clin Pharmacol* 1996; 42: 507–9.

Treatment of Adverse Effects

If overdosage with prazosin occurs activated charcoal should be given if the patient presents within 1 hour of ingestion. Severe hypotension may occur and treatment includes support of the circulation by postural measures and parenteral fluid volume replacement, and if necessary cautious intravenous infusion of a vasopressor. Prazosin is not removed by dialysis.

Precautions

Treatment with prazosin should be introduced cautiously because of the risk of sudden collapse after the initial dose. Extra caution is necessary in patients with hepatic or renal impairment and in the elderly.

Prazosin is not recommended for the treatment of heart failure caused by mechanical obstruction, for example aortic or mitral valve stenosis, pulmonary embolism, and restrictive pericardial disease. It should be used with caution in patients with angina pectoris. Prazosin may cause drowsiness or dizziness; patients so affected should not drive or operate machinery.

Cataract surgery. For a warning about intraoperative floppy iris syndrome during cataract surgery in patients taking alpha blockers, see Cataract Surgery, under Precautions for Tamsulosin Hydrochloride, p. 2369.3.

Cerebral haemorrhage. Hypotension with disturbance of consciousness[1] occurred in 3 patients with recent cerebral haemorrhage after an initial dose of prazosin 500 micrograms.

1. Lin M-S, Hsieh W-J. Prazosin-induced first-dose phenomenon possibly associated with hemorrhagic stroke: a report of three cases. *Drug Intell Clin Pharm* 1987; 21: 723–6.

Tolerance. Although prazosin may be of initial benefit in patients with chronic heart failure, some studies[1,2] have reported the development of tolerance to its haemodynamic effects on prolonged therapy. This may be partly due to upregulation of alpha$_1$ adrenoceptors.[3]

1. Packer M, *et al.* Role of the renin-angiotensin system in the development of hemodynamic and clinical tolerance to long-term prazosin therapy in patients with severe chronic heart failure. *J Am Coll Cardiol* 1986; 7: 671–80.
2. Bayliss J, *et al.* Clinical importance of the renin-angiotensin system in chronic heart failure: double blind comparison of captopril and prazosin. *BMJ* 1985; 290: 1861–5.
3. Kersting F, *et al.* Preliminary evidence for the mechanism underlying the development of tolerance to prazosin in congestive heart failure: the α-agonistic properties of dobutamine unmasked by prazosin treatment. *J Cardiovasc Pharmacol* 1993; 21: 537–43.

Interactions

The hypotensive effects of prazosin may be enhanced by use with diuretics and other antihypertensives, and by alcohol and other drugs that cause hypotension. The risk of first-dose hypotension may be particularly increased in patients receiving beta blockers or calcium-channel blockers.

Analgesics. *Indometacin* reduced prazosin-induced hypotension in 4 of 9 subjects.[1]

1. Rubin P, *et al.* Studies on the clinical pharmacology of prazosin II: the influence of indomethacin and of propranolol on the action and disposition of prazosin. *Br J Clin Pharmacol* 1980; 10: 33–9.

Antidepressants and antipsychotics. A patient who was taking *amitriptyline* and *chlorpromazine* developed acute agitation when given prazosin.[1] The symptoms settled rapidly when prazosin was stopped. Antidepressants and antipsychotics may enhance the hypotensive effect of prazosin and other alpha blockers.

1. Bolli P, Simpson FO. New vasodilator drugs for hypertension. *BMJ* 1974; 1: 637.

Calcium-channel blockers. An enhanced hypotensive effect has been reported in normotensive subjects given prazosin with *verapamil*; the effect may be due in part to enhanced bioavailability of prazosin.[1] Markedly increased hypotensive responses have also been reported with combined use of prazosin and *nifedipine*,[2,3] although the validity of such reports has been questioned.[4]

1. Pasanisi P, *et al.* Combined alpha adrenoceptor antagonism and calcium channel blockade in normal subjects. *Clin Pharmacol Ther* 1984; 36: 716–23.
2. Jee LD, Opie LH. Acute hypotensive response to nifedipine added to prazosin in treatment of hypertension. *BMJ* 1983; 287: 1514.
3. Jee LD, Opie LH. Acute hypotensive response to nifedipine added to prazosin. *BMJ* 1984; 288: 238–9.
4. Elliott HL, *et al.* Acute hypotensive response to nifedipine added to prazosin. *BMJ* 1984; 288: 238.

Digoxin. For reference to the effect of prazosin on serum-digoxin concentrations, see Alpha Blockers under Digoxin, p. 1356.1.

Pharmacokinetics

Prazosin is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 3 hours after an oral dose. The bioavailability is variable and a range of 43 to 85% has been reported. Prazosin is highly bound to plasma proteins. It is extensively metabolised in the liver and some of the metabolites are reported to have hypotensive activity. It is excreted as the metabolites and 5 to 11% as unchanged prazosin mainly in the faeces via the bile. Less than 10% is excreted in the urine. Small amounts are distributed into breast milk. Its duration of action is longer than would be predicted from its relatively short plasma half-life of about 2 to 4 hours. Half-life is reported to be increased to about 7 hours in patients with heart failure.

The elderly. The bioavailability of prazosin was significantly reduced in the elderly, about 40% less unchanged drug reaching the systemic circulation compared with the young.[1] This was attributed to a reduction in the absorption from the gastrointestinal tract. The half-life was also prolonged in the elderly and this was associated with an increase in the volume of distribution at steady state. However, it was considered unlikely that these effects would have major clinical significance.

1. Rubin PC, *et al.* Prazosin disposition in young and elderly subjects. *Br J Clin Pharmacol* 1981; 12: 401–4.

Protein binding. Although a study[1] found that prazosin was about 80 to 85% bound to serum albumin and only about 10 to 30% bound to α_1-acid glycoprotein *in vitro*, potential interactions between the binding proteins *in vivo* were not taken into account; binding to α_1-acid glycoprotein might be more significant in clinical practice. A subsequent study[2] indicated that variations in prazosin protein binding pre- and post-operatively were related to variations in concentration of the glycoprotein.

1. Brunner P, Müller WE. Prazosin binding to human α_1-acid glycoprotein (orosomucoid), human serum albumin, and human serum: further characterisation of the 'single drug binding site' of orosomucoid. *J Pharm Pharmacol* 1985; 37: 305–9.
2. Sager G, *et al.* Binding of prazosin and propranolol at variable α_1-acid glycoprotein and albumin concentrations. *Br J Clin Pharmacol* 1989; 27: 229–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Deciliten; Minipres; ***Austral.***: Minipress; Pratsiol†; Pressin†; ***Austria***: Minipress; ***Belg.***: Minipress: ***Braz.***: Minipress: ***Canad.***: Apo-Prazo; Minipress: Novo-Prazin†; Nu-Prazo; ***Cz.***: Deprazolin†; ***Fin.***: Pratsiol: ***Fr.***: Alpress; Minipress: ***Ger.***: Adversuten†; ***Gr.***: Minipress; ***Hong Kong***: Apo-Prazo; CP-Prazo; Hyprosin†; Minipress; Mizosin†; ***Hung.***: Minipress; ***India***: Cyber; Czopress; Minipress; Prazocip; ***Irl.***: Hypovase†; ***Jpn***: Minipress; ***Malaysia***: Atodel; Minipress; Minison; Mizosin; ***Mex.***: Anapres†; Ensibest; Minipres; Sinozard; ***NZ***: Apo-Prazo; Hyprosin†; Pratsiol†; ***S.Afr.***: Pratsiol; ***Singapore***: Apo-Prazo; Atodel; Minipress; Mizosin; ***Spain***: Minipres; ***Thai.***: Atodel; Hyposin; Lopress; Mima; Minipress; Polypress; Pressin; ***Turk.***: Minipress; ***UK***: Hypovase; ***USA***: Minipress; ***Venez.***: Minpres.

Pharmacopoeial Preparations
BP 2014: Prazosin Tablets;
USP 36: Prazosin Hydrochloride Capsules.

Probucol *(BAN, USAN, rINN)*

DH-581; Probucolum; Пробукол.
4,4′-(Isopropylidenedithio)bis(2,6-di-*tert*-butylphenol).
$C_{31}H_{48}O_2S_2$=516.8.
CAS — 23288-49-5.
ATC — C10AX02.
ATC Vet — QC10AX02.
UNII — 93CTH044XT.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Probucol). A white to off-white, crystalline powder. Insoluble in water; soluble in alcohol and in petroleum spirit; freely soluble in chloroform and in propyl alcohol. Protect from light.

Profile

Probucol is a lipid regulating drug that has been used in the treatment of hyperlipidaemias (p. 1248.1). It lowers total plasma-cholesterol concentrations, mainly by reducing low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein (HDL)-cholesterol concentrations but has little effect on triglyceride or very-low-density lipoprotein (VLDL)-cholesterol concentrations. It has also been used to prevent restenosis after reperfusion and revascularisation procedures (below), and in scleroderma.

Probucol prolongs the QT interval and has been associated with cardiac arrhythmias.

Reperfusion and revascularisation procedures. Restenosis is common after percutaneous coronary revascularisation procedures (p. 1259.2) and various drugs have been tried for its prevention. Probucol, started a few weeks before the procedure, has been reported to reduce the rate of restenosis after coronary angioplasty,[1] and to reduce the need for repeat interventions,[1,2] although another study[3] found no effect.

1. Tardif J-C, *et al.* Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. *N Engl J Med* 1997; 337: 365–72.
2. Daida H, *et al.* Effect of probucol on repeat revascularization rate after percutaneous transluminal coronary angioplasty (from the Probucol Angioplasty Restenosis Trial [PART]). *Am J Cardiol* 2000; 86: 550–2.
3. Nunes GL, *et al.* Role of probucol in inhibiting intimal hyperplasia after coronary stent implantation: a randomized study. Abstract: *Am Heart J* 2006; 152: 914. Full version: http://www.ahjonline.com/article/S0002-8703(06)00463-7/pdf (accessed 07/08/07)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Lorelco†; ***China***: Chang Tai (畅泰); Zhile (之乐); ***Philipp.***: Lorelco; ***Thai.***: Lurselle.

Pharmacopoeial Preparations
USP 36: Probucol Tablets.

Procainamide Hydrochloride

(BANM, rINNM)

Hidrocloruro de procainimida; Novocainamidum; Procainamida, hidrocloruro de; Procainamide, Chlorhydrate de; Procainamidhydrochlorid; Procainamidi Chloridum; Procainamidi hydrochloridum; Prokainiamidihydrokloridi; Prokainamid-hidroklorid; Prokainamid-hydrochlorid; Prokainamid-hydroklorid; Prokainamido hidrochloridas; Prokainamidu chlorowodorek; Прокаинамида Гидрохлорид.
4-Amino-*N*-(2-diethylaminoethyl)benzamide hydrochloride.
$C_{13}H_{21}N_3O$,HCl=271.8.
CAS — 51-06-9 (procainamide); 614-39-1 (procainamide hydrochloride).
ATC — C01BA02.
ATC Vet — QC01BA02.
UNII — S4064O0LX.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Procainamide Hydrochloride). A white or very slightly yellow, hygroscopic, crystalline powder. Very soluble in water; freely soluble in alcohol; slightly soluble in acetone. A 10% solution in water has a pH of 5.6 to 6.3. Store in airtight containers. Protect from light.

USP 36: (Procainamide Hydrochloride). A white to tan, odourless, crystalline powder. Very soluble in water; soluble in alcohol; slightly soluble in chloroform; very slightly soluble in ether and in benzene. A 10% solution in water has a pH of 5.0 to 6.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Stability. Procainamide is more stable in neutral solutions such as sodium chloride, than in acidic solutions such as glucose, but patients requiring intravenous procainamide often have heart failure and cannot tolerate the sodium load associated with sodium chloride injections. The stability of procainamide in glucose 5% is improved by neutralising the glucose using sodium bicarbonate, or storing the admixture at 5 degrees. The concentration of procainamide remained above 90% of the initial concentration for 24 hours if the glucose was first neutralised and this was considered more practical than refrigeration if extended stability was required.[1]

The compound formed by mixing procainamide hydrochloride with glucose 5% was shown to be a mixture of α- and β-glucosylamines[2] and about 10 to 15% of the procainamide was lost in this way after 10 hours at room temperature.

An oral liquid,[3] prepared from procainamide capsules, containing 5, 50, or 100 mg/mL of the hydrochloride was stable for at least 6 months when stored at 4 degrees to 6 degrees.

1. Raymond GG, *et al.* Stability of procainamide hydrochloride in neutralized 5% dextrose injection. *Am J Hosp Pharm* 1988; 45: 2513–17.
2. Sianipar A, *et al.* Chemical incompatibility between procainamide hydrochloride and glucose following intravenous admixture. *J Pharm Pharmacol* 1994; 46: 951–5.
3. Metras JL *et al.* Stability of procainamide hydrochloride in an extemporaneously compounded oral liquid. *Am J Hosp Pharm* 1992; 49: 1720–4.

Uses and Administration

Procainamide is a class Ia antiarrhythmic (p. 1243.1); it has properties similar to those of quinidine (p. 1481.3).

Procainamide is usually reserved for the short-term management of severe or symptomatic ventricular arrhythmias (p. 1266.1) such as those following myocardial infarction. It may also be used in the management of atrial fibrillation.

Therapeutic effect is generally associated with plasma concentrations of 3 to 10 micrograms/mL. The dose of procainamide hydrochloride required will depend on the age, renal and hepatic function, and underlying cardiac condition of the patient: an adult with normal renal function generally requires up to 50 mg/kg daily in divided oral doses every 3 hours. Higher doses may be necessary for atrial arrhythmias. Modified-release preparations are available, and these are usually given at intervals of 6 or 12 hours.

In an emergency and under continuous ECG and blood pressure monitoring, procainamide hydrochloride may be given intravenously. The injection should be diluted in glucose 5% to permit better control of the speed of injection, and should be given in doses of 100 mg every 5 minutes at a rate not exceeding 50 mg/minute until the arrhythmia has been suppressed or a maximum dose of 1 g has been reached. A response may be obtained after 100 to 200 mg has been given and more than 500 or 600 mg is not generally required. Alternatively, procainamide hydrochloride may be given by continuous infusion of 500 to 600 mg over 25 to 30 minutes. Therapeutic plasma concentrations may then be maintained by infusion at a rate of 2 to 6 mg/minute. When transferring to oral therapy, a period of about 3 to 4 hours should elapse between the last intravenous dose and the first oral dose.

Procainamide hydrochloride has also been given intramuscularly.

Procainamide hydrochloride may need to be given in reduced doses or at longer dosing intervals in the elderly and in patients with hepatic or renal impairment. For use in children, see below.

Acecainide (*N*-acetylprocainamide), the active metabolite of procainamide, has class III antiarrhythmic activity and has been used in ventricular arrhythmias.

References.

1. Schreibman DS, *et al.* Usefulness of procainamide challenge for electrophysiologic arrhythmia risk stratification. *Am J Cardiol* 2004; 94: 1435–8.
2. Kochiadakis GE, *et al.* A comparative study of the efficacy and safety of procainamide versus propafenone versus amiodarone for the conversion of recent-onset atrial fibrillation. *Am J Cardiol* 2007; 99: 1721–5.
3. Stiell IG, *et al.* Emergency department use of intravenous procainamide for patients with acute atrial fibrillation or flutter. *Acad Emerg Med* 2007; 14: 1158–64.
4. Contreras ZE, Ximena ZS. Eficacia de procainamida en el tratamiento de la fibrilación ventricular refractaria: descripción de 4 casos clínicos y revisión de la literatura. *Rev Esp Anestesiol Reanim* 2009; 56: 511–4.

Administration in children. Procainamide hydrochloride has been used successfully in children.[1] In a study in 5 children treated with procainamide for various cardiac arrhythmias the mean elimination half-life was found to be 1.7 hours, and the plasma clearance was higher than that reported in adults.[2] In contrast the total serum clearance of procainamide in 3 neonates with supraventricular tachycardia was found to be similar to that in adults and the mean elimination half-life was 5.3 hours.[3] A loading dose of 10 to 12 mg/kg intravenously was given followed by a continuous infusion of 20 to 75 micrograms/kg per minute. Another, retrospective, study[4] in neonates given procainamide by continuous intravenous infusion found that the mean dose to achieve stable therapeutic drug concentrations was between 37 and 38 micrograms/kg per minute. It was considered that the required doses were not significantly different from those in older children, but doses might need to be reduced in premature infants and those with renal impairment; of 5 patients who developed supratherapeutic drug concentrations, 4 were premature and all had creatinine clearance below 30 mL/minute.

An oral dose of 15 to 50 mg/kg (maximum 4 g) daily given every 3 to 6 hours has been used in children.

1. Chang PM, *et al.* Amiodarone versus procainamide for the acute treatment of recurrent supraventricular tachycardia in pediatric patients. *Circ Arrhythm Electrophysiol* 2010; 3: 134–40.
2. Singh S, *et al.* Procainamide elimination kinetics in pediatric patients. *Clin Pharmacol Ther* 1982; 32: 607–11.
3. Bryson SM, *et al.* Therapeutic monitoring and pharmacokinetic evaluation of procainamide in neonates. *DICP Ann Pharmacother* 1991; 25: 68–71.
4. Moffett BS, *et al.* Therapeutic levels of intravenous procainamide in neonates: a retrospective assessment. *Pharmacotherapy* 2006; 26: 1687–93.

Adverse Effects

Cardiac effects occur particularly during intravenous use of procainamide and in overdose. Rapid intravenous dosage may result in severe hypotension, ventricular fibrillation, and asystole. High plasma concentrations are also associated with impaired cardiac conduction.

Hypersensitivity reactions to procainamide are common. Procainamide is a frequent cause of drug-induced SLE and the incidence has been reported to be as high as 30% during long-term use. Antinuclear antibodies may be detected in a high proportion of patients, but they do not necessarily develop the symptoms of SLE, which include arthralgia, arthritis, myalgia, pleural effusion, pericarditis, and fever. Agranulocytosis, eosinophilia, neutropenia, thrombocytopenia, and haemolytic anaemia have been reported. Other symptoms of hypersensitivity not necessarily related to SLE may also occur including hepatomegaly, angioedema, rashes, pruritus, urticaria, flushing, and hypergammaglobulinaemia.

Anorexia, nausea, vomiting, a bitter taste, and diarrhoea are more common with higher oral doses. Effects on the CNS such as mental depression, dizziness, and psychosis with hallucinations, have been reported.

Incidence of adverse effects. Out of 488 hospitalised patients in the Boston Collaborative Drug Surveillance Program who had received procainamide, 45 had acute adverse effects attributed to the drug.[1] Life-threatening reactions included heart block (3), tachyarrhythmias (2), and bradycardia and/or hypotension (2). Other reactions included gastrointestinal upsets (19), pyrexia (8), bradycardia and hypotension (5), tachyarrhythmias (3), heart block (1), eosinophilia (1), and urticaria (1).

1. Lawson DH, Jick H. Adverse reactions to procainamide. *Br J Clin Pharmacol* 1977; 4: 507–11.

Effects on the blood. Adverse haematological effects reported during procainamide therapy include neutropenia,[1-3] agranulocytosis,[2-6] thrombocytopenia,[5] haemolytic anaemia,[7] and pancytopenia.[8] These disorders are usually reversible on withdrawing procainamide although some fatalities have been reported.[3,4] It has been suggested[2,6] that agranulocytosis or severe neutropenia is more likely in patients taking modified-release preparations, but others have found no difference in the incidence between modified-release and conventional-release preparations.[3] An increased risk of agranulocytosis with procainamide has been documented in one large study.[9] Although the precise estimate of excess risk could not be calculated, the order of magnitude was about 3 per million exposed for up to one week. This excess risk was low and of little relevance in the initial choice of therapy.

1. Riker J, *et al.* Bone marrow granulomas and neutropenia associated with procainamide. *Arch Intern Med* 1978; 138: 1731–2.
2. Ellrodt AG, *et al.* Severe neutropenia associated with sustained-release procainamide. *Ann Intern Med* 1984; 100: 197–201.
3. Meyers DG, *et al.* Severe neutropenia associated with procainamide: comparison of sustained release and conventional preparations. *Am Heart J* 1985; 109: 1393–5.
4. Fleet S. Agranulocytosis, procainamide, and phenytoin. *Ann Intern Med* 1984; 100: 616–17.
5. Christensen DJ, *et al.* Agranulocytosis, thrombocytopenia, and procainamide. *Ann Intern Med* 1984; 100: 918.
6. Thompson JF, *et al.* Procainamide agranulocytosis: a case report and review of the literature. *Curr Ther Res* 1988; 44: 872–81.
7. Kleinman S, *et al.* Positive direct antiglobulin tests and immune hemolytic anemia in patients receiving procainamide. *N Engl J Med* 1984; 311: 809–12.
8. Bluming AZ, *et al.* Severe transient pancytopenia associated with procainamide ingestion. *JAMA* 1976; 236: 2520–1.
9. Kelly JP, *et al.* Risks of agranulocytosis and aplastic anemia in relation to the use of cardiovascular drugs: The International Agranulocytosis and Aplastic Anemia Study. *Clin Pharmacol Ther* 1991; 49: 330–41.

Effects on the gastrointestinal tract. Pseudo-obstruction of the bowel occurred in a diabetic patient when given procainamide both orally and intravenously. It was believed that the anticholinergic properties of procainamide and the diabetic state contributed to the severe hypomotility of the gastrointestinal tract.[1]

1. Peterson AM, *et al.* Procainamide-induced pseudo-obstruction in a diabetic patient. *DICP Ann Pharmacother* 1991; 25: 1334–5.

Effects on the heart. Procainamide prolongs the QT interval and has been associated with the development of torsade de pointes,[1,2] and fatal cardiovascular toxicity has been reported[3] in patients with renal impairment. Toxicity appears to be related to accumulation of the major metabolite, *N*-acetylprocainamide, and haemodialysis has been used to reduce plasma concentrations and control symptoms,[1,4] although its benefits have been disputed (see Dialysis, under Treatment of Adverse Effects, below). However, symptoms developed in 1 patient[2] despite plasma concentrations of both procainamide and *N*-acetyl procainamide being within the therapeutic range.

1. Nguyen KPV, *et al.* N-Acetylprocainamide, torsades de pointes, and hemodialysis. *Ann Intern Med* 1986; 104: 283–4.
2. Habbab MA, El-Sherif N. Drug-induced torsades de pointes: role of early afterdepolarizations and dispersion of repolarization. *Am J Med* 1990; 89: 241–6.
3. Vlasses PH, *et al.* Lethal accumulation of procainamide metabolite in severe renal insufficiency. *Am J Nephrol* 1986; 6: 112–16.
4. Stevenson WG, Weiss J. Torsades de pointes due to N-acetylprocainamide. *Pacing Clin Electrophysiol* 1985; 8: 528–31.

Effects on the liver. There have been reports of granulomatous hepatitis[1] and intrahepatic cholestasis[2,3] due to hypersensitivity reactions in patients taking procainamide. Fever and elevation of liver enzyme values also occurred. The reactions were reversible on withdrawing procainamide.

1. Rotmensch HH, *et al.* Granulomatous hepatitis: a hypersensitivity response to procainamide. *Ann Intern Med* 1978; 89: 646–7.
2. Ahn C-S, Tow DE. Intrahepatic cholestasis due to hypersensitivity reaction to procainamide. *Arch Intern Med* 1990; 150: 2589–90.
3. Chuang LC, *et al.* Possible case of procainamide-induced intrahepatic cholestatic jaundice. *Ann Pharmacother* 1993; 27: 434–7.

Effects on mental function. Acute psychosis has been reported[1] in patients receiving therapy with procainamide.

1. Bizjak ED, *et al.* Procainamide-induced psychosis: a case report and review of the literature. *Ann Pharmacother* 1999; 33: 948–51.

Effects on the muscles. Procainamide may affect neuromuscular transmission and there have been reports of severe generalised skeletal muscle weakness[1-3] in patients receiving procainamide. In 2 patients this was associated with respiratory failure[1,2] and developed shortly after starting therapy. Concentrations of procainamide and its *N*-acetyl metabolite exceeded the normal therapeutic ranges and rapid cycling peritoneal dialysis was used to remove the drug in 1 patient.[2] Adverse muscle symptoms are a feature of procainamide-induced lupus erythematosus (see below), but in such instances symptoms usually develop on long-term treatment.

1. Lewis CA, *et al.* Myopathy after short term administration of procainamide. *BMJ* 1986; 292: 593–4.
2. Javaheri S, *et al.* Diaphragmatic paralysis. *Am J Med* 1989; 86: 623–4.
3. Sayler DJ, DeJong DJ. Possible procainamide-induced myopathy. *DICP Ann Pharmacother* 1991; 25: 436.

Lupus erythematosus. Procainamide is a well-known cause of drug-induced lupus erythematosus.[1,2] It occurs in about 20% of patients on long-term therapy,[2] although the majority of patients taking procainamide for more than 1 year have detectable antinuclear antibodies. There is some evidence[3] that slow acetylators are more likely to develop antibodies than rapid acetylators, and that the antibodies appear more rapidly in slow acetylators, but this may not correlate with the development of clinical symptoms.[4] The clinical syndrome may include fever, polyarthritis, arthralgia, myalgia, and pleuropulmonary and pericardial features, and is usually spontaneously reversible on withdrawal of procainamide.

1. Price EJ, Venables PJW. Drug-induced lupus. *Drug Safety* 1995; 12: 283–90.
2. Rubin RL. Drug-induced lupus. *Toxicology* 2005; 209: 135–47.
3. Woosley RL, *et al.* Effect of acetylator phenotype on the rate at which procainamide induces antinuclear antibodies and the lupus syndrome. *N Engl J Med* 1978; 298: 1157–9.
4. Mongey A-B, *et al.* Acetylation status is associated with serological changes but not clinically significant disease in patients receiving procainamide. *J Rheumatol* 1999; 26: 1721–6.

Treatment of Adverse Effects

In overdosage with procainamide treatment is largely symptomatic and supportive. Activated charcoal may be considered if the patient presents within 1 hour of ingestion. The ECG, blood pressure, and renal function should be monitored. Supportive measures include correction of hypotension, assisted ventilation, and electrical pacing. Haemodialysis or haemoperfusion increase the elimination of procainamide and *N*-acetylprocainamide, see below.

SLE will normally respond to withdrawal of procainamide but corticosteroids may be required.

Dialysis. In the UK, the National Poisons Information Service does not recommend the use of haemodialysis or haemofiltration in the treatment of poisoning with class Ia antiarrhythmics. Nonetheless, both procainamide and *N*-acetylprocainamide are removed by haemodialysis, and there are reports[1-4] of the successful use of haemodialysis in patients with procainamide toxicity. However, toxicity has occurred in patients undergoing regular haemodialysis,[2,5,6] suggesting that some accumulation still takes place, and rebound increases in plasma concentrations have also been reported[4,7] after dialysis. Haemoperfusion[5,7] and haemofiltration[6] have also been used, and may be more effective. Peritoneal dialysis may also remove a small amount of procainamide and *N*-acetylprocainamide,[7] and

there has been a report[6] of the successful use of rapid cycling peritoneal dialysis in a patient on maintenance peritoneal dialysis who developed procainamide-induced diaphragmatic paralysis.

1. Atkinson AJ, *et al.* Hemodialysis for severe procainamide toxicity: clinical and pharmacokinetic observations. *Clin Pharmacol Ther* 1976; **20**: 585–92.
2. Stevenson WG, Weiss J. Torsades de pointes due to N-acetylprocainamide. *Pacing Clin Electrophysiol* 1985; **8**: 528–31.
3. Nguyen KPV, *et al.* N-Acetylprocainamide, torsades de pointes, and hemodialysis. *Ann Intern Med* 1986; **104**: 283–4.
4. Rosansky SJ, Brady ME. Procainamide toxicity in a patient with acute renal failure. *Am J Kidney Dis* 1986; **7**: 502–6.
5. Braden GL, *et al.* Hemoperfusion for treatment of N-acetylprocainamide intoxication. *Ann Intern Med* 1986; **105**: 64–5.
6. Domoto DT, *et al.* Removal of toxic levels of N-acetylprocainamide with continuous arteriovenous hemofiltration or continuous arteriovenous hemodiafiltration. *Ann Intern Med* 1987; **106**: 550–2.
7. Low CL, *et al.* Relative efficacy of haemoperfusion, haemodialysis and CAPD in the removal of procainamide and NAPA in a patient with severe procainamide toxicity. *Nephrol Dial Transplant* 1996; **11**: 881–4.
8. Javaheri S, *et al.* Diaphragmatic paralysis. *Am J Med* 1989; **86**: 623–4.

Precautions

Procainamide is contra-indicated in heart block (unless the patient has a pacemaker) and in SLE, and should be used with caution in patients with myocardial damage or severe organic heart disease. It has been advised that procainamide should not be used in heart failure or hypotension. Patients with torsade de pointes may deteriorate if given procainamide. If it is used to treat atrial tachycardia patients may need to be pre-treated with digoxin. Procainamide should preferably not be used in patients with myasthenia gravis or digoxin toxicity. There may be cross-sensitivity between procaine and procainamide.

Accumulation of procainamide may occur in patients with heart failure or hepatic or renal impairment and dosage reduction may be necessary.

Blood counts and screening for lupus erythematosus and serum antinuclear factor should be carried out regularly during therapy.

Intravenous use of procainamide may lead to severe hypotension; it should be injected slowly and blood pressure and ECG should be monitored.

Breast feeding. There was evidence of accumulation of procainamide and *N*-acetylprocainamide in the breast milk of a woman taking procainamide 500 mg four times daily.[1] Milk and serum samples were obtained at three-hourly intervals for 15 hours. Mean serum concentrations of the drug and metabolite were found to be 1.1 and 1.6 micrograms/mL respectively; those in the milk were 5.4 and 3.5 micrograms/mL respectively. The mean milk:serum ratios were 4.3 (range 1.0 to 7.3) and 3.8 (range 1.0 to 6.2) respectively. However, it was considered that the amount ingested by the infant would not yield clinically significant serum concentrations. Although licensed product information states that procainamide should be avoided in breast-feeding women, there have been no reports of adverse effects in infants, and the American Academy of Pediatrics considers[2] that its use is therefore usually compatible with breast feeding.

1. Pittard WB, Glazier H. Procainamide excretion in human milk. *J Pediatr* 1983; **102**: 631–3.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Interactions

Procainamide may enhance the effects of antihypertensives, other antiarrhythmics and arrhythmogenic drugs, antimuscarinics, and neuromuscular blockers, and diminish those of parasympathomimetics, such as neostigmine. Procainamide is actively secreted by kidney tubules and interactions may occur with drugs secreted by the same pathway, such as cimetidine and trimethoprim.

Alcohol. The total body clearance of procainamide is increased by alcohol[1] and the elimination half-life reduced. The acetylation rate of procainamide is also increased resulting in a greater proportion of drug present as the active metabolite *N*-acetylprocainamide.

1. Olsen H, Mørland J. Ethanol-induced increase in procainamide acetylation in man. *Br J Clin Pharmacol* 1982; **13**: 203–8.

Antacids. Procainamide is adsorbed by some antacids and reduced bioavailability has been reported[1] in healthy subjects given procainamide with *kaolin-pectin*; the authors recommended that procainamide and adsorbents should not be used together.

1. Al-Shora HI, *et al.* Interactions of procainamide, verapamil, guanethidine and hydralazine with adsorbent antacids and antidiarrhoeal mixtures. *Int J Pharmaceutics* 1988; **47**: 209–13.

Antiarrhythmics. *Amiodarone* given orally alters the pharmacokinetic properties of an intravenous dose of procainamide,[1] decreasing clearance and prolonging the plasma elimination half-life. The dosage of intravenous procainamide should be reduced by 20 to 30% during concurrent use. Increased serum-procainamide concentrations have also been reported[2] in patients stabilised on oral procainamide who had amiodarone added to their therapy; the dosage of procainamide had to be reduced in some patients due to signs of toxicity. *Quinidine* has also been reported[3] to increase plasma-procainamide concentrations.

1. Windle J, *et al.* Pharmacokinetic and electrophysiologic interactions of amiodarone and procainamide. *Clin Pharmacol Ther* 1987; **41**: 603–10.
2. Saal AK, *et al.* Effect of amiodarone on serum quinidine and procainamide levels. *Am J Cardiol* 1984; **53**: 1264–7.
3. Hughes B, *et al.* Increased procainamide plasma concentrations caused by quinidine: a new drug interaction. *Am Heart J* 1987; **114**: 908–9.

Antibacterials. The renal clearance of procainamide and *N*-acetylprocainamide is reduced by *trimethoprim*[1,2] through competition for renal tubular secretion. Serum concentrations may be increased with a resulting increase in pharmacodynamic response. The fluoroquinolones *ciprofloxacin*,[3] *levofloxacin*,[3] and *ofloxacin*[4] have also been reported to reduce the renal clearance of procainamide.

1. Kosoglou T, *et al.* Trimethoprim alters the disposition of procainamide and N-acetylprocainamide. *Clin Pharmacol Ther* 1988; **44**: 467–77.
2. Vlasses PH, *et al.* Trimethoprim inhibition of the renal clearance of procainamide and N-acetylprocainamide. *Arch Intern Med* 1989; **149**: 1350–3.
3. Bauer LA, *et al.* Levofloxacin and ciprofloxacin decrease procainamide and N-acetylprocainamide renal clearances. *Antimicrob Agents Chemother* 2005; **49**: 1649–51.
4. Martin DE, *et al.* Effects of ofloxacin on the pharmacokinetics and pharmacodynamics of procainamide. *J Clin Pharmacol* 1996; **36**: 85–91.

Histamine H_2-antagonists. Histamine H_2-antagonists compete with other basic drugs for renal tubular secretion. *Cimetidine* reduces the renal clearance of procainamide and *N*-acetylprocainamide[1,2] and a dosage reduction may be necessary. Increases[3,4] and decreases[4] in renal and metabolic clearances of procainamide have occurred with *ranitidine*.

1. Christian CD, *et al.* Cimetidine inhibits renal procainamide clearance. *Clin Pharmacol Ther* 1984; **36**: 221–7.
2. Somogyi A, *et al.* Cimetidine-procainamide pharmacokinetic interaction in man: evidence of competition for tubular secretion of basic drugs. *Eur J Clin Pharmacol* 1983; **25**: 339–45.
3. Somogyi A, Bochner F. Dose and concentration dependent effect of ranitidine on procainamide disposition and renal clearance in man. *Br J Clin Pharmacol* 1984; **18**: 175–81.
4. Rocci ML, *et al.* Ranitidine-induced changes in the renal and hepatic clearances of procainamide are correlated. *J Pharmacol Exp Ther* 1989; **248**: 923–8.

Pharmacokinetics

Procainamide is readily and almost completely absorbed from the gastrointestinal tract. It is widely distributed throughout the body and is only about 15 to 20% bound to plasma proteins. The therapeutic effect of procainamide has been correlated with plasma concentrations of about 3 to 10 micrograms/mL in most patients; progressively severe toxicity is noted at concentrations above 12 micrograms/mL.

Some procainamide undergoes acetylation in the liver to *N*-acetylprocainamide, which also has antiarrhythmic properties. The rate of acetylation of procainamide is genetically determined, there being slow and fast acetylators. Procainamide also undergoes hydrolysis in plasma to para-aminobenzoic acid.

Procainamide is excreted in the urine by active renal secretion, 30 to 70% as unchanged procainamide, with the remainder as *N*-acetylprocainamide and other metabolites. The elimination half-life of procainamide is 2.5 to 5 hours and that of its acetyl metabolite 6 to 7 hours. *N*-Acetylprocainamide may represent a significant fraction of the total drug in the circulation.

Procainamide crosses the placenta and is distributed into breast milk.

References.

1. Grasela TH, Sheiner LB. Population pharmacokinetics of procainamide from routine clinical data. *Clin Pharmacokinet* 1984; **9**: 545–54.

Bioavailability. Modified-release procainamide preparations have been shown[1] to produce similar steady-state serum concentrations of procainamide and *N*-acetylprocainamide when compared with equivalent total doses of immediate-release capsules. However, tablet matrices of a modified-release preparation have been recovered from the stools of a patient with diarrhoea[2] and 3.5 g of procainamide was recovered in these matrices over an 18-hour collection period; the patient had correspondingly low plasma-procainamide concentrations.

1. Vlasses PH, *et al.* Immediate-release and sustained-release procainamide: bioavailability at steady state in cardiac patients. *Ann Intern Med* 1983; **98**: 613–14.
2. Woosley RL, *et al.* Antiarrhythmic therapy: clinical pharmacology update. *J Clin Pharmacol* 1984; **24**: 295–305.

The elderly. Reduced renal clearance of procainamide has been reported in the elderly.[1,2]

1. Reidenberg MM, *et al.* Aging and renal clearance of procainamide and acetylprocainamide. *Clin Pharmacol Ther* 1980; **28**: 732–5.
2. Bauer LA, *et al.* Influence of age, renal function and heart failure on procainamide clearance and n-acetylprocainamide serum concentrations. *Int J Clin Pharmacol Ther Toxicol* 1989; **27**: 213–16.

Hepatic impairment. In 20 healthy subjects and 20 patients with chronic liver disease given a single 500-mg oral dose of procainamide hydrochloride about 64 and 33% respectively of the dose was excreted in the urine within 6 hours.[1] Decreased procainamide acetylation in the patients compared with the control group was not correlated with the severity of liver disease, whereas decreased procainamide hydrolysis and increased procainamide-derived aminobenzoic acid acetylation appeared to be related to the degree of hepatic impairment. It was suggested that the decrease in excretion of procainamide and its metabolites in the urine of the patients with liver disease could be due to an impairment in oral absorption since renal function was within the normal range but the variations in acetylation and hydrolysis were related to hepatic function.

1. du Souich P, Erill S. Metabolism of procainamide and p-aminobenzoic acid in patients with chronic liver disease. *Clin Pharmacol Ther* 1977; **22**: 588–95.

Renal impairment. Procainamide and its active *N*-acetyl metabolite are mainly excreted in the urine and accumulation, particularly of the metabolite, may occur in renal impairment. A study[1] in 20 patients found that procainamide clearance correlated with renal function, and that the ratio of *N*-acetylprocainamide to procainamide in the serum increased as renal function declined. Fatal toxicity in patients with renal impairment and plasma-procainamide concentrations within the therapeutic range has been attributed[2] to accumulation of *N*-acetylprocainamide. Both procainamide and *N*-acetylprocainamide are removed by dialysis, although the benefit of these procedures has been disputed (see Dialysis under Treatment of Adverse Effects, p. 1476.3).

1. Bauer LA, *et al.* Influence of age, renal function and heart failure on procainamide clearance and n-acetylprocainamide serum concentrations. *Int J Clin Pharmacol Ther Toxicol* 1989; **27**: 213–16.
2. Vlasses PH, *et al.* Lethal accumulation of procainamide metabolite in severe renal insufficiency. *Am J Nephrol* 1986; **6**: 112–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Pronestyl†; *Braz.*: Procamide†; *Canad.*: Procan; *Gr.*: Biocoryl; Pronestyl; *India*: Pronestyl; *Irl.*: Pronestyl†; *NZ*: Pronestyl; *S.Afr.*: Pronestyl†; *Singapore*: Pronestyl; *Spain*: Biocoryl; *USA*: Procanbid†.

Pharmacopoeial Preparations

BP 2014: Procainamide Injection; Procainamide Tablets;
USP 36: Procainamide Hydrochloride Capsules; Procainamide Hydrochloride Extended-release Tablets; Procainamide Hydrochloride Injection; Procainamide Hydrochloride Tablets.

Propafenone Hydrochloride

(BANM, USAN, rINNM)

Fenopraine Hydrochloride; Hidrocloruro de fenopraina; Hidrocloruro de propafenona; Propafenon Hidroklorür; Propafenona, hidrocloruro de; Propafénone, chlorhydrate de; Propafenon-hydrochlorid; Propafenonhydrochlorid; Propafenonihydroklorid; Propafenoni Hydrochloridum; Propafenonihydroklorid; Propafenono hidrochloridas; SA-79; WZ-884642; WZ-884643; Пропафенона Гидрохлорид.

2'-(2-Hydroxy-3-propylaminopropoxy)-3-phenylpropiophenone hydrochloride.

$C_{21}H_{27}NO_3$,HCl=377.9

CAS — 54063-53-5 (propafenone); 34183-22-7 (propafenone hydrochloride).

ATC — C01BC03.

ATC Vet — QC01BC03.

UNII — 33XCH0HOCD.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Propafenone Hydrochloride). Colourless crystals or a white or almost white powder. Slightly soluble in cold water; soluble in hot water and in methyl alcohol; practically insoluble in alcohol. A 0.5% solution in water has a pH of 5.0 to 6.2.

USP 36: (Propafenone Hydrochloride). A white powder. Soluble in hot water and in methyl alcohol; slightly soluble in alcohol and in chloroform; very slightly soluble in acetone; insoluble in ether and in toluene. A 0.5% solution in water has a pH of 5.0 to 6.2. Store in airtight containers at a temperature between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Propafenone is a class Ic antiarrhythmic (p. 1243.1) with some negative inotropic and beta-adrenoceptor blocking

activity. It is used in the management of supraventricular and ventricular arrhythmias.

Treatment should be started under close monitoring of the ECG and blood pressure. The usual initial oral dose of propafenone hydrochloride is 150 mg three times daily and this may be increased, if necessary, at intervals of 3 to 4 days up to a maximum of 300 mg three times daily. Reduced doses may be appropriate in patients weighing less than 70 kg and in the elderly; dose reduction may also be necessary in hepatic impairment (see below).

Propafenone hydrochloride is available in some countries as a modified-release preparation. It has also been given by slow intravenous injection or by infusion.

Administration in hepatic impairment. The clearance of propafenone may be reduced in hepatic impairment; careful monitoring is required and lower doses should be considered. US licensed product information states that the dose should be only 20 to 30% of that given in normal hepatic function.

Administration in renal impairment. A study[1] of the disposition of propafenone found that renal function did not affect the pharmacokinetics of propafenone or 5-hydroxypropafenone, and another study[2] suggested that propafenone could be used safely for atrial fibrillation in patients with chronic renal failure. Nevertheless, UK and US licensed product information states that caution is necessary if propafenone is given to patients with renal impairment.

Propafenone does not appear to be removed by haemofiltration.[3]

1. Fromm MF, *et al.* Influence of renal function on the steady-state pharmacokinetics of the antiarrhythmic propafenone and its phase I and phase II metabolites. *Eur J Clin Pharmacol* 1995; 48: 279–83.
2. Napoli C, *et al.* Propafenone in the conversion of atrial fibrillation in patients suffering from chronic renal failure. *Am J Ther* 1997; 4: 130–3.
3. Seto W, *et al.* Propafenone disposition during continuous venovenous hemofiltration. *Ann Pharmacother* 1999; 33: 957–9.

Cardiac arrhythmias. Propafenone is effective in many cardiac arrhythmias.[1,2] It may have a role in the management of supraventricular arrhythmias (see p. 1266.1), including as a single oral loading dose for recent-onset atrial fibrillation.[3,4] It may also be used in ventricular arrhythmias, although in many cases non-pharmacological therapy is preferred. Successful use in children with various arrhythmias has also been reported.[5,6]

1. Capucci A, Boriani G. Propafenone in the treatment of cardiac arrhythmias: a risk-benefit appraisal. *Drug Safety* 1995; 12: 55–72.
2. Reimold SC, *et al.* Propafenone for the treatment of supraventricular tachycardia and atrial fibrillation: a meta-analysis. *Am J Cardiol* 1998; 82: 66N–71N.
3. Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-onset atrial fibrillation. *J Am Coll Cardiol* 2001; 37: 542–7.
4. Boriani G, *et al.* Oral loading with propafenone for conversion of recent-onset atrial fibrillation: a review on in-hospital treatment. *Drugs* 2002; 62: 415–23.
5. Heusch A, *et al.* Clinical experience with propafenone for cardiac arrhythmias in the young. *Eur Heart J* 1994; 15: 1050–6.
6. Janoušek J, Paul T. Safety of oral propafenone in the treatment of arrhythmias in infants and children (European Retrospective Multicenter Study). *Am J Cardiol* 1998; 81: 1121–4.

Adverse Effects

Propafenone can cause disturbances in cardiac conduction which can result in bradycardia, heart block, and sinus arrest. It may aggravate heart failure and may cause hypotension. In common with other antiarrhythmics, propafenone may induce or worsen arrhythmias in some patients.

Among the most common adverse effects are gastrointestinal intolerance, dry mouth, a bitter or metallic taste, dizziness, blurred vision, headache, and fatigue. Convulsions, blood dyscrasias, liver disorders, lupus erythematosus, rashes, impotence, and increased breathlessness and worsening of asthma have also been reported.

Effects on the heart. Propafenone may worsen ventricular arrhythmias and there have been reports[1,2] of fatal exacerbations occurring hours to days after starting treatment. Cardiovascular toxicity may also occur in overdosage.[3] Torsade de pointes has been reported[2,4,5] but appears to be less frequent than with class Ia antiarrhythmics. Toxicity may mimic Brugada syndrome,[6,7] and has been mistaken for acute myocardial infarction.[7] Hypertonic sodium bicarbonate infusion may be effective in treating cardiotoxicity induced by propafenone.[8]

1. Nathan AW, *et al.* Fatal ventricular tachycardia in association with propafenone, a new class IC antiarrhythmic agent. *Postgrad Med J* 1984; 60: 155–6.
2. Buss J, *et al.* Malignant ventricular tachyarrhythmias in association with propafenone treatment. *Eur Heart J* 1985; 6: 424–8.
3. Clarot F, *et al.* Fatal propafenone overdoses: case reports and a review of the literature. *J Anal Toxicol* 2003; 27: 595–9.
4. Rosengarten M, Brooks R. Torsade de pointes ventricular tachycardia in a hypothyroid patient treated with propafenone. *Can J Cardiol* 1987; 3: 234–9.
5. Hii JT, *et al.* Propafenone-induced torsade de pointes: cross-reactivity with quinidine. *Pacing Clin Electrophysiol* 1991; 14: 1568–70.
6. Hasdemir C, *et al.* Brugada-type ECG pattern and extreme QRS complex widening with propafenone overdose. *J Cardiovasc Electrophysiol* 2006; 17: 565–6.
7. Chutani S, *et al.* Propafenone-induced Brugada-like ECG changes mistaken as acute myocardial infarction. *Emerg Med J* 2008; 25: 117–18.
8. Brubacher J. Bicarbonate therapy for unstable propafenone-induced wide complex tachycardia. *CJEM* 2004; 6: 349–56.

Effects on the liver. A review of liver injury secondary to propafenone therapy concluded that it is a rare occurrence and appears to be due to hepatocellular injury, cholestasis, or a combination.[1]

1. Spinler SA, *et al.* Propafenone-induced liver injury. *Ann Pharmacother* 1992; 26: 926–8.

Effects on mental function. Delusions, hallucinations, and paranoia have been reported in an elderly patient after 2 doses of propafenone. The manufacturer had received reports of mania and psychosis.[1] Amnesia developed in a 61-year-old man 6 days after starting treatment with propafenone.[2] Symptoms resolved 6 to 7 hours after stopping the drug.

1. Robinson AJ. Paranoia after propafenone. *Pharm J* 1991; 247: 556.
2. Jones RJ, *et al.* Probable propafenone-induced transient global amnesia. *Ann Pharmacother* 1995; 29: 586–90.

Effects on the nervous system. Myoclonus has been reported in a patient receiving propafenone.[1] In another patient peripheral neuropathy developed 10 months after starting treatment but symptoms had resolved 6 months after stopping the drug.[2] There have also been reports of ataxia.[3]

1. Chua TP, *et al.* Myoclonus associated with propafenone. *BMJ* 1994; 308: 113.
2. Galasso PJ, *et al.* Propafenone-induced peripheral neuropathy. *Mayo Clin Proc* 1995; 70: 469–72.
3. Odeh M, *et al.* Propafenone-induced ataxia: report of three cases. *Am J Med Sci* 2000; 320: 151–3.

Lupus erythematosus. Symptoms of lupus erythematosus and raised antinuclear antibody titres were associated with propafenone therapy on 2 occasions in a 63-year-old woman.[1]

1. Guindo J, *et al.* Propafenone and a syndrome of the lupus erythematosus type. *Ann Intern Med* 1986; 104: 589.

Precautions

Propafenone is contra-indicated in patients with uncontrolled heart failure, conduction disturbances including heart block unless controlled by artificial pacing, cardiogenic shock (unless arrhythmia-induced), severe bradycardia, or pronounced hypotension. It may alter the endocardial pacing threshold and adjustment may be necessary in patients with pacemakers.

Propafenone has beta-blocking activity and may exacerbate obstructive airways disease; it should be used with great caution in such disorders and is contra-indicated in severe disease. Propafenone may aggravate myasthenia gravis and should be avoided in patients with this condition. Electrolyte disturbances should be corrected before beginning treatment. Propafenone should be used with caution in patients with hepatic or renal impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies propafenone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pregnancy and breast feeding. Experience in a patient given propafenone throughout the last trimester of pregnancy indicated that despite transplacental diffusion propafenone could safely be used at this time without harm to the fetus. Propafenone and its metabolite were detected in breast milk at concentrations considered to represent a markedly subtherapeutic dose to an infant.[1]

1. Libardoni M, *et al.* Transfer of propafenone and 5-OH-propafenone to foetal plasma and maternal milk. *Br J Clin Pharmacol* 1991; 32: 527–8.

Interactions

Propafenone is extensively metabolised by the cytochrome P450 enzyme system, mainly by the isoenzyme CYP2D6, although CYP1A2 and CYP3A4 are also involved. Interactions may therefore occur with other drugs that are metabolised by these enzymes. Plasma-propafenone concentrations may be reduced by enzyme inducers such as rifampicin; enzyme inhibitors, such as cimetidine, fluoxetine, quinidine, and HIV-protease inhibitors, may increase plasma-propafenone concentrations. Propafenone itself may alter the plasma concentrations of other drugs, including beta blockers p. 1321.3, ciclosporin p. 1957.2, desipramine p. 406.2, digoxin p. 1356.1, theophylline p. 1234.1, venlafaxine p. 456.3, and warfarin p. 1530.3. The absorption of propafenone may be reduced by orlistat. There may be an increased risk of arrhythmias if propafenone is given with other antiarrhythmics or arrhythmogenic drugs.

Antiarrhythmics. *Quinidine* inhibits the hepatic metabolism of propafenone and has been reported[1] to increase plasma-propafenone concentrations in extensive metabolisers;[1] the plasma concentration of the active 5-hydroxy metabolite was reduced and that of the *N*-depropyl metabolite increased but there was no change in the clinical response. Another study,[2] however, found that quinidine increased the beta-blocking effect of propafenone in extensive metabolisers, and a study[3] in patients with refractory atrial fibrillation found that addition of quinidine to propafenone was as effective and possibly better tolerated than increasing the propafenone dose.

1. Funck-Brentano C, *et al.* Genetically-determined interaction between propafenone and low dose quinidine: role of active metabolites in modulating net drug effect. *Br J Clin Pharmacol* 1989; 27: 435–44.
2. Mörike KE, Roden DM. Quinidine-enhanced beta-blockade during treatment with propafenone in extensive metabolizer human subjects. *Clin Pharmacol Ther* 1994; 55: 28–34.
3. Lau C-P, *et al.* Control of paroxysmal atrial fibrillation recurrence using combined administration of propafenone and quinidine. *Am J Cardiol* 2000; 86: 1327–32.

Antibacterials. *Rifampicin* has lowered steady-state plasma concentrations of propafenone with the reappearance of arrhythmia.[1]

1. Castel JM, *et al.* Rifampicin lowers plasma concentrations of propafenone and its antiarrhythmic effect. *Br J Clin Pharmacol* 1990; 30: 155–6.

Histamine H_2-antagonists. *Cimetidine* has been reported[1] to raise plasma-propafenone concentrations. The mean steady-state concentration increased by 22% but the wide interindividual variability meant this change was not significant.

1. Pritchett ELC, *et al.* Pharmacokinetic and pharmacodynamic interactions of propafenone and cimetidine. *J Clin Pharmacol* 1988; 28: 619–24.

Pharmacokinetics

Propafenone is readily and almost completely absorbed from the gastrointestinal tract. It is metabolised in the liver, largely by the cytochrome P450 isoenzyme CYP2D6, but also to a small extent by CYP1A2 and CYP3A4; the extent of metabolism is genetically determined. In subjects with the extensive metaboliser phenotype there is extensive first-pass metabolism to two active metabolites, 5-hydroxypropafenone and *N*-depropylpropafenone, and to other minor inactive metabolites. In the small proportion of subjects with the slow metaboliser phenotype (lacking CYP2D6) little or no 5-hydroxypropafenone is formed. The bioavailability of propafenone is dependent upon metaboliser phenotype but more importantly on dosage as the first-pass metabolism is saturable. In practice doses are high enough to compensate for differences in phenotype. Propafenone and its metabolites also undergo glucuronidation.

Propafenone is more than 95% protein bound.

Propafenone is excreted in the urine and faeces mainly in the form of conjugated metabolites. The elimination half-life is reported to be 2 to 10 hours in extensive metabolisers and 10 to 32 hours in slow metabolisers.

Propafenone crosses the placenta and is distributed into breast milk.

General references.

1. Hii JTY, *et al.* Clinical pharmacokinetics of propafenone. *Clin Pharmacokinet* 1991; 21: 1–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Normorytmin; *Austria*: Rytmonorma; *Belg.*: Rytmonorm; *Braz.*: Ritmonorm; *Canad.*: Rythmol; *Chile*: Ritmocor; *China*: Rytmonorm (悦复隆); *Cz.*: Prolekofen; Propanorm; Rytmonorm; *Denm.*: Rytmonorm; *Fin.*: Rytmonorm; *Fr.*: Rythmol; *Ger.*: Cuxafenon†; Rytmo-Puren†; Rytmonorm; *Gr.*: Rytmonorm†; *Hong Kong*: Rytmonorm; *Hung.*: Rytmonorm; *Indon.*: Rytmonorm; *Irl.*: Arythmol; *Israel*: Profex; Rythmex; *Ital.*: Cardiofenone; Fenorit; Normarit; Rytmonorm; *Malaysia*: Rytmonorm; *Mex.*: Biopafen; Nistaken; Norfenon; *Neth.*: Rytmonorm; *NZ*: Rytmonorm; *Philipp.*: Rytmocard†; *Pol.*: Polfenon; Rytmonorm; *Port.*: Arythmol; Rytmonorm; *Rus.*: Propanorm (Пропанорм); Ritmonorm (Ритмонорм); Rytmonorm (Ритмонорм)†; *S.Afr.*: Rythmol; *Singapore*: Rytmonorm; *Spain*: Rytmonorm; *Swed.*: Rytmonorm; *Switz.*: Rytmonorm; *Thai.*: Rytmonorm; *Turk.*: Rytmonorm; *UK*: Arythmol; *Ukr.*: Propanorm (Пропанорм); *USA*: Rythmol; *Venez.*: Rytmonorm.

Propatylnitrate *(BAN, rINN)*

ETTN; Ettriol Trinitrate; Propatilnitrato; Propatyl Nitrate (USAN); Propatylnitrat; Propatylnitratum; Propatyylinitraatti; Trinettriol; Win-9317; Пропатилнитрат.

2-Ethyl-2-hydroxymethylpropane-1,3-diol trinitrate.

$C_6H_{11}N_3O_9$=269.2
CAS — 2921-92-8.
ATC — C01DA07.
ATC Vet — QC01DA07.
UNII — AJT2YN495R.

Profile

Propatylnitrate is a vasodilator with general properties similar to those of glyceryl trinitrate (p. 1393.3) that has been used in angina pectoris.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Sustrate.

Propentofylline *(BAN, rINN)*

HWA-285; Propentofilina; Propentofylliini; Propentofyllin; Propentofyllinum; Пропентофиллин.
3-Methyl-1-(5-oxohexyl)-7-propylxanthine.
$C_{15}H_{22}N_4O_3$=306.4
CAS — 55242-55-2.
ATC — N06BC02.
ATC Vet — QC04AD90; QN06BC02; QR03DA90.
UNII — 5RTA398U4H.

Profile

Propentofylline is a xanthine derivative that has been investigated in cerebrovascular disorders including dementia. It is also used in veterinary medicine.

References.

1. Frampton MA, *et al.* Propentofylline for dementia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 22/10/09).
2. Bath PMW, Bath-Hextall FJ. Pentoxifylline, propentofylline and pentifylline for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 22/10/09).

Propranolol Hydrochloride

(BANM, USAN, rINNM) ⊗

AY-64043; Hidrocloruro de propranolol; ICI-45520; NSC-91523; Propanolol-hidroklorid; Propanololi Hydrochloridum; Propranolol, Chlorhydrate de; Propranolol, hidrocloruro de; Propranolol Hidroklorür; Propranolol-hydrochlorid; Propranololhydrochlorid; Propranololhydroklorid; Propranololi Hydrochloridum; Propranololhydroklorid; Propranololio hidrochloridas; Propranololu chlorowodorek; Пропранолола Гидрохлорид.
(±)-1-Isopropylamino-3-(1-naphthyloxy)propan-2-ol hydrochloride.
$C_{16}H_{21}NO_2$,HCl=295.8
CAS — 525-66-6 (propranolol); 13013-17-7 (propranolol); 318-98-9 (propranolol hydrochloride); 3506-09-0 (propranolol hydrochloride).
ATC — C07AA05.
ATC Vet — QC07AA05.
UNII — F8A3652H1V.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Propranolol Hydrochloride). A white or almost white powder. Soluble in water and in alcohol.

USP 36: (Propranolol Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble in water and in alcohol; slightly soluble in chloroform; practically insoluble in ether. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Stability. In aqueous solutions propranolol decomposes with oxidation of the isopropylamine side-chain, accompanied by a reduction in pH and discoloration of the solution. Solutions are most stable at pH 3 and decompose rapidly when alkaline.

Uses and Administration

Propranolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to have membrane-stabilising properties, but does not possess intrinsic sympathomimetic activity.

Propranolol is used as the hydrochloride in the management of hypertension (p. 1251.1), phaeochromocytoma (p. 1278.1), angina pectoris (p. 1254.3), myocardial infarction (p. 1257.1), and cardiac arrhythmias (p. 1266.1). It is also used in hypertrophic cardiomyopathy (p. 1261.3). It is used to control symptoms of sympathetic overactivity in the management of hyperthyroidism (p. 2332.2), anxiety disorders (p. 1028.1), and tremor (p. 1318.3). Other indications include the prophylaxis of migraine (p. 670.3) and of upper gastrointestinal bleeding in patients with portal hypertension (see Variceal Haemorrhage under Monoethanolamine Oleate, p. 2563.1).

Propranolol hydrochloride is usually given orally. In **hypertension** it is given in initial doses of 40 to 80 mg twice daily increased as required to a usual range of 160 to 320 mg daily; some patients may require up to 640 mg daily. Propranolol is *not* suitable for the emergency treatment of hypertension; it should not be given intravenously in hypertension.

In **phaeochromocytoma**, patients treated surgically may be given 60 mg daily on the 3 days before the operation, always with alpha blockade. If the tumour is inoperable prolonged treatment may be given with a daily dose of 30 mg.

In **angina**, initial doses of propranolol hydrochloride 40 mg given 2 or 3 times daily are increased as required to a usual range of 120 to 240 mg daily. Some patients may require up to 320 mg daily.

Propranolol hydrochloride is given within 5 to 21 days of **myocardial infarction** in doses of 40 mg given four times daily for 2 or 3 days followed by 80 mg twice daily. Another regimen is to give 180 to 240 mg daily in divided doses.

Propranolol may be given in doses of 30 to 160 mg daily in divided doses in the long-term management of **cardiac arrhythmias**. For the emergency treatment of cardiac arrhythmias, propranolol hydrochloride may be given by slow intravenous injection over a period of 1 minute, in a dose of 1 mg, repeated if necessary every 2 minutes until a maximum total of 10 mg has been given in conscious patients and 5 mg in patients under anaesthesia. Patients receiving propranolol intravenously should be carefully monitored.

In **hypertrophic cardiomyopathy** the usual dose of propranolol hydrochloride is 10 to 40 mg given three or four times daily.

In **hyperthyroidism** propranolol hydrochloride is given in doses of 10 to 40 mg three or four times daily. If intravenous administration is necessary 1 mg is given over 1 minute, repeated at 2-minute intervals until a response is seen or to a maximum dose of 10 mg in conscious patients or 5 mg in patients under anaesthesia.

The dose for **anxiety** is 40 mg daily; this may be increased to 40 mg two or three times daily.

Essential tremor may be treated with 40 mg given two or three times daily; the dose can be increased at weekly intervals to 160 mg daily although doses up to 320 mg daily may be necessary.

An initial dose of 40 mg two or three times daily is used in **migraine** prophylaxis; the dose can be increased at weekly intervals up to 160 mg daily. Some patients have been given 240 mg daily.

In **portal hypertension**, propranolol hydrochloride should be given in initial doses of 40 mg twice daily; the dose may be increased as required up to 160 mg twice daily.

For the use of propranolol in children, see below.

Administration in children. Propranolol hydrochloride has been used both orally and intravenously in children, although it is not licensed for all indications. Suggested doses are:

for **hypertension**:
- neonates: 250 micrograms/kg orally three times daily, increased as required to a maximum of 2 mg/kg three times daily
- 1 month to 12 years: 0.25 to 1 mg/kg orally three times daily, increased as required to a maximum of 5 mg/kg daily in divided doses
- over 12 years: an adult dose (see above)

for **arrhythmias**, **phaeochromocytoma**, and **hyperthyroidism**:
- neonates: 250 to 500 micrograms/kg orally three times daily. *Alternatively* 20 to 50 micrograms/kg may be given intravenously three or four times daily, injected slowly with appropriate monitoring
- 1 month to 18 years: 250 to 500 micrograms/kg orally three or four times daily, adjusted according to response, to a maximum of 1 mg/kg four times daily or a total daily dose of 160 mg. *Alternatively* 25 to 50 micrograms/kg may be given intravenously three or four times daily, injected slowly with appropriate monitoring

for **prophylaxis of migraine**:
- children up to 12 years: 10 to 20 mg orally two or three times daily
- over 12 years: an adult dose (see above)

for **haemangiomas** and **tetralogy of Fallot**, see below.

Administration in hepatic impairment. A study of the disposition of oral propranolol at steady state in 9 normal subjects and 7 with cirrhosis found a mean threefold increase in unbound blood-propranolol concentrations in patients with cirrhosis when compared with the controls. Mean half-lives for the 2 groups were 11.2 and 4 hours respectively.[1] Another study of propranolol given as a single dose of a 20-mg tablet and as a 160-mg modified-release preparation daily for 7 days in 10 patients with cirrhosis and portal hypertension found higher plasma concentrations in patients with severe liver disease compared with those reported in normal controls.[2] Others have reported similar findings.[3]

In patients with severe liver disease, it has been suggested that propranolol therapy be started at a low dose such as 20 mg three times daily,[2] 80 mg of a modified-release preparation given once daily,[2] or 160 mg of a modified-release preparation given every other day.[3] Monitoring of beta blockade is essential; checking the heart rate[2] or exercise testing[3] have been suggested as suitable methods to assess the extent of beta blockade in patients with cirrhosis.

1. Wood AJJ, *et al.* The influence of cirrhosis on steady-state blood concentrations of unbound propranolol after oral administration. *Clin Pharmacokinet* 1978; 3: 478–87.
2. Arthur MJP, *et al.* Pharmacology of propranolol in patients with cirrhosis and portal hypertension. *Gut* 1985; 26: 14–19.
3. Calès P, *et al.* Pharmacodynamic and pharmacokinetic study of propranolol in patients with cirrhosis and portal hypertension. *Br J Clin Pharmacol* 1989; 27: 763–70.

Administration in renal impairment. A study of the pharmacokinetics of propranolol in 11 patients with chronic renal insufficiency showed no impairment in the elimination kinetics of propranolol compared with 8 subjects with normal renal function.[1] Peak concentrations of propranolol reported in patients with chronic renal failure have been 2 to 3 times higher than those in patients receiving dialysis or in normal subjects.[1,2] Additional studies indicate that there is no pharmacokinetic reason to amend the dosage of propranolol in patients with renal impairment.[3]

Findings from a study in 8 patients on haemodialysis include a slight elevation of plasma-propranolol concentrations, no elevation of plasma concentration of 4-hydroxypropranolol, but extremely high plasma concentrations of other propranolol metabolites.[4]

1. Lowenthal DT, *et al.* Pharmacokinetics of oral propranolol in chronic renal disease. *Clin Pharmacol Ther* 1974; 16: 761–9.
2. Bianchetti G, *et al.* Pharmacokinetics and effects of propranolol in terminal uraemic patients and in patients undergoing regular dialysis treatment. *Clin Pharmacokinet* 1976; 1: 373–84.
3. Wood AJJ, *et al.* Propranolol disposition in renal failure. *Br J Clin Pharmacol* 1980; 10: 561–6.
4. Stone WJ, Walle T. Massive propranolol metabolite retention during maintenance hemodialysis. *Clin Pharmacol Ther* 1980; 28: 449–55.

Haemangioma. Where medical management of infantile haemangiomas (p. 1605.3) is required, it is usually with corticosteroids or antiproliferative drugs, but the response is often unsatisfactory. A rapid therapeutic effect has been reported[1,2] with propranolol when given orally at an initial dose of 2 to 3 mg/kg daily in 2 or 3 divided doses, although some have advocated[3] a lower initial dose of 480 micrograms/kg daily in 3 divided doses, doubled if tolerated to a maximum total daily dose of 2 mg/kg. Propranolol treatment may be particularly useful for haemangiomas with the potential to obstruct the airways.[4-6]

1. Léauté-Labrèze C, *et al.* Propranolol for severe hemangiomas of infancy. *N Engl J Med* 2008; 358: 2649–51.
2. Sans V, *et al.* Propranolol for severe infantile hemangiomas: follow-up report. Abstract: *Pediatrics* 2009; 124: 983. Full version: http://pediatrics.aappublications.org/cgi/reprint/124/3/e423.pdf (accessed 18/01/10)
3. Siegfried EC, *et al.* More on propranolol for hemangiomas of infancy. *N Engl J Med* 2008; 359: 2846.
4. Truong MT, *et al.* Propranolol for the treatment of a life-threatening subglottic and mediastinal infantile hemangioma. *J Pediatr* 2010; 156: 335–8.
5. Denoyelle F, Garabédian EN. Propranolol may become first-line treatment in obstructive subglottic infantile hemangiomas. *Otolaryngol Head Neck Surg* 2010; 142: 463–4.
6. Maturo S, Hartnick C. Initial experience using propranolol as the sole treatment for infantile airway hemangiomas. *Int J Pediatr Otorhinolaryngol* 2010; 74: 323–5.

Tetralogy of Fallot. Beta blockers, particularly propranolol, have been used for the treatment[1] and prophylaxis[1-3] of cyanotic attacks in infants and children with tetralogy of Fallot and reversible right-ventricular outflow tract obstruction, although caution is required since bradycardia may develop.[4] Esmolol may be preferred during surgery.[5-7]

In the UK, licensed prescribing information allows an oral dose of propranolol hydrochloride of up to 1 mg/kg given 3 or 4 times daily. It may also be given intravenously in a dose of up to 100 micrograms/kg 3 or 4 times daily, injected slowly under ECG control.

The *BNFC* recommends the following doses:
- Neonates: 0.25 to 1 mg/kg orally 2 or 3 times daily, to a maximum of 2 mg/kg 3 times daily, or 15 to 20 micrograms/kg (maximum 100 micrograms/kg) intravenously, repeated every 12 hours if necessary
- Children aged 1 month to 12 years: 0.25 to 1 mg/kg orally 3 or 4 times daily, to a maximum of 5 mg/kg daily, or 15 to 20 micrograms/kg (maximum 100 micrograms/kg) intravenously, repeated every 6 to 8 hours if necessary.

1. Cumming GR. Propranolol in tetralogy of Fallot. *Circulation* 1970; 41: 13–15.
2. Eriksson BO, *et al.* Long-term treatment with propranolol in selected cases of Fallot's tetralogy. *Br Heart J* 1969; 31: 37–44.

3. Ponce FE, *et al.* Propranolol palliation of tetralogy of Fallot: experience with long-term drug treatment in pediatric patients. *Pediatrics* 1973; 52: 100–108.
4. Clark DJ, *et al.* Propranolol induced bradycardia in tetralogy of Fallot. *Br Heart J* 1989; 61: 378–9.
5. Nussbaum J, *et al.* Esmolol for the treatment of hypercyanotic spells in infants with tetralogy of Fallot. *J Cardiothorac Anesth* 1989; 3: 200–2.
6. Geary V, *et al.* Esmolol in tetralogy of Fallot. *J Cardiothorac Anesth* 1989; 3: 524–6.
7. Dhir AK, Dhir S. Esmolol in infundibular spasm. *Anaesthesia* 1991; 46: 998.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Breast feeding. Propranolol is distributed into breast milk. A milk/plasma ratio range of 0.33 to 1.65 was reported in a study of 3 women.[1] It was calculated that the maximum dose likely to be ingested by a breast-fed infant would be less than 0.1% of the maternal dose. Other small studies[2,3] have reported similar results. No adverse effects have been seen in breast-fed infants whose mothers were given propranolol and the American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding.

1. Smith MT, *et al.* Propranolol, propranolol glucuronide, and naphthoxylactic acid in breast milk and plasma. *Ther Drug Monit* 1983; 5: 87–93.
2. Karlberg B, *et al.* Excretion of propranolol in human breast milk. *Acta Pharmacol Toxicol (Copenh)* 1974; 34: 222–4.
3. Bauer JH, *et al.* Propranolol in human plasma and breast milk. *Am J Cardiol* 1979; 43: 860–2.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies propranolol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Propranolol is almost completely absorbed from the gastrointestinal tract, but is subject to considerable hepatic-tissue binding and first-pass metabolism. Peak plasma concentrations occur about 1 to 2 hours after an oral dose. Plasma concentrations vary greatly between individuals. Propranolol has high lipid solubility. It crosses the blood-brain barrier and the placenta, and is distributed into breast milk. Propranolol is about 90% bound to plasma proteins. It is metabolised in the liver and at least one of its metabolites (4-hydroxypropranolol) is considered to be active, but the contribution of metabolites to its overall activity is uncertain. The metabolites and small amounts of unchanged drug are excreted in the urine. The plasma half-life of propranolol is about 3 to 6 hours. Propranolol is reported not to be significantly dialysable.

Pregnancy. A study in 6 pregnant patients (32 to 36 weeks' gestation) showed that the disposition of propranolol 120 mg orally and 10 mg intravenously was not altered in pregnancy compared with the postnatal period.[1] Another study[2] in 13 pregnant patients given propranolol to control hypertension showed that the pharmacokinetics of propranolol and most of its major metabolites were not altered during pregnancy. Samples at term[3] in 10 of the women showed that propranolol and all of its known metabolites were present in maternal plasma, cord plasma, and neonatal plasma. At delivery plasma protein binding of propranolol was reported as 87.5% in maternal plasma and 67.2% in cord plasma. Similar results for maternal and cord plasma protein binding have been reported by others.[4]

1. O'Hare MPO, *et al.* Pharmacokinetics of propranolol during pregnancy. *Eur J Clin Pharmacol* 1984; 27: 583–7.
2. Smith MT, *et al.* Chronic propranolol administration during pregnancy: maternal pharmacokinetics. *Eur J Clin Pharmacol* 1983; 25: 481–90.
3. Smith MT, *et al.* Metabolism of propranolol in the human maternal-placental-foetal unit. *Eur J Clin Pharmacol* 1983; 24: 727–32.
4. Wood M, Wood AJJ. Changes in plasma drug binding and α_1-acid glycoprotein in mother and newborn infant. *Clin Pharmacol Ther* 1981; 29: 522–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Inderal; Oposim; Pirimetan; Propaneitor; *Austral.*: Deralin; Inderal; *Austria*: Inderal; *Belg.*: Inderal; *Braz.*: Antitensin; Cardbloc†; Cardix; Hipernolol; Inderal; Pharnolol; Polol; Pradinolol; Pranolal; Propacor; Propanolon; Propanox; Propramed; Rebaten; Sanpronol; Uni Propralol; *Canad.*: Inderal; Novo-Pranol†; *Chile*: Coriodal; *China*: Bai Er Luo (百尔洛); Hang Da Lai (杭达来); Pu Le Xin (普乐欣); Pu Su Xin (普苏欣); *Denm.*: Propal; *Fin.*: Propral; Ranoprin; *Fr.*: Avlocardyl; Hemipralon†; Karnodyl; *Ger.*: Beta-Tablinen†; Dociton; Obsidan; Prophylux†; Propra-ratiopharm; *Gr.*: Betadrenol; Dorizan; Prina; Inderal; Kostalerg; Waucoton; Ziserfin; *Hong Kong*: Deralin†; Inderal; Inpanol; Propa; Synolol†; Uni-Panolol†; *Hung.*: Huma-Pronol; *India*: Betabloc; Betabus; Betacap; Betaspan†; Carnol; Ciplar; Corbeta; Inderal; Lol; Manoprolol; Migrabeta TR; Norten; Propal; *Indon.*: Farmadral; Inderal†; *Irl.*: Beta-Prograne; Half Beta-Prograne; Half Inderal; Inderal; *Israel*: Deralin; Inderal†; Prolol; Slow Deralin; *Ital.*: Inderal; *Malaysia*: Hipranol; Inderal; *Mex.*: Inderalici; Propalem; Sintaser; *Norw.*: Inderal; Pranolol; *NZ*: Angilol; Cardinol; Inderal; *Philipp.*: Duranol; Inderal; Parvilox; Phanerol; *Port.*: Inderal; *Rus.*: Anaprilin (Анаприлин); Obsidan (Обзидан); *S.Afr.*: Cardiblok†; Inderal; Indoblok; Prodorol; Pur-Bloka; Purbloka; *Singapore*: Corbeta; Inderal†; Inpanol; Nalol; Propa; Propanol; Synolol; *Spain*: Sumial; *Swed.*: Inderal; *Switz.*: Inderal; *Thai.*: Alperol; Betalol; Betapress; Cardenol; Chinnolol; CVS; Emforal; Idelol; Inderal; Normpress; P-Parol; Palon; Perlol; Pralol; Prolol; Pronalol; Propanol; Proral; Ropranolol†; Syntonol; *Turk.*: Dideral; *UAE*: Cardilol; *UK*: Angilol; Bedranol; Beta-Prograne; Half Beta-Prograne; Half Inderal; Inderal; Slo-Pro; Syprol; *Ukr.*: Pranolol (Пранолол)†; *USA*: Inderal; InnoPran; *Venez.*: Algoren; Docitral; Inderal.

Multi-ingredient Preparations. *Braz.*: Polol-H; Tenadren; *China*: Di Er Kang Xin (迪尔康欣); *Ger.*: Beta-Turfa†; Dociretic; Docitren; Pertenso N; Propra comp; Triamteren tri-comp†; *India*: Alltop-P; Alprine Plus; Alprine-H; Ambulax-HD; Ambulax-M; Ambulax; Anzi-P; Balmusa Plus; Beptazine-H†; Beptazine†; Calmtec-P; Cam Plus; Cardilax; Ciplar-H; Corbetazine; Diaze-P; Dizepax; Zopax Plus; *Singapore*: Emforal; *Ukr.*: Distonin (Дистонин)†.

Pharmacopoeial Preparations
BP 2014: Prolonged-release Propranolol Capsules; Propranolol Injection; Propranolol Tablets;
USP 36: Propranolol Hydrochloride and Hydrochlorothiazide Extended-release Capsules; Propranolol Hydrochloride and Hydrochlorothiazide Tablets; Propranolol Hydrochloride Extended-release Capsules; Propranolol Hydrochloride Injection; Propranolol Hydrochloride Tablets.

Proscillaridin *(BAN, USAN, rINN)*

2936; A-32686; Proscilaridina; Proscillaridiini; Proscillaridin A; Proscillaridine; Proscillaridinum; PSC-801; Просцилларидин.
14-Hydroxy-3β-(α-L-rhamnopyranosyloxy)-14β-bufa-4,20,22-trienolide.
$C_{30}H_{42}O_8$=530.7
CAS — 466-06-8.
ATC — C01AB01.
ATC Vet — QC01AB01.
UNII — KC6BL281EN.

Profile

Proscillaridin is a cardiac glycoside obtained from *Drimia maritima* (Liliaceae). It is a positive inotrope with general properties similar to those of digoxin (p. 1353.3) and is reported to have a rapid onset and a short duration of action.

Proscillaridin has been given orally in the treatment of heart failure.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Pol.*: Talusin†.

Quinapril Hydrochloride

(BANM, USAN, rINNM)

CI-906 (quinapril); Hidrocloruro de quinapril; Kinapril Hidroklorür; Quinapril, Chlorhydrate de; Quinapril, hidrocloruro de; Quinaprilli Hydrochloridum; Хинаприла Гидрохлорид.
(3*S*)-2-[*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid hydrochloride.
$C_{25}H_{30}N_2O_5$,HCl=475.0
CAS — 85441-61-8 (quinapril); 82586-55-8 (quinapril hydrochloride).
ATC — C09AA06.
ATC Vet — QC09AA06.
UNII — 33067B3N2M.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Quinapril Hydrochloride). A white or almost white or slightly pink, hygroscopic powder. Freely soluble in water and in alcohol; very slightly soluble in acetone. Store in airtight containers at a temperature of 2 degrees to 8 degrees.

USP 36: (Quinapril Hydrochloride). A white to off-white powder, with a pink cast at times. Freely soluble in aqueous solvents.

Suspension. Extemporaneous formulations of quinapril 1 mg/mL made by adding crushed Accupril tablets (*Pfizer US*) to the following vehicles were found to be stable for 6 weeks when stored at 5 degrees:
- *Kphos* 15% (*Beach, US*), *Bicitra* 15% (*Draxis Pharma, US*), *OraSweet* 70% (*Paddock, US*)
- *Kphos* 15%, *Bicitra* 15%, *OraSweet SF* 70%
- *Kphos* 15%, *Bicitra* 15%, simple syrup 70%

The suspension containing *OraSweet SF* was considered to be the formulation of choice.[1]

1. Freed AL, *et al.* The development and stability assessment of extemporaneous pediatric formulations of Accupril. *Int J Pharm* 2005; 304: 135–44.

Uses and Administration

Quinapril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1) and heart failure (p. 1262.3).

Quinapril is converted in the body to its active metabolite quinaprilat. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after about 2 to 4 hours, although the full effect may not develop for 1 to 2 weeks during chronic use. The haemodynamic action persists for about 24 hours, allowing once-daily dosing. Quinapril is given orally as the hydrochloride, but doses are expressed in terms of the base. Quinapril hydrochloride 10.8 mg is equivalent to about 10.0 mg of quinapril.

In the treatment of **hypertension** the initial dose is 10 mg of quinapril once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. An initial dose of 2.5 mg daily is recommended in the elderly, in patients with renal impairment, or in those taking a *diuretic*; if possible, the diuretic should be withdrawn 2 or 3 days before quinapril is started and resumed later if necessary.

The usual maintenance dose is 20 to 40 mg daily, as a single dose or divided into 2 doses, although up to 80 mg daily has been given.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision. Quinapril is given in an initial dose of 2.5 mg daily. Usual maintenance doses range from 10 to 20 mg daily, as a single dose or divided into 2 doses; up to 40 mg daily has been given.

Quinaprilat has been given intravenously.

Reviews.

1. Wadworth AN, Brogden RN. Quinapril: a review of its pharmacological properties, and therapeutic efficacy in cardiovascular disorders. *Drugs* 1991; 41: 378–99.
2. Plosker GL, Sorkin EM. Quinapril: a reappraisal of its pharmacology and therapeutic efficacy in cardiovascular disorders. *Drugs* 1994; 48: 227–52.
3. Culy CR, Jarvis B. Quinapril: a further update of its pharmacology and therapeutic use in cardiovascular disorders. *Drugs* 2002; 62: 339–85.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Breast feeding. After of a single dose of quinapril 20 mg in 6 women, quinapril was detected in the breast milk in a milk to plasma ratio of 0.12; no quinaprilat was detected.[1] It was estimated that the dose received by the infant would only be about 1.6% of the maternal dose.

For advice from UK regulatory authorities against the use of any ACE inhibitor during at least the early weeks of breast feeding see under Precautions of ACE Inhibitors, p. 1287.3.

1. Begg EJ, *et al.* Quinapril and its metabolite quinaprilat in human milk. *Br J Clin Pharmacol* 2001; 51: 478–81.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies quinapril as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Antibacterials. Quinapril has been reported to reduce the absorption of *tetracyclines* due to the presence of magnesium carbonate in the tablet formulation.

Pharmacokinetics

Quinapril acts as a prodrug of the diacid quinaprilat, its active metabolite. About 60% of an oral dose of quinapril is absorbed. Quinapril is metabolised mainly in the liver to quinaprilat and inactive metabolites. Peak plasma concentrations of quinaprilat occur within 2 hours of an oral dose of quinapril. Quinaprilat is about 97% bound to plasma proteins. After an oral dose, quinapril is excreted in the urine and faeces, as quinaprilat, other metabolites, and unchanged drug, with the urinary route predominating; up to 96% of an intravenous dose of quinaprilat is excreted in the urine. The effective half-life for accumulation of quinaprilat is about 3 hours after multiple doses of quinapril; a long terminal phase half-life of 25 hours may represent strong binding of quinaprilat to angiotensin-converting enzyme.

The pharmacokinetics of both quinapril and quinaprilat are affected by renal and hepatic impairment. Dialysis has little effect on the excretion of quinapril or quinaprilat.

Small amounts of quinapril are distributed into breast milk.

References.

1. Begg EJ, *et al.* The pharmacokinetics and pharmacodynamics of quinapril and quinaprilat in renal impairment. *Br J Clin Pharmacol* 1990; 30: 213–20.
2. Halstenson CE, *et al.* The pharmacokinetics of quinapril and its active metabolite, quinaprilat, in patients with various degrees of renal function. *J Clin Pharmacol* 1992; 32: 344–50.
3. Wolter K, Prischka E. Pharmacokinetics and pharmacodynamics of quinaprilat after low dose quinapril in patients with terminal renal failure. *Eur J Clin Pharmacol* 1993; 44 (suppl 1): S53–6.
4. Begg EJ, *et al.* The pharmacokinetics of quinapril and quinaprilat in patients with congestive heart failure. *Br J Clin Pharmacol* 1994; 37: 302–4.
5. Squire IB, *et al.* Haemodynamic response and pharmacokinetics after the first dose of quinapril in patients with congestive heart failure. *Br J Clin Pharmacol* 1994; 38: 117–23.
6. Breslin E, *et al.* A pharmacodynamic and pharmacokinetic comparison of intravenous quinaprilat and oral quinapril. *J Clin Pharmacol* 1996; 36: 414–21.
7. Blumer JL, *et al.* Pharmacokinetics of quinapril in children: assessment during substitution for chronic angiotensin-converting enzyme inhibitor treatment. *J Clin Pharmacol* 2003; 43: 128–32.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Accupril; *Austral.*: Accupril; Acquin; Aquinafil; Asig†; Filpril†; Qpril; *Austria*: Accupro; *Belg.*: Accupril; *Braz.*: Accupril; *Canad.*: Accupril; *Chile*: Accupril; *China*: Yiheng (益恒); *Cz.*: Accupro; *Denm.*: Accupro; Quinacid†; *Fin.*: Accupro; *Fr.*: Acuitel; Korec†; *Ger.*: Accupro; *Gr.*: Accupron; *Hong Kong*: Accupril; *Hung.*: Accupro; Acumerck†; Quiagen; *India*: Acupil; *Indon.*: Accupril; *Irl.*: Accupro; Quinapro†; *Ital.*: Accuprin; Acequin; Quinazil; *Jpn*: Conan; *Mex.*: Acupril; *Neth.*: Acupril; *NZ*: Accupril; *Philipp.*: Accupril; *Pol.*: Accupro; Acurenal; AprilGen; Pulsaren; Q-Pril; *Port.*: Acupril; *Rus.*: Accupro (Аккупро); Quinaphar (Квинафар); *S.Afr.*: Accumax; Accupril; Quinace; Quinagen; Quinaspen; *Singapore*: Accupril; *Spain*: Acuprel; Acuretic†; Ectren; Lidaltrin; *Swed.*: Accupro; *Switz.*: Accupro; Quiril; *Thai.*: Accupril; Quinaril†; Quinsil; *Turk.*: Acuitel; Kinateva; *UK*: Accupro; Quinil; *Ukr.*: Accupro (Аккупро); Acurenal (Акуренал)†; Quinard (Квинард)†; *USA*: Accupril; *Venez.*: Accupril; Quinalar; Solpres.

Multi-ingredient Preparations. *Arg.*: Accuretic; *Austral.*: Accuretic; *Austria*: Accuzide; *Belg.*: Accuretic Co-Quinapril; *Canad.*: Accuretic; *Chile*: Accuretic; *Cz.*: Accuzide; Stadapress; *Fin.*: Accupro Comp; *Fr.*: Acuilix; Koretic†; *Ger.*: Accuzide; QuinaLich comp; Quinaplus†; Quinapril comp†; Quinapril plus†; *Gr.*: Accuretic; Quimea; *Hung.*: Accuzide; Quinanorm Kombi; Quinapril-HCT; *India*: Acupil-H; *Irl.*: Accuretic; *Ital.*: Accuretic; Acequide; Quinazide; *Neth.*: Acuzide; *NZ*: Accuretic; *Philipp.*: Accuzide; *Pol.*: Accuzide; *Port.*: Acuretic; *Rus.*: Accuzide (Аккузид); *S.Afr.*: Accumax Co; Accuretic Adco-Quinaretic; Quinace Co; *Spain*: Bicetil; Lidaltrin Diu; *Swed.*: Accupro Comp; *Switz.*: Accuretic; Quiril comp.; *Thai.*: Accuretic; *Turk.*: Accuzide; *UK*: Accuretic; *Ukr.*: Accuzide (Аккузид); *USA*: Accuretic; Quinaretic; *Venez.*: Accuretic; Quinaretic.

Pharmacopoeial Preparations

USP 36: Quinapril and Hydrochlorothiazide Tablets; Quinapril Tablets.

Quinidine *(BAN)*

Chinidinum; Chinidyna; Kinidiini; Kinidin; Quinidina; Хинидин.

(8*R*,9*S*)-6′-Methoxycinchonan-9-ol; (+)-(α*S*)-α-(6-Methoxy-4-quinolyl)-α-[(2*R*,4*S*,5*R*)-(5-vinylquinuclidin-2-yl)]methanol.

$C_{20}H_{24}N_2O_2$=324.4

CAS — 56-54-2 (anhydrous quinidine); 63717-04-4 (quinidine dihydrate); 72402-50-7 (± quinidine).

ATC — C01BA01.

ATC Vet — QC01BA01.

UNII — ITX08688JL.

Description. Quinidine is an isomer of quinine, obtained from the bark of species of *Cinchona* and their hybrids; it may also be obtained from *Remijia pedunculata*, or prepared from quinine.

Quinidine Bisulfate *(BANM)*

Quinidina, bisulfato de; Quinidine Bisulphate; Хинидина бисульфат.

$C_{20}H_{24}N_2O_2.H_2SO_4$=422.5

CAS — 747-45-5 (anhydrous quinidine bisulfate); 6151-39-9 (quinidine bisulfate tetrahydrate).

ATC — C01BA01.

ATC Vet — QC01BA01.

UNII — 6K043Q65TR.

Pharmacopoeias. In *Br.*

BP 2014: (Quinidine Bisulphate). Colourless, odourless or almost odourless, crystals. It contains not more than 15% of hydroquinidine bisulfate. Freely soluble in water and in alcohol; practically insoluble in ether. A 1% solution in water has a pH of 2.6 to 3.6. Protect from light.

Quinidine Gluconate *(BANM)*

Quinidina, gluconato de; Quinidinium Gluconate; Хинидина глюконат.

$C_{20}H_{24}N_2O_2.C_6H_{12}O_7$=520.6

CAS — 7054-25-3.

ATC — C01BA01.

ATC Vet — QC01BA01.

UNII — R6875N380F.

Pharmacopoeias. In *US.*

USP 36: (Quinidine Gluconate). A white, odourless powder. It contains not more than 20% of hydroquinidine gluconate. Freely soluble in water; slightly soluble in alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Adsorption. More than 40% of a dose of quinidine gluconate was lost when the drug was given by intravenous infusion using a PVC infusion bag and tubing.[1]

1. Darbar D, *et al.* Loss of quinidine gluconate injection in a polyvinyl chloride infusion system. *Am J Health-Syst Pharm* 1996; 53: 655–8.

Quinidine Polygalacturonate

Quinidina, poligalacturonato de; Хинидина полигалактуронат.

Quinidine poly(D-galacturonate) hydrate.

$C_{20}H_{24}N_2O_2.(C_6H_{10}O_7)_n.xH_2O$

CAS — 27555-34-6 (anhydrous quinidine polygalacturonate); 65484-56-2 (quinidine polygalacturonate hydrate).

ATC — C01BA01.

ATC Vet — QC01BA01.

Quinidine Sulfate *(BANM)*

Chinidin sulfat dihydrat; Chinidini sulfas; Chinidino sulfatas; Chinidinsulfat; Chinidinsulfate; Chinidinum Sulfuricum; Chinidyny siarczan; Kinidiinisulfaatti; Kinidin Sülfat; Kinidinsulfat; Kinidin-szulfát; Quinidina, sulfato de; Quinidine, sulfate de; Quinidine Sulphate; Quinidini Sulfas; Quinidini Sulfas Dihydricus; Хинидина сульфат.

$(C_{20}H_{24}N_2O_2)_2.H_2SO_4.2H_2O$=783.0

CAS — 50-54-4 (anhydrous quinidine sulfate); 6591-63-5 (quinidine sulfate dihydrate).

ATC — C01BA01.

ATC Vet — QC01BA01.

UNII — 140CU2322K (anhydrous quinidine sulfate); J13S2394HE (quinidine sulfate dihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Quinidine Sulfate). White or almost white, crystalline powder, or silky, colourless needles. It contains not more than 15% of hydroquinidine sulfate. Slightly soluble in water; soluble in boiling water and in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 6.0 to 6.8. Protect from light.

USP 36: (Quinidine Sulfate). Fine, needle-like, white crystals, frequently cohering in masses, or a fine, white powder. It is odourless and darkens on exposure to light. It contains not more than 20% of hydroquinidine sulfate. Its solutions are neutral or alkaline to litmus. Soluble 1 in 100 of water, 1 in 10 of alcohol, and 1 in 15 of chloroform; insoluble in ether. Protect from light.

Stability. Quinidine sulfate was reported[1] to be stable for up to 60 days in several extemporaneously prepared oral liquid formulations.

1. Allen LV, Erickson MA. Stability of bethanechol chloride, pyrazinamide, quinidine sulfate, rifampin, and tetracycline hydrochloride in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1998; 55: 1804–9.

Uses and Administration

Quinidine is a class Ia antiarrhythmic (p. 1243.1). It also has antimuscarinic and alpha-adrenoceptor blocking properties. Quinidine is used in the management of supraventricular and ventricular arrhythmias, including cardioversion and maintenance of sinus rhythm in atrial fibrillation, but other drugs or methods are usually preferred (see below).

Quinidine is an isomer of quinine and may be used as an alternative to quinine in the treatment of malaria when quinine is not immediately available.

Quinidine is usually given orally and various salts have been used, including the bisulfate, the gluconate, the polygalacturonate, and the sulfate. Strengths of preparations and doses used may be expressed in terms of the salt actually contained in the preparation, but are commonly expressed as the equivalent amount of anhydrous quinidine base or quinidine sulfate dihydrate. Quinidine bisulfate (anhydrous) 260 mg, quinidine gluconate (anhydrous) 321 mg, quinidine sulfate (dihydrate) 241 mg, and quinidine sulfate (anhydrous) 230 mg are each equivalent to about 200 mg of quinidine (anhydrous).

For the management of **cardiac arrhythmias**, a typical dose of *quinidine sulfate dihydrate* is 200 to 400 mg three or four times daily, adjusted according to response; an initial test dose of 200 mg has been recommended for detecting hypersensitivity. Modified-release preparations may be preferred for maintenance.

Quinidine has also been given parenterally but absorption after intramuscular injection is erratic and incomplete, and intravenous use is associated with a risk of severe hypotension. If parenteral use is necessary for acute conversion of supraventricular or ventricular arrhythmias, *quinidine gluconate* may be given by intravenous infusion at a rate no faster than 250 micrograms/kg per minute; most patients respond to a total dose of less than 5 mg/kg, but up to 10 mg/kg may be given if required. ECG and blood pressure should be monitored throughout the infusion.

For the use of quinidine in the management of **malaria**, see below.

General references.

1. Grace AA, Camm AJ. Quinidine. *N Engl J Med* 1998; 338: 35–45.
2. Yang P, *et al.* Quinidine revisited. *Am J Med* 2009; 122: 317–21.

Cardiac arrhythmias. Quinidine is a class Ia antiarrhythmic and has been used in the management of supraventricular and ventricular arrhythmias, but other drugs or non-pharmacological therapies are usually preferred (see Cardiac Arrhythmias, p. 1266.1). Although use of quinidine may have increased after the CAST studies, which found an increased mortality with the use of encainide, flecainide, and moracizine in asymptomatic ventricular arrhythmias, a meta-analysis[1] of studies using quinidine for benign or potentially lethal ventricular arrhythmias found that it was associated with at least as high an incidence of adverse events, including death and early proarrhythmia, as the class Ic drugs flecainide and propafenone. Another meta-analysis[2] found that quinidine was more effective than placebo in maintaining sinus rhythm after cardioversion of atrial fibrillation, but again total mortality was increased. However, some continue to use it for pharmacological cardioversion.[3]

Quinidine has been used[4,5] in patients with Brugada syndrome, a congenital channelopathy that predisposes to ventricular arrhythmias, and may have a role as an alternative to an implantable cardioverter defibrillator. It may also be of use for short QT syndrome,[6] which is characterised by very short QT interval and susceptibility to atrial and ventricular fibrillation.

1. Morganroth J, Goin JE. Quinidine-related mortality in the short-to-medium-term treatment of ventricular arrhythmias: a meta-analysis. *Circulation* 1991; 84: 1977–83.
2. Coplen SE, *et al.* Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. *Circulation* 1990; 82: 1106–16. Correction. *ibid.* 1991; 83: 714.
3. Schwaab B, *et al.* Quinidine for pharmacological cardioversion of atrial fibrillation: a retrospective analysis in 501 consecutive patients. *Ann Noninvasive Electrocardiol* 2009; 14: 128–36.
4. Belhassen B, *et al.* Efficacy of quinidine in high-risk patients with Brugada syndrome. *Circulation* 2004; 110: 1731–7.
5. Viskin S, *et al.* Empiric quinidine therapy for asymptomatic Brugada syndrome: time for a prospective registry. *Heart Rhythm* 2009; 6: 401–4.
6. Kaufman ES. Quinidine in short QT syndrome: an old drug for a new disease. *J Cardiovasc Electrophysiol* 2007; 18: 665–6.

Congenital myasthenia. Although quinidine may exacerbate the symptoms of myasthenia gravis and should be used with great caution in such patients, beneficial responses have been reported in patients with the slow-channel congenital myasthenic syndrome (see p. 685.1).

Hiccup. Quinidine is one of several drugs that have been tried in intractable hiccups. For details of a protocol for the control of hiccups see Chlorpromazine, p. 1046.3.

Malaria. Quinidine may be more potent than quinine as an antimalarial but it is more likely to cause cardiotoxicity

and hypersensitivity and WHO[1,2] has recommended that parenteral formulations of quinidine should only be used when parenteral quinine or artemisinin derivatives are not immediately available. In these situations intravenous infusions of quinidine could be used to begin treatment for severe chloroquine-resistant malaria. Patients should be transferred to oral therapy with quinine as soon as possible to complete a 7-day course; alternatively a single oral treatment of pyrimethamine-sulfadoxine may be given.

In the USA, the CDC[3] have recommended parenteral quinidine gluconate as the drug of choice for the treatment of complicated falciparum malaria, but only because of the lack of availability of parenteral quinine.

Quinidine is given intravenously as the gluconate and doses have been expressed in terms of the base or salt; it should be given under close control, preferably with continuous ECG monitoring and frequent measurements of blood pressure. Regimens used include one[1,3,4] where the equivalent of 15 mg of the base per kg is infused over 4 hours as a loading dose followed by the equivalent of 7.5 mg of the base per kg every 8 hours as infusions over 4 hours. The patient should be transferred to an oral form of antimalarial as soon as possible, to complete a total 3-day course (or a 7-day course if the malaria was acquired in South-East Asia).[3] An alternative regimen[5] consists of a loading dose of 10 mg of quinidine gluconate per kg given by intravenous infusion over a period of 1 to 2 hours followed by a constant intravenous infusion of 20 micrograms/kg per minute for a maximum of 72 hours or until oral therapy with quinine can be instituted to complete an appropriate length of treatment. It is generally recommended that loading doses should not be used if the patient has received quinine or quinidine within the previous 24 hours or mefloquine within the preceding 7 days.

The overall management of malaria is discussed in the chapter on Antimalarials, p. 644.1.

1. WHO. *Management of severe malaria: a practical handbook.* Geneva: WHO,2000. Available at: http://rbm.who.int/docs/hbsm.pdf (accessed 28/07/10)
2. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Also available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 28/07/10) Update (issued April 2011), available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)
3. CDC. Treatment guidelines: treatment of malaria (guidelines for clinicians) (updated April 2011). Available at: http://www.cdc.gov/malaria/resources/pdf/clinicalguidance.pdf (accessed 27/07/11)
4. Phillips RE, *et al.* Intravenous quinidine for the treatment of severe falciparum malaria: clinical pharmacokinetic studies. *N Engl J Med* 1985; 312: 1273–8.
5. Miller KD, *et al.* Treatment of severe malaria in the United States with a continuous infusion of quinidine gluconate and exchange transfusion. *N Engl J Med* 1989; 321: 65–70.

Neurological disorders. For reference to the use of quinidine with dextromethorphan for the management of pseudobulbar affect associated with amyotrophic lateral sclerosis and multiple sclerosis, see p. 1660.3.

Adverse Effects and Treatment

Quinidine and its salts have both cardiac and non-cardiac adverse effects. Gastrointestinal irritation is common, with nausea, vomiting, and diarrhoea.

Hypersensitivity similar to that occurring with quinine may also occur and a test dose has been recommended (see Uses and Administration, p. 1481.3). Reactions include respiratory difficulties, urticaria, pruritus, rashes, purpura, thrombocytopenia and other blood dyscrasias, and, rarely, fever and anaphylaxis. Granulomatous hepatitis and a lupus-like syndrome have been reported.

Quinidine may give rise to cinchonism (see Quinine, p. 666.2) with tinnitus, impaired hearing, visual disturbances, headache, confusion, vertigo, vomiting, and abdominal pain; it is usually associated with large doses, but may occur in idiosyncratic subjects given small doses.

Quinidine may induce hypotension, particularly in overdosage or if intravenous infusions are given too rapidly. It prolongs the QT interval and may precipitate ventricular arrhythmias, including torsade de pointes.

In quinidine overdosage, the cardiac symptoms of intoxication predominate. Quinidine is cumulative in action and inappropriately high plasma concentrations may induce ECG changes, heart block, asystole, ventricular tachycardia, ventricular fibrillation, syncope, seizures, coma, and sometimes death. Treatment of adverse effects and overdosage is symptomatic and supportive. Activated charcoal may be considered if the patient presents within 1 hour of ingestion.

Reviews.

1. Kim SY, Benowitz NL. Poisoning due to class IA antiarrhythmic drugs quinidine, procainamide and disopyramide. *Drug Safety* 1990; 5: 393–420.

Effects on the blood. Quinidine-induced thrombocytopenia is not uncommon and it is one of the best documented causes of drug-dependent thrombocytopenia.[1] It appears to be a hypersensitivity reaction, with quinidine inducing the production of autoantibodies that cause platelet destruction. Highly specific quinidine-dependent antibodies have been detected in patients with thrombocytopenia, and may have a role in diagnosis.[2] The exact mechanism of the reaction is unclear but it is generally thought that binding of quinidine to the platelet surface induces antibody production;[1] alternatively, an antibody-quinidine complex may be formed, which is then deposited on the platelets.[1,3] The antigenic constituent of the platelet membrane may be glycoprotein Ib although other surface glycoproteins have also been implicated.[3,4]

1. van den Bemt PMLA, *et al.* Drug-induced immune thrombocytopenia. *Drug Safety* 2004; 27: 1243–52.
2. Reid DM, Shulman NR. Drug purpura due to surreptitious quinidine intake. *Ann Intern Med* 1988; 108: 206–8.
3. Stricker RB, Shuman MA. Quinidine purpura: evidence that glycoprotein V is a target platelet antigen. *Blood* 1986; 67: 1377–81.
4. Visentin GP, *et al.* Characteristics of quinine-and quinidine-induced antibodies specific for platelet glycoproteins IIb and IIIa. *Blood* 1991; 77: 2668–76.

Effects on the eyes. Corneal deposits resembling those found in keratopathy developed in a patient who had been taking quinidine for 2 years.[1] Symptoms had improved and both corneas had cleared completely within 2 months of stopping the drug.

A small number of patients have also been identified[2] who developed uveitis during quinidine treatment.

1. Zaidman GW. Quinidine keratopathy. *Am J Ophthalmol* 1984; 97: 247–9.
2. Fraunfelder FW, Rosenbaum JT. Drug-induced uveitis: incidence, prevention and treatment. *Drug Safety* 1997; 17: 197–207.

Effects on the joints. Quinidine has been associated with rheumatic disorders.[1] It is a recognised, though uncommon, cause of drug-induced lupus (see below), but there have also been reports[2-4] of reversible, symmetrical polyarthritis developing in patients with no evidence of antinuclear antibodies. Symptoms were generally milder than in drug-induced lupus, and onset was more rapid; recovery occurred within a week of stopping quinidine and in some patients symptoms recurred on rechallenge. Polymyalgia rheumatica-like symptoms have also been reported.[1]

1. Alloway JA, Salata MP. Quinidine-induced rheumatic syndromes. *Semin Arthritis Rheum* 1995; 24: 315–22.
2. Kertes P, Hunt D. Polyarthritis complicating quinidine treatment. *BMJ* 1982; 284: 1373–4.
3. Cohen MG, *et al.* Two distinct quinidine-induced rheumatic syndromes. *Ann Intern Med* 1988; 108: 369–71.
4. Naschitz JE, Yeshurun D. Quinidine and rheumatic syndromes. *Ann Intern Med* 1988; 109: 248–9.

Effects on the liver. Hypersensitivity reactions involving the liver have been reported in about 2% of patients receiving quinidine.[1,2] The main clinical symptom is fever[1-3] but rashes,[1-3] purpura,[2] and hepatomegaly[1] may also occur. Liver enzyme values are raised[1-4] and the platelet count may be reduced.[3] The reaction is reversible on withdrawing quinidine with fever resolving in about 48 hours and liver enzymes values returning to normal within about 2 weeks. Liver biopsy often shows granulomatous hepatitis,[1-3] but other inflammatory changes[2] and cholestatic jaundice[4] have been found.

1. Geltner D, *et al.* Quinidine hypersensitivity and liver involvement: a survey of 32 patients. *Gastroenterology* 1976; 70: 650–2.
2. Knobler H, *et al.* Quinidine-induced hepatitis. *Arch Intern Med* 1986; 146: 526–8.
3. Bramlet DA, *et al.* Granulomatous hepatitis as a manifestation of quinidine hypersensitivity. *Arch Intern Med* 1980; 140: 395–7.
4. Hogan DB, *et al.* Unusual hepatotoxic reaction to quinidine. *Can Med Assoc J* 1984; 130: 973.

Effects on mental state. Gradually progressive cerebral dysfunction characterised by intermittent confusion, agitation, restlessness, personality change, and paranoid features occurred in a 62-year-old man who had taken quinidine for about 15 years.[1] Within 24 hours of stopping quinidine there was a marked improvement and after 5 days he had returned to normal with no cognitive deficits. It was considered that quinidine had precipitated or exacerbated the functional psychosis.

1. Johnson AG, *et al.* A functional psychosis precipitated by quinidine. *Med J Aust* 1990; 153: 47–9.

Effects on the skin. Skin reactions reported with quinidine include exacerbation of psoriasis,[1] blue-grey pigmentation,[2] photosensitivity,[3] and fatal toxic epidermal necrolysis.[4] Purpuric bruising, attributed to inhalation of quinidine dust in the workplace, has also been reported.[5]

1. Harwell WB. Quinidine-induced psoriasis. *J Am Acad Dermatol* 1983; 9: 278.
2. Mahler R, *et al.* Pigmentation induced by quinidine therapy. *Arch Dermatol* 1986; 122: 1062–4.
3. Marx JL, *et al.* Quinidine photosensitivity. *Arch Dermatol* 1983; 119: 39–43.
4. Adornato MC. Toxic epidermal necrolysis associated with quinidine administration. *N Y State Dent J* 2000; 66: 38–40.
5. Salom IL. Purpura due to inhaled quinidine. *JAMA* 1991; 266: 1220.

Hypoglycaemia. Mean plasma-insulin concentrations increased and mean plasma-glucose concentrations decreased in 8 healthy subjects and 10 patients with malaria given quinidine intravenously.[1] Profound hypoglycaemia occurred in 1 patient with cerebral malaria and acute renal failure. These effects were considered to be associated with stimulation of β-cell secretion of insulin by quinidine and it was concluded that hypoglycaemia may occur in any severely ill fasting patient given parenteral quinidine.

1. Phillips RE, *et al.* Hypoglycaemia and antimalarial drugs: quinidine and release of insulin. *BMJ* 1986; 292: 1319–21.

Lupus erythematosus. There are several well-documented reports of quinidine-induced lupus erythematosus.[1-4] The syndrome involves polyarthritis with a positive antinuclear antibody test. Symptoms do not usually occur until several months after starting quinidine and resolve slowly on stopping the drug. A recurrence of lupus-like symptoms has occurred in patients with a previous reaction to procainamide.[2]

1. West SG, *et al.* Quinidine-induced lupus erythematosus. *Ann Intern Med* 1984; 100: 840–2.
2. Amadio P, *et al.* Procainamide, quinidine, and lupus erythematosus. *Ann Intern Med* 1985; 102: 419.
3. Lavie CJ, *et al.* Systemic lupus erythematosus (SLE) induced by quinidine. *Arch Intern Med* 1985; 145: 446–8.
4. Cohen MG, *et al.* Two distinct quinidine-induced rheumatic syndromes *Ann Intern Med* 1988; 108: 369–71.

Oesophageal stricture. Oral quinidine is a recognised cause of oesophageal injury[1,2] and has been associated with ulceration and stricture formation.

1. McCord GS, Clouse RE. Pill-induced esophageal strictures: clinical features and risk factors for development. *Am J Med* 1990; 88: 512–18.
2. Jaspersen D. Drug-Induced oesophageal disorders: pathogenesis incidence, prevention and management. *Drug Safety* 2000; 22: 237–49.

Precautions

Quinidine is contra-indicated in complete heart block (unless the patient has a pacemaker). It should be used with extreme caution in patients with a prolonged QT interval or a history of torsade de pointes, incomplete heart block, uncompensated heart failure, myocarditis, or severe myocardial damage. Patients should be monitored closely for hypersensitivity reactions after the first dose and quinidine should not be given to those who develop a reaction or those with a history of hypersensitivity to quinidine, including patients who have previously developed thrombocytopenia with quinidine or quinine. Antiarrhythmic therapy with quinidine should be begun with extreme caution, if at all, during acute infections or fever as hypersensitivity reactions may be masked. Care is also required in patients with myasthenia gravis as quinidine can exacerbate the symptoms and may reduce the efficacy of parasympathomimetic drugs.

When quinidine is used to treat atrial flutter or fibrillation, the reduction in AV block may result in a very rapid ventricular rate. This can be avoided by prior digitalisation or by use of a rate-limiting calcium-channel blocker or beta blocker. However, quinidine should be avoided in digitalis overdosage as markedly increased plasma concentrations of digoxin may occur.

Reduced dosage should be considered for the elderly, for patients with hepatic or renal impairment, and on the occasions when it is used in heart failure.

Breast feeding. A woman[1] receiving 2.1 g quinidine daily throughout pregnancy had milk and serum concentrations 5 days after delivery of 6.4 and 9.0 micrograms/mL respectively, giving a milk to serum ratio of 0.71. It was estimated that the amount of quinidine that would be ingested by an infant would be far below the therapeutic range for its weight. No adverse effects have been reported in infants and the American Academy of Pediatrics considers[2] that quinidine is therefore usually compatible with breast feeding.

1. Hill LM, Malkasian GD. The use of quinidine sulfate throughout pregnancy. *Obstet Gynecol* 1979; 54: 366–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction, *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies quinidine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pregnancy. In a report[1] on the use of quinidine sulfate by a woman throughout pregnancy, concentrations in the infant's serum at delivery were similar to the mother's although amniotic fluid concentrations were raised. The infant's weight, ECG, haemoglobin concentration, and platelet count were all found to be within normal limits.

1. Hill LM, Malkasian GD. The use of quinidine sulfate throughout pregnancy. *Obstet Gynecol* 1979; 54: 366–8.

Interactions

Quinidine has the potential for both pharmacodynamic and pharmacokinetic interactions with many other drugs.

Use of quinidine with drugs that increase the QT interval or have arrhythmogenic effects should generally be avoided, since there is an increased risk of toxicity. Although quinidine is sometimes given with other antiarrhythmics, caution is required since there may be both pharmacodynamic and pharmacokinetic interactions (see below). Interactions may also occur with other drugs because of the antimuscarinic and alpha-adrenoceptor blocking properties of quinidine; potentiation of the effects of neuromuscular blockers has also been reported.

Quinidine is metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, and may interact with inhibitors or inducers of this isoenzyme. Rifampicin, phenobarbital, and phenytoin increase the metabolism of quinidine and increased doses may be required; HIV-protease inhibitors, which inhibit CYP3A4, may produce toxic concentrations of quinidine.

Urinary excretion of quinidine is dependent on urinary pH; drugs that increase urinary pH such as sodium bicarbonate, some antacids, and carbonic anhydrase inhibitors tend to increase the plasma concentration of quinidine since the proportion of nonionised drug in the urine is increased allowing greater renal tubular reabsorption.

Quinidine itself may also have effects on other drugs; it inhibits cytochrome P450 isoenzyme CYP2D6 and may affect drugs metabolised by this route. Examples of further drugs that may be affected by quinidine include oral anticoagulants, beta blockers, and digoxin; more details are given under the monographs for these drugs. Quinidine is used with dextromethorphan (see Neurological Disorders, p. 1660.3) for its ability to inhibit the metabolism of the latter.

Antiarrhythmics. *Amiodarone* may increase the plasma concentration of quinidine, increasing the risk of toxicity; prolongation of the QT interval with torsade de pointes has been reported.[1] This is probably because amiodarone inhibits hepatic or renal clearance of quinidine or displaces quinidine from binding sites. If the two drugs are used together the dose of quinidine may need to be reduced and the patient should be closely monitored. *Verapamil* given intravenously has been reported[2] to cause severe hypotension in patients also taking quinidine orally. Studies *in vitro* suggest this is due to the additive blockade of α-adrenergic receptors by both drugs and the simultaneous blockade of calcium channels by verapamil; verapamil may also increase the plasma concentration of quinidine. Quinidine itself may increase the plasma concentration of some other antiarrhythmics (see Ajmaline, p. 1295.3, Digoxin, p. 1356.2, Disopyramide, p. 1365.1, Flecainide Acetate, p. 1384.3, Procainamide, p. 1477.1, and Propafenone Hydrochloride, p. 1478.3).

1. Lesko LJ. Pharmacokinetic drug interactions with amiodarone. *Clin Pharmacokinet* 1989; 17: 130–40.
2. Maisel AS, *et al.* Hypotension after quinidine plus verapamil. *N Engl J Med* 1985; 312: 167–70.

Antibacterials. Torsade de pointes has been reported[1] in a patient taking *erythromycin* with quinidine. Like quinidine, erythromycin prolongs the QT interval, and the effect may be greater if the drugs are given together;[2] there is also some evidence[3-5] that erythromycin reduces quinidine clearance.

1. Lin JC, Quasny HA. QT prolongation and development of torsades de pointes with the concomitant administration of oral erythromycin base and quinidine. *Pharmacotherapy* 1997; 17: 626–30.
2. Stanford RH, *et al.* Effect of oral erythromycin on quinidine pharmacodynamics in healthy volunteers. *Pharmacotherapy* 1997; 17: 1111.
3. Spinler SA, *et al.* Possible inhibition of hepatic metabolism of quinidine by erythromycin. *Clin Pharmacol Ther* 1995; 57: 89–94.
4. Stanford RH, *et al.* Effect of oral erythromycin on quinidine pharmacokinetics in healthy volunteers. *Pharmacotherapy* 1998; 18: 426–7.
5. Damkier P, *et al.* Effect of diclofenac, disulfiram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinidine. *Br J Clin Pharmacol* 1999; 48: 829–38.

Antifungals. *Ketoconazole* temporarily increased the plasma-quinidine concentration in a patient through reduced hepatic elimination.[1] Another antifungal that inhibits hepatic metabolism, *itraconazole*, has also been reported[2] to increase plasma-quinidine concentrations.

1. McNulty RM, *et al.* Transient increase in plasma quinidine concentrations during ketoconazole-quinidine therapy. *Clin Pharm* 1989; 8: 222–5.
2. Kaukonen K-M, *et al.* Itraconazole increases plasma concentrations of quinidine. *Clin Pharmacol Ther* 1997; 62: 510–17.

Beta blockers. Quinidine and beta blockers may have additive adverse effects, and pharmacokinetic interactions may also occur. Sinus bradycardia has been reported in a patient prescribed oral quinidine and *timolol* eye drops,[1] and orthostatic hypotension has occurred when quinidine was used with *atenolol*.[2] Use of quinidine or the beta blocker alone was well tolerated in each case with no adverse effects.

1. Dinai Y, *et al.* Bradycardia induced by interaction between quinidine and ophthalmic timolol. *Ann Intern Med* 1985; 103: 890–1.
2. Manolis AS, Estes NAM. Orthostatic hypotension due to quinidine and atenolol. *Am J Med* 1987; 82: 1083–4.

Calcium-channel blockers. *Nifedipine* has been reported[1] to reduce plasma-quinidine concentrations and increasing the dose of quinidine to up to 20 mg/kg failed to increase the plasma concentration. Withdrawal of nifedipine resulted in a doubling of the quinidine concentration. A pharmacokinetic and pharmacodynamic study in healthy subjects, however, failed to show that modified-release *felodipine* or nifedipine had any effect on quinidine disposition.[2] Another study in healthy subjects suggested that quinidine may inhibit nifedipine metabolism.[3] *Diltiazem* has also been reported[4] to decrease the clearance and increase the half-life of quinidine in healthy subjects, although it was noted that another study had failed to show any interaction.

For the effects of *verapamil* used with quinidine, see Antiarrhythmics, above.

1. Green JA, *et al.* Nifedipine-quinidine interaction. *Clin Pharm* 1983; 2: 461–5.
2. Bailey DG, *et al.* Quinidine interaction with nifedipine and felodipine: pharmacokinetic and pharmacodynamic evaluation. *Clin Pharmacol Ther* 1993; 53: 354–9.
3. Bowles SK, *et al.* Evaluation of the pharmacokinetic and pharmacodynamic interaction between quinidine and nifedipine. *J Clin Pharmacol* 1993; 33: 727–31.
4. Laganière S, *et al.* Pharmacokinetic and pharmacodynamic interactions between diltiazem and quinidine. *Clin Pharmacol Ther* 1996; 60: 255–64.

Diuretics. *Carbonic anhydrase inhibitors* increase urinary pH and may increase plasma-quinidine concentrations by increasing renal tubular reabsorption. *Thiazides* and *loop diuretics* may increase the risk of arrhythmias by causing hypokalaemia. Arrhythmias occurred in 4 of 10 patients receiving *amiloride* when given quinidine,[1] possibly due to additive sodium-channel blockade.

1. Wang L, *et al.* Amiloride-quinidine interaction: adverse outcomes. *Clin Pharmacol Ther* 1994; 56: 659–67.

Histamine H_2-antagonists. *Cimetidine* inhibits the hepatic metabolism of quinidine and increases in plasma concentration and half-life with a reduction in clearance have been reported.[1-3]

1. Hardy BG, *et al.* Effect of cimetidine on the pharmacokinetics and pharmacodynamics of quinidine. *Am J Cardiol* 1983; 52: 172–5.
2. Kolb KW, *et al.* Effect of cimetidine on quinidine clearance. *Ther Drug Monit* 1984; 6: 306–12.
3. MacKichan JJ, *et al.* Effect of cimetidine on quinidine bioavailability. *Biopharm Drug Dispos* 1989; 10: 121–5.

Pharmacokinetics

Quinidine is rapidly absorbed from the gastrointestinal tract; the time to peak plasma concentration depends on the salt and formulation but is about 2 hours for quinidine sulfate immediate-release tablets. Bioavailability is variable, owing to first-pass metabolism in the liver.

Quinidine is metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, to several metabolites, at least some of which are pharmacologically active. It is excreted in the urine, mainly in the form of its metabolites. The proportion excreted unchanged is dependent on urinary pH; in acidic urine about 20% is excreted as unchanged quinidine but in alkaline urine this is reduced to about 5% due to increased renal tubular reabsorption.

Quinidine is widely distributed throughout the body and is 80 to 90% bound to plasma proteins including α_1-acid glycoprotein. It has a plasma half-life of about 6 to 8 hours but this may show wide variation. Its therapeutic effect has been correlated with plasma concentrations of about 1 to 6 micrograms/mL, depending on the assay method used; older methods that do not differentiate quinidine from its metabolites may give misleading results.

Quinidine crosses the placenta and is distributed into breast milk. Only small amounts are removed by haemodialysis.

Considerable intersubject and intrasubject variability in the pharmacokinetics of quinidine has been noted;[1] in one study the half-life ranged from about 1 to 16 hours regardless of whether the drug was given as a tablet, capsule, oral solution, or intramuscular injection. There may also be considerable variations in absorption depending upon the formulation and the salt used.[2,3] The effect of food on absorption is not clear.[4,5] The heart condition being treated or associated with the arrhythmia may alter quinidine's pharmacokinetics[4,7] as may the age of the patient.[8-10] Hepatic impairment may affect protein binding and prolong quinidine's half-life.[11] Protein binding increases in patients with renal impairment, although it returns to normal during dialysis procedures.[12] Accumulation of quinidine metabolites may occur in patients with renal dysfunction.[13-15]

1. Mason WD, *et al.* Comparative plasma concentrations of quinidine following administration of one intramuscular and three oral formulations to 13 human subjects. *J Pharm Sci* 1976; 65: 1325–9.
2. Prigo GM, *et al.* Comparison of quinidine plasma concentration curves following oral administration of some short- and long-acting formulations. *Br J Clin Pharmacol* 1977; 4: 449–54.
3. Mahon WA, *et al.* Comparative bioavailability study of three sustained release quinidine formulations. *Clin Pharmacokinet* 1987; 13: 118–24.
4. Woo E, Greenblatt DJ. Effect of food on enteral absorption of quinidine. *Clin Pharmacol Ther* 1980; 27: 188–93.
5. Martinez MN, *et al.* Effect of dietary fat content on the bioavailability of a sustained release quinidine gluconate tablet. *Biopharm Drug Dispos* 1990; 11: 17–29.
6. Ueda CT, Drindzio BS. Quinidine kinetics in congestive heart failure. *Clin Pharmacol Ther* 1978; 23: 158–64.
7. Ueda CT, Drindzio BS. Bioavailability of quinidine in congestive heart failure. *Br J Clin Pharmacol* 1981; 11: 571–7.
8. Drayer DE, *et al.* Prevalence of high (3S)-3-hydroxyquinidine/quinidine ratios in serum, and clearance of quinidine in cardiac patients with age. *Clin Pharmacol Ther* 1980; 27: 72–5.
9. Szefler SJ, *et al.* Rapid elimination of quinidine in pediatric patients. *Pediatrics* 1982; 70: 370–5.
10. Pickoff AS, *et al.* Age-related differences in the protein binding of quinidine. *Dev Pharmacol Ther* 1981; 3: 108–15.
11. Kessler KM, *et al.* Quinidine pharmacokinetics in patients with cirrhosis or receiving propranolol. *Am Heart J* 1978; 96: 627–35.
12. Kessler KM, Perez GO. Decreased quinidine plasma protein binding during haemodialysis. *Clin Pharmacol Ther* 1981; 30: 121–6.
13. Kessler KM, *et al.* Quinidine elimination in patients with congestive heart failure or poor renal function. *N Engl J Med* 1974; 290: 706–9.
14. Drayer DE, *et al.* Steady-state serum levels of quinidine and active metabolites in cardiac patients with varying degrees of renal function. *Clin Pharmacol Ther* 1978; 24: 31–9.
15. Hall K, *et al.* Clearance of quinidine during peritoneal dialysis. *Am Heart J* 1982; 104: 646–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Kinidin†; *Braz.*: Quinicardine; *Canad.*: Apo-Quin-G†; *Fin.*: Kiniduron; *Gr.*: Kinidin; Kinidine; Longaquin; *India*: Natcardine; *Irl.*: Kinidin†; *Ital.*: Chinteina†; Longachin; *Philipp.*: Kinidin†; *Rus.*: Kinidin (Хинидин); *S.Afr.*: Quinaglute†; *Turk.*: Longacor; Natisedine; Quinicardine.

Multi-ingredient Preparations. *Fr.*: Quinimax; *Ger.*: Cordichin; *USA*: Nuedexta.

Pharmacopoeial Preparations

BP 2014: Quinidine Sulphate Tablets;

USP 36: Quinidine Gluconate Extended-release Tablets; Quinidine Gluconate Injection; Quinidine Sulfate Capsules; Quinidine Sulfate Extended-release Tablets; Quinidine Sulfate Oral Suspension; Quinidine Sulfate Tablets.

Ramipril *(BAN, USAN, rINN)*

Hoe-498; Ramiprilli; Ramiprilis; Ramiprilum; Рамиприл.

(2*S*,3a*S*,6a*S*)-1-[*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]perhydrocyclopenta[*b*]pyrrole-2-carboxylic acid.

$C_{23}H_{32}N_2O_5$=416.5

CAS — 87333-19-5.

ATC — C09AA05.

ATC Vet — QC09AA05.

UNII — E35JN3I7SJ.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Ramipril). A white or almost white, crystalline powder. Sparingly soluble in water; freely soluble in methyl alcohol. Protect from light.

USP 36: (Ramipril). A white to almost white, crystalline powder. Sparingly soluble in water; freely soluble in methyl alcohol. Store in airtight containers.

Uses and Administration

Ramipril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1), heart failure (p. 1262.3), and after myocardial infarction (p. 1257.1) to improve survival in patients with clinical evidence of heart failure. It is also used to reduce the risk of cardiovascular events in patients with certain risk factors (see Cardiovascular Risk Reduction, p. 1246.1).

Ramipril owes its activity to ramiprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 to 2 hours of a single oral dose and the maximum effect occurs after about 3 to 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic effect is maintained for at least 24 hours, allowing once-daily dosing.

In the treatment of **hypertension** an initial oral dose of 2.5 mg once daily is given (or 1.25 mg in those on diuretics or otherwise at risk of profound hypotension). Since there may be a precipitous fall in blood pressure when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Patients taking diuretics should, if possible, have the diuretic stopped 2 to 3 days before starting ramipril, and resumed later if necessary. The usual maintenance dose is 2.5 to 5 mg daily as a single dose,

although up to 10 mg daily may be required. In the USA an initial dose of 2.5 mg once daily in hypertensive patients not taking a diuretic and a maintenance dose of 2.5 to 20 mg daily, as a single dose or in two divided doses, have been suggested.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision; high doses of diuretics should be reduced before starting ramipril. Ramipril is given in an initial dose of 1.25 mg once daily. The usual maximum dose is 10 mg daily; doses of 2.5 mg or more daily may be taken in 1 or 2 divided doses.

After **myocardial infarction**, treatment with ramipril may be started in hospital 3 to 10 days after the infarction at a usual initial dose of 2.5 mg twice daily, increased after two days to 5 mg twice daily. The usual maintenance dose is 2.5 to 5 mg twice daily.

In the treatment of diabetic and non-diabetic **nephropathy**, an initial oral dose of 1.25 mg once daily may be given, doubled at intervals of 2 weeks to a maintenance dose of 5 mg once daily.

For the **prophylaxis of cardiovascular events** in patients considered to be at high risk, ramipril is given in an initial dose of 2.5 mg once daily. The dose should be increased, if tolerated, to 5 mg once daily after 1 week, then to the usual maintenance dose of 10 mg once daily after a further 3 weeks. In patients with hypertension or recent myocardial infarction it may also be given in divided doses.

A reduction in dosage of ramipril may be necessary in patients with impaired hepatic or renal function (see below).

References.

1. Todd PA, Benfield P. Ramipril: a review of its pharmacological properties and therapeutic efficacy in cardiovascular disorders. *Drugs* 1990; 39: 110–35.
2. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993; 342: 821–8.
3. Frampton JE, Peters DH. Ramipril: an updated review of its therapeutic use in essential hypertension and heart failure. *Drugs* 1995; 49: 440–66.
4. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342: 145–53.
5. Warner GT, Perry CM. Ramipril: a review of its use in the prevention of cardiovascular outcomes. *Drugs* 2002; 62: 1381–1405.
6. Vuong AD, Annis LG. Ramipril for the prevention and treatment of cardiovascular disease. *Ann Pharmacother* 2003; 37: 412–19.
7. Rokoss MJ, Teo KK. Ramipril in the treatment of vascular diseases. *Expert Opin Pharmacother* 2005; 6: 1911–19.
8. Anderson VR, *et al.* Ramipril: a review of its use in preventing cardiovascular outcomes in high-risk patients. *Am J Cardiovasc Drugs* 2006; 6: 417–32.
9. Lüders S, *et al.* The PHARAO study: prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure - a prospective, randomized, controlled prevention trial of the German Hypertension League. *J Hypertens* 2008; 26: 1487–1496.
10. Yusuf S, *et al.* ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; 358: 1547–59.

Administration in children. Ramipril was a safe and effective antihypertensive and antiproteinuric drug when given to 31 children and adolescents aged from about 2 to 20 years with chronic renal disease and hypertension or proteinuria.[1] A single daily oral starting dose of 1.5 mg/m² was adjusted to a range of 1.2 to 5.7 mg/m² (mean dose 2.5 mg/m²). Similar results were also seen with a fixed oral dose of 6 mg/m² in 397 children aged from 3 to 18 years with chronic renal failure.[2]

1. Seeman T, *et al.* Ramipril in the treatment of hypertension and proteinuria in children with chronic kidney diseases. *Am J Hypertens* 2004; 17: 415–20.
2. Wühl E, *et al.* ESCAPE Trial Group. Antihypertensive and antiproteinuric efficacy of ramipril in children with chronic renal failure. *Kidney Int* 2004; 66: 768–76.

Administration in hepatic or renal impairment. UK licensed product information for ramipril states that in patients with hepatic impairment the maximum oral daily dose is 2.5 mg. In renal impairment, the following dosage adjustments are required depending on creatinine clearance (CC):

- CC 30 to 60 mL/min: a maximum maintenance dose of 5 mg daily
- CC 10 to 30 mL/min (and haemodialysis patients): an initial dose of 1.25 mg daily and a maximum maintenance dose of 5 mg daily. Doses should be given a few hours after haemodialysis

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ramipril as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Ramipril acts as a prodrug of the diacid ramiprilat, its active metabolite. After oral doses at least 50 to 60% is absorbed. Ramipril is metabolised in the liver to ramiprilat; other metabolites are inactive. Peak plasma concentrations of ramiprilat occur 2 to 4 hours after an oral dose of ramipril. Ramiprilat is about 56% bound to plasma proteins. After oral doses ramipril is excreted mainly in the urine, as ramiprilat, other metabolites, and some unchanged drug. About 40% of an oral dose appears in the faeces; this may represent both biliary excretion and unabsorbed drug. The effective half-life for accumulation of ramiprilat is 13 to 17 hours after multiple doses of ramipril 5 to 10 mg, but is much longer for doses of 1.25 to 2.5 mg daily; the difference relates to the long terminal half-life associated with saturable binding to the angiotensin-converting enzyme. The clearance of ramiprilat is reduced in renal impairment.

Reviews.

1. Meisel S, *et al.* Clinical pharmacokinetics of ramipril. *Clin Pharmacokinet* 1994; 26: 7–15.
2. van Griensven JMT, *et al.* Pharmacokinetics, pharmacodynamics and bioavailability of the ACE inhibitor ramipril. *Eur J Clin Pharmacol* 1995; 47: 513–8.
3. Fillastre JP, *et al.* Kinetics, safety, and efficacy of ramipril after long-term administration in hemodialyzed patients. *J Cardiovasc Pharmacol* 1996; 27: 269–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lostapres; Tritace; ***Austral.***: Prilace; Ramace; Tritace; Tryzan; ***Austria***: Hypren; Lannapril; Tritace; ***Belg.***: Tritace; ***Braz.***: Atensec; Ecator; Naprix; Triatec; ***Canad.***: Altace; ***Chile***: Ramipres; Triatec; ***China***: Ruisutan (瑞素坦); Tritace (瑞素); ***Cz.***: Acesial; Amprilan; Hartil; Medoram; Miril; Piramil; Ramicard; Ramigamma; Ramil; Ramistada†; Ramitren†; Tritace; Vivokar†; ***Denm.***: Alarimed; Mariram; Rolam; Sylerasamed; Triatec; Yamasiv; ***Fin.***: Cardace; ***Fr.***: Triatec; Triateckit†; ***Ger.***: Delix; Ramicard†; Ramiclair; Ramigamma; RamiLich; Vesdil†; ***Gr.***: Piramil; Stibenyl; Triatec; ***Hong Kong***: Tritace; ***Hung.***: Amprilan; Corpril†; Emren; Hartil; Meramyl; Piramil†; Ramace; Ramicard; Ramigamma; Ramiwin†; Tritace; ***India***: Acepril; Alvace; Cardace; Cardiopril; Conram; Cordimil; Corpril; Dexace; Ecator; Emipril; Etoril; Gopril; Hecril; Hopace; Hopecard; Hoperam; Kapril; Megapril; Odipril; Preface; R-Pril; Ramcor; Ramipres; Sclerace; ***Indon.***: Cardace; Hyperil; Ramixal; Redutens; Tenapril†; Triatec; Vivace; ***Irl.***: Bellramil; ByTrite; Loavel; Ramic; Ramilo; Ramitace; Ramyte†; Tritace; ***Israel***: Ramitens; Tritace; ***Ital.***: Norapril; Quark; Ramieca; Triatec; Unipril; ***Malaysia***: Tripril; Tritace; ***Mex.***: Intemipril; Lastace; Ramace; Tritace; Venesden; ***Neth.***: Tritace; ***Norw.***: Triatec; ***NZ***: Tritace†; ***Philipp.***: Ramipro; Tritace; ***Pol.***: Ampril; Apo-Rami; Axtil; Mitrip; Piramil; Polpril; Ramicor; Ramve; Tritace; Vivace; ***Port.***: Brefit; Prilamil; Ramgen†; Romace; Triatec; Verzatec; ***Rus.***: Amprilan (Амприлан); Hartil (Хартил); Piramil (Пирамил); Ramitren (Рамитрен); Tritace (Тритаце); ***S.Afr.***: Ramace; Ramiwin; Rampil; Retace; Tritace; ***Singapore***: Tritace; ***Spain***: Acovil; Carasel; ***Swed.***: Triatec; ***Switz.***: Triatec; ***Thal.***: Acetate; Corpril; Gempril; Mediram; Piramil†; Ramicard; Ramiril†; Ramtace; Tritace; ***Turk.***: Blokace; Dellx; Race; Raliks; Revil; Sandace; ***UK***: Tritace; ***Ukr.***: Ampril (Амприл); Hartil (Хартил); Polapril (Полаприл); Rami (Рами); Ramihexal (Рамигексал)†; Ramizes (Рамизес); ***USA***: Altace; ***Venez.***: Altace; Piramil.

Multi-ingredient Preparations. ***Arg.***: Triacor; Tritace-HCT; ***Austral.***: Triasyn; ***Austria***: Hypren plus; Lannapril plus; Lasitace; Ramicomp; Tritazide; ***Belg.***: Co-Ramipril; Tazko; Tritazide; ***Braz.***: Ecator H; Naprix A; Naprix D; Ramipress HCT; Triatec D; ***Canad.***: Altace HCT; Altace Plus Felodipine; ***Cz.***: Amprilan H; Hartil-H; Medoram plus H; Miril plus H; Ramil H; Ramipril H; Ramixa Plus H†; Triasyn; Tritazide; ***Denm.***: Marilamed; Ramiad†; Ranid; Tiavase; Triatec Comp†; Xeviram†; ***Fin.***: Cardace Comp; Unimax; ***Fr.***: Cotriatec; ***Ger.***: Arelix ACE†; Delix Plus; Delmuno; Rami-Q comp†; Ramicard Plus†; Ramiclair Plus; Ramigamma HCT; RamiLich comp; Ramiplus†; Ramipril comp; Ramipril HCT†; Ramipril HCTad†; Ramipril Plus†; Ramitanid†; Unimax; Vesdil plus†; ***Gr.***: Piramil Plus; Stibenyl HCT; Triacor; Triatec Plus; Unitens; ***Hung.***: Amprilan HD; Amprilan HL; Hartil HCT; Meramyl HCT; Ramace Plusz; Ramiwin HCT†; Triasyn; Tritace-HCT; ***India***: Acepril-A; Alis-AT; Alis-R; Amlo-R; Amlokos-R; Ampine-RL; Asomex-R; Cardace-H; Conram H; Corpril-AM; Dexace-H; Diakit-3; Diakit-4; Ecator-H; Esam R; Eslo-Ril; Etotan-HR; Etotan-R; Hopace-AM; Hopace-H; Hopecard AM; Hopecard H; Kapril-H; Loram-H; Loram; Losanorm-HR; Loscom-R; LR; Odipril-H; Olmy-R; Ramcor H; Ramipres H; ***Irl.***: Trialix; Triapin; ***Israel***: Ramipril Plus; Ramitens Plus†; Tritace Comp; ***Ital.***: Idroquark; Prilace; Triapin; Triatec HCT; Uniprildiur; ***Mex.***: Dynyel; Triacor; Tritazide; ***Neth.***: Delitab-HCT†; Prilitab-HCT†; Prilitaril-HCT; Ramitab-HCT†; Triapin; Tritazide; ***Philipp.***: Triapin; ***Pol.***: Ampril HD; Ampril HL; Delmuno; Ramicor Comb†; Tritace Comb; ***Port.***: Ramicor D†; Triapin; Triatec Composto; Unimax†; ***Rus.***: Amprilan ND (Амприлан НД); Amprilan NL (Амприлан НЛ); Hartil-D (Хартил-Д); Ramazid H (Рамазид Н); ***S.Afr.***: Tri-Plen; ***Spain***: Triapin; ***Swed***: Triatec Comp; ***Switz.***: Co-Ramipril; Ramipril HCT; Trialix; Triatec Comp; Unimax†; ***Thal.***: Tritazide; ***Turk.***: Blokace Plus; Delix Plus; Race Plus; Revil Plus; ***UK***: Triapin; ***Ukr.***: Ampril HD (Амприл HD); Ampril HL (Амприл HL); Hartil-H (Хартил-Н); Mipril H (Миприл Н); Rami Compositum (Рами Композитум); Rami-Asomex (Рами-Азомекс); Ramihexal Compositum (Рами гексал Композитум)†; Ramizes Com (Рамизес Ком); Tritace Plu (Тритаце Плюс); ***Venez.***: Altace Plus.

Pharmacopoeial Preparations

BP 2014: Ramipril Capsules; Ramipril Tablets;
USP 36: Ramipril Capsules.

Ranolazine *(BAN, USAN, rINN)*

CVT-303; Ran-D; Ran4; Ranolazina; Ranolazinum; RS-43285-003; Ранолазин.

(±)-*N*-(2,6-Dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-1-piperazineacetamide.

$C_{24}H_{33}N_3O_4$=427.5

CAS — 95635-55-5.
ATC — C01EB18.
ATC Vet — QC01EB18.
UNII — A6IEZ5M406.

Ranolazine Hydrochloride *(USAN, rINNM)*

Hidrocloruro de ranolazina; Ranolazina, hidrocloruro de; Ranolazine, Chlorhydrate de; Ranolazini Hydrochloridum; RS-43285; Ранолазина Гидрохлорид.

$C_{24}H_{33}N_3O_4.2HCl$=500.5

CAS — 95635-56-6.
ATC — C01EB18.
ATC Vet — QC01EB18.
UNII — F71253DJUN.

Uses and Administration

Ranolazine is an antianginal drug. Its mechanism of action is unclear but may involve inhibition of the late sodium current in cardiac myocytes; it also inhibits fatty acid oxidation, but this does not appear to occur at therapeutic plasma concentrations. It is given orally, as a modified-release dose-form, for the treatment of stable angina pectoris (p. 1254.3).

In the UK, ranolazine is indicated in patients who are unable to tolerate or who have not responded satisfactorily to other antianginals, and should be given as an adjunct to standard therapy. It is given in an initial dose of 375 mg twice daily, increased after 2 to 4 weeks to 500 mg twice daily. The dose may be further increased to a maximum of 750 mg twice daily depending on response; dose reduction may be necessary if adverse effects occur.

In the USA, ranolazine may be used alone or as an adjunct to other antianginal drugs. The initial dose is 500 mg twice daily, increasing to a maximum of 1 g twice daily if necessary. The dose should be limited to 500 mg twice daily in patients taking some interacting drugs (see Interactions, p. 1485.1).

Reviews.

1. Tafreshi MJ, Fisher E. Ranolazine: a new approach to management of patients with angina. *Ann Pharmacother* 2006; 40: 689–93.
2. Chaitman BR. Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. *Circulation* 2006; 113: 2462–72.
3. Zerumsky K, McBride BF. Ranolazine in the management of chronic stable angina. *Am J Health-Syst Pharm* 2006; 63: 2331–8.
4. Keating GM. Ranolazine: a review of its use in chronic stable angina pectoris. *Drugs* 2008; 68: 2483–2503.
5. Aslam S, Gray D. Ranolazine (Ranexa) in the treatment of chronic stable angina. *Adv Therapy* 2010; 27: 193–201.
6. Reffelmann T, Kloner RA. Ranolazine: an anti-anginal drug with further therapeutic potential. *Expert Rev Cardiovasc Ther* 2010; 8: 319–29.

Diabetes mellitus. Ranolazine treatment for acute coronary syndrome has been found to be associated with a reduction in HbA_{1c} both in patients with diabetes mellitus (p. 459.1) and those with no history of the disease;[1] the mechanism was uncertain.

1. Morrow DA, *et al.* Evaluation of the glycometabolic effects of ranolazine in patients with and without diabetes mellitus in the MERLIN-TIMI 36 randomized controlled trial. *Circulation* 2009; 119: 2032–9.

Adverse Effects and Precautions

Adverse effects most commonly seen with ranolazine are nausea, constipation, dizziness, and headache. Palpitations, tinnitus, vertigo, dry mouth, abdominal pain, vomiting, peripheral oedema, and dyspnoea have also been reported. Rarely reported effects include bradycardia, haematuria, paraesthesia, hypotension, and blurred vision. Acute renal failure has also been reported.

Dose-related prolongation of the QT interval may occur; ranolazine should be used with caution in patients with pre-existing QT prolongation, and in those at increased risk of

QT prolongation: it is contra-indicated in patients with significant hepatic impairment and those taking interacting drugs (see Interactions, below). Plasma concentrations are increased in renal impairment and UK licensed product information contra-indicates ranolazine in patients with creatinine clearance below 30 mL/minute.

Interactions

Ranolazine is mainly metabolised by the P450 isoenzyme CYP3A4 and may interact with other drugs that affect or are affected by this enzyme. Ranolazine is contra-indicated with potent inhibitors of CYP3A4, such as ketoconazole and related antifungals, clarithromycin and telithromycin, HIV-protease inhibitors, and nefazodone. It may be used with caution in patients taking moderate CYP3A4 inhibitors or P-glycoprotein inhibitors, such as diltiazem, verapamil, fluconazole, erythromycin, ciclosporin, and grapefruit juice or grapefruit products; US licensed product information recommends a maximum dose of 500 mg twice daily if such combinations are given. Use of ranolazine with CYP3A4 or P-glycoprotein inducers should be avoided.

Ranolazine may itself act as an inhibitor of some enzymes. Plasma concentrations of simvastatin, which is metabolised by CYP3A4, are reported to be doubled when given with ranolazine. Plasma concentrations of digoxin, a P-glycoprotein substrate, may also be increased and dose adjustment may be required; dose reductions may also be needed for drugs metabolised by CYP2D6, such as tricyclic antidepressants and some antipsychotics.

Ranolazine may theoretically interact with other drugs that increase the QT-interval. UK licensed product information contra-indicates its use with class Ia or class III antiarrhythmics.

Pharmacokinetics

Absorption of ranolazine is highly variable and peak plasma concentrations occur about 2 to 5 hours after an oral dose of the modified-release preparation. Ranolazine is extensively metabolised in the gastrointestinal tract and liver. Four main metabolites have been identified. Protein binding of ranolazine is about 62%. About 75% of a dose is excreted in the urine with the remainder in the faeces, with less than 5% as unchanged drug. The apparent terminal half-life for the modified-release preparation of ranolazine is 7 hours, and steady state occurs within 3 days.

Reviews.
1. Jerling M. Clinical pharmacokinetics of ranolazine. *Clin Pharmacokinet* 2006; 45: 469–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Ranexa; ***Cz.***: Ranexa; ***Ger.***: Ranexa; ***Gr.***: Ranexa; ***India***: Caroza; ***Irl.***: Ranexa; ***Israel***: Ranexa; ***Neth.***: Ranexa; ***Pol.***: Ranexa; ***Port.***: Ranexa; ***Spain***: Ranexa; ***Switz.***: Ranexa; ***UK***: Ranexa; ***USA***: Ranexa.

Raubasine

Ajmalicina; Ajmalicine; Alkaloid F; Raubasiini; Raubasin; Raubasina; Raubasinum; δ-Yohimbine; Аймалицин; Рауба-зин.

Methyl 16,17-didehydro-19α-methyl-18-oxayohimban-16-carboxylate.

$C_{21}H_{24}N_2O_3$=352.4

CAS — 483-04-5.

UNII — 4QJL8OX71Z.

Pharmacopoeias. In *Chin.*

Profile

Raubasine is an alkaloid obtained from *Rauwolfia serpentina* (Apocynaceae). It is a vasodilator related chemically to reserpine (below) and has been given orally and by injection in peripheral and cerebral vascular disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Lamuran.

Multi-ingredient Preparations. ***China***: Duxil (都可喜); ***Fr.***: Iskedyl; ***Hong Kong***: Duxaril; ***Philipp.***: Duxaril; ***Singapore***: Duxaril; ***Thai.***: Duxaril†.

Rauwolfia Serpentina

Chotachand; Rauvolfia; Rauwolfia; Rauwolfiae Radix; Rauwolfiawurzel; Раувольфия Змеиная.

CAS — 8063-17-0 (rauwolfia).

ATC — C02AA04.

ATC Herb — HC02AA5001 (Rauwolfia serpentina: root).

UNII — 3P7VF1UYMO (Rauwolfia serpentina); H192N84N1G (Rauwolfia serpentina root).

Pharmacopoeias. In *Ger.* and *US.*

USP 36: (Rauwolfia Serpentina). The dried roots of *Rauwolfia serpentina* (Apocynaceae). It contains not less than 0.15% of reserpine-rescinnamine group alkaloids calculated as reserpine. Store at 15 degrees to 30 degrees in a dry place.

Profile

Rauwolfia serpentina contains numerous alkaloids, the most active as hypotensive agents being the ester alkaloids, reserpine and rescinnamine. Other alkaloids present have structures related to reserpic acid, but are not esterified, and include ajmaline (rauwolfine), ajmalinine, ajmalicine, isoajmaline (isorauwolfine), serpentine, rauwolfinine, and sarpagine. The actions of rauwolfia serpentina are those of its alkaloids and it has been used for the same purposes as reserpine, below. It has been given orally as the powdered whole root.

Rauwolfia vomitoria has also been used.

A crude form of rauwolfia serpentina has been used in India for centuries as preparations such as Sarpagandha, in the treatment of insomnia and certain forms of mental illness.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Raunatine (Раунатин).

Multi-ingredient Preparations. ***India***: Arjin; Confido; Lukol; Memtone; Nevromine; ***Rus.***: Speman Forte (Спеман Форте); ***Ukr.***: Confido (Конфидо)†.

Homoeopathic Preparations. ***Austria***: Homviotensin; ***Ger.***: Antihypertonicum N†; Homviotensin; Lowe-Komplex Nr 3; RauwolfiaViscomp; Viscum album H†; ***Rus.***: Crataegus-Plus (Крателгус-Плюс); ***Ukr.***: Homviotensin (Хомвиотензин).

Pharmacopoeial Preparations
USP 36: Rauwolfia Serpentina Tablets.

Regadenoson *(BAN, USAN, rINN)*

CVT-3146; Regadenosón; Régadénoson; Regadenosonum; Регаденозон.

1-(6-Amino-9-β-D-ribofuranosyl-9*H*-purin-2-yl)-*N*-methyl-1*H*-pyrazole-4-carboxamide monohydrate.

$C_{15}H_{18}N_8O_5$, H_2O=408.4

CAS — 313348-27-5 (regadenoson); 875148-45-1 (regadenoson monohydrate).

ATC — C01EB21.

ATC Vet — QC01EB21.

UNII — 2XLN4Y044H.

Uses and Administration

Regadenoson has similar properties to adenosine (p. 1291.1) but has a greater selectivity for the adenosine A_{2A}-receptor. It is a coronary vasodilator and increases coronary blood flow and is used to provide a pharmacological stress as an adjunct to radionuclide myocardial perfusion imaging. It is given intravenously in a single dose of 400 micrograms by rapid injection over about 10 seconds, followed by 5 mL of sodium chloride 0.9%; the radionuclide should be given 10 to 20 seconds after the sodium chloride.

References.
1. Hendel RC, *et al.* Initial clinical experience with regadenoson, a novel selective A_{2A} agonist for pharmacologic stress single-photon emission computed tomography myocardial perfusion imaging. *J Am Coll Cardiol* 2005; 46: 2069–75.
2. Iskandrian AE, *et al.* Adenosine versus regadenoson comparative evaluation in myocardial perfusion imaging: results of the ADVANCE phase 3 multicenter international trial. *J Nucl Cardiol* 2007; 14: 645–58.
3. Buhr C, *et al.* Regadenoson in the detection of coronary artery disease. *Vasc Health Risk Manag* 2008; 4: 337–40.
4. Thomas GS, *et al.* The RegEx trial: a randomized, double-blind, placebo- and active-controlled pilot study combining regadenoson, a selective A_{2A} adenosine agonist, with low-level exercise, in patients undergoing myocardial perfusion imaging. *J Nucl Cardiol* 2009; 16: 63–72.
5. Al Jaroudi W, Iskandrian AE. Regadenoson: a new myocardial stress agent. *J Am Coll Cardiol* 2009; 54: 1123–30.
6. Garnock-Jones KP, Curran MP. Regadenoson. *Am J Cardiovasc Drugs* 2010; 10: 65–71.

Adverse Effects, Treatment, and Precautions

As for Adenosine, p. 1291.3. Regadenoson may be used with caution in patients with asthma or chronic obstructive pulmonary disease.

Interactions

As for Adenosine, p. 1292.1.

Pharmacokinetics

After intravenous injection of regadenoson, peak plasma concentrations occur within 1 to 4 minutes and decline in a multi-exponential fashion. The initial half-life is about 2 to 4 minutes, followed by an intermediate stage with a half-life of about 30 minutes, during which the pharmacodynamic effect is lost; the half-life during the terminal phase is about 2 hours. Regadenoson does not appear to be metabolised; about 57% of a dose is excreted unchanged in the urine.

References.
1. Gordi T, *et al.* A population pharmacokinetic/pharmacodynamic analysis of regadenoson, an adenosine A_{2A}-receptor agonist, in healthy male volunteers. *Clin Pharmacokinet* 2006; 45: 1201–12.
2. Gordi T, *et al.* Regadenoson pharmacokinetics and tolerability in subjects with impaired renal function. *J Clin Pharmacol* 2007; 47: 825–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Rapiscan; ***Irl.***: Rapiscan; ***Neth.***: Rapiscan; ***Pol.***: Rapiscan; ***Port.***: Rapiscan; ***UK***: Rapiscan; ***USA***: Lexiscan.

Rescinnamine *(BAN, rINN)*

Rescinamina; Rescinnamin; Rescinnaminum; Resinnamiini; Рецинниамин.

Methyl *O*-(3,4,5-trimethoxycinnamoyl)reserpate.

$C_{35}H_{42}N_2O_9$=634.7

CAS — 24815-24-5.

ATC — C02AA01.

ATC Vet — QC02AA01.

UNII — Q6W1F7DJ2D.

Profile

Rescinnamine is an ester alkaloid isolated from the root of *Rauwolfia serpentina* or *R. vomitoria*. It has properties similar to those described under reserpine (below) and has been used in the treatment of hypertension.

Reserpine *(BAN, rINN)*

Reserpiini; Reserpin; Reserpina; Réserpine; Reserpinum; Reszerpin; Rezerpin; Rezerpina; Rezerpinas; Резерпин.

Methyl 11,17α-dimethoxy-18β-(3,4,5-trimethoxybenzoyloxy)-3β,20α-yohimbane-16β-carboxylate; Methyl *O*-(3,4,5-trimethoxybenzoyl)reserpate.

$C_{33}H_{40}N_2O_9$=608.7

CAS — 50-55-5.

ATC — C02AA02.

ATC Vet — QC02AA02.

UNII — 8B1QWR724A.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Reserpine). It occurs as small, white to slightly yellow crystals or a crystalline powder. It darkens slowly on exposure to light. Practically insoluble in water; very slightly soluble in alcohol. Protect from light.

USP 36: (Reserpine). A white or pale buff to slightly yellowish, odourless, crystalline powder. It darkens slowly on exposure to light, but more rapidly when in solution. Insoluble in water; soluble 1 in 1800 of alcohol and 1 in 6 of chloroform; freely soluble in acetic acid; very slightly soluble in ether; slightly soluble in benzene. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Stability. Reserpine is unstable in the presence of alkalis, particularly when the drug is in solution.

Uses and Administration

Reserpine is an alkaloid obtained from the roots of certain species of *Rauwolfia* (Apocynaceae), mainly *Rauwolfia serpentina* and *R. vomitoria*, or by synthesis. The material obtained from natural sources may contain closely related alkaloids.

Reserpine is an antihypertensive drug that causes depletion of noradrenaline stores in peripheral sympathetic nerve terminals and depletion of catecholamine and serotonin stores in the brain, heart, and many other organs resulting in a reduction in blood pressure, bradycardia, and CNS depression. The hypotensive effect is mainly due to a reduction in cardiac output and a reduction in peripheral resistance. Cardiovascular reflexes are partially inhibited, but orthostatic hypotension is rarely a problem at the doses used in hypertension. When given orally the full effect is only reached after several weeks of treatment and persists for up to 6 weeks after treatment is stopped.

Reserpine has been used in the management of hypertension (p. 1251.1) and in chronic psychoses (p. 1030.2) such as schizophrenia. It has also been used in the treatment of Raynaud's syndrome (see Vasospastic Arterial Disorders, p. 1275.3).

In **hypertension**, reserpine may be given orally in an initial dose of up to 500 micrograms daily for about 2 weeks, subsequently reduced to the lowest dose necessary to maintain the response; some sources recommend an initial dose of 50 to 100 micrograms. A maintenance dose of about 100 to 250 micrograms daily may be adequate and 500 micrograms should not normally be exceeded. To reduce adverse effects and tolerance smaller doses of reserpine may be used with a thiazide diuretic.

Reserpine has been used in chronic **psychoses** in daily doses of up to 1 mg.

References.
1. Shamon SD, Perez ML. Blood pressure lowering efficacy of reserpine for primary hypertension. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 27/10/09).

Adverse Effects

Adverse effects commonly include nasal congestion, headache and CNS symptoms including depression, drowsiness, dizziness, lethargy, nightmares, and symptoms of increased gastrointestinal tract motility including diarrhoea, abdominal cramps, and, at higher doses, increased gastric acid secretion. Respiratory distress, cyanosis, anorexia, and lethargy may occur in infants whose mothers have taken reserpine before delivery.

Higher doses may cause flushing, bradycardia, severe depression which may lead to suicide, and extrapyramidal effects. Hypotension, coma, convulsions, respiratory depression, and hypothermia also occur in overdosage. Hypotension is also more common in patients after a cerebrovascular accident.

Breast engorgement and galactorrhoea, gynaecomastia, increased prolactin concentrations, decreased libido, impotence, sodium retention, oedema, decreased or increased appetite, weight gain, miosis, dry mouth, sialorrhoea, dysuria, rashes, pruritus, and thrombocytopenic purpura have also been reported.

Large doses of reserpine have been shown to be tumorigenic in *rodents*. Several reports have suggested an association between reserpine and the development of neoplasms of the breast (see below) but other surveys have failed to confirm this.

Neoplasms of the breast. Although early studies suggested that the incidence of breast cancer was up to 3 to 4 times greater in hypertensive women treated with rauwolfia preparations than in control groups, analysis[1] of both prospective and case-control studies found only a low-grade association between use of rauwolfia preparations and risk of malignancy.

1. Grossman E, *et al.* Antihypertensive therapy and the risk of malignancies. *Eur Heart J* 2001; 22: 1343–52.

Treatment of Adverse Effects

Withdrawal of reserpine or reduction of the dosage causes the reversal of many adverse effects although mental disorders may persist for months and hypotensive effects may persist for weeks after the cessation of treatment. If overdosage occurs activated charcoal may be considered within 1 hour of ingestion. Treatment is generally supportive and symptomatic. Severe hypotension may respond to placing the patient in the supine position with the feet raised. Direct-acting sympathomimetics may be effective for treatment of severe hypotension, but should be given with caution. The patient must be observed for at least 72 hours.

Precautions

Reserpine should not be used in patients with depression or a history of depression, with active peptic ulcer disease or ulcerative colitis, or in patients with Parkinson's disease. It should also be avoided in phaeochromocytoma.

It should be used with caution in debilitated or elderly patients, and in the presence of cardiac arrhythmias, myocardial infarction, renal insufficiency, gallstones, epilepsy, or allergic conditions such as bronchial asthma.

Reserpine is contra-indicated in patients having ECT and an interval of at least 7 to 14 days should be allowed between the last dose of reserpine and the start of any ECT.

It is probably not necessary to stop reserpine during anaesthesia, although the effects of CNS depressants may be enhanced by reserpine.

Interactions

Patients taking reserpine may be hypersensitive to adrenaline and other direct-acting sympathomimetics, which should not be given except to antagonise reserpine.

The effects of indirect-acting sympathomimetics such as ephedrine may be decreased by reserpine. The hypotensive effects of reserpine are enhanced by thiazide diuretics and other antihypertensives. Reserpine may cause excitation and hypertension in patients receiving MAOIs. Use of digitalis or quinidine with reserpine may cause cardiac arrhythmias. Reserpine may enhance the effects of CNS depressants.

Antiparkinsonian drugs. For the inhibitory effect of reserpine on the antiparkinsonian actions of *levodopa*, see Antihypertensives, p. 907.2.

Pharmacokinetics

Reserpine is absorbed from the gastrointestinal tract with a bioavailability of 50%. It is extensively metabolised and is excreted slowly in the urine and faeces. In the first 4 days, about 8% is excreted in the urine, mainly as metabolites, and about 60% in the faeces, mainly unchanged. Reserpine crosses the placenta and the blood-brain barrier and also appears in breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Resapin†; Serpasil.

Multi-ingredient Preparations. *Austria*: Brinerdin; *Braz.*: Higroton Reserpina; *China*: Fufang Lixueping (复方利血平); No 0 (0号); *Cz.*: Crystepin†; Neocrystepin†; *Fr.*: Tensionorme; *Ger.*: Briserin N; Triniton†; *Gr.*: Aditasin; Bestocalm; Hygroton-Reserpine; Neourizine; Renese R; Santapertas; Tensiplex; *India*: Adelphane-Esidrex; Adelphane; Genophane; *Indon.*: Deliasidrex†; Ser-Ap-Es; *Ital.*: Brinerdina; Igroton-Reserpina; *Jpn*: Behyd-RA; *Mex.*: Higroton-Res; *Pol.*: Normatens; *Rus.*: Adelphane-Esidrex (Адельфан-эзидрекс); Brinerdin (Бринердин); Crystepin (Кристепин); Normatens (Нормитенс); Triresid K (Трирезид К)†; *S.Afr.*: Brinerdin; Protensin-M†; *Switz.*: Brinerdine; Hygroton-Reserpine†; *Thai.*: Bedin; Brinerdin; Briscotin†; Hydrares; Mano-Ap-Es; Reser; Ser-Ap-Es†; *Turk.*: Adelphan-Esidrex†; Adelphan†; Regroton; *Ukr.*: Adelphane-Esidrex (Адельфан-Эзидрекс); Normatens (Нормитенс); *USA*: Demi-Regroton; Diupres; Hydropres; Marpres; Regroton.

Homoeopathic Preparations. *Austria*: Homviotensin; *Ger.*: dysto-loges N; dysto-loges S; *Ukr.*: Homviotensin (Хомвиотензин).

Pharmacopoeial Preparations

USP 36: Reserpine and Chlorothiazide Tablets; Reserpine and Hydrochlorothiazide Tablets; Reserpine Elixir; Reserpine Injection; Reserpine Tablets; Reserpine, Hydralazine Hydrochloride, and Hydrochlorothiazide Tablets.

Reteplase *(BAN, USAN, rINN)*

BM-06.022; Reteplaasi; Reteplas; Reteplasa; Rétéplase; Reteplasum; rPA; Ретеплаза.

173-L-Serine-174-L-tyrosine-175-L-glutamine-173–527-plasminogen activator (human tissue-type).

$C_{1736}H_{2653}N_{499}O_{522}S_{22}$=39571.6

CAS — 133652-38-7.

ATC — B01AD07.

ATC Vet — QB01AD07.

UNII — DQA630RIE9.

Description. Reteplase is a nonglycosylated protein produced by recombinant DNA technology. It consists of selected domains of human tissue plasminogen activator.

Incompatibility. Reteplase may precipitate out of solution if it is given with heparin in the same intravenous line.[1] Reteplase and heparin must therefore be given separately; if a single intravenous line is used it must be flushed thoroughly with sodium chloride 0.9% or with glucose 5% before, and after, reteplase injection.

1. CSM/MCA. Reteplase (Rapilysin): incompatibility with heparin. *Current Problems* 2000; 26: 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 20/06/06)

Uses and Administration

Reteplase is a thrombolytic drug. It converts plasminogen to plasmin, resulting in fibrinolysis and dissolution of clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p. 1124.3. Reteplase has some fibrin specificity (see Thrombolytics, p. 1245.3).

Reteplase is used similarly to streptokinase (p. 1503.1) in acute myocardial infarction (p. 1257.1). It is given intravenously as soon as possible after the onset of symptoms. The dose is 10 units given by slow intravenous injection (but over not more than 2 minutes), and this dose of 10 units is repeated once, 30 minutes after the start of the first injection.

General references.
1. Noble S, McTavish D. Reteplase: a review of its pharmacological properties and clinical efficacy in the management of acute myocardial infarction. *Drugs* 1996; 52: 589–605.
2. Wooster MB, Luzier AB. Reteplase: a new thrombolytic for the treatment of acute myocardial infarction. *Ann Pharmacother* 1999; 33: 318–24.
3. Llevador J, *et al.* Bolus fibrinolytic therapy in acute myocardial infarction. *JAMA* 2001; 286: 442–9.
4. Simpson D, *et al.* Reteplase: a review of its use in the management of thrombotic occlusive disorders. *Am J Cardiovasc Drugs* 2006; 6: 265–85.

Catheters and cannulas. Reteplase has been used[1] successfully to clear thrombi in central venous catheters. A single dose of 0.4 units of reteplase was given as a 1 unit/mL solution, further diluted to the volume required to fill the catheter. The minimum dwell time was 30 minutes and the solution was aspirated after treatment. A second dose of 0.4 units was given if necessary.

1. Owens L. Reteplase for clearance of occluded venous catheters. *Am J Health-Syst Pharm* 2002; 59: 1638–40.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p. 1505.1. Allergic reactions may be less likely to occur with reteplase than with streptokinase.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies reteplase as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Streptokinase, p. 1507.1.

Pharmacokinetics

Based on fibrinolytic activity, reteplase is reported to have an initial half-life of about 14 minutes and a terminal half-life of 1.6 hours in patients with myocardial infarction.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Rapilysin; *Austria*: Rapilysin; *Belg.*: Rapilysin; *Canad.*: Retavase; *China*: Pai Tong Xin (派通欣); Rui Tong Li (瑞通立); *Cz.*: Rapilysin; *Denm.*: Rapilysin; *Fin.*: Rapilysin; *Fr.*: Rapilysin; *Ger.*: Rapilysin; *Gr.*: Rapilysin; *Hong Kong*: Rapilysin; *Irl.*: Rapilysin; *Ital.*: Rapilysin; *Neth.*: Rapilysin; *Norw.*: Rapilysin; *NZ*: Rapilysin; *Pol.*: Rapilysin; *Port.*: Rapilysin; *Singapore*: Rapilysin; *Spain*: Rapilysin; *Swed.*: Rapilysin; *Switz.*: Rapilysin; *Turk.*: Rapilysin; *UK*: Rapilysin; *USA*: Retavase.

Reviparin Sodium *(BAN, rINN)*

Reviparilninatrium; Reviparina sódica; Révlparine Sodique; Reviparinnatrium; Reviparinum Natricum; Ревипарин Натрий.

CAS — 9041-08-1.

ATC — B01AB08.

ATC Vet — QB01AB08.

UNII — 5XQ9UBJ16W.

Description. Reviparin sodium is prepared by nitrous acid depolymerisation of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-*O*-sulfo-2,5-anhydro-D-mannitol structure at the reducing end of their chain. The mass-average molecular mass ranges between 3150 and 5150 with a characteristic value of about 4150. The degree of sulfation is about 2.1 per disaccharide unit.

Units

As for Low-molecular-weight Heparins, p. 1426.2.

Uses and Administration

Reviparin sodium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant activity. It is used in the prevention and treatment of venous thromboembolism (p. 1274.1) and has been used to prevent coagulation during haemodialysis.

Doses are expressed in terms of anti-factor Xa activity (anti-Xa units) although different values may be encountered in the literature depending upon the reference preparation used.

In the prophylaxis of venous thromboembolism during surgery, reviparin sodium is given subcutaneously in a usual dose of about 1750 or 4200 units once daily, depending on risk, with the first dose given 2 to 4 hours before surgery with the lower dose, or 12 hours before surgery with the higher dose. In the treatment of venous

thromboembolism, a subcutaneous dose of about 175 units/kg is given daily in 2 divided doses.

References.
1. Wellington K, *et al.* Reviparin: a review of its efficacy in the prevention and treatment of venous thromboembolism. *Drugs* 2001; 61: 1185–209.
2. Yusuf S, *et al.* CREATE Trial Group Investigators. Effects of revtparin, a low-molecular-weight heparin, on mortality, reinfarction, and strokes in patients with acute myocardial infarction presenting with ST-segment elevation. *JAMA* 2005; 293: 427–35.

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p. 1426.3.

Severe bleeding with reviparin sodium may be reduced by the slow intravenous injection of protamine sulfate; 1.2 mg of protamine sulfate has been stated to inhibit the effect of about 100 units of reviparin sodium.

Interactions

As for Low-molecular-weight Heparins, p. 1427.2.

Pharmacokinetics

Reviparin sodium is absorbed after subcutaneous doses with a bioavailability of about 95%. Peak plasma concentrations occur after about 3 hours. Reviparin sodium is excreted mainly in the urine; the elimination half-life is about 3 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Clivarin (诺易平); Cz.: Clivarin†; *Fr.*: Clivarine†; *Ger.*: Clivarin; *Gr.*: Clivarin; *Hong Kong*: Clivarine†; *Hung.*: Clivarin†; *India*: Clivarine; *Ital.*: Clivarina; *Pol.*: Clivarin†.

Rilmenidine Phosphate *(rINNM)*

Fosfato de rilmenidina; Oxaminozoline Phosphate; Rilmenidiinidivetyfosfaatti; Rilmenidin Dihdrojen Fosfat; Rilmenidin fosfát; Rilmenidina, fosfato de; Rilmenidin-dihidrogénfoszfát; Rilmenidindihydrogenphosphat; Rilmenidindivätefosfat; Rilmenidine Acid Phosphate; Rilmenidine Dihydrogen Phosphate; Riménidine, dihydrogénophosphate de; Rilmenidine Hydrogen Phosphate; Riménidine, Phosphate de; Rilmenidini Dihydrogenophosphas; Rilmenidini Phosphas; Rilmenidino divandenillo fosfatas; S-3341-3; Рильменидина Фосфат.

2-[(Dicyclopropylmethyl)amino]-2-oxazoline phosphate.

$C_{10}H_{16}N_2O.H_3PO_4$=278.2

CAS — 54187-04-1 (rilmenidine); 85409-38-7 (rilmenidine phosphate).

ATC — C02AC06.

ATC Vet — QC02AC06.

UNII — 59QD64Q32M.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Rilmenidine Dihydrogen Phosphate). A white or almost white powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane.

Profile

Rilmenidine is a centrally acting antihypertensive that appears to act through stimulation of central imidazoline receptors and also has alpha$_2$-adrenoceptor agonist activity. It has general properties similar to those of clonidine (p. 1339.1), but is reported to cause less sedation and central adverse effects. In the management of hypertension (p. 1251.1) it has been given as the phosphate, but doses are expressed in terms of the base. Rilmenidine phosphate 1.5 mg is equivalent to about 1 mg of rilmenidine. The dose is 1 mg daily, as a single oral dose; this may be increased if necessary, after 1 month, to 2 mg daily in divided doses.

References.
1. Bousquet P, Feldman J. Drugs acting on imidazoline receptors: a review of their pharmacology, their use in blood pressure control and their potential interest in cardioprotection. *Drugs* 1999; 58: 799–812.
2. Reid JL. Rilmenidine: a clinical overview. *Am J Hypertens* 2000; 13: 106S–111S.
3. Reid JL. Update on rilmenidine: clinical benefits. *Am J Hypertens* 2001; 14: 322S–324S.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Hyperium; *Austria*: Iterium; *Braz.*: Hyperium; *China*: Iperdix (爱博克); Cz.: Albarel†; Tenaxum; *Fr.*: Hyperium; *Gr.*: Hyperium; *Hong Kong*: Iperdix†; *Hung.*: Hyperlex; Tenaxum; *Philipp.*: Hyperdix†; *Pol.*: Tenaxum; *Port.*: Hyperium; *Rus.*: Albarel (Альбарел); Tenaxum (Тенаксум); *Thai.*: Hyperdix†; *Turk.*: Hyperium; *Ukr.*: Tenaxum (Тенаксум)†; *Venez.*: Hyperium.

Riociguat *(USAN, rINN)*

BAY-63-2521; Riociguatum; Риоцигуат.

Methyl *N*-(4,6-diamino-2-{1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl}pyrimidin-5-yl)-*N*-methylcarbamate.

$C_{20}H_{19}FN_8O_2$=422.4

CAS — 625115-55-1.

UNII — RU3FE2Y4XL.

Profile

Riociguat is a guanylate cyclase stimulator which acts on nitric oxide receptors to produce vasodilatation. It is used in the treatment of pulmonary arterial hypertension and persistent or recurrent chronic thromboembolic pulmonary hypertension, either after surgical treatment or in inoperable cases (p. 1278.2). It is given orally in 3 divided doses. The usual initial dose is 3 mg daily; patients who do not tolerate the hypotensive effects of riociguat may be given an initial dose of 1.5 mg daily. Thereafter, the dose may be increased in steps of 1.5 mg, at intervals of at least 2 weeks, to a maximum of 7.5 mg daily, provided systolic blood pressure remains greater than 95 mmHg and the patient has no signs or symptoms of hypotension. The dose should be decreased in steps of 1.5 mg in those who develop symptoms of hypotension.

Riociguat is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP); it is mainly metabolised by the cytochrome P450 isoenzymes CYP1A1, CYP3A, CYP2C8, and CYP2J2. When used with potent P450 isoenzyme or P-gp/BCRP inhibitors such as azole antifungals and HIV-protease inhibitors, the increase in riociguat exposure may result in hypotension; consequently, initial doses should be reduced to 1.5 mg daily. A decrease in riociguat exposure may occur with potent inducers of CYP3A, although there are no recommendations on dosage adjustments in the licensed product information. Tobacco smoking also induces hepatic metabolic enzymes and may decrease the plasma levels of riociguat; if tolerated, doses higher than 7.5 mg daily may be considered for smokers. Conversely, lower doses may be required in those who stop smoking. Riociguat should not be used with nitrates or nitric oxide donors (such as amyl nitrite), or phosphodiesterase (PDE) inhibitors, including both specific PDE-5 inhibitors (such as sildenafil, tadalafil, and vardenafil) and non-specific PDE inhibitors (such as dipyridamole and theophylline), because of additive hypotensive effects.

Riociguat has been shown to be teratogenic and embryotoxic in *animals* and is therefore contra-indicated in pregnant patients. Pregnancy should be excluded before starting therapy, and avoided during and for 1 month after stopping treatment; monthly pregnancy tests are recommended.

Serious bleeding, including haemoptysis and haemorrhage, has been reported with riociguat therapy.

References.
1. Frey R, *et al.* Riociguat (BAY 63-2521) and warfarin: a pharmacodynamic and pharmacokinetic interaction study. *J Clin Pharmacol* 2011; 51: 1051–60.
2. Schermuly RT, *et al.* Riociguat for the treatment of pulmonary hypertension. *Expert Opin Invest Drugs* 2011; 20: 567–76.
3. Bonderman D, *et al.* Left Ventricular Systolic Dysfunction associated with Pulmonary Hypertension Riociguat Trial (LEPHT) Study Group. Riociguat for patients with pulmonary hypertension caused by systolic left ventricular dysfunction: a phase IIb double-blind, randomized, placebo-controlled, dose-ranging hemodynamic study. *Circulation* 2013; 128: 502–11.
4. Ghofrani HA, *et al.* CHEST-1 Study Group. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2013; 369: 319–29.
5. Ghofrani HA, *et al.* PATENT-1 Study Group. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2013; 369: 330–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Adempas.

Rivaroxaban *(BAN, USAN, rINN)*

Bay-59-7939; Rivaroxabán; Rivaroxabana; Rivaroxabanum; Ривароксабан.

5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide.

$C_{19}H_{18}ClN_3O_5S$=435.9

CAS — 366789-02-8.

ATC — B01AF01.

ATC Vet — QB01AF01.

UNII — 9NDF7JZ4M3.

Uses and Administration

Rivaroxaban is a direct inhibitor of factor Xa (activated factor X) with a dose-dependent effect on prothrombin time. It is used for the treatment of deep-vein thrombosis or pulmonary embolism (p. 1274.1) and to prevent recurrence after initial treatment, or for the prophylaxis of venous thromboembolism in patients undergoing hip or knee replacement surgery. It is also used for the prevention of stroke and systemic embolisation in patients with non-valvular atrial fibrillation, and for the prevention of atherothrombotic events in patients after an acute coronary syndrome. Rivaroxaban is given orally; doses of 10 mg can be taken with or without food, whereas larger doses should be taken with food (see also Pharmacokinetics, p. 1488.1).

The recommended dose for the initial treatment of acute deep-vein thrombosis or pulmonary embolism is 15 mg twice daily for the first three weeks, followed by 20 mg once daily for continued treatment and prevention of recurrence.

For prophylaxis of venous thromboembolism in patients undergoing hip or knee replacement surgery, rivaroxaban is given in a dose of 10 mg once daily. The initial dose should be given 6 to 10 hours after surgery, providing haemostasis has been established, and treatment should be continued for 5 weeks after hip surgery and for 12 to 14 days after knee surgery.

For the prevention of stroke in atrial fibrillation, rivaroxaban is given in a dose of 20 mg once daily with the evening meal.

For the prevention of atherothrombotic events in patients after an acute coronary syndrome, rivaroxaban is given either with aspirin alone or with aspirin plus clopidogrel or ticlopidine. The recommended dose of rivaroxaban is 2.5 mg twice daily, started as soon as possible after stabilisation but at least 24 hours after admission to hospital and at the time when parenteral anticoagulation is stopped.

Recommendations for a missed dose depend on the dosing schedule being followed.

- For patients taking 15 mg twice daily: take rivaroxaban immediately to ensure intake of 30 mg per day; two 15-mg tablets may be taken at once if required. The patient should continue with 15 mg twice daily on the following day.
- For patients taking 10 or 20 mg once daily: take rivaroxaban immediately and continue on the following day with the once daily dose as recommended. The dose should not be doubled within the same day to make up for a missed dose.
- For patients taking 2.5 mg twice daily: continue with the next usual dose of rivaroxaban. The dose should not be doubled to make up for a missed dose.

If anticoagulation must be withdrawn to reduce the risk of bleeding with surgical or other procedures, rivaroxaban should be stopped at least 24 hours before the procedure. It may be restarted after the procedure as soon as haemostasis has been established.

For administration and dose adjustments in renal impairment, see below.

General references.
1. Fassiadis N. Rivaroxaban, the first oral, direct factor Xa inhibitor. *Expert Opin Pharmacother* 2009; 10: 2945–6.
2. NICE. Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (TA170, issued April 2009). Available at: http://www.nice.org.uk/nicemedia/live/12133/43811/43811.pdf (accessed 19/09/13)
3. Perzborn E, *et al.* Rivaroxaban: a new oral factor Xa inhibitor. *Arterioscler Thromb Vasc Biol* 2010; 30: 376–81.
4. NICE. Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation (TA256, issued May 2012). Available at: http://www.nice.org.uk/nicemedia/live/13746/59295/59295.pdf (accessed 19/09/13)
5. NICE. Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism (TA261, issued July 2012). Available at: http://www.nice.org.uk/nicemedia/live/13805/60040/60040.pdf (accessed 19/09/13)
6. Cohen AT, Dobromirski M. The use of rivaroxaban for short- and long-term treatment of venous thromboembolism. *Thromb Haemost* 2012; 107: 1035–43.
7. Duggan ST. Rivaroxaban: a review of its use for the prophylaxis of venous thromboembolism after total hip or knee replacement surgery. *Am J Cardiovasc Drugs* 2012; 12: 57–72.
8. Ahrens I, Bode C. Rivaroxaban for stroke prevention in atrial fibrillation and secondary prevention in patients with a recent acute coronary syndrome. *Future Cardiol* 2012; 8: 533–41.
9. Turpie AG, *et al.* Management consensus guidance for the use of rivaroxaban–an oral, direct factor Xa inhibitor. *Thromb Haemost* 2012; 108: 876–86.
10. NICE. Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism (TA287, issued June 2013). Available at: http://www.nice.org.uk/nicemedia/live/14192/64274/64274.pdf (accessed 19/09/13)
11. Palareti G, *et al.* Clinical management of rivaroxaban-treated patients. *Expert Opin Pharmacother* 2013; 14: 655–67.
12. Carter NJ, Plosker GL. Rivaroxaban: a review of its use in the prevention of stroke and systemic embolism in patients with atrial fibrillation. *Drugs* 2013; 73: 715–39.

Administration in renal impairment. Exposure to rivaroxaban is increased in patients with renal impairment. The usual oral doses can be used in those with mild renal impairment (creatinine clearance (CC) from 50 to 80 mL/minute), but dose adjustments may be needed for some indications in those with moderate (CC from 30 up to 50 mL/minute) to severe (CC from 15 up to 30 mL/minute) impairment.

- For the treatment of deep-vein thrombosis and pulmonary embolism and the prevention of recurrence in

patients with moderate to severe renal impairment, EU licensed product information recommends a reduced initial dose of 15 mg twice daily for the first 3 weeks. Thereafter, the usual recommended dose of 20 mg once daily may be taken, but a reduction to 15 mg once daily should be considered if the risk of bleeding outweighs the risk for recurrent deep-vein thrombosis or pulmonary embolism. In the USA, rivaroxaban is not recommended in patients with severe impairment and the usual dose may be given to those with moderate impairment.

- For the prevention of stroke and systemic embolism in atrial fibrillation in patients with moderate to severe renal impairment, a reduced dose of rivaroxaban 15 mg once daily is suggested.
- For prophylaxis of venous thromboembolism in patients undergoing hip or knee replacement surgery, rivaroxaban is not recommended in patients with severe impairment.

Rivaroxaban should not be used in patients with a CC less than 15 mL/minute, regardless of indication.

Caution is required in patients with renal impairment who are also taking other medication that may increase exposure to rivaroxaban, see Interactions, below.

Adverse Effects and Treatment

The most common adverse effect with rivaroxaban is bleeding. Nausea and increases in liver enzyme values may also occur; other gastrointestinal effects, pruritus, rashes, and renal impairment have been reported but are uncommon. There is no known antidote to rivaroxaban. Haemorrhagic complications should be treated with standard measures; use of factor VIIa may be considered in severe haemorrhage but clinical experience is lacking.

Precautions

Rivaroxaban should not be used in patients with clinically significant bleeding or with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. It should be used with caution in other patients at increased risk of bleeding. Plasma concentrations are increased in hepatic or renal impairment and the risk of bleeding may be increased; a reduced dose may be required in renal impairment, see Administration in Renal Impairment, p. 1487.3. There appears to be a possible rebound increased risk of stroke when stopping rivaroxaban in atrial fibrillation, and adequate cover with alternative anticoagulants may be needed. Although rivaroxaban does not require anticoagulant monitoring, it may falsely increase INR values on conversion with another anticoagulant such as warfarin.

Studies in *animals* have shown reproductive toxicity and distribution of rivaroxaban into breast milk and it is therefore contra-indicated in pregnancy and breast feeding.

Interactions

Rivaroxaban is metabolised by the cytochrome P450 isoenzyme CYP3A4 and is also a substrate for P-glycoprotein. It should not be given with potent inhibitors of both CYP3A4 and P-glycoprotein, such as ketoconazole, itraconazole, posaconazole, voriconazole, or HIV-protease inhibitors, although it may be used cautiously with fluconazole. Drugs that inhibit only one of these pathways or are less potent inhibitors, such as clarithromycin and erythromycin, do not appear to have clinically relevant effects. Potent inducers of CYP3A4, such as rifampicin, may reduce the effect of rivaroxaban.

Caution is needed if rivaroxaban is given with other anticoagulants or with drugs that affect bleeding, including NSAIDs and antiplatelet drugs. (However, another anticoagulant may need to be given when stopping rivaroxaban, see Precautions, above.)

Pharmacokinetics

When given orally, rivaroxaban is rapidly absorbed and peak plasma concentrations occur after 2 to 4 hours. The bioavailability of rivaroxaban is dose-dependent; it is about 80 to 100% for the 2.5-mg and 10-mg doses and is unaffected by food. With larger doses, bioavailability is lower but is increased with food. Plasma protein binding is about 92 to 95%. Rivaroxaban is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2J2 and by other mechanisms. About two-thirds of an oral dose is metabolised, with the metabolites excreted equally in the urine and faeces; the remaining third is excreted unchanged in the urine, mainly by active renal secretion. After an intravenous dose of rivaroxaban the elimination half-life is about 4.5 hours, but on oral dosage elimination is limited by the rate of absorption and the terminal elimination half-life is about 7 to 11 hours.

General references.

1. Mueck W, *et al.* Population pharmacokinetics and pharmacodynamics of rivaroxaban—an oral, direct factor Xa inhibitor—in patients undergoing major orthopaedic surgery. *Clin Pharmacokinet* 2008; 47: 203–16.
2. Weinz C, *et al.* Metabolism and excretion of rivaroxaban, an oral, direct factor Xa inhibitor, in rats, dogs, and humans. *Drug Metab Dispos* 2009; 37: 1056–64.
3. Kubitza D, *et al.* Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. *Br J Clin Pharmacol* 2010; 70: 703–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Xarelto; *Austral.*: Xarelto; *Austria*: Xarelto; *Belg.*: Xarelto; *Braz.*: Xarelto; *Canad.*: Xarelto; *Chile*: Xarelto; *China*: Xarelto (拜瑞妥); *Cz.*: Xarelto; *Denm.*: Xarelto; *Fr.*: Xarelto; *Ger.*: Xarelto; *Gr.*: Xarelto; *Hong Kong*: Xarelto; *Hung.*: Xarelto; *Indon.*: Xarelto; *Irl.*: Xarelto; *Israel*: Xarelto; *Ital.*: Xarelto; *Jpn*: Xarelto; *Malaysia*: Xarelto; *Neth.*: Xarelto; *Norw.*: Xarelto; *NZ*: Xarelto; *Philipp.*: Xarelto; *Pol.*: Xarelto; *Port.*: Xarelto; *Rus.*: Xarelto (Ксарелто); *Singapore*: Xarelto; *Spain*: Xarelto; *Swed.*: Xarelto; *Switz.*: Xarelto; *Thai.*: Xarelto; *UK*: Xarelto; *Ukr.*: Xarelto (Ксарелто); *USA*: Xarelto.

Rosuvastatin Calcium

(BANM, USAN, rINNM)

Calcii Rosuvastatinum; Rosuvastatina calcica; Rosuvastatine Calcique; S-4522; ZD-4522 (rosuvastatin); Кальций Розувастатин.

(*E*)-(3*R*,5*S*)-7-[4-(4-Fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid calcium (2:1).

$(C_{22}H_{27}FN_3O_6S)_2Ca$=1001.1

CAS — 287714-41-4 (rosuvastatin); 147098-20-2 (rosuvastatin calcium).

ATC — C10AA07.

ATC Vet — QC10AA07.

UNII — 83MVU38M7Q.

Uses and Administration

Rosuvastatin, a hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p. 1489.2). It is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the management of hyperlipidaemias (p. 1248.1), including primary hypercholesterolaemia (type IIa), mixed dyslipidaemia (type IIb), and hypertriglyceridaemia (type IV), as well as in patients with homozygous familial hypercholesterolaemia. It may be used to reduce the progression of atherosclerosis in patients with elevated total- or LDL-cholesterol concentrations, and also for the primary prevention of cardiovascular disease in those at high risk.

Rosuvastatin is given orally as the calcium salt, although doses are expressed in terms of the base; 10.4 mg of rosuvastatin calcium is equivalent to about 10 mg of base.

The usual initial dose of rosuvastatin is 5 or 10 mg once daily, depending on plasma-cholesterol concentrations, cardiovascular risk factors, and risk factors for adverse effects. The maintenance dose ranges from 5 to 40 mg once daily, although the 40-mg dose is reserved for patients with high cardiovascular risk who do not achieve their target cholesterol concentration at lower doses and who do not have risk factors for adverse effects. Specific dosage recommendations vary; for dosage in renal impairment, see below.

UK licensed product information recommends an initial dose of 5 or 10 mg once daily; elderly patients, Asian patients, and those taking fibrates or otherwise at risk of myopathy should be given the 5-mg dose. The dose may be increased at intervals of 4 weeks, if necessary, to a usual maximum of 20 mg once daily. A higher dose of 40 mg once daily may be given under specialist supervision in severe hypercholesterolaemia, but should not be given to patients at high risk of myopathy, including those receiving fibrates, and Asian patients; use with *ciclosporin* or *protease inhibitors* is contra-indicated.

US licensed product information recommends a usual initial dose of 10 mg once daily. However, a lower initial dose of 5 mg once daily may be adequate and is recommended for patients at risk of myopathy, including Asian patients; patients with marked hypercholesterolaemia, such as those with homozygous familial hypercholesterolaemia, may be started on 20 mg once daily. The dose should be adjusted after 2 to 4 weeks, to a usual maximum of 20 mg once daily; a dose of 40 mg once daily may be necessary in some patients. Patients receiving *ciclosporin* may be given a maximum of 5 mg once daily, and in those receiving *gemfibrozil* or *ritonavir-boosted lopinavir* the maximum dose is 10 mg once daily; dosage increases should be made with caution in Asian patients.

For doses in children, see below.

General reviews.

1. Chong PH, Yim BT. Rosuvastatin for the treatment of patients with hypercholesterolemia. *Ann Pharmacother* 2002; 36: 93–101.
2. Carswell CI, *et al.* Rosuvastatin. *Drugs* 2002; 62: 2075–85.
3. White CM. A review of the pharmacologic and pharmacokinetic aspect of rosuvastatin. *J Clin Pharmacol* 2002; 42: 963–70.
4. McKenney JM. Efficacy and safety of rosuvastatin in treatment o dyslipidemia. *Am J Health-Syst Pharm* 2003; 60: 1033–47.
5. Olsson AG. Expanding options with a wider range of rosuvastatin doses *Clin Ther* 2006; 28: 1747–63.
6. Kapur NK. Rosuvastatin: a highly potent statin for the prevention an management of coronary artery disease. *Expert Rev Cardiovasc Ther* 2007 5: 161–75.
7. Schuster H. The GALAXY Program: an update on studies investigating efficacy and tolerability of rosuvastatin for reducing cardiovascular risk *Expert Rev Cardiovasc Ther* 2007; 5: 177–93.
8. Crouse JR. An evaluation of rosuvastatin: pharmacokinetics, clinica efficacy and tolerability. *Expert Opin Drug Metab Toxicol* 2008; 4: 287–304
9. Rizzo M, *et al.* Quantitative and qualitative effects of rosuvastatin or LDL-cholesterol: what is the clinical significance? *Int J Clin Pract* 2009; 63: 478–85.
10. Rubba P, *et al.* Efficacy and safety of rosuvastatin in the management o dyslipidemia. *Vasc Health Risk Manag* 2009; 5: 343–52.

Administration in children. Rosuvastatin may be given to adolescent boys of Tanner stage II and above, and girls at least 1 year post-menarche, and who are aged 10 years and over, in the management of heterozygous familial hypercholesterolaemia. The usual initial oral dose is 5 mg once daily, which may be adjusted at intervals of at least 4 weeks to a maximum maintenance dose of 20 mg once daily.

Administration in renal impairment. Patients with renal impairment have an increased risk of developing myopathy and statins should be used with caution, particularly in higher doses. In severe renal impairment plasma-rosuvastatin concentrations may be increased and dosage reduction may be necessary.

UK licensed product information recommends the following oral doses according to creatinine clearance (CC):

- CC 30 to 60 mL/minute: initial oral dose of 5 mg once daily and a maximum dose of 20 mg once daily
- CC below 30 mL/minute: contra-indicated

In the USA usual doses (see above) are allowed in moderate impairment but an initial dose of 5 mg once daily and a maximum dose of 10 mg once daily is recommended in those with CC below 30 mL/minute per 1.73 m^2.

Adverse Effects and Precautions

As for Simvastatin, p. 1492.1 and p. 1494.1, respectively. Systemic exposure to rosuvastatin may be higher in Asian patients (see Ethnicity under Pharmacokinetics, p. 1489.1) and lower doses are advised in Asian patients and in others at high risk of myopathy (see Uses and Administration, above).

Incidence of adverse effects. An analysis[1] of adverse effects reported to the FDA in the first year of marketing found that rosuvastatin was significantly more likely to be associated with severe adverse effects than some other statins. However, further analyses of data from clinical studies[2] and postmarketing studies[3,4] suggest that the risk of adverse effects is similar for all the statins. Another observational study[5] with a median treatment period of 9.8 months found that rosuvastatin was generally well tolerated, although 17.5% of patients stopped taking the drug, with myalgia being the most common reason. Abnormal liver function tests were more common in patients taking higher doses.

1. Alsheikh-Ali AA, *et al.* The safety of rosuvastatin as used in common clinical practice: a postmarketing analysis. *Circulation* 2005; 111: 3051–7.
2. Shepherd J, *et al.* Safety of rosuvastatin: update on 16,876 rosuvastatin-treated patients in a multinational clinical trial program. *Cardiology* 2007; 107: 433–43.
3. Goettsch WG, *et al.* Results from a rosuvastatin historical cohort study in more than 45 000 Dutch statin users, a PHARMO study. *Pharmacoepidemiol Drug Safety* 2006; 15: 435–43.
4. McAfee AT, *et al.* The comparative safety of rosuvastatin: a retrospective matched cohort study in over 48 000 initiators of statin therapy. *Pharmacoepidemiol Drug Safety* 2006; 15: 444–53.
5. Kashiwal R, *et al.* Safety profile of rosuvastatin: results of a prescription-event monitoring study of 11 680 patients. *Drug Safety* 2007; 30: 157–70.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rosuvastatin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions of statins with other drugs are described under simvastatin, p. 1494.2. Rosuvastatin undergoes limited metabolism, principally by the cytochrome P450 isoenzyme CYP2C9, and may not have the same interactions with enzyme inhibitors as simvastatin. However, increased plasma-rosuvastatin concentrations have been reported with ciclosporin, HIV-protease inhibitors, eltrombopag, and, to a lesser extent, with gemfibrozil, and if such combinations cannot be avoided lower doses of rosuvastatin should be used (see Uses and Administra-

tion, p. 1488.2); in UK licensed product information, rosuvastatin is contra-indicated with ciclosporin.

Pharmacokinetics

Rosuvastatin is incompletely absorbed from the gastrointestinal tract, with an absolute bioavailability of about 20%. Peak plasma concentrations occur about 5 hours after an oral dose. It is taken up extensively by the liver, its primary site of action, and undergoes limited metabolism, mainly by the cytochrome P450 isoenzyme CYP2C9. It is about 90% bound to plasma proteins. The plasma elimination half-life of rosuvastatin is about 19 hours. About 90% of an oral dose of rosuvastatin appears in the faeces, including absorbed and non-absorbed drug, and the remainder is excreted in the urine; about 5% of a dose is excreted unchanged in urine.

Ethnicity. A pharmacokinetic study[1] found that plasma exposure to rosuvastatin and its metabolites was significantly higher in Asian (Chinese, Malay, or Indian) than in Caucasian subjects and lower doses should be used (see Uses and Administration, p. 1488.2).

1. Lee E, *et al.* Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. *Clin Pharmacol Ther* 2005; 78: 330–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Astende; Bilip; Colerragin; Crestor; Lipoglutaren; Nodis; Reovex; Rosedex; Rosimol; Rosustatin; Rosuvast; Rovartal; Roxolan; Sinlip; ***Austral.***: Crestor; Visacor; ***Austria***: Crestor; ***Belg.***: Crestor; ***Braz.***: Crestor; Rosucor; Rosustatin; Rosuvast; Rusovas; Vivacor; ***Canad.***: Crestor; ***Chile***: Cresadex; Crestor; Rosumed; Rosvel; Rux; ***China***: Crestor (可定); Soltan (舒夫坦); *Cz.*: Crestor; Mertenil; Rosucard; Rosumop; Sorvasta; Zahron; ***Denm.***: Crestor; Provisacor; Simestat†; Visacor; ***Fin.***: Crestor; ***Fr.***: Crestor; ***Ger.***: Crestor; ***Gr.***: Crestor; ***Hong Kong***: Crestor; ***Hung.***: Crestor; Xeter; ***India***: Bestor; Crestor; Fortius; LDNil; Novastat; Razel; Rosuvas; ***Indon.***: Crestor; ***Irl.***: Crestor; Rosuva; ***Israel***: Crestor; Stator; ***Ital.***: Crestor; Provisacor; Simestat; ***Jpn***: Crestor; ***Malaysia***: Crestor; ***Mex.***: Crestor; ***Neth.***: Cirantan; Crestor; Provisacor; ***Norw.***: Crestor; ***NZ***: Crestor; ***Philipp.***: Crestor; Rosucol; Rustor; ***Pol.***: Crestor; Rosucard; Suvardio; Zahron; Zaranta; ***Port.***: Crestor; Visacor; ***Rus.***: Crestor (Крестор); Mertenil (Мертенил); ***S.Afr.***: Crestor; ***Singapore***: Crestor; ***Spain***: Crestor; Provisacor; ***Swed.***: Crestor; Visacor†; ***Switz.***: Crestor; ***Thai.***: Crestor; ***Turk.***: Colnar; Crestor; Rosutech; Stage; Ultrox; ***UK***: Crestor; ***Ukr.***: Crestor (Крестор); Mertenil (Мертенил); Rosart (Розарт); Rosulip (Розулип); Roxera (Роксера); Rozucard (Розукард); ***USA***: Crestor; ***Venez.***: Crestor.

Sarpogrelate Hydrochloride *(rINNM)*

Hidrocloruro de sarpogrelato; MCI-9042; Sarpogrélate, Chlorhydrate de; Sarpogrelati Hydrochloridum; Sarpogrelato, hidrocloruro de; Сарпогрелата Гидрохлорид.

(±)-2-(Dimethylamino)-1-[[o-(*m*-methoxyphenethyl)phenoxy]methyl]ethyl hydrogen succinate hydrochloride.

$C_{24}H_{31}NO_6$,HCl=466.0

CAS — 125926-17-2 (sarpogrelate); 135159-51-2 (sarpogrelate hydrochloride).

Profile

Sarpogrelate is a serotonin 5-HT_2-receptor antagonist used as an inhibitor of platelet aggregation in thromboembolic disorders. It is given for occlusive arterial disease (p. 1272.3) in oral doses of 100 mg of the hydrochloride three times daily.

References.

1. Doggrell SA. Sarpogrelate: cardiovascular and renal clinical potential. *Expert Opin Invest Drugs* 2004; 13: 865–74.
2. Norgren L, *et al.* European MCI-9042 Study Group. Sarpogrelate, a 5-HT_{2A} receptor antagonist in intermittent claudication: a phase II European study. *Vasc Med* 2006; 11: 75–83.
3. Tamura A, *et al.* Comparison of sarpogrelate and ticlopidine in bare metal coronary stent implantation. *Int J Cardiol* 2008; 126: 79–83.
4. Shinohara Y, *et al.* S-ACCESS Study Group. Sarpogrelate-Aspirin Comparative Clinical Study for Efficacy and Safety in Secondary Prevention of Cerebral Infarction (S-ACCESS): a randomized, double-blind, aspirin-controlled trial. *Stroke* 2008; 39: 1827–33.
5. Shinohara Y, Nishimaru K. S-ACCESS study group. Sarpogrelate versus aspirin in secondary prevention of cerebral infarction: differential efficacy in diabetes? Subgroup analysis from S-ACCESS. *Stroke* 2009; 40: 2862–5.
6. Hanawa K, *et al.* Development of sarpogrelate external preparation for intractable pain control. I. Pre-formulation study on application of modified beta-cyclodextrins. *Chem Pharm Bull (Tokyo)* 2010; 58: 45–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Anplag (安步乐克); ***Jpn***: Anplag.

Saruplase *(BAN, rINN)*

Prourokinase, Non-glycosylated; Recombinant Human Single-Chain Urokinase-type Plasminogen Activator; Saruplasa; Saruplasum; scuPA; Саруплаза.

Prourokinase (enzyme-activating) (human clone pUK4/pUK18), non-glycosylated.

$C_{2031}H_{3121}N_{585}O_{601}S_{31}$=46343.7

CAS — 99149-95-8.

ATC — B01AD08.

ATC Vet — QB01AD08.

NOTE. The term prourokinase has been used for both saruplase and the related compound nasaruplase.

Profile

Saruplase is a thrombolytic drug. It is a urokinase-type plasminogen activator with a single chain structure prepared via recombinant DNA technology and is converted to urokinase (p. 1520.3) in the body by plasmin. It also has some intrinsic plasminogen-activating properties. Saruplase has been investigated in acute myocardial infarction.

References.

1. Tebbe U, *et al.* Randomized, double-blind study comparing saruplase with streptokinase therapy in acute myocardial infarction: the COMPASS equivalence trial. *J Am Coll Cardiol* 1998; 31: 487–93.
2. Vermeer F, *et al.* Saruplase is a safe and effective thrombolytic agent: observations in 1,698 patients: results of the PASS study. *J Thromb Thrombolysis* 1999; 8: 143–50.
3. Spiecker M, *et al.* Thrombolysis with saruplase versus streptokinase in acute myocardial infarction: five-year results of the PRIMI trial. *Am Heart J* 1999; 138: 518–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Gemase (Гемаза); Purolase (Пуролаза).

Semuloparin Sodium *(USAN, rINN)*

AVE-5026; Semuloparina Sódica; Sémuloparine Sodique; Semuloparinum Natricum; Семулопарин Натрия.

CAS — 9041-08-1.

UNII — V5T10N50RD.

Description. Semuloparin sodium is prepared by phosphazene-promoted depolymerisation of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 4-deoxy-2-*O*-sulfo-α-L-*threo*-hex-4-enopyranosuronic acid structure at the non-reducing end and a 2-deoxy-6-*O*-sulfo-2-(sulfoamino)-D-glucopyranose structure at the reducing end of their chain. The average molecular weight is about 2000 to 3000; no more than 40% of the components are less than 1600 and no more than 11% are more than 4500. The degree of sulfation is about 2 per disaccharide unit.

Profile

Semuloparin sodium is an ultra-low-molecular-weight heparin with anticoagulant activity. It is under investigation for the prevention of venous thromboembolism in patients with cancer, or who have undergone orthopaedic surgery.

References.

1. Agnelli G, *et al.* Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *N Engl J Med* 2012; 366: 601–9.

Simvastatin *(BAN, USAN, rINN)*

L-644128-000U; MK-733; Simvastatiini; Simvastatina; Simvastatinas; Simvastatine; Simvastatinum; Sinvinolina; Synvinolin; Szimvasztatin; Velastatin; Velastatina; Симвастатин.

(1*S*,3*R*,7*S*,8*S*,8a*R*)-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8-[2-[(2*R*,4*R*)-tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl]ethyl]-1-naphthyl 2,2-dimethylbutyrate.

$C_{25}H_{38}O_5$=418.6

CAS — 79902-63-9.

ATC — C10AA01.

ATC Vet — QC10AA01.

UNII — AGG2FN16EV.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Simvastatin). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol; very soluble in dichloromethane. Store under nitrogen in airtight containers. Protect from light.

USP 36: (Simvastatin). A white to off-white powder. Practically insoluble in water; freely soluble in alcohol, in chloroform, and in methyl alcohol; sparingly soluble in propylene glycol; very slightly soluble in petroleum spirit. Store at a temperature between 15 degrees and 30 degrees, or at 2 degrees to 8 degrees.

Uses and Administration

Simvastatin is a lipid regulating drug; it is a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the rate-determining enzyme for cholesterol synthesis. Inhibition of HMG-CoA reductase leads to reduced cholesterol synthesis in the liver and lower intracellular cholesterol concentrations; this stimulates an increase in low-density-lipoprotein (LDL)-cholesterol receptors on hepatocyte membranes, thereby increasing the clearance of LDL from the circulation. HMG-CoA reductase inhibitors (also called statins) reduce total cholesterol, LDL-cholesterol, and very-low-density lipoprotein (VLDL)-cholesterol concentrations in plasma. They also tend to reduce triglycerides and to increase high-density lipoprotein (HDL)-cholesterol concentrations.

Simvastatin is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the treatment of hyperlipidaemias (p. 1248.1). It is used in hypercholesterolaemias, primary (type IIa) or mixed (type IIb) hyperlipidaemia, hypertriglyceridaemia (type IV), and primary dysbetalipoproteinaemia (type III), and may also be used as adjunct therapy in patients with homozygous familial hypercholesterolaemia. Simvastatin is also used for cardiovascular risk reduction (p. 1246.1).

Simvastatin is given orally and doses range from 5 to 80 mg daily, although high doses of 80 mg should be limited to those patients with severe hypercholesterolaemia and high cardiovascular risk, who have not achieved their target cholesterol concentrations at lower doses, provided benefits outweigh the potential risks. For the treatment of **hyperlipidaemias**, the usual initial dose is 10 to 20 mg once daily in the evening; an initial dose of 40 mg may be used in patients who require a large reduction in cholesterol or who are at high cardiovascular risk. The dose may be adjusted at intervals of not less than 4 weeks up to a maximum of 80 mg once daily in the evening. Patients with homozygous familial hypercholesterolaemia may be treated initially with 40 mg once daily in the evening, up to a maximum of 80 mg once daily in the evening.

For **cardiovascular risk reduction** in high-risk patients, such as those with atherosclerotic cardiovascular disease or diabetes mellitus, the usual dose is 20 to 40 mg once daily in the evening.

A lower dose of simvastatin may be needed in patients at risk of myopathy, including patients with severe renal impairment (see p. 1490.3).

Changes to therapy may be required when patients are taking other drugs that interact with simvastatin see Interactions, p. 1494.2, although recommendations vary between countries. UK licensed product information advises:

- simvastatin should not be used with potent inhibitors of cytochrome P450 isoenzyme CYP3A4 or the fibrate gemfibrozil (see below for other fibrates)
- a maximum dose of simvastatin 10 mg once daily for patients also taking fibrates other than gemfibrozil; fenofibrate is an exception and there are no such restrictions but caution is advised
- a maximum dose of simvastatin 20 mg once daily for patients also taking the CYP3A4 inhibitors *amiodarone*, *amlodipine*, *diltiazem*, and *verapamil*
- close monitoring of patients who require *fusidic acid*, withholding simvastatin therapy if necessary
- a maximum dose of simvastatin 40 mg once daily for patients also taking *ticagrelor*, a weak inhibitor of CYP3A4

In the USA, simvastatin dosing should be reduced by half when starting treatment with lomitapide, a CYP3A4 inhibitor, with a maximum daily dose of 20 mg (or 40 mg in those who previously tolerated simvastatin 80 mg daily for at least 1 year).

For the use of simvastatin in children, see p. 1490.2.

General reviews.

1. Mauro VF, MacDonald JL. Simvastatin: a review of its pharmacology and clinical use. *DICP Ann Pharmacother* 1991; 25: 257–64.
2. Plosker GL, McTavish D. Simvastatin: a reappraisal of its pharmacology and therapeutic efficacy in hypercholesterolaemia. *Drugs* 1995; 50: 334–63.
3. Schectman G, Hiatt J. Dose-response characteristics of cholesterol-lowering drug therapies: implications for treatment. *Ann Intern Med* 1996; 125: 990–1000.
4. White CM. Pharmacological effects of HMG CoA reductase inhibitors other than lipoprotein modulation. *J Clin Pharmacol* 1999; 39: 111–18.
5. Mata P, *et al.* Benefits and risks of simvastatin in patients with familial hypercholesterolaemia. *Drug Safety* 2003; 26: 769–86.
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Action. The effects of statins on *plasma lipids* are well established.[1-4] Their primary action is to inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis. Cholesterol is an important precursor for synthesis of several substances by the liver, and reduced intracellular concentrations stimulate an increase in the expression of low-density lipoprotein (LDL) receptors in the liver. This leads to increased uptake of LDL-cholesterol from the plasma

into liver cells, with a subsequent reduction in both LDL and total cholesterol. Triglycerides are also decreased, due to decreased synthesis of very-low-density lipoprotein (VLDL), while high-density lipoprotein (HDL)-cholesterol is either modestly increased or unchanged, leading to an improvement in the LDL:HDL ratio. An effect on LDL-cholesterol may also occur independent of the effect on receptors; some statins have been shown to lower LDL-cholesterol in patients with homozygous familial hypercholesterolaemia, despite their lack of functional LDL receptors. Statins generally provide a greater reduction in LDL-cholesterol than other classes of lipid regulating drugs, but where large reductions are required combination therapy may be necessary. Statins have been used with bile-acid binding resins and with ezetimibe; they have also been given with fibrates or nicotinic acid, although the increased risk of adverse effects needs to be considered. Cholesterol synthesis in the liver peaks during the early morning (midnight to 3 a.m.) and there is some evidence that statins with short half-lives, such as simvastatin, should be taken in the evening.[5]

Statins have several additional (pleiotropic) actions,[1-4,6,7] although whether these contribute to their cardiovascular effects is controversial.[8]

In *atherosclerosis* they have beneficial effects on endothelial function, which may be partly independent of their effect on lipids, and also appear to stabilise atherosclerotic plaques. Studies[9,10] have also shown that statins reduce concentrations of C-reactive protein (CRP), a marker of inflammation that is raised in atherosclerosis, and there is some evidence that the reduction in CRP is independently associated with a reduction in cardiovascular events[11,12] and regression of atherosclerotic lesions.[13] There is also some evidence of symptomatic improvement in patients with *chronic occlusive peripheral arterial disease* (p. 1272.3). However, studies with statins in calcific aortic stenosis, a condition with similarities to atherosclerosis, have shown mixed results.[14] Statins have some actions that may be beneficial in *heart failure*,[15] but detrimental effects are also possible and their role specifically for heart failure is unclear.[16] Evidence from cohort studies[17-19] suggests statins may improve mortality in heart failure, and analyses of cardiovascular risk reduction studies[20,21] also suggest benefit. However, a randomised study[22] of rosuvastatin in patients with heart failure of ischaemic origin failed to show an effect on mortality, although there were fewer hospitalisations in patients given the active drug. Statins may also have *antihypertensive*[23] and *antiarrhythmic* effects; they reduce the incidence of atrial fibrillation,[24] and have also been associated with a reduced risk of ventricular arrhythmias,[25,26] although this requires confirmation. Beneficial effects have also been reported on some measures of *haemostasis*,[27] and a reduced incidence of venous thromboembolism has been noted in some studies.[28,29] A study[29] has shown that the use of higher doses of statins (rosuvastatin ≥10 mg daily and lovastatin, simvastatin, or atorvastatin 40 mg daily) is associated with a greater antithrombotic effect and that the use of a statin with antiplatelet therapy further reduces the incidence of venous thromboembolism.

Statins also appear to have anti-inflammatory and immunomodulatory actions and these may contribute to their beneficial effects. There is evidence from epidemiological studies that they reduce the risk of bacterial infections, although this has been attributed to a 'healthy-user' effect,[30,31] and they may also reduce mortality in patients with sepsis.[31] Benefit has also been reported in *rheumatoid arthritis* and other inflammatory arthropathies.[32-35] In patients with *organ transplantation*, both cardiovascular and immunomodulatory actions may be of benefit (see p. 1492.1). However, the use of statins in these diseases remains to be confirmed.

For discussion of the use of statins in other non-cardiovascular disorders, including dementia, kidney disorders, malignant neoplasms, and osteoporosis, see from p. 1491.2.

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Administration in children. The management of hyperlipidaemias in children and adolescents is controversial and is usually reserved for those with familial hyperlipidaemias who have a high risk of premature cardiovascular disease. Dietary measures and bile-acid binding resins have traditionally been first-line therapy in children, but may be poorly tolerated or inadequate. Studies with statins in children aged 8 to 18 years with familial hypercholesterolaemia have shown[1,2] that they effectively lower total cholesterol and low-density lipoprotein (LDL)-cholesterol and they are now increasingly preferred where drug therapy is indicated.[3,4] However, there have been concerns about the potential adverse effects of statins on growth and sexual development, since these patients require life-long treatment. Although this does not appear to be a problem, most studies have been relatively short-term, and longer follow-up is needed to confirm statin safety;[3,4] pravastatin was well tolerated in a cohort of 185 children with familial hypercholesterolaemia who were followed for a mean of about 2 years.[5] Preliminary evidence suggests that statins may also be effective in children with hyperlipidaemia related to nephrotic syndrome[6] or organ transplantation.[3,4]

Licensed product information for simvastatin allows its use in children aged 10 to 17 years with familial heterozygous hypercholesterolaemia in an initial oral dose of 10 mg at night, increased at intervals of at least 4 weeks as required to a maximum dose of 40 mg daily. A placebo-controlled study[7] in 173 such children found that simvastatin given orally in a dose of up to 40 mg daily for 48 weeks effectively reduced LDL-cholesterol and was well tolerated, with no effect on growth or sexual development.

The *BNFC* recommends the following oral doses for children with hyperlipidaemia:

- age 5 to 10 years: initial dose 10 mg at night, increased if necessary at intervals of at least 4 weeks to a maximum dose of 20 mg at night
- age 10 to 18 years: initial dose 10 mg at night, increased if necessary at intervals of at least 4 weeks to a maximum dose of 40 mg at night

Doses should be reduced in children who are taking drugs that may interact with simvastatin (see Interactions p. 1494.2).

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Administration in renal impairment. Statins appear to be safe and effective in patients with dyslipidaemia and renal impairment, and there is some evidence that they may have beneficial effects on renal function (see Kidney Disorders, p. 1491.3). However, patients with severe renal impairment may be at increased risk of developing myopathy or rhabdomyolysis and lower doses may be appropriate in such patients. Dose reduction may also be needed for statins that are excreted by the kidneys.

Simvastatin does not undergo significant renal excretion and no dose modification is required in patients with mild or moderate renal impairment. However, in patients with severe renal impairment (creatinine clearance below 30 mL/minute) the recommended initial oral dose is 5 mg once daily and doses above 10 mg once daily should be used with caution.

Cardiovascular risk reduction. Lipid regulating drugs have an important role in cardiovascular risk reduction (p. 1246.1), and statins are widely used for both primary and secondary prevention. The rationale for their use has been the established link between hypercholesterolaemia and atherosclerosis, but they may have additional actions that contribute to their effect (see Action, p. 1489.3). The efficacy of statins in reducing cardiovascular events has been established in a wide range of patient groups and is generally believed to be a class effect, although outcome studies have not been performed for all the statins in every case.

In patients with established ischaemic heart disease, statins reduce the risk of further cardiovascular events, and also reduce both cardiovascular and overall mortality.[1] Statins shown to be effective for secondary prevention in large, randomised studies include simvastatin,[2] pravastatin,[3,4] and fluvastatin.[5,6] For primary prevention in patients at high risk but without prior cardiovascular events, a similar reduction in cardiovascular events, cardiovascular mortality, and overall mortality has been shown.[7] Benefit has been established in studies using pravastatin,[8,9] lovastatin,[10] simvastatin,[11] atorvastatin,[12] and rosuvastatin;[13] the negative results of the ALLHAT-LLT study[14] with pravastatin were attributed to the substantial use of statins in the control group.

Although the main benefit of statins is to reduce mortality and major coronary events, there may also be a reduction in the incidence[15-19] and severity[20] of stroke. (An increase in the risk of haemorrhagic stroke has been suggested,[17] but has not been confirmed.[19]) The incidence of peripheral vascular disease may also be reduced,[21] and some studies have also shown a reduction in coronary[21,22] and peripheral[21,23] ischaemic symptoms. Observational studies have suggested that statins may also reduce postoperative mortality in patients with high cardiovascular risk undergoing surgery, although this remains to be confirmed,[24,25] and there is some evidence that statins may reduce the risk of myocardial damage in patients undergoing percutaneous interventions,[26] although they have not been shown to affect restenosis.[27,28] Early use of statins may also have a role in patients with acute coronary syndromes; one meta-analysis[29] found no evidence of benefit at 1 or 4 months after the initial event, but another[30] reported a reduction in cardiovascular events with statin therapy for 6 months or longer, and some studies[31] have suggested earlier benefit with high-dose regimens.

The main effect of statins appears to relate to their action on lipid concentrations, and increased benefit has been reported[32,33] with the use of intensive lipid lowering regimens, including a reduction in mortality in patients with acute coronary syndromes.[34] However, studies have shown that statins improve outcomes in patients with both raised[8,29] and average[3,4,10,12] cholesterol concentrations, and

meta-analyses[35,36] have concluded that the absolute benefit of statin treatment depends on both the initial cardiovascular risk and the degree of cholesterol reduction achieved. Most benefit has been reported in patients at the highest risk; subgroups in whom particular benefit has been reported include patients with metabolic syndrome compared with those without,[37] and diabetics compared with non-diabetics.[38] Diabetics with renal disease also benefit,[39] although this may not be the case for those with end-stage disease receiving haemodialysis.[40] Another study[41] in patients receiving haemodialysis for end-stage renal disease from various causes similarly found no benefit with statins despite the high risk of cardiovascular events in this subgroup. Early studies included mainly middle-aged men, but later studies and meta-analyses have confirmed that statins also improve outcomes in women[11,35,42] and in the elderly.[9,11,35,43,44] Observational studies[45,46] have confirmed that these benefits extend to the clinical situation.

Statins differ in potency,[47-49] but evidence that they differ in efficacy for cardiovascular risk reduction when given at comparable lipid-lowering doses is limited.[50] Patients who do not achieve target lipid concentrations or who have adverse effects with one statin may find an alternative statin effective and tolerable, although recurrence of myalgia is not uncommon.[51]

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Dementia. Epidemiological studies have reported[1,2] that the prevalence of dementia (p. 388.1) is lower in patients taking statins (prevalence may also be reduced in patients taking fibrates).[2] Some longitudinal studies have reported[3,4] that statins also reduce the incidence of dementia, but others have found no evidence of a reduction in risk,[5-7] and it has been suggested[5] that inappropriate analysis may explain the positive results. There has also been some evidence that statins[8-10] and other lipid regulating drugs[10] may reduce the progression of cognitive decline in patients with dementia, but the effect has generally been small and negative effects on mental function have been reported with some statins (see under Adverse Effects, p. 1493.1).

Although a plausible mechanism can be inferred for a possible beneficial effect of statins on dementia, a systematic review[11] concluded that there was good evidence that statins given in later life have no effect in preventing Alzheimer's disease and dementia, and that they should not be prescribed to that end.

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9. Bernick C, *et al.* Cardiovascular Health Study Collaborative Research Group. Statins and cognitive function in the elderly: the Cardiovascular Health Study. *Neurology* 2005; 65: 1388–94.
10. Masse I, *et al.* Lipid lowering agents are associated with a slower cognitive decline in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2005; 76: 1624–9.
11. McGuinness B, *et al.* Statins for the prevention of dementia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 17/08/09).

Kidney disorders. Although proteinuria has been reported with statins (see Effects on the Kidney under Adverse Effects, p. 1492.3) there is also some evidence that statins modestly reduce the progression of proteinuria and loss of renal function.[1-4] However, further studies are required to confirm these effects.

1. Sandhu S, *et al.* Statins for improving renal outcomes: a meta-analysis. *J Am Soc Nephrol* 2006; 17: 2006–16.
2. Douglas K, *et al.* Meta-analysis: the effect of statins on albuminuria. *Ann Intern Med* 2006; 145: 117–24.
3. Agarwal R. Effects of statins on renal function. *Mayo Clin Proc* 2007; 82: 1381–90.
4. Strippoli GFM, *et al.* Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. *BMJ* 2008; 336: 645. Available at: http://www.bmj.com/content/336/7645/645 (accessed 10/02/12) Correction. *ibid.* 2009; 339: b2952. Available at: http://www.bmj.com/content/339/bmj.b2951 (accessed 10/02/12)

Malignant neoplasms. Although studies in *animals* suggest[1] that statins could be carcinogenic, evidence for a detrimental effect in humans is limited, and some studies have suggested that statins may be protective. Low plasma-cholesterol concentrations have been associated with cancer, and an increased incidence of cancer was reported in a randomised study of pravastatin for cardiovascular risk reduction in elderly patients,[2] although this was attributed to chance. Conversely, several observational studies have reported[3-7] that statins reduce the incidence of cancer, although the effect has generally been small. Meta-analyses have generally found no association between the use of statins and the incidence of cancer. Analyses including only randomised studies[8,9] have found no significant effect on overall risk, although follow-up may not have been long enough in most studies to be conclusive; there is also little evidence of a protective effect for specific cancers.[10-12] However, another large cohort study[13] in elderly patients found no evidence that statins either increased or reduced the risk, and longer follow-up in a randomised study[14] using simvastatin also found no significant effect.

1. Newman TB, Hulley SB. Carcinogenicity of lipid-lowering drugs. *JAMA* 1996; 275: 55–60.
2. Shepherd J, *et al.* Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; 360: 1623–30.
3. Blais L, *et al.* 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and the risk of cancer: a nested case-control study. *Arch Intern Med* 2000; 160: 2363–8.
4. Graaf MR, *et al.* The risk of cancer in users of statins. *J Clin Oncol* 2004; 22: 2388–94.
5. Poynter JN, *et al.* Statins and the risk of colorectal cancer. *N Engl J Med* 2005; 352: 2184–92.
6. Khurana V, *et al.* Statins reduce the risk of lung cancer in humans: a large case-control study of US veterans. *Chest* 2007; 131: 1282–8.
7. Karp I, *et al.* Statins and cancer risk. *Am J Med* 2008; 121: 302–9.
8. Dale KM, *et al.* Statins and cancer risk: a meta-analysis. *JAMA* 2006; 295: 74–80.
9. Bonovas S, *et al.* Statins and cancer risk: a literature-based meta-analysis and meta-regression analysis of 35 randomized controlled trials. *J Clin Oncol* 2006; 24: 4808–17.
10. Bonovas S, *et al.* Use of statins and breast cancer: a meta-analysis of seven randomized clinical trials and nine observational studies. *J Clin Oncol* 2005; 23: 8606–12.
11. Bonovas S, *et al.* Statins and the risk of colorectal cancer: a meta-analysis of 18 studies involving more than 1.5 million patients. *J Clin Oncol* 2007; 25: 3462–8.
12. Bonovas S, *et al.* Use of statins and risk of haematological malignancies: a meta-analysis of six randomized clinical trials and eight observational studies. *Br J Clin Pharmacol* 2007; 64: 255–62.
13. Setoguchi S, *et al.* Statins and the risk of lung, breast, and colorectal cancer in the elderly. *Circulation* 2007; 115: 27–33.
14. Strandberg TE, *et al.* Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). *Lancet* 2004; 364: 771–7.

Multiple sclerosis. It has been suggested[1-3] that statins might be of benefit in the treatment of multiple sclerosis (p. 996.3) but any definite role remains to be established. There is a report of *increased* disease activity in patients taking beta interferon for relapsing-remitting disease when atorvastatin was added to therapy,[4] although others have suggested that statins had no effect on beta interferon.[5]

1. Neuhaus O, *et al.* Are statins a treatment option for multiple sclerosis? *Lancet Neurol* 2004; 3: 369–71.
2. Neuhaus O, *et al.* Evaluation of HMG-CoA reductase inhibitors for multiple sclerosis: opportunities and obstacles. *CNS Drugs* 2005; 19: 833–41.
3. Neuhaus O, Hartung HP. Evaluation of atorvastatin and simvastatin for treatment of multiple sclerosis. *Expert Rev Neurother* 2007; 7: 547–56.

4. Birnbaum G, *et al.* Combining beta interferon and atorvastatin may increase disease activity in multiple sclerosis. *Neurology* 2008; 71: 1390–5.
5. Rudick RA, *et al.* Effect of statins on clinical and molecular responses to intramuscular interferon beta-1a. *Neurology* 2009; 72: 1989–93.

Organ and tissue transplantation. Cardiovascular disease is an important cause of morbidity and mortality after organ transplantation and statins are useful for cardiovascular risk reduction in these patients. They may also have immunomodulatory effects and have reduced the risk of rejection in some studies.[1] Some evidence also suggests that they may reduce the risk of sepsis and post-transplantation infections.[2] A meta-analysis of patients who had undergone heart transplantation (p. 1938.2) considered that treatment with a statin within 3 months of transplantation reduced allograft rejection with haemodynamic compromise and reduced 1-year mortality;[3] it was calculated that one life was saved for every 8.5 treated heart transplant patients. There is some tentative evidence that statin therapy may also reduce acute rejection and the development of obliterative bronchiolitis in patients who have undergone lung transplantation (p. 1941.3),[4] although prospective controlled studies are lacking.

1. Paraskevas KI. Applications of statins in cardiothoracic surgery: more than just lipid-lowering. *Eur J Cardiothorac Surg* 2008; 33: 377–90.
2. Sun H-Y, Singh N. Antimicrobial and immunomodulatory attributes of statins: relevance in solid-organ transplant recipients. *Clin Infect Dis* 2009; 48: 745–55.
3. Mehra MR, Raval NY. Metaanalysis of statins and survival in de novo cardiac transplantation. *Transplant Proc* 2004; 36: 1539–41.
4. Johnson BA, *et al.* Statin use is associated with improved function and survival of lung allografts. *Am J Respir Crit Care Med* 2003; 167: 1271–8.

Osteoporosis. Statins appear to have effects on bone metabolism and preliminary studies[1,2] have suggested that some statins may increase bone mineral density. However, the clinical relevance of any effect is unclear.[3] Several case-control studies[4–6] have also suggested that use of statins may protect against fractures, but another case-control study[7] and an observational study[8] failed to support such an association. A review[9] of 4 further observational studies found that the risk of fracture was lower in women taking statins, but analysis of data from randomised studies of statins for cardiovascular disease[10,11] failed to confirm any effect, and controlled studies are needed[3,12] to confirm the role of statins in the management of osteoporosis (p. 1168.1).

1. Edwards CJ, *et al.* Oral statins and increased bone-mineral density in postmenopausal women. *Lancet* 2000; 355: 2218–9.
2. Watanabe S, *et al.* Effects of 1-year treatment with fluvastatin or pravastatin on bone. *Am J Med* 2001; 110: 584–7.
3. Jadhav SB, Jain GK. Statins and osteoporosis: new role for old drugs. *J Pharm Pharmacol* 2006; 58: 3–18.
4. Chan KA, *et al.* Inhibitors of hydroxymethylglutaryl-coenzyme A reductase and risk of fracture among older women. *Lancet* 2000; 355: 2185–8.
5. Meier CR, *et al.* HMG-CoA reductase inhibitors and the risk of fractures. *JAMA* 2000; 283: 3205–10.
6. Wang PS, *et al.* HMG-CoA reductase inhibitors and the risk of hip fractures in elderly patients. *JAMA* 2000; 283: 3211–16.
7. van Staa T-P, *et al.* Use of statins and risk of fractures. *JAMA* 2001; 285: 1850–55. Correction. *ibid.*; 286: 674.
8. LaCroix AZ, *et al.* Statin use, clinical fracture, and bone density in postmenopausal women: results from the Women's Health Initiative Observational Study. *Ann Intern Med* 2003; 139: 97–104.
9. Bauer DC, *et al.* Use of statins and fracture: results of 4 prospective studies and cumulative meta-analysis of observational studies and controlled trials. *Arch Intern Med* 2004; 164: 146–52.
10. Reid IR, *et al.* Effect of pravastatin on frequency of fracture in the LIPID study: secondary analysis of a randomised controlled trial. *Lancet* 2001; 357: 509–12.
11. Pedersen TR, Kjekshus J. 4S Study Group. Statin drugs and the risk of fracture. *JAMA* 2000; 284: 1921–2.
12. Coons JC. Hydroxymethylglutaryl-coenzyme A reductase inhibitors in osteoporosis management. *Ann Pharmacother* 2002; 36: 326–30.

Adverse Effects

The commonest adverse effects of therapy with simvastatin and other statins are gastrointestinal disturbances. Other adverse effects are generally rare but include headache, rash, dizziness, insomnia, hyperglycaemia and diabetes mellitus, peripheral neuropathy, reversible cognitive impairment, depression, interstitial lung disease, sexual dysfunction, and alopecia. Hypersensitivity reactions have occurred, including anaphylaxis, angioedema, urticaria, photosensitivity, fever, flushing, dyspnoea, thrombocytopenia, toxic epidermal necrolysis, dermatomyositis, vasculitis, and lupus-like syndrome. Reversible increases in serum-transaminase concentrations may occur. Hepatitis, hepatic failure, and pancreatitis have been reported. Dose-related myopathy, characterised by myalgia and muscle weakness and associated with increased creatine phosphokinase concentrations, has been reported. Drug interactions may increase the risk of myopathy, see Interactions, p. 1494.2. Rarely, rhabdomyolysis with acute renal failure may develop.

General references.

1. Farmer JA, Torre-Amione G. Comparative tolerability of the HMG-CoA reductase inhibitors. *Drug Safety* 2000; 23: 197–213.
2. Davidson MH. Safety profiles for the HMG-CoA reductase inhibitors: treatment and trust. *Drugs* 2001; 61: 197–206.
3. Pasternak RC, *et al.* ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Circulation* 2002; 106: 1024–8. Also available at: http://circ.ahajournals.org/cgi/reprint/106/8/1024.pdf (accessed 29/05/08)
4. Karthikeyan VJ. Adverse effects of statins: an update. *Adverse Drug React Bull* 2005; (Aug): 895–8.
5. McKenney JM, *et al.* Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. *Am J Cardiol* 2006; 97(Issue 8 suppl 1): 89C–94C.
6. Armitage J. The safety of statins in clinical practice. *Lancet* 2007; 370: 1781–90.
7. Brown WV. Safety of statins. *Curr Opin Lipidol* 2008; 19: 558–62.
8. Beltowski J, *et al.* Adverse effects of statins–mechanisms and consequences. *Curr Drug Saf* 2009; 4: 209–28.
9. Naci H, *et al.* Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. *Circ Cardiovasc Qual Outcomes* 2013; 6: 390–9.

Incidence of adverse effects. By February 1992 the UK CSM had received 738 reports of adverse effects associated with simvastatin,[1] from an estimated 257 000 prescriptions. Abnormal hepatic function and myalgia were 2 of the most frequently reported reactions, with 36 and 48 reports respectively, including 5 reports of hepatitis and 2 of jaundice. Other muscle effects included 3 reports of myositis, 10 of myopathy, and 7 reports of asymptomatic increases in serum creatine kinase concentrations. Gastrointestinal adverse effects accounted for 20% of the reports; skin, neurological and musculoskeletal effects for 15% each; psychiatric effects for 10%; liver effects for 7%; and visual effects for 4%. A systematic review[2] of data from clinical studies confirmed that the risk of liver transaminase elevation was increased by statins but there was no significant increase in the incidence of myalgia (reported in about 15% of patients), creatine kinase elevation (0.9%), or rhabdomyolysis (0.2%), compared with placebo. The incidence of adverse effects may be greater with high-dose therapy.[3,4]

1. CSM. Simvastatin. *Current Problems* 33 1992. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024451&RevisionSelectionMethod=LatestReleased (accessed 30/05/08)
2. Kashani A, *et al.* Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation* 2006; 114: 2788–97.
3. Davidson MH, Robinson JG. Safety of aggressive lipid management. *J Am Coll Cardiol* 2007; 49: 1753–62.
4. Silva M, *et al.* Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. *Clin Ther* 2007; 29: 253–60.

Carcinogenicity. For discussion of the effects of statins on the risk of cancer, see Malignant Neoplasms under Uses, p. 1491.3.

Effects on the blood. *Thrombocytopenia* has been reported rarely with statin therapy. Serious thrombocytopenic purpura has occurred with simvastatin, with the onset ranging from 1 or 2 days[1,2] to 11 or 12 months[3,4] after starting treatment. Platelet counts improved after stopping simvastatin in each case, although most patients were given corticosteroids, immunoglobulins, or plasma exchange. There has also been a similar report with atorvastatin,[5] which recurred on rechallenge; the patient had previously taken simvastatin without developing thrombocytopenia, suggesting an idiosyncratic reaction.

A case of *haemolytic anaemia* has been reported[6] in a patient taking lovastatin; no adverse effect was seen when the patient was given simvastatin.

Statins have effects on coagulation and fibrinolysis but these are generally beneficial (see Action under Uses, p. 1489.3); there have been rare reports of *ocular haemorrhage*,[7] but the association with statins is not established.

1. McCarthy LJ, *et al.* Thrombotic thrombocytopenic purpura and simvastatin. *Lancet* 1998; 352: 1284–5.
2. Sundram F, *et al.* Thrombotic thrombocytopenic purpura associated with statin treatment. *Postgrad Med J* 2004; 80: 551–2.
3. Possamai G, *et al.* Thrombocytopenic purpura during therapy with simvastatin. *Haematologica* 1992; 77: 357–8.
4. Groneberg DA, *et al.* Simvastatin-induced thrombocytopenia. *Am J Hematol* 2001; 67: 277.
5. González-Ponte ML, *et al.* Atorvastatin-induced severe thrombocytopenia. *Lancet* 1998; 352: 1284.
6. Robbins MJ, *et al.* Lovastatin-induced hemolytic anemia: not a class-specific reaction. *Am J Med* 1995; 99: 328–9.
7. Praunfelder FW. Ocular hemorrhage possibly the result of HMG-CoA reductase inhibitors. *J Ocul Pharmacol Ther* 2004; 20: 179–82.

Effects on the eyes. Studies in *animals* have suggested that some statins could cause cataracts, but this has not been confirmed in humans. Although a study[1] with lovastatin found lens opacities in 13 of 101 patients after treatment for 18 weeks, no deterioration in visual function was found in 11 of these who continued lovastatin and were followed up for an average of 26 months from the start of treatment. Similarly, no differences were found in the development of lens opacities or in changes in visual acuity between patients treated with lovastatin for 48 weeks and patients taking placebo in a study of 8245 patients.[2] A large case-control study[3] found no evidence that use of therapeutic statin doses was associated with the development of cataracts, although the risk did appear to be increased in patients taking simvastatin with erythromycin. Further observational studies have suggested that statins may have beneficial effects; in one study[4] there was no effect on the overall incidence of cataract but the risk of developing nuclear cataract appeared to be decreased, while another study[5] reported a reduction in the overall incidence but this was not significant for any specific cataract type.

For mention of ocular haemorrhage in patients taking statins, see Effects on the Blood, above.

1. Hunninghake DB, *et al.* Lovastatin: follow-up ophthalmologic data. *JAMA* 1988; 259: 354–5.
2. Laties AM, *et al.* The human lens after 48 weeks of treatment with lovastatin. *N Engl J Med* 1990; 323: 683–4.
3. Schlienger RG, *et al.* Risk of cataract in patients treated with statins. *Arch Intern Med* 2001; 161: 2021–6.
4. Klein BEK, *et al.* Statin use and incident nuclear cataract. *JAMA* 2006; 295: 2752–8.
5. Tan JSL, *et al.* Statin use and the long-term risk of incident cataract: the Blue Mountains Eye Study. *Am J Ophthalmol* 2007; 143: 687–9.

Effects on the hair. Between its introduction in Australia and 1993, 16 cases of alopecia associated with the use of simvastatin had been reported to the Adverse Drug Reactions Advisory Committee.[1] Most cases involved either excessive hair loss or hair thinning, although 2 cases of hair loss in patches and 1 resembling alopecia areata were reported. Onset occurred between 3 days and 15 months after starting therapy. Progressive hair loss has also been reported[2] in a woman within 6 weeks of starting atorvastatin; the hair regrew when atorvastatin was stopped but alopecia recurred when therapy was restarted 5 months later.

1. Anonymous. Simvastatin and alopecia. *Aust Adverse Drug React Bull* 1993; 12: 7.
2. Segal AS. Alopecia associated with atorvastatin. *Am J Med* 2002; 113: 171.

Effects on the kidneys. *Proteinuria* was reported in 10 patients taking simvastatin 40 mg daily.[1] The protein loss was of a pattern typical for increased glomerular permeability. In 2 patients proteinuria disappeared when simvastatin was withdrawn and recurred on its subsequent reintroduction. Proteinuria has also been seen with rosuvastatin, and was found to be dose-dependent.[2] However, there is also some evidence that statins may improve proteinuria (see Kidney Disorders under Uses, p. 1491.3).

Acute tubulointerstitial *nephritis* developed[3] in a patient receiving high-dose therapy with rosuvastatin. It resolved over 3 weeks when rosuvastatin was stopped, but recurred 2 weeks after rechallenge. A similar reaction was noted with atorvastatin, but improved with dose reduction, and the patient was finally stabilised on simvastatin without a further recurrence.

Renal failure due to rhabdomyolysis has been reported rarely (see under Effects on Skeletal Muscle, p. 1493.2).

1. Deslypere JP, *et al.* Proteinuria as complication of simvastatin treatment. *Lancet* 1990; 336: 1453.
2. Agarwal R. Effects of statins on renal function. *Am J Cardiol* 2006; 97: 748–55.
3. van Zyl-Smit R, *et al.* Renal tubular toxicity of HMG-CoA reductase inhibitors. *Nephrol Dial Transplant* 2004; 19: 3176–9.

Effects on the liver. Statins cause dose-related increases in liver enzymes but the incidence appears to be low with low to moderate doses[1] and serious hepatic effects appear to be rare.[2] Although monitoring of liver function tests is advised, the value of routine assessment has been questioned.[3] There is some evidence[4] that the incidence of hepatic reactions may be higher with fluvastatin than with other statins, but this is not yet established.

There have also been case reports[5–8] of cholestasis and acute hepatitis in patients receiving statins.

1. de Denus S, *et al.* Statins and liver toxicity: a meta-analysis. *Pharmacotherapy* 2004; 24: 584–91.
2. Charles ED, *et al.* Evaluation of cases of severe statin-related transaminitis within a large health maintenance organization. *Am J Med* 2005; 118: 618–24.
3. Kostner K, Howes LG. Statins and monitoring of liver function tests. *Drug Safety* 2007; 30: 1–4.
4. Conforti A, *et al.* Fluvastatin and hepatic reactions: a signal from spontaneous reporting in Italy. *Drug Safety* 2006; 29: 1163–72.
5. Jiménez-Alonso J, *et al.* Atorvastatin-induced cholestatic hepatitis in a young woman with systemic lupus erythematosus. *Arch Intern Med* 1999; 159: 1811–12.
6. Wierzbicki AS, Crook MA. Cholestatic liver dysfunction. *Lancet* 1999; 354: 954.
7. Batey RG, Harvey M. Cholestasis associated with the use of pravastatin sodium. *Med J Aust* 2002; 176: 561.
8. Rahier JF, *et al.* Severe acute cholestatic hepatitis with prolonged cholestasis and bile-duct injury following atorvastatin therapy: a case report. *Acta Gastroenterol Belg* 2008; 71: 318–20.

Effects on the lungs. Interstitial lung disorders, including hypersensitivity pneumonitis, have been reported with several statins.[1–5] In some cases the condition improved when the statin was stopped[2] but treatment with corticosteroids and immunosuppressants was required in some patients[1–4] and progressive disease and fatalities have occurred.[4]

1. de Groot REB, *et al.* Interstitial lung disease with pleural effusion caused by simvastin [sic]. *J Intern Med* 1996; 239: 361–3.
2. Liebhaber ML *et al.* Polymyalgia, hypersensitivity pneumonitis and other reactions in patients receiving HMG-CoA reductase inhibitors: a report of ten cases. *Chest* 1999; 115: 886–9.