6. Miller DW, Slovis CM. Hypophosphatemia in the emergency department therapeutics. *Am J Emerg Med* 2000; 18: 457–61.
7. Charron T, *et al.* Intravenous phosphate in the intensive care unit: more aggressive repletion regimens for moderate and severe hypophosphatemia. *Intensive Care Med* 2003; 29: 1273–8.

Osteomalacia. Vitamin D deficiency, or its abnormal metabolism, is the most usual cause of osteomalacia and rickets (p. 1168.1); however, phosphate depletion may also contribute, and phosphate supplementation may be given as appropriate.

A suggested oral dose for vitamin-D-resistant hypophosphataemic osteomalacia in adults is 65 to 100 mmol phosphate daily. The *BNFC* suggests the following oral phosphate doses:

- for neonates, 1 mmol/kg daily given as a single dose or in 2 divided doses; alternatively it may be given via fortified breast milk
- older children may be given 2 to 3 mmol/kg daily, in 2 to 4 divided doses; a maximum dose of 48 mmol daily is recommended in those up to 5 years of age, and a maximum of 97 mmol daily for those aged 5 years and over.

If parenteral administration is indicated, an intravenous infusion of 1 mmol/kg daily may be given to neonates, 0.7 mmol/kg daily to children aged 1 month to 2 years, and 0.4 mmol/kg daily to those aged 2 to 18 years. Doses should be adjusted as necessary.

RICKETS OF PREMATURITY. Dietary deficiency of phosphorus is unusual, but can occur in small premature infants fed exclusively on human breast milk. The phosphate intake in these infants appears to be inadequate to meet the needs of bone mineralisation, and hypophosphataemic rickets can develop. This condition, variably called metabolic bone disease of prematurity, or rickets of prematurity, can be prevented by ensuring an adequate phosphate intake by very low-birth-weight babies. Adequate intake of calcium and vitamin D is also essential. Phosphate supplementation, with calcium and vitamin D, may be given orally either in formula feeds or as fortification of human breast milk, or intravenously in parenteral nutrition solutions.[1,2]

Dosage recommendations for phosphate may vary, but the *BNFC* suggests a daily dose of 1 mmol/kg; if given orally, this may be as a single dose or in 2 divided doses.

1. Ryan S. Nutritional aspects of metabolic bone disease in the newborn. *Arch Dis Child Fetal Neonatal Ed* 1996; 74: F145–8.
2. Harrison CM, *et al.* Osteopenia of prematurity: a national survey and review of practice. *Acta Paediatr* 2008; 97: 407–13.

Adverse Effects and Treatment

Excessive doses of intravenous phosphate cause hyperphosphataemia, particularly in patients with renal failure. Hyperphosphataemia leads in turn to hypocalcaemia, which may be severe, and to ectopic calcification, particularly in patients with initial hypercalcaemia. Tissue calcification may cause hypotension and organ damage and result in acute renal failure. Hyperphosphataemia, hypocalcaemia, and tissue calcification are rare after oral or rectal doses (but see Effects on Electrolytes, and Effects on the Kidneys, below).

Adverse effects of oral phosphates may include nausea, vomiting, diarrhoea, and abdominal pain. When they are being used for indications other than their laxative effects, diarrhoea may necessitate a reduction in dosage. Sodium phosphates given rectally for bowel evacuation may cause local irritation.

Phosphates are given as the potassium or sodium salts or both, and may thus be associated with hyperkalaemia, and hypernatraemia and dehydration. Sodium phosphate may cause hypokalaemia.

Treatment of adverse effects involves withdrawal of phosphate, general supportive measures, and correction of serum-electrolyte concentrations, especially calcium. Measures to remove excess phosphate such as oral phosphate binders and haemodialysis may be required (see also Hyperphosphataemia, p. 1776.3).

Effects on electrolytes. Although less common than after intravenous therapy, hyperphosphataemia, accompanied by hypocalcaemia or other severe electrolyte disturbances and resulting in tetany[1,2] and even death,[2] has been reported after the use of phosphate enemas. Similar effects have also been reported with the use of oral phosphate laxatives,[3–7] and in the USA, the FDA has issued warnings of the risk of electrolyte disturbances after the use of high oral doses of sodium phosphate, particularly in vulnerable patients.[8] Infants or children,[2,9,10] the elderly,[4,11] and those with renal impairment,[1,4,11] or congestive heart failure[4] have often had these adverse effects. Licensed product information for one oral sodium phosphate bowel cleanser (*Visicol; Salix, USA*) states that there have been reports of generalised tonic-clonic seizures and/or loss of consciousness in patients with no history of seizures; these cases were associated with electrolyte abnormalities, and low serum osmolality.

Hyperphosphataemia may precipitate nephrocalcinosis, causing an acute phosphate nephropathy, see Effects on the Kidneys, below.

1. Haskell LP. Hypocalcaemic tetany induced by hypertonic-phosphate enema. *Lancet* 1985; ii: 1433.
2. Martin RR, *et al.* Fatal poisoning from sodium phosphate enema: case report and experimental study. *JAMA* 1987; 257: 2190–2.
3. Peixoto Filho AJ, Lassman MN. Severe hyperphosphatemia induced by a phosphate-containing oral laxative. *Ann Pharmacother* 1996; 30: 141–3.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Electrolyte disturbances with oral phosphate bowel preparations. *Aust Adverse Drug React Bull* 1997; 16: 2. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9702.htm (accessed 04/08/08)
5. Ullah N, *et al.* Fatal hyperphosphatemia from a phosphosoda bowel preparation. *J Clin Gastroenterol* 2002; 34: 457–8.
6. Woo YM, *et al.* A life threatening complication after ingestion of sodium phosphate bowel preparation. *BMJ* 2006; 333: 589–90.
7. Domico MB, *et al.* Severe hyperphosphatemia and hypocalcemic tetany after oral laxative administration in a 3-month-old infant. *Pediatrics* 2006; 118: e1580–e1583. Also available at: http://pediatrics.aappublications.org/cgi/reprint/118/5/e1580 (accessed 13/12/06)
8. FDA. Safety of Sodium Phosphates Oral Solution (Issued 17th September, 2001). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm173897.htm (accessed 20/08/10)
9. McCabe M, *et al.* Phosphate enemas in childhood: cause for concern. *BMJ* 1991; 302: 1074.
10. Harrington L, Schuh S. Complications of Fleet enema administration and suggested guidelines for use in the pediatric emergency department. *Pediatr Emerg Care* 1997; 13: 225–6.
11. Boivin MA, Kahn SR. Symptomatic hypocalcemia from oral sodium phosphate: a report of two cases. *Am J Gastroenterol* 1998; 93: 2577–9.

Effects on the kidneys. Acute renal failure and nephrocalcinosis have been reported after the use of oral phosphate-based cathartics for bowel cleansing.[1,2] Although relatively rare with oral preparations, this acute phosphate nephropathy is a serious adverse effect; most patients were left with chronic renal insufficiency, and some developed end-stage renal disease. Potential contributing factors include inadequate hydration, increased age, a history of hypertension and arteriosclerosis, and concurrent use of ACE inhibitors, angiotensin receptor antagonists, diuretics, or NSAIDs.[2] The FDA has issued warnings[3] about the use of oral sodium phosphate products, especially in patients with impaired renal function, hypovolaemia, decreased intravascular volume, or dehydration, or in those taking drugs likely to contribute to the risk of nephropathy. Patients with bowel obstruction or active colitis may also be at risk. Patient advice includes the need to take the correct dose of oral sodium phosphate, to drink sufficient liquid during bowel cleansing, and to avoid other phosphate-containing laxatives. Patients at increased risk should have their electrolytes and renal function monitored.

Nephrocalcinosis has also been reported in children with hypophosphataemic rickets treated with calcitriol and phosphate supplements; this was found to be associated with the phosphate dose.[4]

1. Desmeules S, *et al.* Acute phosphate nephropathy and renal failure. *N Engl J Med* 2003; 349: 1006–7.
2. Markowitz GS, *et al.* Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an underrecognized cause of chronic renal failure. *J Am Soc Nephrol* 2005; 16: 3389–96.
3. FDA. Oral sodium phosphate (OSP) products for bowel cleansing (marketed as Visicol and OsmoPrep, and oral sodium phosphate products available without a prescription) (issued 12th November, 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103354.htm (accessed 20/08/10)
4. Verge CF, *et al.* Effects of therapy in X-linked hypophosphatemic rickets. *N Engl J Med* 1991; 325: 1843–8.

Local toxicity. Rectal gangrene has been associated with the use of phosphate enemas in elderly patients and was believed to be due to a direct necrotising effect of the phosphate on the rectum.[1]

1. Sweeney JL, *et al.* Rectal gangrene: a complication of phosphate enema. *Med J Aust* 1986; 144: 374–5.

Precautions

Phosphates should not generally be given to patients with severe renal impairment. They should be avoided in patients who may have low serum-calcium concentrations, as these may decrease further, and in patients with infected phosphate renal calculi. Potassium phosphates should be avoided in patients with hyperkalaemia and sodium phosphates should generally be avoided in patients with congestive heart failure, hypertension, and oedema. Serum electrolytes and renal function should be monitored during therapy, particularly if phosphates are given parenterally.

Oral or rectal sodium phosphate preparations for bowel evacuation should not be used in patients with gastrointestinal obstruction, inflammatory bowel disease, and conditions where there is likely to be increased colonic absorption. They should be used cautiously in elderly and debilitated patients, and in those with pre-existing electrolyte disturbances (see Effects on Electrolytes, above).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies potassium and sodium phosphates as not porphyrinogenic; they may be used as drugs 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

Oral phosphate supplements should not be used with aluminium, calcium, or magnesium salts as these will bind phosphate and reduce its absorption. Vitamin D increases the gastrointestinal absorption of phosphates and therefore increases the potential for hyperphosphataemia.

Hyperphosphataemia, hypocalcaemia, and hypernatraemia are more likely to occur with phosphate enemas or oral laxatives if these are given to patients receiving diuretics or other drugs that may affect serum electrolytes. The risk of ectopic calcification may be increased by concurrent use of calcium supplements or calcium-containing antacids.

The risk of hyperkalaemia is increased if potassium phosphates are given with drugs that can increase serum-potassium concentrations.

Pharmacokinetics

About two-thirds of ingested phosphate is absorbed from the gastrointestinal tract. Excess phosphate is mainly excreted in the urine, the remainder being excreted in the faeces.

References.

1. Larson JE, *et al.* Laxative phosphate poisoning: pharmacokinetics of serum phosphorus. *Hum Toxicol* 1986; 5: 45–9.

Human Requirements

Phosphorus requirements are usually regarded as equal to those of calcium.

Most foods contain adequate amounts of phosphate, particularly meat and dairy products, hence deficiency is virtually unknown except in certain disease states, in patients receiving total parenteral nutrition, or in those who have received phosphate-binding drugs for prolonged periods; for further details see under Hypophosphataemia, p. 1777.1.

UK and US recommended dietary intake. In the UK dietary reference values (DRV—see Human Requirements, p. 2046.1)[1] and in the USA dietary reference intakes including recommended dietary allowances (RDA)[2] have been published for phosphorus. In the UK the reference nutrient intake (RNI) for adults is about 550 mg (17.5 mmol) daily; no additional amount is recommended for pregnancy although an additional amount of about 440 mg (14.3 mmol) daily is advised during lactation. In the USA the RDA is 1250 mg daily for those aged 9 to 18 years and 700 mg daily in adults; no increase in RDA is recommended during pregnancy and lactation. A tolerable upper intake level of 4 g daily has been set in adults aged up to 70 years; in those older than 70 a maximum of 3 g daily is recommended.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*. Washington, DC: National Academy Press, 1999. Also available at: http://www.nap.edu/openbook.php?isbn=0309063507 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Denverlax; Dicofan; Enemol; Fosfacol; Fosfafarma†; Fosfalax; Fosfo-Dom; Fosfoadital; Fosfobarigraf; Gadolax; Kritel Enema; Prontonema; Sliaxa; Tekfema; *Austral.*: Celloids PP 85†; Celloids SP 96†; Diacol; Fleet Phospho-Soda; Fleet Ready-to-Use; Phosphate-Sandoz; Phosphoprep†; *Austria*: Fleet Phospho-Soda; Relaxyl†; *Belg.*: Colexklysma; Fleet Enema; Fleet Phospho-Soda; Kaliphos; Sodiphos; *Braz.*: Fleet Enema; Phosfoenema; *Canad.*: Enema; Fleet Enema; Phoslax; Phosphates; Relieve†; *Chile*: Fabulaxol; Fleet Enema; Fleet Fosfosoda; *China*: Fleet Enema (辉力); Fleet Phospho-Soda (辉灵); Gu Ping (固平); Qing Ke Long (清可隆); *Denm.*: Fleet; Phosphoral; *Fin.*: Phosphoral; *Fr.*: Colokit; Fleet Phospho-Soda; *Ger.*: Fleet Phospho-Soda; Freka-Clyss†; Isogutt†; *Gr.*: Bioklysm; Enema Cooper; Fleet Enema; Fleet Ready-to-Use; Fosfolax; Klysmol; *Hong Kong*: Enemol†; Fleet Enema; Fleet Phospho-Soda; Unima; *Hung.*: Fleet Phospho-Soda; Optacid; *India*: Exelyte; Exit; *Indon.*: Fleet Enema; Fleet Phosposoda; *Irl.*: Fleet Phospho-Soda; Fleet; *Israel*: Fleet Enema; *Malaysia*: Fleet Enema; Fleet Phospho-Soda; *Mex.*: Fleet Enema Fosf-Sodio; Fleet PS; *Neth.*: Fleet Gebruiksklaar Klysma†; Phosphoral; *Norw.*: Fleet Phospho-Soda; Phosphoral; *NZ*: Fleet Phosphate Enema; Fleet Phospho-Soda; *Philipp.*: Fleet Enema; Oksna†; Phospho-Soda; *Pol.*: Enema; Fleet Phospho-Soda; Phospho-Laxative†; Rectanal; *Port.*: Fleet Enema; Fleet Phospho-Soda; *Rus.*: Fleet Phospho-Soda (Флит Фосфосода); *Singapore*: Fleet Enema; Fleet Phospho-Soda; Phosphates; *Spain*: Fosfoevac; Fosfosoda; Lainema; *Swed.*: Phosphoral; *Switz.*: Freka-Clyss; *Thai.*: Patar 88 Enema; RISS;

Turk.: BT Enema; Fleet Enema; Fleet Fosfo Soda; *UK*: Diafalk; Fleet Phospho-Soda; Fleet Ready-to-Use; OsmoPrep; *Ukr.*: Fleet (Флит); *USA*: Fleet Enema; Fleet Phospho-Soda†; K-Phos Original; OsmoPrep; Pedia-Lax; Visicol; *Venez.*: Fleet Enema; Fleet Fosfosoda.

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

Homoeopathic Preparations. *Austral.*: Hangover Relief; Nervatona Focus; *Austria*: Lakrima; *Canad.*: Alfalfa Tonic; Barijodeel†; Bioactiv E†; Bioactiv S†; Biochemic Phosphates; Biomag†; Calms Forte; Combinaison†; Comp-Drops 7 Sleepless†; Diamite; Eczema L87; Formula FA 224†; Homeoknop Ikoplex 13†; Hylands Bioplasma; Hylands Formula CF; Hylands Formula NT; Hylands Insomnia; Ikoplex 11 Digestion Aid†; Ikoplex 21†; Ikoplex 5†; Melange†; Minerals+; Nerve Tonic; Nervita; Nuage Bioplasma†; Rexorubia†; Selenium Homaccord†; Sore Throat L39†; Ton 1 Complex†; Ursical Formula†; Urticalcin; *Chile*: Anacardio con Fosforo; Bioactiv E; Bioactiv F; Bioactiv M; Ikoplex No 10; Ikoplex No 11; Ikoplex No 13; Ikoplex No 15; Ikoplex No 18; Ikoplex No 19; Ikoplex No 1; Ikoplex No 20; Ikoplex No 21; Ikoplex No 22; Ikoplex No 24; Ikoplex No 2; Ikoplex No 5; Ikoplex No 8; Ikoplex No 9; *Fr.*: Acidum Phosphoricum Compose†; Billerol; Biomag; Boripharm No 12†; Boripharm No 15†; Boripharm No 31; Boripharm No 3; Cistus Canadensis Complexe No 86†; Diabene; Diacure; Kalium Phosphoricum Complexe No 100; Mercurius Solubilis Complexe No 39; Natrum Carbonicum Complexe No 10†; Rexorubia; Scabiosa Complexe No 87; Stressdoron; Triphosphates; Zenalia; *Ger.*: Cefasept N; Cefasept†; Cefasept; Dormi-cyl L Ho-Len-Complex; Drufusan N†; Drufusan; Girheulit HM†; HanoOxygen E; Infi-China; Influvit; Neurodoron; Refesan T; Rufebran allergo†; Rufebran regeno†; Tondinel; Viscum album H†; Zappelin N; *Neth.*: Apo-STOM; Cerebrum comp; Lymfelite; Nervival; *S.Afr.*: Kalium Phos Comp†; *Switz.*: Urticalcin; *UK*: New Era Nervone; *Ukr.*: Kindinorm (Киндинорм).

Pharmacopoeial Preparations

BP 2014: Dipotassium Hydrogen Phosphate Injection; Phosphate Oral Solution; Phosphates Enema; Potassium Dihydrogen Phosphate Oral Solution; Sterile Potassium Dihydrogen Phosphate Concentrate;

Ph. Eur.: Anticoagulant Citrate-Phosphate-Glucose Solution (CPD);

USP 36: Anticoagulant Citrate Phosphate Dextrose Adenine Solution; Anticoagulant Citrate Phosphate Dextrose Solution; Multiple Electrolytes and Invert Sugar Injection Type 1; Potassium Phosphates Injection; Sodium Phosphates Injection; Sodium Phosphates Oral Solution; Sodium Phosphates Rectal Solution.

Potassium

Kalium; Potasio; Калий.

K=39.0983

UNII — RWP5GA015D (potassium); 295O53K152 (potassium ion).

Description. Potassium salts covered in this section are those principally given as a source of potassium ions, but consideration should also be given to the effect of the anion. Phosphate salts of potassium are covered under Phosphate, p. 1790.3, and the bicarbonate and citrate salts under Bicarbonate, p. 1780.3.

Potassium Acetate

Acetato potásico; E261; Kalii Acetas; Kalio acetatas; Kaliumacetat; Kálium-acetát; Kaliumasetaatti; Octan draselný; Potasio, acetato de; Potassium, acétate de; Potasu octan; Калия Ацетат; Уксуснокислый Калий.

CH_3CO_2K=98.14

CAS — 127-08-2.

ATC — B05XA17.

ATC Vet — QB05XA17.

UNII — M911911U02.

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

Ph. Eur. 8: (Potassium Acetate). Deliquescent white or almost white, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol. A 5% solution in water has a pH of 7.5 to 9.0. Protect from moisture.

USP 36: (Potassium Acetate). Colourless, monoclinic crystals, or a white crystalline powder. It is odourless or has a faint acetous odour. Deliquesces on exposure to moist air. Soluble 1 in 0.5 of water, 1 in 0.2 of boiling water, and 1 in 3 of alcohol. pH of a 5% solution in water is between 7.5 and 8.5. Store in airtight containers.

Equivalence. Each g of potassium acetate (anhydrous) represents about 10.2 mmol of potassium. Potassium acetate (anhydrous) 2.51 g is equivalent to about 1 g of potassium.

Potassium Aspartate

Aspartate monopotassique hémihydraté; Kalii Hydrogenoaspartas Hemihydricus; Kalio-divandenillo aspartatas hemihidratas; Kaliumhydrogenaspartat-Hemihydrat; Kaliumhydrogen-aspartát hemihydrát; Kaliumvateaspartathemihydraatti; Kaliumvetyaspartaatti hemihydraatti; Potassium Hydrogen Aspartate Hemihydrate; Калия Аспарат.

Potassium aminosuccinate hemihydrate.

$C_4H_6KNO_4.½H_2O$=180.2

CAS — 7259-25-8 (hemihydrate).

UNII — OC4598NZEO.

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

Ph. Eur. 8: (Potassium Hydrogen Aspartate Hemihydrate). A white or almost white, powder or crystalline powder, or colourless crystals. Very soluble in water; practically insoluble in alcohol and in dichloromethane. pH of a 2.5% solution in water is between 6.0 and 7.5.

Equivalence. Each g of potassium aspartate represents about 5.5 mmol of potassium. Potassium aspartate 4.61 g is equivalent to about 1 g of potassium.

Potassium Chloride

Chlorid draselný; Cloreto de Potássio; Cloruro potásico; E508; Kalii chloridum; Kalio chloridas; Kalium Chloratum; Kaliumchlorid; Kaliumklorid; Kálium-klorid; Kaliumkloridi; Potasio, cloruro de; Potassium, chlorure de; Potasu chlorek; Хлорид Калия.

KCl=74.55

CAS — 7447-40-7.

ATC — A12BA01; B05XA01.

ATC Vet — QA12BA01; QB05XA01.

UNII — 660YQ98I10.

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

Ph. Eur. 8: (Potassium Chloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; practically insoluble in dehydrated alcohol.

USP 36: (Potassium Chloride). Colourless, elongated, prismatic, or cubical crystals, or a white, granular powder. Is odourless. Soluble 1 in 2.8 of water, and 1 in 2 of boiling water; insoluble in alcohol. Its solutions are neutral to litmus.

Equivalence. Each g of potassium chloride represents about 13.4 mmol of potassium. Potassium chloride 1.91 g is equivalent to about 1 g of potassium.

Potassium Gluconate

E577; Gluconato potásico; Potasio, gluconato de; Калия Глюконат.

Potassium D-gluconate.

$CH_2OH.[CH(OH)]_4.CO_2K$=234.2

CAS — 299-27-4 (anhydrous potassium gluconate); 35398-15-3 (potassium gluconate monohydrate).

ATC — A12BA05.

ATC Vet — QA12BA05.

UNII — 12H3K5QKN9.

Pharmacopoeias. In *Fr.*

US permits anhydrous or the monohydrate.

USP 36: (Potassium Gluconate). It is anhydrous or contains one molecule of water of hydration. A white or yellowish-white, odourless, crystalline powder or granules. Soluble 1 in 3 of water; practically insoluble in dehydrated alcohol, in chloroform, in ether, and in benzene. Its solutions are slightly alkaline to litmus. Store in airtight containers.

Equivalence. Each g of potassium gluconate (anhydrous) represents about 4.3 mmol of potassium. Each g of potassium gluconate (monohydrate) represents about 4 mmol of potassium. Potassium gluconate (anhydrous) 5.99 g and potassium gluconate (monohydrate) 6.45 g are each equivalent to about 1 g of potassium.

Potassium Sulfate *(USAN)*

E515; Kalii Sulfas; Kalio sulfatas; Kalium Sulfuricum; Kaliumsulfaatti; Kaliumsulfat; Potasio, sulfato de; Potassii Sulphas; Potassium, sulfate de; Potassium Sulphate; Síran draselný; Sulfato potásico; Tartarus Vitriolatus; Калия Сульфат.

K_2SO_4=174.3

CAS — 7778-80-5.

UNII — 1K573LC5TV.

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

Ph. Eur. 8: (Potassium Sulfate). A white or almost white, crystalline powder or colourless crystals. Soluble in water; practically insoluble in dehydrated alcohol.

Equivalence. Each g of potassium sulfate represents about 11.5 mmol of potassium. Potassium sulfate 2.23 g is equivalent to about 1 g of potassium.

Potassium Tartrate

E336; Potasio, tartrato de; Potasu winian; Tartrato potásico; Тартрат Калия.

$C_4H_4K_2O_6.½H_2O$=235.3

CAS — 921-53-9 (anhydrous potassium tartrate).

UNII — O9WLL1ZL8S.

Equivalence. Each g of potassium tartrate (hemihydrate) represents about 8.5 mmol of potassium. Potassium tartrate (hemihydrate) 3.00 g is equivalent to about 1 g of potassium.

Uses and Administration

Potassium salts in this section are used for the prevention and treatment of potassium depletion and/or **hypokalaemia** (p. 1777.2) and have been used in the prevention of **diuretic-induced hypokalaemia** (see Hydrochlorothiazide, Effects on Electrolyte Balance, p. 1404.2). Doses may be expressed in terms of mmol or mEq of potassium, mass (mg) of potassium, or mass of potassium salt (for comparative purposes see Table 3, below). Treatment should be monitored by plasma-potassium estimations because of the risk of inducing hyperkalaemia, especially where there is renal impairment.

Potassium chloride is probably the most commonly used potassium salt; this is because hypochloraemic alkalosis, which is often associated with hypokalaemia, can be corrected by the chloride ions. An alkalinising salt such as potassium acetate, potassium bicarbonate, or potassium citrate may be preferable if a metabolic acidosis, such as occurs in renal tubular acidosis, accompanies the hypokalaemia (see p. 1775.2). Other salts that are or have been used in the management of potassium deficiency include potassium ascorbate, potassium aspartate, potassium benzoate, potassium gluceptate, potassium gluconate, potassium phosphate, and potassium tartrate. Typical doses for the prevention of hypokalaemia may be up to 50 mmol daily and similar doses may be adequate in mild potassium deficiency. However, higher doses may be needed in more severe deficiency. Patients with renal impairment should receive correspondingly lower doses. *Oral* treatment is used for prophylaxis and is also suitable for treating most cases of hypokalaemia. Oral potassium salts are more irritating than the corresponding sodium salts; they should be taken with or after meals with plenty of fluid; liquid preparations are preferable.

An *intravenous* potassium salt may be required in severe acute hypokalaemia. This normally entails infusing a solution containing 20 mmol of potassium in 500 mL over 2 to 3 hours under ECG control. A recommended maximum dose is 2 to 3 mmol/kg of potassium in 24 hours. Higher concentrations have been given when an infusion pump has been used (see Administration p. 1794.1). Adequate urine flow must be ensured and careful monitoring of plasma-potassium and other electrolyte concentrations is essential. Potassium chloride is the salt most commonly used and solutions intended for intravenous use that are in a concentrated form (such as 1.5 or 2 mmol/mL) *must* be diluted to the appropriate concentration before use. There should be careful and thorough mixing when adding concentrated potassium chloride solutions to infusion fluids. Potassium chloride is also available as premixed infusions with sodium chloride and/or glucose containing 10 to 40 mmol/litre of potassium (but see also Administration, p. 1794.1). Potassium acetate is also given intravenously.

Amongst **other uses**, the sulfate, and tartrate salts of potassium have been given orally as osmotic laxatives (p. 1804.1).

Some potassium salts are used as sodium-free condiments when sodium intake must be restricted.

Potassium chloride is sometimes used as an excipient in pharmaceutical formulations.

Table 3. Some potassium salts and their potassium content.

	Potassium content per g		
Potassium salt	mg	mmol	mEq
Potassium acetate (anhydrous)	398	10.2	10.2
Potassium aspartate	217	5.5	5.5
Potassium bicarbonate	391	10.0	10.0
Potassium chloride	524	13.4	13.4
Potassium citrate (anhydrous)	383	9.8	9.8
Potassium citrate (monohydrate)	361	9.3	9.3
Potassium gluconate (anhydrous)	167	4.3	4.3
Potassium gluconate (monohydrate)	155	4.0	4.0
Potassium sulfate (anhydrous)	449	11.5	11.5
Potassium tartrate (hemihydrate)	332	8.5	8.5

Administration. The standard concentration and rate of administration of potassium chloride for infusion is discussed in Uses and Administration, p. 1793.3. However, higher concentrations (200 or 300 mmol/litre) and faster infusion rates have been used, via an infusion pump, for cases of severe symptomatic hypokalaemia, especially with fluid overload.[1,2]

There has been controversy regarding the preferred route of administration of these higher concentrations of potassium chloride.[1] The central route avoids the problems of pain and phlebitis when potassium is given peripherally. However, it has been suggested that high concentrations of potassium given centrally may carry a greater risk of cardiac toxicity if the infusion is carried directly to the heart. Use of lidocaine has improved tolerability of peripheral administration of potassium chloride.[2]

Intravenous potassium is usually given in sodium chloride and/or glucose infusion. However, it has been pointed out that glucose can reduce serum-potassium concentrations, and that glucose-free solutions should be used for the initial intravenous administration of potassium in hypokalaemia.[3]

1. Kruse JA, Carlson RW. Rapid correction of hypokalemia using concentrated intravenous potassium chloride infusions. *Arch Intern Med* 1990; 150: 613–17.
2. Pucino F, *et al.* Patient tolerance to intravenous potassium chloride with and without lidocaine. *Drug Intell Clin Pharm* 1988; 22: 676–9.
3. Agarwal A, Wingo CS. Treatment of hypokalaemia. *N Engl J Med* 1999; 340: 154–5.

Diabetic ketoacidosis. As discussed under Diabetic Emergencies on p. 465.3, potassium replacement is given in diabetic ketoacidosis to restore total body stores of potassium and thereby prevent the hypokalaemia induced by insulin.

Hypertension. A meta-analysis[1] has reported that potassium supplementation reduces both systolic and diastolic blood pressure. The size of the effect in hypertensive patients was great enough to suggest a possible role in the treatment of hypertension (p. 1251.1); effects in normotensive subjects were less marked but consistent with a similar role for preventing hypertension. Most studies have used potassium chloride, but an effect has also been found with the aspartate[2] and the citrate.[3]

1. Whelton PK, *et al.* Effects of oral potassium on blood pressure: meta-analysis of randomized controlled clinical trials. *JAMA* 1997; 277: 1624–32.
2. Pranzoni F, *et al.* Antihypertensive effect of oral potassium aspartate supplementation in mild to moderate arterial hypertension. *Biomed Pharmacother* 2005; 59: 25–9.
3. He FJ, *et al.* Effect of short-term supplementation of potassium chloride and potassium citrate on blood pressure in hypertensives. *Hypertension* 2005; 45: 571–4.

Myocardial infarction. A glucose, insulin, and potassium infusion has been investigated in acute myocardial infarction (see p. 482.3).

Termination of pregnancy. Solutions of potassium chloride are used to reduce fetal numbers in multifetal pregnancies[1-3] or for severe fetal malformation by abolishing the fetal cardiac activity. The solution is injected into the thorax of the fetus without affecting the others, which are allowed to continue to term. Alternatively, potassium chloride may be injected into the umbilical vein when access to the fetal heart is difficult. A retrospective comparison[4] found both techniques to be effective. Significantly smaller doses were required for the umbilical route, possibly because a sustained dose is delivered directly to the fetal heart and myocardium, compared with intraventricular injection.

1. Wapner RJ, *et al.* Selective reduction of multifetal pregnancies. *Lancet* 1990; 335: 90–3.
2. Berkowitz RL, *et al.* The current status of multifetal pregnancy reduction. *Am J Obstet Gynecol* 1996; 174: 1265–72.
3. De Catte L, Foulon W. Obstetric outcome after fetal reduction to singleton pregnancies. *Prenat Diagn* 2002; 22: 206–10.
4. Bhide A, *et al.* Comparison of feticide carried out by cordocentesis versus cardiac puncture. *Ultrasound Obstet Gynecol* 2002; 20: 230–2.

Adverse Effects

Excessive doses of potassium may lead to the development of hyperkalaemia (p. 1777.1), especially in patients with renal impairment. Symptoms include paraesthesia of the extremities, muscle weakness, paralysis, cardiac arrhythmias, heart block, cardiac arrest, and confusion. Cardiac toxicity is of particular concern after intravenous dosage.

Pain or phlebitis may occur when given intravenously via peripheral veins, particularly at higher concentrations.

Nausea, vomiting, diarrhoea, and abdominal cramps may occur with oral potassium salts. There have been numerous reports of gastrointestinal ulceration, sometimes with haemorrhage and perforation or with the late formation of strictures, after the use of enteric-coated tablets of potassium chloride. Ulceration has also occurred after the use of sustained-release tablets.

Treatment of Adverse Effects

The treatment of hyperkalaemia discussed on p. 1777.1 also applies when hyperkalaemia occurs during potassium therapy. However, in mild hyperkalaemia that has developed on long-term treatment, stopping the potassium supplement and other drugs that may increase plasma-potassium concentrations, and avoidance of foods with a high potassium content may be sufficient to correct the hyperkalaemia.

In cases of acute oral overdosage of potassium supplements, the stomach should be emptied by gastric lavage in addition to the measures described on p. 1777.1.

Precautions

Potassium salts should be given with considerable care to patients with cardiac disease or conditions predisposing to hyperkalaemia such as renal or adrenocortical insufficiency, acute dehydration, or extensive tissue destruction as occurs with severe burns. Excessive use of potassium-containing salt substitutes or potassium supplements may lead to accumulation of potassium especially in patients with renal insufficiency. Regular monitoring of clinical status, serum electrolytes, and the ECG is advisable in patients receiving potassium therapy, particularly those with cardiac or renal impairment.

Liquid or effervescent preparations are preferred to solid dosage forms for oral use; use of the former, with or after food, may reduce gastric irritation. Solid oral dosage forms of potassium salts should not be given to patients with gastrointestinal ulceration or obstruction. They should be given with care to patients in whom passage through the gastrointestinal tract may be delayed, as in pregnant patients. Treatment should be stopped if severe nausea, vomiting, or abdominal distress develops.

Potassium chloride should not be used in patients with hyperchloraemia.

Direct injection of potassium chloride concentrates without appropriate dilution may cause instant death. For the view that glucose-containing solutions should not be used for the initial intravenous administration of potassium in hypokalaemia see Administration, above.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies potassium chloride 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

Potassium supplements should be used with caution, if at all, in patients receiving drugs that increase serum-potassium concentrations. These include potassium-sparing diuretics, ACE inhibitors, ciclosporin, and drugs that contain potassium such as the potassium salts of penicillin. Similarly, the concomitant use of potassium-containing salt substitutes for flavouring food should be avoided. Antimuscarinics delay gastric emptying and consequently may increase the risk of gastrointestinal adverse effects in patients receiving solid oral dosage forms of potassium.

Pharmacokinetics

Potassium salts other than the phosphate, sulfate, and tartrate are generally readily absorbed from the gastrointestinal tract. Potassium is excreted mainly by the kidneys; it is secreted in the distal tubules in exchange for sodium or hydrogen ions. Some potassium is excreted in the faeces and small amounts may also be excreted in sweat.

Human Requirements

Potassium is an essential body electrolyte. However, requirements are difficult to determine and have been estimated from the amount accumulated during growth and reported urinary and faecal excretion.

Over 90% of dietary potassium is absorbed from the gastrointestinal tract. Potassium is particularly abundant in vegetables, potatoes, and fruit.

UK and US recommended dietary intake. In the UK dietary reference values (DRV—see Human Requirements, p. 2046.1)[1] have been estimated for potassium. The reference nutrient intake (RNI) for adults is 3.5 g (90 mmol) daily. In the USA, no recommended dietary allowance (RDA) has been established for potassium. However a daily intake of 1.6 to 2 g (40 to 50 mmol) is considered adequate for adults.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Co-Salt; Control K; Gluco-K; Kaon; Orakit; Potamkim; *Austral.*: Celloids PC 73†; Celloids PS 29†; Chlorvescent; Duro-K; Slow-K; Span-K; *Austria*: KCl-retard; Micro-Kalium; *Belg.*: Chloropotassuril; Kali-Sterop; Steropotassium; Ultra-K; *Braz.*: Clotassio; Decorfen; Slow-K; *Canad.*: Apo-K; Essential Liquid Mineral; K-10; K-Dur; K-Lyte/Cl†; Micro-K; Odan K-20; Pro-600K; Proflavanol C†; Riva K; Slo-Pot; Slow-K; *Chile*: Kaion Retard; Sal Dietetica; Slow-K; Yonka; *China*: Budaxiu (补达秀); Di Jia (迪佳); Lai Ding Jia (莱丁甲); Lejia (乐甲); Li Bei Jia (立贝甲); Panangin (潘南金); Xian Jia (先甲); Xin Jian Ju (欣健聚); *Cz.*: Kaldyum; Kalnormin; *Denm.*: Kaleorid; *Fin.*: Kaleorid; Kalinorm†; Kalisol; *Fr.*: Diffu-K; Kaleorid; Nati-K; *Ger.*: Kalinor-retard P; KCl-retard; Rekawan; *Gr.*: Acronitol; Acroser; Sopa-K; *Hong Kong*: Apo-K; KSR; Slow-K; Span-K; *Hung.*: Kaldyum; Kalium Durules†; Kalium-R; *India*: K-Card; Kay Ciel; Keylyte; Potklor; *Indon.*: Aspar-K; Kalipar; KSR; *Irl.*: Diarrest RF†; Kay-Cee-L; Slow-K; *Israel*: Moviprep; Slow-K; *Ital.*: K-Flebo; Kadalex; Lento-Kalium; *Malaysia*: Apo-K; Beacon K; Slow-K; *Mex.*: Ceposil†; Clor-K-Zaf; Corpotasin GK; Corpotasin LP; Efilat; K-Dur; Kaliollte; Kelefusin; Potasoral†; *Neth.*: Slow-K; *Norw.*: Kaleorid; *NZ*: Chlorvescent; Slow-K†; Span-K; *Philipp.*: Ion-O-Trate†; Kalium; *Pol.*: Kaldyum; Kalimat†; Kalipoz; *S.Afr.*: Flexivial; Micro-K†; Plenish-K; Sandoz K; Slow-K; *Singapore*: Apo-K; Dorama-neo; Slow-K; *Spain*: AP-Inyect; Boi-K Aspartico; Boi-K; Potasion Solucion; Potasion; *Swed.*: Kaleorid; Kalium Retard†; *Switz.*: Kaliglutol†; Plus Kalium retard; *Thai.*: Addi-K; Enpot; Kaliject; Kaylyte; Potassride; Strong Pot Chloride; *Turk.*: Kadaleks; *UK*: Kay-Cee-L; Slow-K; *Ukr.*: Caldium (Кальциум)†; Gik (Гик); Kalium-Normin (Калий-Нормин); *USA*: Adolphs Salt Substitute; Cena-K; Gen-K; K + 10; K-Dur; K-G Elixir; K-Lor; K-Lyte/Cl; K-Tab; Kaon-Cl; Kaon; Klor-Con; Klorvess; Klotrix; Micro-K; Potasalan; Ten-K.

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

Homoeopathic Preparations. *Austria*: Tonsillopas; *Canad.*: Combinaison†; Diamite; Earache; Formula PC 223†; Homeoknop Ikoplex 13†; Hylands Bioplasma; Ikoplex 21†; Melange†; Nuage Bioplasma†; Optalia†; Sinus Ease; Sinuspax†; *Chile*: Ikoplex No 13; Ikoplex No 15; Ikoplex No 17; Ikoplex No 18; Ikoplex No 19; Ikoplex No 20; Ikoplex No 21; Ikoplex No 22; Ikoplex No 23; Ikoplex No 3; Ikoplex No 5; Ikoplex No 8; Ikoplex No 9; *Fr.*: Boripharm No 10†; Boripharm No 22†; Kalium Muriaticum Complexe No 41†; Sinuspax; *Ger.*: Drufusan N†; Drufusan; Hevertotox; Hevertotox; Jowidarmin; NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†; Odonton-Bchtroplex; Pyrogenium; Sinusyx; Tonsillopas; *UK*: New Era Nervone.

Pharmacopoeial Preparations

BP 2014: Bumetanide and Prolonged-release Potassium Tablets; Compound Sodium Lactate Infusion; Effervescent Potassium Chloride Tablets; Oral Rehydration Salts; Potassium Ascorbate Eye Drops; Potassium Chloride and Glucose Infusion; Potassium Chloride and Sodium Chloride Infusion; Potassium Chloride Oral Solution; Potassium Chloride, Sodium Chloride and Glucose Infusion; Prolonged-release Potassium Chloride Tablets; Sterile Potassium Chloride Concentrate;

USP 36: Half-strength Lactated Ringer's and Dextrose Injection; Lactated Ringer's and Dextrose Injection; Lactated Ringer's Injection; Minerals Capsules; Minerals Tablets; Multiple Electrolytes and Dextrose Injection Type 1; Multiple Electrolytes and Dextrose Injection Type 2; Multiple Electrolytes and Dextrose Injection Type 3; Multiple Electrolytes and Invert Sugar Injection Type 1; Multiple Electrolytes and Invert Sugar Injection Type 2; Multiple Electrolytes and Invert Sugar Injection Type 3; Multiple Electrolytes Injection Type 1; Multiple Electrolytes Injection Type 2; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Tablets; Oral Rehydration Salts; PEG 3350 and Electrolytes for Oral Solution; Potassium Acetate Injection; Potassium Bicarbonate and Potassium Chloride Effervescent Tablets for Oral Solution; Potassium Bicarbonate and Potassium Chloride for Effervescent Oral Solution; Potassium Chloride Extended-release Capsules; Potassium Chloride Extended-release Tablets; Potassium Chloride for Injection Concentrate; Potassium Chloride for Oral Solution; Potassium Chloride in Dextrose and Sodium Chloride Injection; Potassium Chloride in Dextrose Injection; Potassium Chloride in Lactated Ringer's and Dextrose Injection; Potassium Chloride in Sodium Chloride Injection; Potassium Chloride Oral Solution; Potassium Chloride, Potassium Bicarbonate, and Potassium Citrate Effervescent Tablets for Oral Solution; Potassium Gluconate and Potassium Chloride for Oral Solution; Potassium Gluconate and Potassium Chloride Oral Solution; Potassium Gluconate and Potassium Citrate Oral Solution; Potassium Gluconate Elixir; Potassium Gluconate Tablets; Potassium Gluconate, Potassium Citrate, and Ammonium Chloride Oral Solution; Ringer's and Dextrose Injection; Trikates Oral Solution; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Sodium

Natrium; Sód; Sodio; Натрий.
Na=22.98976928
UNII — 9NEZ333N27 (sodium); LYR4M0NH37 (sodium ion).

Description. Sodium chloride is the principal sodium salt used as a source of sodium ions. Sodium salts used chiefly as sources of bicarbonate ions, such as the acetate, bicarbonate, citrate, and lactate, are covered under Bicarbonate, p. 1780.3. Phosphate salts of sodium are covered under Phosphate, p. 1790.3.

Sodium Chloride

Chlorid sodný; Chlorure de Sodium; Cloreto de Sódio; Cloruro sódico; Natrii Chloridum; Natrio chloridas; Natrium-chlorid; Natriumklorid; Nátrium-klorid; Natriumkloridi; Salt; Sodio, cloruro de; Sodium, chlorure de; Sodu chlorek; Sodyum Klorür; Натрия Хлорид.
NaCl=58.44
CAS — 7647-14-5.
ATC — A12CA01; B05CB01; B05XA03.
ATC Vet — QA12CA01; QB05CB01; QB05XA03.
UNII — 451W47IQ8X.

NOTE. An aqueous solution of sodium chloride 0.9% is often known as physiological saline.

SALINE is a code approved by the BP 2014 for use on single unit doses of eye drops containing sodium chloride 0.9% where the individual container may be too small to bear all the appropriate labelling information. HECL is a similar code approved for hyetellose and sodium chloride eye drops.

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

Ph. Eur. 8: (Sodium Chloride). A white or almost white, crystalline powder or colourless crystals or white or almost white pearls. Freely soluble in water; practically insoluble in dehydrated alcohol.

USP 36: (Sodium Chloride). Colourless cubic crystals or white crystalline powder. Soluble 1 in 2.8 of water, 1 in 2.7 of boiling water, and 1 in 10 of glycerol; slightly soluble in alcohol.

Equivalence. Each g of sodium chloride represents about 17.1 mmol of sodium and of chloride. Sodium chloride 2.54 g is equivalent to about 1 g of sodium.

Storage. Solutions of some sodium salts, including sodium chloride, when stored, may cause separation of solid particles from glass containers and solutions containing such particles must not be used.

Uses and Administration

Sodium chloride is used in the management of deficiencies of sodium and chloride ions in salt-losing conditions (see Hyponatraemia, p. 1778.1). Sodium chloride solutions are used as a source of sodium chloride and water for hydration.

A 0.9% solution in water is iso-osmotic, and thus in most cases isotonic with serum and lachrymal secretions. Doses may be expressed in terms of mEq or mmol of sodium, mass (mg) of sodium, or mass of sodium salt (for comparative purposes, see Table 4, below).

A typical oral replacement dose of sodium chloride in **chronic salt-losing conditions** is about 2.4 to 4.8 g (about 40 to 80 mmol of sodium) daily as a modified-release preparation, accompanied by a suitable fluid intake; doses of up to 12 g daily may be necessary in severe cases. Oral supplements are also used for the prevention of muscle cramps during routine haemodialysis (p. 1779.3); a suggested dose is about 6 to 10 g of a modified-release preparation per dialysis session.

Glucose facilitates the absorption of sodium from the gastrointestinal tract, and solutions containing sodium chloride and glucose usually with additional electrolytes (see p. 1780.1) are used for oral rehydration in acute diarrhoea (p. 1805.2).

Table 4. Some sodium salts and their sodium content.

Sodium salt	Sodium content per g		
	mg	mmol	mEq
Sodium acetate (anhydrous)	280	12.2	12.2
Sodium acetate (trihydrate)	169	7.3	7.3
Sodium acid citrate	175	7.6	7.6
Sodium bicarbonate	274	11.9	11.9
Sodium chloride	394	17.1	17.1
Sodium citrate (anhydrous)	267	11.6	11.6
Sodium citrate (dihydrate)	235	10.2	10.2
Sodium lactate	205	8.9	8.9

The concentration and dosage of sodium chloride solutions for intravenous use is determined by several factors including the age, weight, and clinical condition of the patient and in particular the patients' hydration state. Serum-electrolyte concentrations should be carefully monitored. In severe sodium depletion, 2 to 3 litres of sodium chloride 0.9% may be given over 2 to 3 hours and thereafter at a slower rate. If there is combined water and sodium depletion a 1 to 1 mixture of sodium chloride 0.9% and glucose 5% may be appropriate. Although hypertonic sodium chloride solutions may be used in certain patients with severe acute dilutional hyponatraemia, over-rapid correction may have severe neurological adverse effects (see Hyponatraemia, p. 1778.1). Solutions containing 1.8 to 5% are available.

In **hypernatraemia** with volume depletion (p. 1778.1), sodium chloride 0.9% may be used to maintain plasma-sodium concentrations with expanding fluid volume. Sodium chloride 0.9% (or rarely, in marked hypernatraemia, 0.45%) is used for fluid replacement in diabetic ketoacidosis (see Diabetic Emergencies, p. 465.3).

Among its **other uses**, sodium chloride solution 0.9%, being isotonic, is a useful fluid for sterile irrigations, for example, of the eye or bladder, and general skin or wound cleansing. The 0.9% concentration is also widely used as a vehicle or diluent for the parenteral administration of other drugs. Nasal drops of sodium chloride 0.9% are used to relieve nasal congestion. A mouthwash containing sodium chloride is also available for oral hygiene.

Sodium chloride in the form of sea water or sea salt (see p. 2612.1) has been also used for nasal irrigations.

Sodium chloride solutions should *not* be used to induce emesis; this practice is dangerous and deaths from resulting hypernatraemia have been reported.

Sodium chloride is sometimes used as an excipient in capsules and tablets.

Homoeopathy

Sodium chloride has been used in homoeopathic medicines under the following names: Natrium muriaticum; Nat. Mur.; Natrii chloridum; Natricum chloratum; Natrum muriaticum.

NOTE. Do not confuse Natricum chloratum with sodium chlorate (p. 2618.1).

Catheters and cannulas. For reference to sodium chloride 0.9% being used to maintain the patency of catheters and cannulas, and to its equivalent efficacy to heparin, see Catheters and Cannulas under Uses and Administration of Heparin, p. 1398.1.

Cystic fibrosis. Inhalation of 4 mL of a hypertonic solution of sodium chloride (7%) twice daily for 48 weeks in 82 patients with stable cystic fibrosis (p. 177.2) was associated with a moderate but sustained improvement in lung function and a marked reduction in the number of exacerbations and need for antibacterials, when compared with 80 placebo-treated patients.[1] There was, however, no difference in the rate of change of lung function. Each inhalation was preceded by a bronchodilator to minimise airway narrowing; adverse reactions to the active treatment were nonetheless reported in 14 patients and included cough, chest tightness or pharyngitis, sinusitis, haemoptysis, sneezing, and vomiting. As a result, 6 patients withdrew from the study, but the effects resolved in the remainder without the need for dose reduction or interruption. Hypertonic saline was considered to be an inexpensive and safe adjunctive therapy in patients with cystic fibrosis.

1. Elkins MR, *et al.* A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med* 2006; 354: 229–40.

Termination of pregnancy. Trans-abdominal intra-amniotic instillation of sodium chloride 20% (maximum volume 200 to 250 mL) has been used for the termination of second-trimester pregnancy. However, serious adverse effects have occurred (see below), and other methods are generally preferred (p. 2131.3).

Adverse Effects

Adverse effects of sodium salts are attributable to electrolyte imbalances from excess sodium; there may also be effects due to the specific anion.

Retention of excess sodium in the body usually occurs when there is defective renal sodium excretion. This leads to the accumulation of extracellular fluid to maintain normal plasma osmolality, which may result in pulmonary and peripheral oedema and their consequent effects.

Hypernatraemia (a rise in plasma osmolality) is usually associated with inadequate water intake, or excessive water losses (see p. 1778.1). It rarely occurs after therapeutic doses of sodium chloride, but has occurred with the use of hypertonic saline for induction of emesis or for gastric lavage and after errors in the formulation of infant feeds. Hypernatraemia may also occur after inappropriate intravenous use of hypertonic saline.

The most serious effect of hypernatraemia is dehydration of the brain which causes somnolence and confusion progressing to convulsions, coma, respiratory failure, and death. Other symptoms include thirst, reduced salivation and lachrymation, fever, sweating, tachycardia, hypertension or hypotension, headache, dizziness, restlessness, irritability, weakness, and muscular twitching and rigidity.

Gastrointestinal effects associated with acute oral ingestion of hypertonic solutions or excessive amounts of sodium chloride include nausea, vomiting, diarrhoea, and abdominal cramps.

Excessive use of chloride salts may cause a loss of bicarbonate with an acidifying effect.

Intra-amniotic injection of hypertonic solutions of sodium chloride, which has been used for termination of pregnancy, has been associated with serious adverse effects including disseminated intravascular coagulation, renal necrosis, cervical and uterine lesions, haemorrhage, pulmonary embolism, pneumonia, and death.

General references.

1. Moder KG, Hurley DL. Fatal hypernatremia from exogenous salt intake: report of a case and review of the literature. *Mayo Clin Proc* 1990; 65: 1587–94. Correction. *ibid.* 1991; 66: 439.
2. Martos Sánchez I, *et al.* Hipernatremia grave por administración accidental de sal común. *An Esp Pediatr* 2000; 53: 495–8.
3. Adeleye O, *et al.* Hypernatremia in the elderly. *J Natl Med Assoc* 2002; 94: 701–5.
4. Coulthard MG, Haycock GB. Distinguishing between salt poisoning and hypernatraemic dehydration in children. *BMJ* 2003; 326: 157–60. Correction. *ibid.*: 497.

Treatment of Adverse Effects

In patients with mild sodium excess, drinking water and restricting sodium intake is sufficient. However, in the event of recent acute oral overdose of sodium chloride, gastric lavage should be carried out along with general symptomatic and supportive treatment. Serum-sodium concentrations should be measured, and if severe hypernatraemia is present this should be treated (see p. 1778.1).

Precautions

Sodium salts should be used with caution in patients with hypertension, heart failure, peripheral or pulmonary oedema, renal impairment, pre-eclampsia, or other conditions associated with sodium retention.

When sodium supplements are given orally, adequate water intake should be maintained. Modified-release tablets should not be given to patients with gastrointestinal disorders associated with strictures or diverticula because of the risk of obstruction.

Sodium chloride solutions should *not* be used to induce emesis; this practice is dangerous and deaths from resulting hypernatraemia have been reported.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sodium chloride 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)

Pharmacokinetics

Sodium chloride is well absorbed from the gastrointestinal tract. Excess sodium is mainly excreted by the kidney, and small amounts are lost in the faeces and sweat.

Human Requirements

The body contains about 4 mol (92 g) of sodium of which about one-third is found in the skeleton and about half is present in the extracellular fluid.

The body can adapt to a wide range of intakes by adjustment of renal excretion through physical and hormonal factors. Loss through the skin is significant only if excessive sweating occurs. Sodium requirements may be increased with exercise or exposure to high ambient temperatures in the short term, until the body adjusts.

Sodium is widely available in foods and is also added as salt during processing, cooking, and at the table. Dietary deficiency of sodium is therefore extremely rare and more concern has been expressed that current intakes are excessive. Restriction of sodium intake, by limiting the amount of culinary salt consumed, may be a useful aid in the management of some patients with hypertension (p. 1251.1).

UK and US recommended dietary intake. In the UK dietary reference values (DRV—see Human Requirements, p. 2046.1)[1] have been published for sodium. The reference nutrient intake (RNI) for adults is 1.6 g of sodium (70 mmol) daily, which is about 4 g of sodium chloride. In

the USA, it has been recommended that daily intakes of sodium be limited to 2.4 g (6 g of sodium chloride) or less.[2] Dietary intake is often in excess of these recommendations, and may be a factor in essential hypertension,[3] and osteoporosis.[4] A possible association with cardiovascular disease has also been suggested by the long-term follow-up of two hypertension studies.[5] Results found that reducing sodium intake may also reduce the risk of cardiovascular events.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Subcommittee on the tenth edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Council. *Recommended dietary allowances*. 10th ed. Washington, DC: National Academy Press, 1989. Also available at: http://www.nap.edu/openbook.php?isbn=0309046335 (accessed 21/07/08)
3. Midgley JP, *et al.* Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. *JAMA* 1996; 275: 1590–7.
4. Devine A, *et al.* A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women. *Am J Clin Nutr* 1995; 62: 740–5.
5. Cook NR, *et al.* Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). Abridged version: *BMJ* 2007; 334: 885–8. Full version: http://www.bmj.com/cgi/reprint/334/7599/885 (accessed 13/03/09)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aqua Lent Limpia Cristales; Cutidermin Bebe Gel Nasal†; Hypersol; Larmabak; Muro 128; Oftalook; Relente; Suaviler; Xylisol; Yusin Tears I; *Austral.*: Dimetapp Infants Nasal Relief; Ear Clear Ear Cleanser; Fess; Hypergel; Lens Plus; Mesalt; Narium; Normlgel; Otrivin Saline Baby; Sensitive Eyes Saline; Slow-Sodium; *Austria*: Kochsalz; SmartDose†; *Belg.*: Natriclo; Physiologica; Physiorhine; *Braz.*: Advnasal†; Afrin Natural; Alive; Conidrin Baby; Conidrin Salina; Deltasoro; Descodrin; Fisiorinus; Fluimare; Fluimucil Solucao Nasal; Maresis; Maxidrate; Multisoro; Naridrin Bebe; Naridrin H; Narisoro; Neorino; Neosoro H; Neosoro Infantil; Novo Rino-S; Pratsorin; Rinoben; Rinoflux†; Rinosoft S; Rinosoro; Salsep; Sinustrat Solucao Natural; Snif; Sonarin (INF); Sorine Pediatrico; Sorine; Sorofar; Soroliv; Soroneo; *Canad.*: Hypergel; Mesalt; Muro 128; Nebusal; Normigel; Rhinaris Sinus; Salinex; Sea Clens†; Softwear†; Thalanex†; Thalaris†; *Chile*: Fisiolimp; Larmabak†; Pediasea; Printan; Respirex†; Rinodan; Rinokid; Rinosteryl; Sinus; *China*: Ai Na Duo (艾那多); *Fin.*: Natrosteril†; Selutrio; *Fr.*: Erjean; Hypergel; Jelly-wash; Larmabak; Larmes Artificielles; Multilarm†; Normlgel; Physiologica†; Polyrinse†; Selgine; *Ger.*: Adsorbonac†; Freka-Drainjet†; Hylase; Isogutt akut; Isotone Kochsalz; Isotonische Kochsalzlosung; Olynth salin; Omni-Sorb; Tetrisal; Tussamag Nasenspray Pur†; Urgo sterile; *Gr.*: Babynose; Clinofar; Larmabak; Otrisalin; Phy-O; Rhinodose; Selva N; *Hong Kong*: Ayr Saline†; Earinse; Larmabak; Nasal Physiological Solution; Physiodose; Unison Enema; *Hung.*: Rins-Sal; Salsol A†; *India*: Hold; Hynasal; Hypersol; Hytosol; Izabel; Libna; Nam Cold-NS; Nasalt; Nasivion-S; Nasoclear; Nipit; Nos-Air Saline; Ocutone; Osmogel; Otrivin-S; *Indon.*: Breathy; Infusan-NS; Otsu-NS; Wida NS; Wida NSI; *Irl.*: Diarrest RF†; *Israel*: Af-Kid; Af-Tiponet; Alrin Baby; Baby AF; Baby Saline†; Clean-AF; L'Batzeket; Moviprep; Normasol; Ocean Spray; Otrivini; Tinok AF; Tipotaf; *Ital.*: Adsorbonac†; Hydrabak; Libenar; Narhinel; Otrivin Baby†; Physiodose; Respifree Baby; Rinowash; *Mex.*: Corni Limp; Hiperton; Muro 123; Phylarm; *Mon.*: Unilarm; *NZ*: Narium; *Philipp.*: Hypersalt; Hyperton-Opta; Larmabak†; Muconase; SalinaGel; Salinase; Snif; *Pol.*: Oftarinol; Solnasin†; *Port.*: Extraneal; *Rus.*: Aquamaster (Аквамастер); Rizosin (Ризосин); Salin (Салин); *S.Afr.*: Polyrinse†; Vicks Vapomist†; *Singapore*: Adsorbonac†; Dorama-neo; Larmabak; Normasol; Oftalmolosa Cusi Antiedema†; Otrivin Saline Nasal Spray; Salacyn; *Spain*: Antiedema; Apiroserum Clorurado; Fisiologica†; Fisiologico Bieffe Medital†; Fisiologico Braun; Fisiologico Mein; Fisiologico Serra Pamies†; Fisiologico Vitulia†; Fisiologico†; Flebobag Fisio; Fleboflex Salina Fisiologica†; Fleboplast Fisio; Freeflex Cloruro Sodico; Hidrathea; Meinvenil Fisiologico†; Plast Apyr Fisiologico; Solucion Fisiologica Respitol; Suero Fisiologico; Suero Fisiologico; *Switz.*: Physiologic; Physiosoin†; Serophy; *Thai.*: Patar Enema; Royal-C; U-Enema; Unison Enema; *Turk.*: Berko-Fiz; Droser; Fizyolen; Fizyolik; Fizyosol; Larmabak; Otrisalin; Physiodese; Physiologica Gifrer; Ser Damla†; Serum Fizyolojik; *UAE*: Normaline; *UK*: Askina; Equaleze; Irriclens; Irripod; Miniversol; MucoClear; Nasosal; Nebusal; Normasol; Slow-Sodium; SodiClor; Stericlens; Steripod; Tubilux; Uriflex S; Uro-Tainer M; Versol; *Ukr.*: No-Sol (Но-Соль); *USA*: Adsorbonac†; Ak-NaCl; Ayr Saline; Breathe Free; Broncho Saline; Dristan Saline Spray; Entsol; HuMist Nasal Mist; Marlin Salt System†; Muro 128; Muroptic; Nasal Moist; NaSal; Normaline; Ocean; Pretz; Rhinaris; Salinex; SeaMist; Sochlor; Your Choice†; *Venez.*: Larmabak; Nafavine.

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

Homoeopathic Preparations. *Austral.*: Allergy Relief; Childrens Runny Nose Relief; Respatona Head Cold; Vitatona Energy†; *Austria*: Globuli gegen Hautausschlage; *Canad.*: Adrisin†; Calms Forte 4 Kids; Cold Sores & Fever Blisters; Combinaison†; Diamite; Eczema; Hives; Homeoknop Bioactiv O Weight Loss Aid†; Homeoknop Ikoplex 13†; Hylands Bioplasma; Hylands Vaginitis†; Hylavir FB†; Ikoplex 11 Digestion Aid†; Ikoplex 14†; Melange†; Nuage Bioplasma†; Sore Throat L39†; Sorinoheel; *Chile*: Anacardio con Fosforo; Bioactiv M; Bioactiv O; Bioactiv P; Ikoplex No 11; Ikoplex No 13; Ikoplex No 14; Ikoplex No 17; Ikoplex No 19; Ikoplex No 6; Ikoplex No 7; Ikoplex No 8; *Fr.*: Billerol; Pulsatilla Complexe No 60†; Soludor; *Ger.*: Derivatio H; Drufusan N†; Drufusan; Herpes-Gastreu R68; Hewelymphon N†; Muco-cyl L Ho-Len-Complex; Nuxal comp; Schleimhaut-Komplex L Ho-Fu-Complex; *Neth.*: Ailgeno spag; Hemorrolite; Urtizon complex; *Rus.*: Diet-Comfort (Диет-Комфорт); *Switz.*: Regenaplex Nr 28b.

Pharmacopoeial Preparations

BP 2014: Compound Glucose, Sodium Chloride and Sodium Citrate Oral Solution; Compound Sodium Chloride Mouthwash; Compound Sodium Lactate Infusion; Oral Rehydration Salts; Potassium Chloride and Sodium Chloride Infusion; Potassium Chloride, Sodium Chloride and Glucose Infusion; Sodium Chloride and Glucose Infusion; Sodium Chloride Eye Drops; Sodium Chloride Eye Lotion; Sodium Chloride Eye Ointment; Sodium Chloride Infusion; Sodium Chloride Irrigation Solution; Sodium Chloride Nebuliser Solution; Sodium Chloride Oral Solution; Sodium Chloride Solution; Soluble Sodium Chloride Tablets;

USP 36: Bacteriostatic Sodium Chloride Injection; Cimetidine in Sodium Chloride Injection; Cisplatin for Injection; Dextran 40 in Sodium Chloride Injection; Dextran 70 in Sodium Chloride Injection; Dextrose and Sodium Chloride Injection; Fructose and Sodium Chloride Injection; Half-strength Lactated Ringer's and Dextrose Injection; Inulin in Sodium Chloride Injection; Lactated Ringer's and Dextrose Injection; Lactated Ringer's Injection; Mannitol in Sodium Chloride Injection; Multiple Electrolytes and Dextrose Injection Type 1; Multiple Electrolytes and Dextrose Injection Type 2; Multiple Electrolytes and Dextrose Injection Type 3; Multiple Electrolytes and Dextrose Injection Type 4; Multiple Electrolytes and Invert Sugar Injection Type 1; Multiple Electrolytes and Invert Sugar Injection Type 2; Multiple Electrolytes and Invert Sugar Injection Type 3; Multiple Electrolytes Injection Type 1; Multiple Electrolytes Injection Type 2; Oral Rehydration Salts; PEG 3350 and Electrolytes for Oral Solution; Potassium Chloride in Dextrose and Sodium Chloride Injection; Potassium Chloride in Lactated Ringer's and Dextrose Injection; Potassium Chloride in Sodium Chloride Injection; Ringer's and Dextrose Injection; Sodium Chloride and Dextrose Tablets; Sodium Chloride Inhalation Solution; Sodium Chloride Injection; Sodium Chloride Irrigation; Sodium Chloride Ophthalmic Ointment; Sodium Chloride Ophthalmic Solution; Sodium Chloride Tablets for Solution; Sodium Chloride Tablets.

Gases

This chapter includes monographs on gases with medical or pharmaceutical uses and applications (such as oxygen, carbon dioxide, helium, and nitrogen) and some whose main medical interest is management of their toxicity or adverse effects (such as carbon monoxide or hydrogen sulfide). Also included are some compressed and liquefied gases used as refrigerants and aerosol propellants. Nitric oxide gas is used in bronchopulmonary disorders and is discussed in Cardiovascular Drugs (p. 1457.1). Other gases with medical uses can be found in Disinfectants and Preservatives (p. 1730.1) and General Anaesthetics (p. 1896.1).

Refrigerants and Aerosol Propellants

Some gases have properties that make them suitable for use as refrigerants and as aerosol propellants; these include nitrogen, nitrous oxide, carbon dioxide, and hydrocarbons such as propane, and the butanes. Chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs) have been widely used but are generally being phased out due to their environmental effects, particularly depletion of the ozone layer. Nonchlorinated fluorocarbons (hydrofluorocarbons; HFCs) do not affect the ozone layer (although they may contribute to global warming) and are a possible alternative; however, their physical properties may be less suitable. Ammonia gas (see p. 2441.2) may be used as an industrial refrigerant.

The evaporation of propellants such as halogenated hydrocarbons and dimethyl ether produces an intense cold. Topical application has a numbing effect on tissues and has been used for analgesia (see Rubefacients and Topical Analgesia, p. 6.3), although cold injury, including frostbite, has been reported.

Refrigerants and aerosol propellants have been subject to deliberate abuse. They have similar effects to volatile solvents (see Abuse, under Adverse Effects of Toluene, p. 2216.3), and both acute and chronic toxicity may occur. Inhalation of high concentrations of halogenated hydrocarbons for their euphoriant effect may result in CNS depression, cardiac arrhythmias, respiratory depression, and death, while propane and butane can act as simple asphyxiants. Toxicity may also result from decomposition products, such as hydrogen chloride and phosgene from heating halogenated hydrocarbons.

Toxicity. The toxicity resulting from abuse by deliberate inhalation of propellants has been reviewed.[1-4] Further references relevant to the toxicity of individual agents are given in the monographs.

1. Kurtzman TL, *et al.* Inhalant abuse by adolescents. *J Adolesc Health* 2001; 28: 170–80.
2. Brouette T, Anton R. Clinical review of inhalants. *Am J Addict* 2001; 10: 79–94.
3. Anderson CE, Loomis GA. Recognition and prevention of inhalant abuse. *Am Fam Physician* 2003; 68: 869–74.
4. Williams JF, Storck M. American Academy of Pediatrics Committee on Substance Abuse. Inhalant abuse. *Pediatrics* 2007; 119: 1009–17.

Argon

Argón; Argonum; E938; Аргон.
CAS — 7440-37-1.
UNII — 67XQY1V3KH.

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

Ph. Eur. 8: (Argon). A colourless gas. Soluble 1 in about 29 of water by volume at 20 degrees and at a pressure of 101 kPa. Store as a compressed gas or liquid in appropriate containers.

Profile

Argon is an inert gas and is used to replace air in containers containing oxidisable substances.

Bromochlorodifluoromethane

Bromoclorodifluorometano; Halon 1211; R-12B1; Бромхлордифторметан.
$CBrClF_2$=165.4
CAS — 353-59-3.
UNII — 915X8AJX5.

Profile

Bromochlorodifluoromethane is a halogenated hydrocarbon that has been used as a fire-extinguishing agent. Like chlorofluorocarbons it causes ozone depletion and other environmental effects and its use is generally being phased out.

Toxicity has been reported after the misuse or abuse of fire extinguishers containing bromochlorodifluoromethane,[1-3] and in persons exposed in other ways.[4,5]

1. Steadman C, *et al.* Abuse of fire-extinguishing agent and sudden death in adolescents. *Med J Aust* 1984; 141: 115–17.
2. Lerman Y, *et al.* Fatal accidental inhalation of bromochlorodifluoromethane (Halon 1211). *Hum Exp Toxicol* 1991; 10: 125–8.
3. Gerhardt RT. Acute Halon (bromochlorodifluoromethane) toxicity by accidental and recreational inhalation. *Am J Emerg Med* 1996; 14: 675–7.
4. Matrat M, *et al.* Reactive airways dysfunction syndrome caused by bromochlorodifluoromethane from fire extinguishers. *Occup Environ Med* 2004; 61: 712–14.
5. Lo SH, *et al.* Grand rounds: outbreak of hematologic abnormalities in a community of people exposed to leakage of fire extinguisher gas. *Environ Health Perspect* 2006; 114: 1713–17.

Butane

n-Butané; Butano; E943a; Бутан.
C_4H_{10}=58.12
CAS — 106-97-8.
UNII — 6LV4FOR43R.

Pharmacopoeias. In *USNF.*

USNF 31: (Butane). A colourless gas. It is highly flammable and explosive. Store in airtight cylinders at a temperature not exceeding 40 degrees.

Profile

Butane is used as an aerosol propellant (above). It is widely used as a fuel.

Abuse. Toxicity has been reported with the abuse of butane.[1-10]

1. Gunn J, *et al.* Butane sniffing causing ventricular fibrillation. *Lancet* 1989; i: 617.
2. Siegel E, Wason S. Sudden death caused by inhalation of butane and propane. *N Engl J Med* 1990; 323: 1638.
3. Roberts MJD, *et al.* Asystole following butane gas inhalation. *Br J Hosp Med* 1990; 44: 294.
4. Williams DR, Cole SJ. Ventricular fibrillation following butane gas inhalation. *Resuscitation* 1998; 37: 43–5.
5. Rieder-Scharinger J, *et al.* Multiorganversagen nach Butangasinhalation: ein Fallbericht. *Wien Klin Wochenschr* 2000; 112: 1049–52.
6. Wehner F, *et al.* Tödliche Inhalation von Butan-Propan-Gas. *Arch Kriminol* 2002; 209: 164–8.
7. El-Menyar AA, *et al.* A teenager with angiographically normal epicardial coronary arteries and acute myocardial infarction after butane inhalation. *Eur J Emerg Med* 2005; 12: 137–41.
8. Harris D, Mirza Z. Butane encephalopathy. *Emerg Med J* 2005; 22: 676–7.
9. Doogue M, Barclay M. Death due to butane abuse—the clinical pharmacology of inhalants. *N Z Med J* 2005; 118: U1732.
10. Girard F, *et al.* Fibrillation ventriculaire par inhalation de spray déodorant. *Ann Fr Anesth Reanim* 2008; 27: 83–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Frionex.

Carbon Dioxide

Anglies dioksidas; Anhídrido carbónico; Carbone, dioxyde de; Carbonei Dioxidum; Carbonei Dioxydum; Carbonic Acid Gas; Carbonique; Hiilidioksidi; Kohlendioxid; Koldioxid; Oxid uhličitý; Szén-dioxid; Węgla dwutlenek; Диоксид Углерода; Двуокись Углерода; Углекислый Газ.
CO_2=44.01
CAS — 124-38-9.
ATC — V03AN02.
ATC Vet — QV03AN02.
UNII — 142M471B3J.

NOTE. Carbon dioxide is about 1½ times as heavy as air.

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

Ph. Eur. 8: (Carbon Dioxide). A colourless gas. Soluble 1 in about 1 of water by volume at 20 degrees and at a pressure of 101 kpA. Store liquefied under pressure in suitable containers.

The BP 2014 directs that carbon dioxide should be kept in approved metal cylinders which are painted grey and carry a label stating 'Carbon Dioxide'. In addition, 'Carbon Dioxide' or the symbol 'CO_2' should be stencilled in paint on the shoulder of the cylinder.

USP 36: (Carbon Dioxide). A colourless, odourless gas. Its solutions are acid to litmus. One volume dissolves in about 1 volume of water. Store in cylinders.

Uses and Administration

Carbon dioxide is a product of respiration and blood concentrations are normally kept within strict physiological limits. Manipulation of carbon dioxide concentrations has been used therapeutically (see below) but hypocapnia is not always desirable and carbon dioxide has been added to the oxygen in pump oxygenators to prevent hypocapnia developing.

Carbon dioxide acts as a respiratory stimulant, but is rarely used therapeutically for this purpose. However, inhalation of low concentrations has been tried in the management of neonatal apnoea (p. 1204.3).

Carbon dioxide may be used as the insufflating gas for laparoscopy, and to flood the surgical field to prevent formation of gas emboli during cardiac surgery. It may also be used as a contrast agent in radiography (p. 1580.1).

Solid carbon dioxide, or 'dry ice' has a temperature of -80 degrees and has been used to treat warts (p. 1689.3) and naevi by cryotherapy.

Pharmaceutically, carbon dioxide is used as an aerosol propellant and as a replacement for air to preserve oxidisable substances. Carbonated vehicles are useful for masking the unpleasant taste of some medicinal preparations.

Manipulation of carbon dioxide concentrations in the blood may be achieved by ventilatory techniques and has been used therapeutically. Examples include the use of hyperventilation in the management of raised intracranial pressure (p. 1271.3) and breath-holding or rebreathing for intractable hiccup (p. 1046.3).

Adverse Effects

Carbon dioxide has direct toxic effects and also acts as an asphyxiant. Above a concentration of about 6%, it causes headache, dizziness, confusion, palpitations, hypertension, dyspnoea, increased depth and rate of respiration, and CNS depression. Concentrations of about 20% and higher produce convulsions and loss of consciousness; inhalation of 50% carbon dioxide is reported to produce central effects similar to anaesthetics. The inhalation of high concentrations may produce respiratory acidosis.

Abrupt withdrawal of carbon dioxide after prolonged inhalation may produce malaise, pallor, headache, and nausea or vomiting.

Skin contact with solid carbon dioxide may cause frostbite.

References.

1. Halpern P, *et al.* Exposure to extremely high concentrations of carbon dioxide: a clinical description of a mass casualty incident. *Ann Emerg Med* 2004; 43: 196–9.
2. Langford NJ. Carbon dioxide poisoning. *Toxicol Rev* 2005; 24: 229–35.
3. Srisont S, *et al.* A carbon dioxide fatality from dry ice. *J Forensic Sci* 2009; 54: 961–2.
4. Leikin JB, *et al.* Carbon dioxide-induced narcosis due to dry ice exposure in a patient with sleep apnea. *Ann Intern Med* 2009; 150: 361–2.
5. Dunford JV, *et al.* Asphyxiation due to dry ice in a walk-in freezer. *J Emerg Med* 2009; 36: 353–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Carbogen.

Carbon Monoxide *(USAN)*

Anglies monoksidas; Carbone, monoxyde de; Carbonei Monoxidum; Hiilimonoksidi; Karbon Monoksit; Kolmonoxid; Monóxido de carbono; Węgla tlenek; Монооксид Углерода; Окись Углерода; Угарный Газ.
CO=28.01
CAS — 630-08-0.
UNII — 7U1EE4V452.

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

Ph. Eur. 8: (Carbon Monoxide). A colourless, flammable gas obtained by steam reforming (catalytic oxidation) of hydrocarbons. Soluble 2.266 in 100 of water by volume at 20 degrees and at a pressure of 101 kPa. Store as a compressed gas in appropriate containers.

Uses

Carbon monoxide has been used in low concentrations as a tracer gas in measurements of lung function. It is also reported to have anti-inflammatory properties and is under investigation for various medical uses, including the management of delayed graft function. It appears to have a physiological role as a signalling molecule. Carbon

monoxide labelled with carbon-11 may be used to assess the blood volume.

General references.

1. Foresti R, *et al.* Use of carbon monoxide as a therapeutic agent: promises and challenges. *Intensive Care Med* 2008; 34: 649–58.
2. Bauer I, Pannen BH. Bench-to-bedside review: carbon monoxide—from mitochondrial poisoning to therapeutic use. *Crit Care* 2009; 13: 220.
3. Ghosh S, *et al.* Carbon monoxide: endogenous mediator, potential diagnostic and therapeutic target. *Ann Med* 2010; 42: 1–12.

Adverse Effects

Carbon monoxide is produced by incomplete combustion of organic materials and is highly toxic when inhaled; infants, small children, and elderly people are particularly susceptible. Although the number of cases of poisoning in countries such as the UK has fallen as the availability of coal gas has declined and as changes have been made to motor vehicles to improve their exhaust fumes, carbon monoxide is still a major cause of poisoning. Common sources of carbon monoxide include poorly maintained and ventilated heating systems and improperly burnt fuel in domestic fires.

When inhaled, carbon monoxide combines with haemoglobin in the blood to form carboxyhaemoglobin; this complex is unable to transport oxygen, and cellular hypoxia therefore results. Most of the symptoms of poisoning are due to anoxia, but carbon monoxide also has a direct toxic effect on cells, which may contribute. The skin and tissues may turn a classic cherry red in patients poisoned with carbon monoxide although this is seen most often after death.

The symptoms of carbon monoxide poisoning are varied and depend on the degree and duration of exposure, although there is wide variation between individuals. Unconsciousness may occur suddenly but is commonly preceded by headache, dizziness, weakness, nausea, and vomiting, which may be misdiagnosed as a viral illness or food poisoning. Other symptoms may include skin lesions, excessive sweating, pyrexia, increased respiration, mental dullness and confusion, visual disturbances, convulsions, hypotension, tachycardia or other cardiac arrhythmias, myocardial ischaemia, and possibly myocardial infarction. Death may result from respiratory failure, pulmonary oedema, cardiovascular failure, or cerebral damage. Carboxyhaemoglobin concentrations are a guide to the severity of poisoning, although they are not a reliable measure of toxicity; the lethal concentration of carboxyhaemoglobin in the blood is about 50% or more. Concentrations over 1000 ppm of carbon monoxide in inspired air may be fatal in 1 hour. Neurological and psychiatric sequelae may develop some weeks later in the survivors of severe poisoning and therefore a prolonged follow-up of such patients is advised; symptoms include memory impairment, apathy, mutism, irritability, personality change, gait disturbance, and urinary and faecal incontinence. Chronic carbon monoxide exposure may present as a non-specific illness with headache, nausea, and flu-like symptoms.

General references.

1. WHO. Carbon Monoxide. *Environmental Health Criteria 213*. Geneva: WHO, 1999. Available at: http://www.inchem.org/documents/ehc/ehc/ehc213.htm (accessed 05/07/04)
2. Satran D, *et al.* Cardiovascular manifestations of moderate to severe carbon monoxide poisoning. *J Am Coll Cardiol* 2005; 45: 1513–16.
3. Kao LW, Nañagas KA. Toxicity associated with carbon monoxide. *Clin Lab Med* 2006; 26: 99–125.
4. Cevik AA, *et al.* Interrelation between the Poisoning Severity Score, carboxyhaemoglobin levels and in-hospital clinical course of carbon monoxide poisoning. *Int J Clin Pract* 2006; 60: 1558–64.
5. Prockop LD, Chichkova RI. Carbon monoxide intoxication: an updated review. *J Neurol Sci* 2007; 262: 122–30.
6. Grieb G, *et al.* The diversity of carbon monoxide intoxication: medical courses can differ extremely—a case report. *Inhal Toxicol* 2008; 20: 911–5.
7. Weaver LK. Carbon monoxide poisoning. *N Engl J Med* 2009; 360: 1217–25.

Treatment of Adverse Effects

The patient should be removed from the contaminated atmosphere and an effective airway established. Oxygen (100%) should be given until the blood carboxyhaemoglobin concentration has fallen below dangerous levels (usually 5%). Management is then usually symptomatic and supportive with attention being given to the possible need to treat or correct any cardiovascular disorders, metabolic acidosis, or cerebral oedema. Hyperbaric oxygen therapy may be considered in pregnant patients or in severe poisoning (if the patient is, or has been, unconscious, or if there are neurological symptoms or cardiac complications) but is of unproven benefit (see below) and its use is controversial.

Hyperbaric oxygen therapy. The use of hyperbaric oxygen therapy in the management of carbon monoxide poisoning is controversial.[1-3] The rationale for using hyperbaric oxygen is that it increases the rate at which carboxyhaemoglobin dissociates, shortening the half-life from about 2 hours with normobaric 100% oxygen to about 30 minutes with hyperbaric oxygen. Theoretically, this should be of benefit, and retrospective studies have shown improved symptoms in patients given hyperbaric oxygen, particularly in terms of neurological outcomes.[6] However, controlled studies have had conflicting results, and systematic reviews[1-4] have found insufficient evidence to determine the value of hyperbaric oxygen. Although hyperbaric oxygen has been widely recommended, particularly in severe poisoning, availability is limited and it remains unclear which patients should be considered for therapy. There is some evidence that older patients, and those with loss of consciousness, prolonged exposures, or high carboxyhaemoglobin concentrations gain most benefit,[7] but this is not established. It is also unclear whether use in pregnancy should be recommended, since few studies have included pregnant patients. Case reports suggest that hyperbaric oxygen is safe in pregnancy,[8] and there is a theoretical basis for therapy since fetal carboxyhaemoglobin concentrations are higher than maternal concentrations, but evidence is limited and successful outcomes without the use of hyperbaric oxygen have also been reported.[9]

1. Juurlink DN, *et al.* Hyperbaric oxygen for carbon monoxide poisoning. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 20/06/08).
2. Buckley NA, *et al.* Hyperbaric oxygen for carbon monoxide poisoning: a systematic review and critical analysis of the evidence. *Toxicol Rev* 2005; 24: 75–92.
3. Domachevsky L, *et al.* Hyperbaric oxygen in the treatment of carbon monoxide poisoning. *Clin Toxicol* 2005; 43: 181–8.
4. Silver S, *et al.* Should hyperbaric oxygen be used for carbon monoxide poisoning? *CJEM* 2006; 8: 43–6.
5. Wolf SJ, *et al.* American College of Emergency Physicians. Clinical policy: critical issues in the management of adult patients presenting to the emergency department with acute carbon monoxide poisoning. *Ann Emerg Med* 2008; 51: 138–52.
6. Hawkins M, *et al.* Severe carbon monoxide poisoning: outcome after hyperbaric oxygen therapy. *Br J Anaesth* 2000; 84: 584–6.
7. Weaver LK, *et al.* Carbon monoxide poisoning: risk factors for cognitive sequelae and the role of hyperbaric oxygen. *Am J Respir Crit Care Med* 2007; 176: 491–7.
8. Van Hoesen KB, *et al.* Should hyperbaric oxygen be used to treat the pregnant patient for acute carbon monoxide poisoning: a case report and literature review. *JAMA* 1989; 261: 1039–43. Correction. *Ibid.* 1990; 263: 2750.
9. Bar B, *et al.* Pre-labor exposure to carbon monoxide: should the neonate be treated with hyperbaric oxygenation? *Clin Toxicol* 2007; 45: 579–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Lung Diffusion Test Mix No Ne Co; Lung Diffusion Test Mixture Gas.

Chlorofluorocarbons

CFCs; Clorofluorocarbonos; Хлорофтороуглеводороды; Хлорфторуглероды.

Cryofluorane (*rINN*)

CFC-114; Criofluorano; Cryofluoranum; Dichlorotetrafluoroethane; Propellant 114; Refrigerant 114; Tetrafluorodichloroethane; Криофлуоран.

1,2-Dichloro-1,1,2,2-tetrafluoroethane.

$C_2Cl_2F_4$=170.9

CAS — 76-14-2.

UNII — 6BSWT93AR.

Pharmacopoeias. In *USNF.*

USNF 31: (Dichlorotetrafluoroethane). A clear, colourless gas having a faint ethereal odour. Store in airtight cylinders at a temperature not exceeding 40 degrees.

Dichlorodifluoromethane

CFC-12; Diclorodifluorometano; Difluorodichloromethane; Propellant 12; Refrigerant 12; Дифтордихлорметан; Дихлордифторметан.

CCl_2F_2=120.9

CAS — 75-71-8.

UNII — OFM06SG1KO.

Pharmacopoeias. In *USNF.*

USNF 31: (Dichlorodifluoromethane). A clear, colourless gas having a faint ethereal odour. Store in airtight cylinders at a temperature not exceeding 40 degrees.

Trichlorofluoromethane

CFC-11; Fluorotrichloromethane; Fluorotriclorometano; Propellant 11; Refrigerant 11; Trichloromonofluoromethane; Triclorofluorometano; Tricloromonofluorometano; Фтортрихлорметан.

CCl_3F=137.4

CAS — 75-69-4.

UNII — 990TYB331R.

NOTE. Trichlorofluoromethane is a gas above 24 degrees.

Pharmacopoeias. In *USNF.*

USNF 31: (Trichloromonofluoromethane). A clear, colourless gas having a faint ethereal odour. Store in airtight cylinders at a temperature not exceeding 40 degrees.

Profile

Chlorofluorocarbons are halogenated hydrocarbons that contain only chlorine, fluorine, and carbon. They have been widely used as refrigerants and as aerosol propellants (p. 1797.1), but have been phased out in most countries due to their effects on atmospheric ozone. Medicinally, they have been used in metered dose inhalers and in cold sprays for topical anaesthesia, but alternatives are now preferred.

References.

1. WHO. Fully halogenated chlorofluorocarbons. *Environmental Health Criteria 113*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc113.htm (accessed 08/06/09)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Algispray; *Austral.*: Derm-Freeze†; *USA*: Aerofreeze†; Fluro-Ethyl†.

Dimethyl Ether

Dimethyl Oxide; Éter dimetílico; Methoxymethane; Oxybismethane; Простой Диметиловый Эфир; Диметилэфир.

C_2H_6O=46.07

CAS — 115-10-6.

UNII — AM13FS69BX.

Profile

Dimethyl ether is used as a refrigerant, aerosol propellant (p. 1797.1), and topical anaesthetic. It has also been used as a fuel.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: ActiFreeze.

Multi-ingredient Preparations. *Ger.*: Wartner; *Irl.*: Wartner; *Israel*: Wartner†; *NZ*: Wartner; *Singapore*: Wartner; *Switz.*: Wartner; *UK*: Histofreezer; PR Freeze Spray; Ralgex Freeze Spray†; Wartner; *USA*: Compound W Freeze Off.

Helium

E939; Helio; Hélium; Гелий.

He=4.002602

CAS — 7440-59-7.

ATC — V03AN03.

ATC Vet — QV03AN03.

UNII — 206GF3GB41.

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

Ph. Eur. 8: (Helium). A colourless, inert gas. Store as a compressed gas or liquid at cryogenic temperatures, in appropriate containers.

USP 36: (Helium). A colourless, odourless, tasteless gas which is not combustible and does not support combustion. Very slightly soluble in water. Store in cylinders.

Profile

As helium is less dense than nitrogen, breathing a mixture of 80% helium and 20% oxygen requires less effort than breathing air. Thus mixtures containing various concentrations of oxygen ('Heliox') have been used in patients with respiratory disorders. Mixtures of helium and oxygen have also been used as an alternative to compressed air by divers or others working under high pressure, to prevent the development of nitrogen narcosis. Helium has been used in pulmonary function testing.

Breathing helium increases vocal pitch and causes voice distortion. Cerebral artery gas embolism has been reported after inhalation of helium from a pressurised container.

Although individual studies may have shown benefit, systematic reviews of the use of helium and oxygen mixtures (heliox) in various respiratory disorders have generally failed to find convincing evidence of value.

References to the use of helium or heliox.

1. Rodrigo GJ, *et al.* Heliox for treatment of exacerbations of chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 22/02/10).
2. Rodrigo GJ, *et al.* Heliox for nonintubated acute asthma patients. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 22/02/10).
3. Colebourn CL, *et al.* Use of helium-oxygen mixture in adult patients presenting with exacerbations of asthma and chronic obstructive pulmonary disease: a systematic review. *Anaesthesia* 2007; 62: 34–42.
4. Harris PD, Barnes R. The uses of helium and xenon in current clinical practice. *Anaesthesia* 2008; 63: 284–93.
5. McGarvey JM, Pollack CV. Heliox in airway management. *Emerg Med Clin North Am* 2008; 26: 905–20.

6. Migliori C, *et al.* The effects of helium/oxygen mixture (heliox) before and after extubation in long-term mechanically ventilated very low birth weight infants. *Pediatrics* 2009; 123: 1524–8.
7. Vorwerk C, Coats T. Heliox for croup in children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2010 (accessed 22/02/10).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Heliox; Lung Diffusion Test Mixture Gas.

Hydrochlorofluorocarbons

HCFCs; Hidroclorofluorocarbonos; Гидрохлорфторуглероды.

Chlorodifluoroethane

Clorodifluoroetano; Propellant 142b; Refrigerant 142b; Дифтормонохлорэтан.
1-Chloro-1,1-difluoroethane.
$C_2H_3ClF_2$=100.5
CAS — 75-68-3.

Chlorodifluoromethane

Clorodifluorometano; Propellant 22; Refrigerant 22; Дифтормонохлорметан; Хлордифторметан.
$CHClF_2$=86.47
CAS — 75-45-6.

Profile

Hydrochlorofluorocarbons are hydrogenated chlorofluorocarbons. They have been used similarly to chlorofluorocarbons as refrigerants and as aerosol propellants (p. 1797.1) but share the same environmental effects and have been or are being phased out in most countries.

References to toxicity.

1. Dekant W. Toxicology of chlorofluorocarbon replacements. *Environ Health Perspect* 1996; 104 (suppl 1): 75–83.
2. Kubota T, Miyata A. Acute inhalational exposure to chlorodifluoromethane (freon-22): a report of 43 cases. *Clin Toxicol* 2005; 43: 305–8.
3. Koreeda A, *et al.* An accidental death due to Freon 22 (monochlorodifluoromethane) inhalation in a fishing vessel. *Forensic Sci Int* 2007; 168: 208–11.
4. Lee J, *et al.* Uncontrolled occupational exposure to 1,1-dichloro-1-fluoroethane (HCFC-141b) is associated with acute pulmonary toxicity. *Chest* 2009; 135: 149–55.

Hydrofluorocarbons

HFAs; HFCs; Hidrofluoroalcanos; Hidrofluorocarbonos; Hydrofluoralkanes; Гидрофторуглероды.

Apaflurane *(BAN, rINN)*

Apaflurano; Apafluranum; Heptafluoropropane; HFA-227; HFC-227; Апафлуран.
1,1,1,2,3,3,3-Heptafluoropropane.
C_3HF_7=170.0
CAS — 431-89-0.
UNII — R40P36GDK6.

Difluoroethane

Difluoroetano; Ethylene Fluoride; Fluoruro de etileno; HFC-152a; Propelente 152a; Propellant 152a; Refrigerant 152a; Refrigerante 152a; Дифторэтан.
1,1-Difluoroethane.
$C_2H_4F_2$=66.05
CAS — 75-37-6.
UNII — 0B1U8K2ME0.

Norflurane *(BAN, USAN, rINN)*

Fluorocarbon 134a; Fluorocarbono 134a; GR-106642X; HFA-134a; HFC-134a; Norflurano; Norfluranum; Propellant 134a; Refrigerant 134a; Норфлуран.
1,1,1,2-Tetrafluoroethane.
$C_2H_2F_4$=102.0
CAS — 811-97-2.
UNII — DH9E53K1Y8.

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

Ph. Eur. 8: (Norflurane). A clear, colourless gas, liquid under pressure. At 20 degrees and at a pressure of 101 kPa, slightly soluble in water; freely soluble in alcohol. Relative density about 1.23, for the gas in the liquid phase. B.p. about -26 degrees. It is a hygroscopic, non-flammable gas.

Pentafluoropropane

HFC-245fa; R-245fa; Пентафторпропан.
1,1,1,3,3-Pentafluoropropane.
$C_3H_3F_5$=134.0
CAS — 460-73-1.
UNII — TA9UOF49CY.

Profile

Hydrofluorocarbons are halogenated hydrocarbons that contain only hydrogen, fluorine, and carbon. They do not affect atmospheric ozone and have been used as replacements for chlorofluorocarbons and hydrochlorofluorocarbons as refrigerants and as aerosol propellants (p. 1797.1). Apaflurane and norflurane are also used in metered dose inhalers. Norflurane and pentafluoropropane have been used as topical anaesthetics.

References to abuse and toxicity.

1. Dekant W. Toxicology of chlorofluorocarbon replacements. *Environ Health Perspect* 1996; 104 (suppl 1): 75–83.
2. Kuspis DA, Krenzelok EP. Oral frostbite injury from intentional abuse of a fluorinated hydrocarbon. *J Toxicol Clin Toxicol* 1999; 37: 873–5.
3. Sasaki C, *et al.* A fatality due to inhalation of 1,1-difluoroethane (HFC-152a) with a peculiar device. *Forensic Toxicol* 2009; 27: 45–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Wartner Kids†.

Multi-ingredient Preparations. *USA*: Gebauers Spray & Stretch.

Hydrogen Sulfide

Ácido sulfhídrico; Hydrogen Sulphide; Siarkowodór; Sulfuro de hidrógeno; Sulphuretted Hydrogen; Сульфид Водорода; Сероводород.
H_2S=34.08
CAS — 7783-06-4.
UNII — YY9FVM7NSN.

Description. Hydrogen sulfide is a colourless flammable gas with a characteristic odour.

Uses

Hydrogen sulfide is used in industrial processes as a source of sulfur and in the manufacture of other chemicals, although it is mainly encountered as a byproduct. It appears to have a physiological role as a signalling molecule and has been investigated for therapeutic use.

Adverse Effects

Hydrogen sulfide is a common industrial hazard and is encountered in such places as chemical works, mines, sewage works, and stores of decomposing protein. Concentrations of 0.1 to 0.2% in the atmosphere may be fatal in a few minutes. At concentrations of about 0.005% and above hydrogen sulfide causes anosmia and its unpleasant odour is no longer detectable. Pulmonary irritation, oedema, and respiratory failure usually occur after acute poisoning; prolonged exposure to low concentrations may cause severe conjunctivitis with photophobia and corneal opacity, irritation of the respiratory tract, cough, nausea, vomiting and diarrhoea, pharyngitis, headache, dizziness, and lassitude. There are some similarities to poisoning with cyanides.

General references.

1. WHO. Hydrogen Sulfide. *Environmental Health Criteria 19*. Geneva: WHO, 1981. Available at: http://www.inchem.org/documents/ehc/ehc/ehc019.htm (accessed 05/07/04)

Treatment of Adverse Effects

In poisoning with hydrogen sulfide the patient should be removed from the contaminated atmosphere and an effective airway established. Inhalation of amyl nitrite or parenteral therapy with sodium nitrite have been suggested for severe poisoning; this produces methaemoglobin, which may bind sulfide. Oxygen should be given; hyperbaric oxygen therapy has also been suggested. The conjunctival sacs should be carefully washed out if eye irritation is severe. Management is then usually symptomatic and supportive.

Isobutane

E943b; Isobutano; 2-Methylpropane; 2-Metilpropano; Изобутан.
C_4H_{10}=58.12
CAS — 75-28-5.
UNII — BXR49TP611.

Pharmacopoeias. In *USNF.*

USNF 31: (Isobutane). A colourless gas. It is highly flammable and explosive. Store in airtight cylinders at a temperature not exceeding 40 degrees.

Profile

Isobutane is used as an aerosol propellant (p. 1797.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: Histofreezer; *USA*: Compound W Freeze Off.

Nitrogen

Azot; Azotas; Azote; Dusík; E941; Kvävgas; Nitrogén; Nitrogenium; Nitrógeno; Nitrogenum; Stickstoff; Typpi; Азот.
N_2=28.014
CAS — 7727-37-9.
ATC — V03AN04.
ATC Vet — QV03AN04.
UNII — N762921K75.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Nitrogen). The monograph applies to nitrogen for medicinal use. A colourless, odourless gas. Soluble 1 in about 62 of water and 1 in about 10 of alcohol by volume at 20 degrees and at a pressure of 101 kpA. Store as a compressed gas or a liquid in appropriate containers.

The BP 2014 directs that nitrogen should be kept in approved metal cylinders, the shoulders of which are painted black and the remainder grey. The cylinder should carry a label stating 'Nitrogen'.

Ph. Eur. 8: (Nitrogen, Low-oxygen). The monograph applies to nitrogen used in the production of an inert atmosphere for finished medicinal products that are particularly sensitive to degradation by oxygen. A colourless, odourless gas. Soluble 1 in about 62 of water and 1 in about 10 of alcohol by volume at 20 degrees and at a pressure of 101 kpA. Store as a compressed gas or a liquid in appropriate containers.

USNF 31: (Nitrogen). A colourless, odourless, tasteless gas. It is non-flammable and does not support combustion. Soluble 1 in about 65 of water v/v and 1 in about 9 of alcohol v/v at 20 degrees and at a pressure of 760 mmHg. Store in cylinders.

USNF 31: (Nitrogen 97 Percent). It contains not less than 97% v/v of nitrogen. Store in cylinders or in a low-pressure collecting tank.

Uses and Administration

Nitrogen is used as a diluent for pure oxygen or other active gases and as an inert gas to replace air in containers holding oxidisable substances. It is also used as an aerosol propellant. Liquid nitrogen is used as a cryotherapeutic agent for the removal of warts (p. 1689.3) and for preservation of tissues and organisms.

Adverse Effects

Nitrogen narcosis has been reported after use of nitrogen mixtures (such as air) at high pressure, for example in deep-water diving. Under high pressure, nitrogen dissolves in blood and lipid. If decompression is too rapid, nitrogen effervesces from body stores producing gas emboli and leads to the syndrome of decompression sickness. High inhaled concentrations of nitrogen are asphyxiant. Skin contact with liquid nitrogen causes frostbite or burns.

References.

1. Roblin P, *et al.* Liquid nitrogen injury: a case report. *Burns* 1997; 23: 638–40.
2. Kernbach-Wighton G, *et al.* Clinical and morphological aspects of death due to liquid nitrogen. *Int J Legal Med* 1998; 111: 191–5.
3. Koplewitz BZ, *et al.* Gastric perforation attributable to liquid nitrogen ingestion. *Pediatrics* 2000; 105: 121–3.
4. Kim DH, Lee HJ. Evaporated liquid nitrogen-induced asphyxia: a case report. *J Korean Med Sci* 2008; 23: 163–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Airapy; *Neth.*: Airapy.

Multi-ingredient Preparations. *Canad.*: Lung Diffusion Test Mix No Ne Co; Lung Diffusion Test Mixture Gas; *Denm.*: Airapy; *Fin.*: Airapy.

Oxygen

Deguonis; E948; Happi; Kyslík; Ossigeno; Oxigén; Oxigeno; Oxygène; Oxygenium; Oxygenum; Sauerstoff; Tlen; Кислород.
O_2=31.998.

CAS — 7782-44-7.
ATC — V03AN01.
ATC Vet — QV03AN01.
UNII — S88TT14065.

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

Ph. Eur. 8: (Oxygen). A colourless gas. Soluble 1 in about 32 of water by volume at 20 degrees and at a pressure of 101 kPa. Store as a compressed gas or liquid in appropriate containers. Oils and grease are not to be used unless oxygen-compatible.

The BP 2014 directs that oxygen should be kept in approved metal cylinders, the shoulders of which are painted white and the remainder black. The cylinder should carry a label stating 'Oxygen'. In addition, 'Oxygen' or the symbol 'O_2' should be stencilled in paint on the shoulder of the cylinder.

Ph. Eur. 8: (Oxygen (93 per cent)). It contains 90.0% v/v to 96.0% v/v of O_2, the remainder mainly consisting of argon and nitrogen. A colourless gas. It is normally used on the site where it is produced. It is fed directly into a medicinal gas pipeline or administration system. Where authorised, it may be stored in suitable containers. Oils and grease are not to be used unless oxygen-compatible.

Ph. Eur. 8: (Air, Medicinal; Aer Medicinalis; Medical Air BP 2014). It is compressed ambient air containing not less than 20.4% and not more than 21.4% of oxygen. A colourless, odourless gas. Soluble 1 in about 50 of water by volume at 20 degrees and at a pressure of 101 kPa. Store as a gas in suitable containers.

Ph. Eur. 8: (Air, Synthetic Medicinal; Aer Medicinalis Artificiosus; Synthetic Air BP 2014). It is a mixture of nitrogen and oxygen containing between 21.0% and 22.5% of oxygen. A colourless, odourless gas. Soluble 1 in about 50 of water by volume at 20 degrees and at a pressure of 101 kPa. Store as a compressed gas in suitable containers.

USP 36: (Oxygen). A colourless, odourless, tasteless gas that supports combustion more energetically than does air. Soluble 1 in about 32 of water v/v and 1 in about 7 of alcohol v/v at 20 degrees and at a pressure of 760 mmHg. Store in cylinders or in a pressurised storage tank.

USP 36: (Medical Air). A natural or synthetic mixture of gases consisting largely of nitrogen and oxygen. It contains not less than 19.5% and not more than 23.5% of oxygen. Store in cylinders or in a low pressure collecting tank.

USP 36: (Oxygen 93 Percent). It contains not less than 90% v/v and not more than 96% v/v of oxygen, the remainder consisting mostly of argon and nitrogen. Store in cylinders or in a low-pressure collecting tank.

Uses and Administration

Oxygen comprises about 21% of ambient air (at sea level) and is essential for human life. Supplementary inhaled oxygen may be necessary to prevent or correct hypoxaemia and increase oxygen delivery to the tissues in situations where the ambient air is unable to meet the body's demands. It is used in respiratory failure (p. 1801.1), as an adjunct to specific treatment of the underlying cause and general measures such as correction of anaemia or repositioning of the patient. It is also used in situations where the oxygen content of the air breathed is inadequate, for example in the management of high-altitude disorders (p. 1276.2).

Oxygen is of value in the treatment of poisoning with several substances, including carbon monoxide (p. 1798.1), cyanides (see under Hydrocyanic Acid, p. 2156.2), and dichloromethane (p. 2181.2). It is also used in inhalation injury and in poisoning with asphyxiant gases. Workers in pressurised spaces and divers may breathe oxygen rather than air to reduce the risk of nitrogen narcosis, although mixtures of oxygen with an inert gas such as helium may be preferred to reduce the risk of oxygen toxicity. Oxygen is also used as a diluent of volatile and gaseous anaesthetics.

Supplementary oxygen is usually provided at a concentration of 100% as a compressed gas in metal cylinders, but is also available as liquid oxygen, supplied at low temperatures in insulated containers. Oxygen concentrators, which extract oxygen from the air, can provide concentrations of 95 to 98% and are useful for domiciliary therapy, especially in patients using large quantities of oxygen. Oxygen is used in varying concentrations, and this is controlled by the flow rate and delivery system. In general, the exact concentration inhaled is not critical, and most delivery systems work by adjusting the flow rate to provide an approximate dose. Nasal cannulae deliver concentrations of 24 to 40% at flow rates of 1 to 4 litres/minute and are widely used, particularly for domiciliary therapy. Standard face masks deliver concentrations of 40 to 60% at flow rates of 5 to 10 litres/minute, while reservoir masks allow flow rates of 10 to 15 litres/minute and oxygen concentrations of 60 to 90%. Where more precise dosage is required Venturi masks may be used; these provide a set oxygen concentration independent of the flow rate and are available for a range of concentrations between 24 and 60%. If very high doses are required, endotracheal tubes or oxygen tents can be used to deliver concentrations of up to 100%.

The concentration of inspired oxygen used has generally been determined by the condition being treated, but for acute therapy it is now considered preferable to adjust the concentration in line with the patient's oxygen saturation. For most patients, the **target oxygen saturation**, measured by pulse oximetry, should be 94 to 98%. However, for patients with hypercapnia or at risk of hypercapnia, a lower target range of 88 to 92% is recommended (see Chronic Lung Disorders under Precautions, p. 1802.1). Suggested initial concentrations and delivery systems are as follows:

- critically ill patients, including those with carbon monoxide poisoning: **high** concentration oxygen (reservoir mask at flow rate of 15 litres/minute)
- patients with acute hypoxaemia due to conditions such as acute asthma, pneumonia, pulmonary embolism, and postoperatively: **moderate** concentration therapy
  - oxygen saturation below 85%: reservoir mask at flow rate of 10 to 15 litres/minute
  - oxygen saturation 85% or higher: nasal cannulae or simple face mask at flow rate of 2 to 10 litres/minute
- patients with chronic obstructive pulmonary disease or otherwise at risk of hypercapnia: low concentration (controlled) oxygen therapy
  - if oxygen saturation unknown: 28% at 4 litres/minute, or 24% at 2 to 4 litres/minute if there is a history of hypercapnia (via Venturi mask)
  - oxygen saturation below 88%: nasal cannulae at 2 to 6 litres/minute or simple face mask at 5 litres/minute

Hyperbaric oxygen therapy, in which oxygen is given at pressures greater than 1 atmosphere, has an established role in the management of decompression sickness and gas emboli. It may also be used in carbon monoxide poisoning, severe anaerobic infection, and several other conditions, although this is more controversial; for further discussion, see below.

General references.

1. Bateman NT, Leach RM. ABC of oxygen: acute oxygen therapy. *BMJ* 1998; 317: 798–801.
2. Rees PJ, Dudley F. ABC of oxygen: oxygen therapy in chronic lung disease. *BMJ* 1998; 317: 871–4.
3. Rees PJ, Dudley F. ABC of oxygen: provision of oxygen at home. *BMJ* 1998; 317: 935–8.
4. Treacher DF, Leach RM. ABC of oxygen: oxygen transport: basic principles. *BMJ* 1998; 317: 1302–6.
5. Leach RM, Treacher DF. ABC of oxygen: oxygen transport: tissue hypoxia. *BMJ* 1998; 317: 1370–3.
6. Kallstrom TJ. American Association for Respiratory Care (AARC). AARC clinical practice guideline: oxygen therapy for adults in the acute care facility—2002 revision & update. *Respir Care* 2002; 47: 717–20. Also available at: http://www.rcjournal.com/cpgs/pdf/06.02.717.pdf (accessed 26/02/10)
7. American Association for Respiratory Care (AARC). AARC clinical practice guideline: oxygen therapy in the home or alternate site health care facility—2007 revision & update. *Respir Care* 2007; 52: 1063–8. Also available at: http://www.rcjournal.com/cpgs/pdf/08.07.1063.pdf (accessed 26/02/10)
8. O'Driscoll BR, *et al.* British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. *Thorax* 2008; 63 (suppl 6): vi1–vi68. Correction. *ibid.* 2009; 64: 91. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Emergency%20Oxygen/Emergency%20oxygen%20guideline/THX-63-Suppl_6.pdf (accessed 03/06/09)
9. Balfour-Lynn IM, *et al.* British Thoracic Society. BTS guidelines for home oxygen in children. *Thorax* 2009; 64 (suppl 2): ii1–ii26. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Home%20Oxygen/Home%20Oxygen%20Guideline/HomeOxygen-in-children-full-guideline.pdf (accessed 26/02/10)

Cluster headache. Randomised studies[1,2] and case series[3] have suggested that inhalation of 100% oxygen can provide rapid and effective treatment of cluster headache attacks (p. 670.1), although the evidence is limited.[4] Treatment with 100% oxygen should therefore be considered in all patients,[5] although practical issues may limit its use.

1. Fogan L. Treatment of cluster headache: a double-blind comparison of oxygen v air inhalation. *Arch Neurol* 1985; 42: 362–3.
2. Cohen AS, *et al.* High-flow oxygen for treatment of cluster headache: a randomized trial. *JAMA* 2009; 302: 2451–7.
3. Rozen TD. High oxygen flow rates for cluster headache. *Neurology* 2004; 63: 593.
4. Bennett MH, *et al.* Normobaric and hyperbaric oxygen therapy for migraine and cluster headache. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 21/08/08).
5. Scottish Intercollegiate Guidelines Network. Diagnosis and management of headache in adults (issued November 2008). Available at: http://www.sign.ac.uk/pdf/sign107.pdf (accessed 26/01/09)

Hyperbaric oxygen therapy. Hyperbaric oxygen therapy[1-3] involves the inhalation of 100% oxygen at a pressure of greater than 1 atmosphere and is given by enclosing the patient in a special high-pressure chamber. The optimum pressure and duration of treatment depend on the indication, but pressures of 2.5 to 3 atmospheres for periods from 45 minutes to 2 hours are commonly used. A single session may be adequate for some indications, but treatment is usually repeated once or twice daily and up to 40 sessions may be required. Hyperbaric oxygen therapy is generally safe, but adverse effects may occur (see p. 1801.3); intermittent replacement of oxygen with air as the inspired gas may reduce the risk of oxygen toxicity.[2]

Hyperbaric oxygen therapy appears to act by 2 main mechanisms. The increased pressure has a physical effect, reducing the size of gas bubbles within the circulation, which is of benefit in decompression sickness and gas embolism. In addition, the amount of oxygen dissolved in the blood increases under pressure, increasing tissue oxygen supply. This hyperoxia has various physiological and biochemical effects, including stimulation of wound healing and tissue repair and improved resistance to infection.

Therapy with hyperbaric oxygen has been tried in many disorders, but for most there have been few controlled studies and evidence of benefit is therefore limited. However, there are several accepted indications, and research continues in many other disorders.

The role of hyperbaric oxygen therapy as a safe and effective primary therapy for *decompression sickness* and *air or gas embolism* is well established. Reduction in bubble size is the main action, although the increase in oxygenation may also be beneficial. Pressures are generally similar to those used for other indications (initially about 2.8 atmospheres), although up to 6 atmospheres may be required. The pressure may then be gradually reduced at a safe rate.

Hyperbaric oxygen therapy has been widely recommended for *carbon monoxide poisoning* but its precise role remains unclear (see p. 1798.1); it may be considered in selected patients. Its mechanism of action is not fully understood; it increases the rate at which carboxyhaemoglobin concentrations decline, increases intracellular delivery of oxygen, and may also reduce lipid peroxidation and thus spare neuronal cell membranes.

In the management of *wounds and infections*, hyperbaric oxygen has various applications.[4] It is used as adjunctive therapy in *clostridial infections (gas gangrene)* (p. 182.2). Early treatment appears to reduce systemic toxic reactions (probably by inhibiting the production of alpha toxin by the anaerobic bacteria, *Clostridium*) thus enabling patients to tolerate surgery more readily; additionally there is a clearer demarcation of viable and nonviable tissue. *Necrotising fasciitis* (p. 193.1) is another infection in which hyperbaric oxygen therapy may be useful, although evidence is limited. Other infections in which hyperbaric oxygen therapy may be used include osteomyelitis, and intracranial abscesses.

There is some evidence that hyperbaric oxygen may be useful in non-infected wounds where hypoxia contributes to poor healing.[5,6] In *problem wounds*, including venous ulcers, therapy may increase the tissue oxygen tension and stimulate angioneogenesis but it is emphasised that it is adjunctive therapy and not a replacement for meticulous local care. Hyperbaric oxygen therapy might also reduce the risk of major amputation in patients with chronic *diabetic foot ulcer*.[7,8] Improved healing of leg ulcers has been reported[9] with use of hyperbaric oxygen therapy in patients with livedoid vasculopathy. Other wounds in which therapy may be beneficial include thermal burns and compromised skin grafts and flaps. The management of burns and wounds is described on p. 1683.1 and p. 1690.1, respectively. Hyperbaric oxygen may also be of benefit in patients with acute trauma and *crush injuries*;[10] it reduces oedema by causing vasoconstriction and may reverse ischaemia by increasing oxygen delivery.

In patients with malignancy, hyperbaric oxygen may have a role in the treatment of *radiation-induced tissue damage*;[11] radiation therapy can damage normal adjacent tissue resulting in tissue hypoxia and eventual cell death but hyperbaric oxygen therapy appears to aid in salvaging such tissue by stimulating angioneogenesis in marginally viable tissue. There is some evidence of benefit in osteoradionecrosis, soft-tissue damage, and radiation-induced haemorrhagic cystitis (p. 2347.3), although a randomised study[12] failed to confirm this in patients with jaw osteoradionecrosis. Hyperbaric oxygen has also been tried as an adjunct to standard treatment for malignant neoplasms but does not yet have an established role.[13]

Evidence to support the use of hyperbaric oxygen in *neurological disorders* is limited. Benefits have been reported in children with *cerebral palsy*, but this has not been established, and there is some evidence that it is no better than pressurised air.[14] Improvement has been reported in neonates with hypoxic-ischaemic encephalopathy,[15] but again further research is needed. A study of hyperbaric 24% oxygen in children with autism has also suggested benefits.[16]

Hyperbaric oxygen may also have a limited role in the management of severe anaemia (p. 1121.2) due to massive blood loss, since it enables sufficient oxygen to be dissolved in the blood to meet tissue demands, independent of haemoglobin. However, practical issues mean that other treatments are generally preferred.

1. Tibbles PM, Edelsberg JS. Hyperbaric-oxygen therapy. *N Engl J Med* 1996; 334: 1642–8.

2. Leach RM, *et al.* ABC of oxygen: hyperbaric oxygen therapy. *BMJ* 1998; 317: 1140–3.
3. Gill AL, Bell CNA. Hyperbaric oxygen: its uses, mechanisms of action and outcomes. *Q J Med* 2004; 97: 385–95.
4. Kaide CG, Khandelwal S. Hyperbaric oxygen: applications in infectious disease. *Emerg Med Clin North Am* 2008; 26: 571–95.
5. Thackham JA, *et al.* The use of hyperbaric oxygen therapy to treat chronic wounds: a review. *Wound Repair Regen* 2008; 16: 321–30.
6. Kulikovsky M, *et al.* Hyperbaric oxygen therapy for non-healing wounds. *Isr Med Assoc J* 2009; 11: 480–5.
7. Wang C, *et al.* Hyperbaric oxygen for treating wounds: a systematic review of the literature. *Arch Surg* 2003; 138: 272–9.
8. Roeckl-Wiedmann I, *et al.* Systematic review of hyperbaric oxygen in the management of chronic wounds. *Br J Surg* 2005; 92: 24–32.
9. Juan W-H, *et al.* Livedoid vasculopathy: long-term follow-up results following hyperbaric oxygen therapy. *Br J Dermatol* 2006; 154: 251–5.
10. Garcia-Covarrubias L, *et al.* Adjuvant hyperbaric oxygen therapy in the management of crush injury and traumatic ischemia: an evidence-based approach. *Am Surg* 2005; 71: 144–51.
11. Pasquier D, *et al.* Hyperbaric oxygen therapy in the treatment of radio-induced lesions in normal tissues: a literature review. *Radiother Oncol* 2004; 72: 1–13.
12. Annane D, *et al.* Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized, placebo-controlled, double-blind trial from the ORN96 study group. *J Clin Oncol* 2004; 22: 4893–4900.
13. Daruwalla J, Christophi C. Hyperbaric oxygen therapy for malignancy: a review. *World J Surg* 2006; 30: 2112–31.
14. McDonagh MS, *et al.* Systematic review of hyperbaric oxygen therapy for cerebral palsy: the state of the evidence. *Dev Med Child Neurol* 2007; 49: 942–7.
15. Liu Z, *et al.* Clinical effectiveness of treatment with hyperbaric oxygen for neonatal hypoxic-ischaemic encephalopathy: systematic review of Chinese literature. *BMJ* 2006; 333: 374–6.
16. Rossignol DA, *et al.* Hyperbaric treatment for children with autism: a multicenter, randomized, double-blind, controlled trial. *BMC Pediatr* 2009; 9: 21.

Respiratory failure. Respiratory failure is a clinical condition in which the arterial plasma partial pressure of oxygen (P_aO_2) and of carbon dioxide (P_aCO_2) cannot be maintained within normal physiological limits. It may result from an abnormality in any part of the respiratory system, including airways, alveoli, CNS, respiratory muscles, and circulation, and may be associated with various underlying disorders; it may be acute or chronic. In type I respiratory failure P_aO_2 is low (hypoxaemia) but P_aCO_2 may be normal or low, whereas in type II respiratory failure $P_aO_2$is low but $P_aCO_2$is raised (hypercapnia). Type I respiratory failure is most common and can occur in most acute lung disorders; examples include pulmonary oedema, pneumonia, and pulmonary haemorrhage. Type II respiratory failure (also known as ventilatory failure) is associated with conditions such as drug overdosage, neuromuscular disorders, and chronic obstructive airways disease. Patients with asthma may develop either type of respiratory failure.

The signs and symptoms of respiratory failure are those of the underlying condition plus any associated hypoxaemia or hypercapnia. Dyspnoea (painful or difficult breathing) is common, and patients may also have tachypnoea, tachycardia and other arrhythmias, signs of cyanosis, and neurological symptoms such as confusion and somnolence.

Management of respiratory failure mainly involves giving oxygen to reverse hypoxaemia, and specific therapy for any underlying condition. Invasive or non-invasive ventilatory support may be required in severe cases. Respiratory stimulants have a limited role but may be considered in some situations.

In acute respiratory failure, oxygen is the mainstay of therapy.[1,2] The concentration given should be the minimum required to reverse hypoxaemia and, ideally, should be determined by blood gas measurements or pulse oximetry. Use of oxygen in patients who are not hypoxaemic is not generally recommended,[3] and there is no evidence that it is beneficial for dyspnoea associated with causes such as cancer or heart failure.[4]

In ***type I respiratory failure*** high initial oxygen concentrations are given using nasal cannulae or face masks and target oxygen saturations are 94 to 98%. Ventilatory support may be required if adequate saturations cannot be maintained using reservoir masks.

In ***type II respiratory failure*** initial oxygen concentrations depend on the risk of exacerbating hypercapnia and acidosis:

- In *acute severe asthma* (p. 1195.2), hypercapnia is not a barrier to oxygen therapy and oxygen should be given from a reservoir mask, at a flow rate of 10 to 15 litres/minute (if oxygen saturation is below 85%), or from nasal cannulae or a simple face mask at a flow rate of 2 to 10 litres/minute if oxygen saturation is 85% or higher.[3] (The *BNF* notes that if the P_aCO_2 remains high despite other treatment, intermittent positive-pressure ventilation needs to be considered urgently.)
- In exacerbations of chronic respiratory disorders such as *chronic obstructive pulmonary disease* (COPD, p. 1199.1), cystic fibrosis (p. 177.2), or neuromuscular disorders, high concentrations of oxygen may exacerbate hypercapnia (see Precautions, p. 1802.1), particularly if given for a long period. Controlled delivery of low concentrations (24 to 28%) is therefore recommended for initial therapy,[3,5] although this is based on consensus opinion rather than controlled studies.

Ventilatory support is required in patients with respiratory failure when hypoxaemia persists or if hypercapnia and acidosis worsen. This generally involves endotracheal intubation and invasive ventilation, but the use of non-invasive methods is increasing and may be preferred in many situations, particularly in exacerbations of chronic conditions.[6] Use of gas mixtures that are less dense than air, such as mixtures of helium and oxygen, has been tried in acute respiratory failure to reduce the work of breathing, but is not of established benefit.[7] In extreme cases of respiratory failure, such as acute respiratory distress syndrome, extracorporeal membrane oxygenation (ECMO) may be tried,[8] although evidence for benefit is limited.

Respiratory stimulants such as doxapram have been used in respiratory failure but their role is limited. In patients with exacerbations of chronic ventilatory failure, the central drive to respiratory muscles is already increased and stimulants have little effect, although they may be tried in patients who are unsuitable for mechanical ventilation or where this is unavailable. Respiratory stimulants may also be considered in the management of *postanaesthetic hypoventilation*. Specific antagonists such as naloxone and flumazenil may have a role if respiratory depression is due to drugs such as opioids or benzodiazepines, respectively, although care is needed since therapeutic effects may be reduced.

Severe respiratory failure in *neonates* may result from various disorders. Use of surfactant or inhaled nitric oxide may be of benefit in some cases but ECMO may be required.[9]

In **chronic respiratory failure**, management involves treating the underlying cause and dealing with acute exacerbations, but oxygen therapy may have a role in some patients with stable disease. Long-term oxygen therapy, given by nasal cannulae, may improve survival in patients with severe chronic obstructive pulmonary disease and persistent hypoxaemia, and should be given for at least 15 hours each day.[5,10] Patients may also use intermittent, 'short-burst' oxygen to improve symptoms associated with exercise, although benefit is not established.[5,10] There is also limited evidence to support the use of nocturnal oxygen in patients with nocturnal hypoxaemia.[5]

1. Chakrabarti B, Calverley PM. Management of acute ventilatory failure. *Postgrad Med J* 2006; 82: 438–45.
2. Goldring JJP, Wedzicha JA. Managing acute on chronic respiratory failure: a guide to non-invasive ventilation. *Br J Hosp Med* 2008; 69: 444–9.
3. O'Driscoll BR, *et al.* British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. *Thorax* 2008; 63 (suppl 6): vi1–vi68. Correction. *ibid.* 2009; 64: 91. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Emergency%20Oxygen/Emergency%20oxygen%20guideline/THX-63-Suppl_6.pdf (accessed 03/06/09)
4. Cranston JM, *et al.* Oxygen therapy for dyspnoea in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 01/03/10).
5. Abramson M, *et al.* The COPDX plan: Australian and New Zealand guidelines for the management of chronic obstructive pulmonary disease 2009. Available at: http://www.copdx.org.au/guidelines/documents/COPDX_V2_18.pdf (accessed 01/03/10)
6. Garpestad E, *et al.* Noninvasive ventilation for critical care. *Chest* 2007; 132: 711–20.
7. Colebourn CL, *et al.* Use of helium-oxygen mixture in adult patients presenting with exacerbations of asthma and chronic obstructive pulmonary disease: a systematic review. *Anaesthesia* 2007; 62: 34–42.
8. Schuerer DJ, *et al.* Extracorporeal membrane oxygenation: current clinical practice, coding, and reimbursement. *Chest* 2008; 134: 179–84.
9. Barrington KJ, Finer NN. Care of near term infants with respiratory failure. *BMJ* 1997; 315: 1215–18.
10. National Collaborating Centre for Chronic Conditions. Chronic obstructive pulmonary disease: national clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax* 2004; 59 (suppl 1): 1–232. Also available at: http://www.nice.org.uk/nicemedia/pdf/CG012_niceguideline.pdf (accessed 16/04/10)

Wounds. Hyperbaric oxygen therapy may have a role in the management of infected and problem wounds (see p. 1800.2). Supplemental normobaric oxygen has also been tried in the prevention of postoperative wound infections. Although the results of individual studies remain contradictory, a meta-analysis[1] concluded that oxygen, at 80%, provided a beneficial effect. However, a more recent multicentre study[2] found no reduced risk of infection after 80% rather than 30% oxygen, during, and for 2 hours after, surgery.

Oxygen has also been applied topically to wounds.[3]

1. Qadan M, *et al.* Perioperative supplemental oxygen therapy and surgical site infection: a meta-analysis of randomized controlled trials. *Arch Surg* 2009; 144: 359–66.
2. Meyhoff CS, *et al.* Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: the PROXI randomized clinical trial. *JAMA* 2009; 302: 1543–50.
3. Gordillo GM, Sen CK. Evidence-based recommendations for the use of topical oxygen therapy in the treatment of lower extremity wounds. *Int J Low Extrem Wounds* 2009; 8: 105–11.

Adverse Effects

Oxygen is essential for life but inhalation of high concentrations may have adverse effects, particularly with prolonged exposure at higher pressures. Both pulmonary and CNS effects may occur. Pulmonary toxicity usually results from prolonged or repeated exposure. Symptoms include cough, dyspnoea, and substernal discomfort, and there may also be a reduction in vital capacity; alveolar collapse (absorption atelectasis), pulmonary oedema, and pneumonitis have also been reported. CNS toxicity is usually only seen at pressures above 2 atmospheres absolute but generally precedes pulmonary toxicity; the risk is higher in wet conditions and with physical activity. Symptoms include nausea, mood changes, vertigo, twitching, convulsions, and loss of consciousness. Toxic effects on the eyes may also occur (see Hyperbaric Oxygen Therapy, and Retinopathy of Prematurity, below).

The mechanism of oxygen toxicity is not clear, but may involve an increase in oxygen free radicals. Hyperoxaemia may also have adverse physiological effects related to cerebral and coronary vasoconstriction. It is also increasingly recognised that high inhaled concentrations of oxygen may be detrimental in patients with chronic lung disorders due to the effects of oxygen on ventilation (see Precautions, p. 1802.1).

Hyperbaric oxygen therapy. CNS toxicity is an important and unpredictable adverse effect with inhalation of oxygen at pressures higher than atmospheric, both during hyperbaric oxygen therapy and when used by divers.[1] Hyperbaric oxygen is also associated with pulmonary toxicity, particularly after repeated treatments. Complications related to the increased pressure also occur.[2-5] Barotrauma affecting the middle ear and sinuses is relatively common, and tympanic membrane rupture may result. Pulmonary barotrauma and pneumothorax have been reported, and dental barotrauma may rarely cause pain under a dental filling. Visual changes including myopia may occur, but are reversible once treatment is stopped; cataracts have been reported but there is no evidence that hyperbaric oxygen is the cause. Psychological adverse effects such as claustrophobia may also occur.

1. Bitterman N. CNS oxygen toxicity. *Undersea Hyperb Med* 2004; 31: 63–72.
2. Grim PS, *et al.* Hyperbaric oxygen therapy. *JAMA* 1990; 263: 2216–20.
3. Plafki C, *et al.* Complications and side effects of hyperbaric oxygen therapy. *Aviat Space Environ Med* 2000; 71: 119–24.
4. Gill AL, Bell CN. Hyperbaric oxygen: its uses, mechanisms of action and outcomes. *Q J Med* 2004; 97: 385–95.
5. Huang K-C, *et al.* Hyperbaric oxygen therapy in orthopedic conditions: an evaluation of safety. *J Trauma* 2006; 61: 913–17.

Retinopathy of prematurity. The role of oxygen in the development of retinopathy of prematurity has been controversial.[1,2] In the 1940s and 1950s an epidemic of retinopathy of prematurity, affecting perhaps 10 000 babies, was attributed to excessive use of oxygen in neonates. This resulted in the use of oxygen being reduced or curtailed and the incidence of the condition fell dramatically. However, other complications increased and use of oxygen was later liberalised, possibly contributing to a resurgence of cases in the 1970s, although other factors such as the improved survival of very preterm neonates were probably more important. It is now generally accepted that very low birth-weight and extreme prematurity are the major risk factors for retinopathy of prematurity, but that excessive oxygen use also has an important role.[3] Retinal development occurs late in gestation and depends to some extent on the relative hypoxia of the uterine environment. Supplementary oxygen inhibits production of vascular endothelial growth factor, thereby inhibiting retinal vascularisation. The lack of retinal blood vessels then leads to hypoxia, which stimulates excessive neovascularisation, leading to retinal fibrosis and detachment in severe cases. Generation of reactive oxygen species may also play a role.

The optimum approach to oxygen supplementation in infants and neonates remains unclear (see under Precautions, p. 1802.2). Studies[4,5] have suggested that policies in which oxygen use is adjusted for the individual neonate to maintain oxygen saturation (measured by pulse oximetry) within specific limits, avoiding both hyperoxia and hypoxia, can reduce the incidence of retinopathy, and one study[6] found that this had no deleterious effect on development at 18 months. The most appropriate oxygen saturation has not been determined, but may depend on the age of the infant: target saturations of 85 to 92% for gestational age less than 34 weeks and 92 to 97% for gestational age 34 weeks and above have been suggested.[7] For infants who develop signs of retinopathy, higher saturations may also be appropriate; a study[8] of supplemental oxygen for treating pre-threshold retinopathy suggested that therapy was safe, but a beneficial effect could not be confirmed.

1. Saugstad OD. Oxygen and retinopathy of prematurity. *J Perinatol* 2006; 26 (suppl 1): S46–S50.
2. Harrell SN, Brandon DH. Retinopathy of prematurity: the disease process, classifications, screening, treatment, and outcomes. *Neonatal Netw* 2007; 26: 371–8.
3. Tin W, *et al.* Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001; 84: F106–F110.

4. Chow LC, *et al.* Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? *Pediatrics* 2003; 111: 339–45.
5. Wright KW, *et al.* A physiologic reduced oxygen protocol decreases the incidence of threshold retinopathy of prematurity. *Trans Am Ophthalmol Soc* 2006; 104: 78–84.
6. Deulofeut R, *et al.* Avoiding hyperoxia in infants ≤1250 g is associated with improved short- and long-term outcomes. *J Perinatol* 2006; 26: 700–705.
7. Sears JE, *et al.* A change in oxygen supplementation can decrease the incidence of retinopathy of prematurity. *Ophthalmology* 2009; 116: 513–18.
8. The STOP-ROP Multicenter Study Group. Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. *Pediatrics* 2000; 105: 295–310.

Precautions

Any fire or spark is highly dangerous in the presence of increased oxygen concentrations especially when oxygen is used under pressure.

Metal cylinders containing oxygen should be fitted with a reducing valve by which the rate of flow can be controlled. It is important that the reducing valve should be free from all traces of oil or grease (unless it is oxygen-compatible) as otherwise a violent explosion may occur. Combustible material soaked in liquid oxygen is potentially explosive and the low temperature of liquid oxygen may cause unsuitable equipment to become brittle and crack. Liquid oxygen should not be allowed to come into contact with the skin as it produces severe 'cold burns'.

Oxygen intended for aviation or mountain rescue must have a sufficiently low moisture content to avoid blocking of valves by ice at low temperatures.

Excessive oxygen may be detrimental in some patients with chronic lung disorders and in neonates, and high initial concentrations should generally be avoided until oxygen saturations are known (see below). Prophylactic oxygen is given in many acute situations but there is some evidence that it may be detrimental in non-hypoxic patients and routine use may not be advisable (see Myocardial Infarction and Pregnancy, below).

Oxygen should be avoided in the initial management of paraquat poisoning since it may increase pulmonary damage. Pulmonary toxicity associated with bleomycin toxicity may also be exacerbated by oxygen use.

Chronic lung disease. Breathless patients are frequently treated with 100% oxygen but, paradoxically, this may be detrimental in those with chronic lung disorders.[1-3] In chronic obstructive pulmonary disease and in patients with chest wall deformities or musculoskeletal disorders, high concentrations of inhaled oxygen may lead to carbon dioxide retention (hypercapnia) and acidosis, which may in turn lead to organ dysfunction. The mechanism by which this occurs is complex but probably involves a reduction in hypoxic drive and an increased mismatching of blood flow and gas flow to the lungs. A lower target oxygen saturation of 88 to 92% is recommended in such patients[3] and initial oxygen concentrations of 24 to 28% should be used until oxygen saturation is known.

1. New A. Oxygen: kill or cure? Prehospital hyperoxia in the COPD patient. *Emerg Med J* 2006; 23: 144–6.
2. Beasley R, *et al.* Is it time to change the approach to oxygen therapy in the breathless patient? *Thorax* 2007; 62: 840–1.
3. O'Driscoll BR, *et al.* British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. *Thorax* 2008; 63 (suppl 6): vi1–vi68. Correction. *Ibid.* 2009; 64: 91. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Emergency%20Oxygen/Emergency%20oxygen%20guideline/THX-63-Suppl_6.pdf (accessed 03/06/09)

Myocardial infarction. Oxygen is routinely recommended for patients with acute myocardial infarction (see p. 1257.1). However, a systematic review[1] found that studies were lacking, and the very limited evidence available indicated that the use of high-flow oxygen in myocardial infarction might increase infarct size and raise the risk of mortality, possibly due to a reduction in coronary blood flow. The authors concluded that there was insufficient evidence to support the practice, and that further study was urgently needed.

1. Wijesinghe M, *et al.* Routine use of oxygen in the treatment of myocardial infarction: systematic review. *Heart* 2009; 95: 198–202.

Neonates and infants. The use of supplemental oxygen in neonates and infants is controversial.[1-3] For the *resuscitation* of asphyxiated term neonates, use of 100% oxygen has been standard, but there is some evidence that the use of room air (21% oxygen) is equally effective and possibly safer. However, a systematic review[4] concluded that there was insufficient evidence for recommendations to be made. Guidelines[5,6] for neonatal resuscitation recommend the use of either air or blended oxygen to achieve target oxygen saturations,[5,6] although increasing to 100% oxygen might be suitable for those who remain bradycardic after 90 seconds of resuscitation at lower concentrations.[6] Pulse oximetry should be used to guide treatment, with care taken to avoid both hypoxia and hyperoxia.[5,6] A study[7] in preterm neonates found that room air (21% oxygen) was insufficient to maintain adequate oxygen saturations and the authors suggested that an initial oxygen concentration of 30 to 40% might be more appropriate.

For *respiratory support* in preterm neonates and infants, oxygen use should be closely monitored. Excessive use of supplementary oxygen has been associated with retinopathy of prematurity and chronic lung disease,[8] and there is some evidence for a link between neonatal oxygen supplementation and childhood cancer,[9] although this remains to be confirmed. However, untreated hypoxia may result in permanent brain injury or death,[3] and it has been suggested that oxygen supplementation improves sleep and respiratory patterns in healthy preterm infants.[10] Unrestricted use of inhaled oxygen is therefore not advised, and the concentration given should be adjusted individually based on arterial-oxygen saturation measured by pulse oximetry. The optimum saturation range is not entirely clear,[11] but target saturations of between 85 and 93 to 94% have been suggested[2,3] for preterm neonates.

1. Higgins RD, *et al.* Executive summary of the workshop on oxygen in neonatal therapies: controversies and opportunities for research. *Pediatrics* 2007; 119: 790–6.
2. Sola A, *et al.* Oxygen as a neonatal health hazard: call for détente in clinical practice. *Acta Paediatr* 2007; 96: 801–12.
3. Walsh BK, *et al.* Oxygen therapy in the neonatal care environment. *Respir Care* 2009; 54: 1193–202.
4. Tan A, *et al.* Air versus oxygen for resuscitation of infants at birth. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 07/06/06).
5. Resuscitation Council (UK). 2010 Resuscitation Guidelines: newborn life support. Available at: http://www.resus.org.uk/pages/nls.pdf (accessed 09/02/11)
6. The American Heart Association. Part 15: neonatal resuscitation: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010; 122 (suppl 3): S909–S919. Also available at: http://circ.ahajournals.org/cgi/reprint/122/18_suppl_3/S909.pdf (accessed 09/02/11)
7. Wang CL, *et al.* Resuscitation of preterm neonates by using room air or 100% oxygen. *Pediatrics* 2008; 121: 1083–9.
8. Askie LM, *et al.* Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 25/02/10).
9. Spector LG, *et al.* Childhood cancer following neonatal oxygen supplementation. *J Pediatr* 2005; 147: 27–31.
10. Simakajornboon N, *et al.* Effect of supplemental oxygen on sleep architecture and cardiorespiratory events in preterm infants. *Pediatrics* 2002; 110: 884–8.
11. Tin W, Gupta S. Optimum oxygen therapy in preterm babies. *Arch Dis Child Fetal Neonatal Ed* 2007; 92: F143–7.

Pregnancy. Oxygen has commonly been given to women during labour as a treatment for fetal distress; however, a systematic review[1] found little evidence to support its use. Furthermore, prophylactic oxygen given during labour may be harmful to the fetus,[2] and guidelines[3] therefore do not recommend this practice.

1. Pawole B, Hofmeyr GJ. Maternal oxygen administration for fetal distress. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 01/05/09).
2. Simpson KR. Intrauterine resuscitation during labor: should maternal oxygen administration be a first-line measure? *Semin Fetal Neonatal Med* 2008; 13: 362–7.
3. O'Driscoll BR, *et al.* British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. *Thorax* 2008; 63 (suppl 6): vi1–vi68. Correction. *Ibid.* 2009; 64: 91. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Emergency%20Oxygen/Emergency%20oxygen%20guideline/THX-63-Suppl_6.pdf (accessed 03/06/09)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Airapy; *Cz.*: Conoxia; *Denm.*: Conoxia; *Fin.*: Conoxia; *Ger.*: Conoxia; *Ital.*: Aria; *Neth.*: Airapy; Conoxia; Keol-C; Loxmed; Mediox; *Norw.*: Conoxia; *Spain*: Conoxia; Keol-S.

Multi-ingredient Preparations. *Belg.*: Kalinox; *Canad.*: Alnox; Carbogen; Entonox; Heliox; Liqui-Med; Lung Diffusion Test Mix No Ne Co; Lung Diffusion Test Mixture Gas; *Cz.*: Entonox; *Denm.*: Airapy; Kalinox; Livopan; Medimix; *Fin.*: Airapy; Livopan; *Fr.*: Antasol; Entonox; Kalinox; Oxynox; *Ger.*: Livopan; *Irl.*: Entonox; *Neth.*: Donopa; Relivopan; *Pol.*: Entonox; *S.Afr.*: Entonox; *Spain*: Entonox; Kalinox; *Swed.*: Livopan; Medimix; *Switz.*: Entonox; Kalinox; Medimix†; *UK*: Entonox; Equanox.

Propane

Dimethylmethane; E944; Propano; Propyl Hydride; Пропан.

C_3H_8=44.10

CAS — 74-98-6.

UNII — T75W9911L6.

Pharmacopoeias. In *USNF*.

USNF 31: (Propane). A colourless gas. It is highly flammable and explosive. Store in airtight cylinders at a temperature not exceeding 40 degrees.

Profile

Propane is used as a refrigerant and as an aerosol propellant (p. 1797.1). It is also widely used as a fuel.

Toxicity has been reported[1-8] with the abuse or misuse of propane.

1. James NK, Moss ALH. Cold injury from liquid propane. *BMJ* 1989; 299: 950–1.
2. Siegel E, Wason S. Sudden death caused by inhalation of butane and propane. *N Engl J Med* 1990; 323: 1638.
3. Tsoukali H, *et al.* Death during deliberate propane inhalation. *Forensic Sci Int* 1998; 93: 1–4.
4. McLennan JJ, *et al.* Propane-associated autoerotic fatalities. *Am J Forensic Med Pathol* 1998; 19: 381–6.
5. Grosse K, Grosse J. Propanmissbrauch: extreme Dosissteigerung durch Toleranzentwicklung. *Nervenarzt* 2000; 71: 50–3.
6. Jackowski C, *et al.* Autoerotic accident by inhalation of propane-butane gas mixture. *Am J Forensic Med Pathol* 2005; 26: 355–9.
7. Stemberga V, *et al.* Propane-associated autoerotic asphyxiation: accident or suicide? *Coll Antropol* 2007; 31: 625–7.
8. Bonamonte D, *et al.* Cold burn from contact with a propane and butane gas blend inside a spray canister used as a booter. *Contact Dermatitis* 2008; 59: 61–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ger.*: Olbas; Wartner; *Irl.*: Wartner; *Israel*: Wartner†; *NZ*: Wartner; *Singapore*: Wartner; *Switz.*: Wartner; *UK*: Histofreezer; Wartner; *USA*: Compound W Freeze Off.

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This chapter describes the principal drugs used in the treatment of gastrointestinal disorders, and the choice of treatment for some of the main disorders.

Gastrointestinal Drug Groups

Antacids

Antacids are basic compounds that neutralise hydrochloric acid in the gastric secretions. They are used in the symptomatic management of gastrointestinal disorders associated with gastric hyperacidity such as dyspepsia (p. 1806.3), gastro-oesophageal reflux disease (p. 1807.2), and peptic ulcer disease (see p. 1813.2).

Antacids do not reduce the volume of hydrochloric acid secreted and elevation of the gastric pH may actually promote an increase in acid secretion. However, this is usually minor and short-lived except after large doses of calcium carbonate. Antacids are normally given between meals and at bedtime when symptoms of gastric hyperacidity usually occur; the presence of food in the stomach can prolong the neutralising activity. Some calculate doses as mEq or mmol of acid-neutralising capacity, but the relationship between neutralising capacity and beneficial effect is not straightforward. Other factors, including formulation (liquid preparations are more effective than solids) and duration of action (relatively insoluble antacids are longer acting) are also important.

Aluminium salts tend to produce constipation and to delay gastric emptying, while magnesium salts have the reverse effect; a combination of the two may reduce adverse gastrointestinal effects. Another advantage of combined antacid formulations is that a slow-acting antacid such as aluminium hydroxide may be combined with a more rapidly acting drug such as magnesium hydroxide to improve the onset and duration of effect. Alternatively, complexes containing both aluminium and magnesium may be used, such as almasilate, hydrotalcite, and magaldrate. Other drugs that may be combined with antacid formulations include simeticone, which acts as a defoaming agent to reduce excess gas in the stomach, and alginates, which form a gel or foam on the surface of the stomach contents thereby impeding reflux and protecting the oesophageal mucosa from acid attack.

Calcium carbonate and sodium bicarbonate are both rapidly acting but have disadvantages: calcium carbonate is usually reserved for short-term treatment because of the risks of rebound acid secretion and metabolic alkalosis, while sodium bicarbonate is absorbed and is contra-indicated in patients who must control sodium intake (e.g. in heart failure, hypertension, renal failure, cirrhosis, or pregnancy).

Antacids may interact with numerous other drugs, affecting the rate and extent of their absorption, and in some cases their renal elimination. Changes in gastric pH affect the dissolution of other drugs, and together with altered gastric emptying can markedly influence absorption. Aluminium compounds in particular are noted for their propensity to adsorb other drugs and to form insoluble complexes that are not absorbed. Antacids that alter urinary pH will affect renal clearance of drugs that are weak acids or bases. Several mechanisms may play a part in any particular interaction. Interactions can be minimised by giving antacids and other medication 2 to 3 hours apart.

Antacids in this chapter include aluminium salts, magnesium salts, and calcium carbonate. For sodium bicarbonate, see p. 1781.1.

Described in this chapter are

- Aceglutamide Aluminium, p. 1814.3
- Alexitol Sodium, p. 1815.1
- Almagate, p. 1815.3
- Almasilate, p. 1815.3
- Aloglutamol, p. 1816.2
- Aluminium Glycinate, p. 1817.2
- Aluminium Hydroxide, p. 1817.2
- Aluminium Hydroxide-Magnesium Carbonate Co-dried Gel, p. 1818.2
- Aluminium Phosphate, p. 1818.3
- Aluminium Sodium Silicate, p. 1818.3
- Basic Aluminium Carbonate, p. 1817.1
- Bismuth Compounds, p. 1821.3
- Calcium Carbonate, p. 1824.3
- Dihydroxyaluminum Sodium Carbonate, p. 1835.2
- Hydrotalcite, p. 1845.2
- Magaldrate, p. 1856.1
- Magnesium Carbonate, p. 1856.2
- Magnesium Hydroxide, p. 1857.2
- Magnesium Oxide, p. 1857.3
- Magnesium Trisilicate, p. 1858.1

Antidiarrhoeals

Antidiarrhoeals are used as adjuncts in the symptomatic treatment of diarrhoea (see p. 1805.2), although the main aim in the management of *acute* diarrhoea is the correction of fluid and electrolyte depletion with rehydration therapy; this is especially important in infants and young children and antidiarrhoeals are not generally recommended for this age group. Their use is also limited in *chronic* diarrhoea since treatment aimed at the underlying disorder will often alleviate the diarrhoea.

Described in this chapter are drugs that reduce intestinal motility such as the opioid analogues diphenoxylate and loperamide, and adsorbents such as attapulgite and kaolin. Bulking agents (which include bran and ispaghula) have also been used for diarrhoea and for adjusting faecal consistency in patients with colostomies.

Described in this chapter are

- Albumin Tannate, p. 1815.1
- Attapulgite, p. 1820.1
- Bismuth Compounds, p. 1821.3
- Bran, p. 1823.3
- Chalk, p. 1826.3
- Crofelemer, p. 1833.3
- Difenoxin, p. 1835.2
- Diphenoxylate, p. 1835.3
- Ispaghula, p. 1849.1
- Kaolin, p. 1850.1
- Lidamidine, p. 1853.1
- Loperamide, p. 1854.2
- Racecadotril, p. 1881.3
- Smectites, p. 1887.1
- Zaldaride, p. 1895.3

Antiemetics

Antiemetics are a diverse group of drugs used to treat or prevent nausea and vomiting, including that associated with cancer therapy, anaesthesia, and motion sickness (see p. 1811.3).

The choice of drug depends partly on the cause of nausea and vomiting. For example, hyoscine or an antihistamine are used in motion sickness whereas dopamine antagonists (such as metoclopramide and domperidone) and serotonin 5-HT_3-receptor antagonists (5-HT_3 antagonists), such as ondansetron, are ineffective. Conversely, nausea and vomiting associated with cancer chemotherapy is often hard to control and special regimens have been devised including the use of the 5-HT_3 antagonists, dexamethasone, and, more recently, the neurokinin-1 receptor antagonists aprepitant and casopitant.

Described in this chapter are

- Alizapride, p. 1815.2
- Aprepitant, p. 1819.2
- Azasetron, p. 1820.2
- Bromopride, p. 1824.2
- Casopitant, p. 1826.2
- Cerium Oxalate, p. 1826.2
- Clebopride, p. 1833.1
- Difenidol, p. 1835.1
- Dolasetron, p. 1837.2
- Domperidone, p. 1838.1
- Dronabinol, p. 1840.1
- Fosaprepitant, p. 1843.2
- Ginger, p. 1844.1
- Granisetron, p. 1844.3
- Hyoscine, p. 1845.3
- Indisetron, p. 1848.3
- Itopride, p. 1850.1
- Mecloxamine Citrate, p. 1859.1
- Metoclopramide, p. 1862.2
- Metopimazine, p. 1865.1
- Nabilone, p. 1865.2
- Ondansetron, p. 1872.1
- Palonosetron, p. 1875.1
- Ramosetron, p. 1881.3
- Tropisetron, p. 1894.1

Antisecretory drugs

Antisecretory drugs are used in the treatment and prophylaxis of peptic ulcer disease (p. 1813.2); some are also employed in other disorders associated with gastric hyperacidity such as gastro-oesophageal reflux disease (p. 1807.2) and dyspepsia (p. 1806.3). They may generally be divided into:

- *Histamine H_2-receptor antagonists* (H_2-antagonists), which act by blocking histamine H_2-receptors on gastric parietal cells, thereby antagonising the normal stimulatory effect of endogenous histamine on gastric acid production. Those described in this chapter include cimetidine, famotidine, nizatidine, and ranitidine.
- *Proton pump inhibitors*, which act by blocking the enzyme system responsible for active transport of protons into the gastrointestinal lumen, namely the hydrogen/potassium adenosine triphosphatase (H^+/K^+ ATPase) of the gastric parietal cell, also known as the 'proton pump'. Those described in this chapter include lansoprazole, omeprazole, pantoprazole, and rabeprazole.
- *Selective antimuscarinics*, which block cholinergic stimulation of gastric acid production with fewer adverse effects than less selective antimuscarinics (see Action of Antimuscarinics, p. 1310.3), but have largely been superseded. Pirenzepine is an example.
- *Prostaglandin analogues*, which inhibit gastric acid secretion by a direct action on the parietal cell and may also inhibit gastrin release and possess cytoprotective properties. Misoprostol (p. 2140.3) is an example.

Described in this chapter are

- Cimetidine, p. 1827.1
- Dexlansoprazole, p. 1834.2
- Eseridine Salicylate, p. 1840.3
- Esomeprazole, p. 1841.1
- Famotidine, p. 1842.1
- Ilaprazole, p. 1848.2
- Lafutidine, p. 1851.3
- Lansoprazole, p. 1851.3
- Nizatidine, p. 1866.1
- Omeprazole, p. 1867.2
- Pantoprazole, p. 1875.3
- Pirenzepine, p. 1878.2
- Proglumide, p. 1880.1
- Rabeprazole, p. 1881.1
- Ranitidine, p. 1882.1
- Ranitidine Bismuth Citrate, p. 1883.3
- Revaprazan, p. 1884.2
- Roxatidine, p. 1884.3
- Tenatoprazole, p. 1893.3
- Urogastrone, p. 1894.3

Antispasmodics

Antispasmodics are drugs used for their relaxant action on smooth muscle, either direct or through an antimuscarinic action on the parasympathetic innervation. They play a role in the management of gastrointestinal spasm (p. 1807.1) and irritable bowel syndrome (p. 1810.3) as well as other disorders associated with smooth muscle spasm. Those described in this chapter are mainly antimuscarinics; drugs in other chapters that may be used for relaxation of smooth muscle include calcium-channel blockers (p. 1244.2) and nitrates (p. 1245.2), as well as drugs with less well defined mechanisms of action such as papaverine (p. 2362.2).

Described in this chapter are

- Alverine Citrate, p. 1819.1
- Butropium Bromide, p. 1824.3
- Cidonium Bromide, p. 1827.1
- Cimetropium Bromide, p. 1831.3
- Clidinium Bromide, p. 1833.2
- Dicycloverine Hydrochloride, p. 1834.2
- Difemerine Hydrochloride, p. 1835.1
- Dihexyverine Hydrochloride, p. 1835.2
- Diisopromine Hydrochloride, p. 1835.3
- Drofenine Hydrochloride, p. 1839.3
- Hyoscine, p. 1845.3
- Hyoscine Butylbromide, p. 1845.3
- Hyoscine Hydrobromide, p. 1845.3
- Hyoscine Methobromide, p. 1846.1
- Hyoscine Methonitrate, p. 1846.1
- Hyoscyamine, p. 1848.1
- Hyoscyamine Hydrobromide, p. 1848.1
- Hyoscyamine Sulfate, p. 1848.1
- Isopropamide Iodide, p. 1848.3
- Mebeverine Hydrochloride, p. 1858.3
- Mepenzolate Bromide, p. 1859.1
- Methanthelinium Bromide, p. 1861.3
- Methylbenactyzium Bromide, p. 1861.3
- Octatropine Methylbromide, p. 1866.2
- Oxapium Iodide, p. 1874.3
- Oxyphencyclimine Hydrochloride, p. 1875.1
- Oxyphenonium Bromide, p. 1875.1
- Pargeverine Hydrochloride, p. 1877.1
- Peppermint Leaf, p. 1877.1
- Peppermint Oil, p. 1877.1
- Pipenzolate Bromide, p. 1878.1

Piperidolate Hydrochloride, p. 1878.1
Pipethanate Ethobromide, p. 1878.2
Platyphylline Acid Tartrate, p. 1878.3
Poldine Metilsulfate, p. 1879.1
Prifinium Bromide, p. 1879.3
Propantheline Bromide, p. 1880.1
Tiemonium, p. 1893.3
Timepidium Bromide, p. 1894.1
Tiquizium Bromide, p. 1894.1
Valethamate Bromide, p. 1895.2

Laxatives

Laxatives (purgatives or cathartics) promote defaecation and are used in the treatment of constipation (see below) and for bowel evacuation before investigational procedures, such as endoscopy or radiological examination, or before surgery.

Laxatives are frequently used for self-medication. Abuse of laxatives is a well-known phenomenon that may occasionally lead to toxicity.

Laxatives may be classified according to their mode of action. There is, however, a degree of overlap between the various groups and in some cases the precise mechanisms of action are not fully understood. Many traditionally used laxatives have fallen from use owing to the violence of their action or their adverse effect profile.

- *Bulk laxatives* (bulk-forming laxatives or bulking agents) cause retention of fluid and an increase in faecal mass resulting in stimulation of peristalsis. Owing to their hydrophilic nature, bulk laxatives may also be used to control diarrhoea and to regulate the consistency of effluent in colostomy patients. Those described in this chapter include bran, ispaghula, and sterculia.
- *Stimulant laxatives* (contact laxatives) act by directly stimulating nerve endings in the colonic mucosa, thereby increasing intestinal motility. It is this group of laxatives which is most commonly associated with abuse. Those described in this chapter include bisacodyl, cascara, phenolphthalein, senna, and sodium picosulfate.
- *Osmotic laxatives* act by increasing intestinal osmotic pressure thereby promoting retention of fluid within the bowel. Those described in this chapter include saline laxatives such as magnesium citrate, magnesium hydroxide, and sodium sulfate (for magnesium sulfate and sodium phosphate see p. 1787.3 and p. 1791.1 respectively). Lactulose may also be classified as an osmotic laxative because its breakdown products exert a similar effect. Also included in this group are the hyperosmotic laxatives such as glycerol (p. 2517.2) and sorbitol (p. 2092.1), and the macrogols (p. 2547.3).
- *Faecal softeners* (emollient laxatives) are claimed to act by decreasing surface tension and increasing penetration of intestinal fluid into the faecal mass. Those described in this chapter include docusate (which is also believed to have a stimulant action).

For the lubricant laxative liquid paraffin see p. 2191.2.

Described in this chapter are

Aloes, p. 1816.1
Aloin, p. 1816.2
Bisacodyl, p. 1821.1
Bisoxatin, p. 1823.2
Bran, p. 1823.3
Buckthorn, p. 1824.2
Casanthranol, p. 1826.1
Cascara, p. 1826.1
Cassia Pulp, p. 1826.2
Colocynth, p. 1833.3
Dantron, p. 1833.3
Docusates, p. 1836.2
Euonymus, p. 1842.1
Fig, p. 1843.2
Frangula, p. 1843.3
Ispaghula, p. 1849.1
Jalap, p. 1850.1
Lactitol, p. 1850.3
Lactulose, p. 1850.3
Liquorice, p. 1853.2
Magnesium Citrate, p. 1857.1
Magnesium Hydroxide, p. 1857.2
Magnesium Oxide, p. 1857.3
Manna, p. 1858.2
Pentaerythritol, p. 1877.1
Phenolphthalein, p. 1877.3
Polycarbophil, p. 1879.1
Potassium Acid Tartrate, p. 1879.2
Potassium Sodium Tartrate, p. 1879.3
Prune, p. 1881.1
Psyllium Seed, p. 1849.1
Rhubarb, p. 1884.2
Senna, p. 1885.1
Sodium Picosulfate, p. 1887.2
Sodium Sulfate, p. 1888.1
Sodium Tartrate, p. 1888.2
Sterculia, p. 1888.3
Tamarind, p. 1892.2

Mucosal protectants

Cytoprotective drugs (mucosal protectants) play a role in the management of peptic ulcer disease (p. 1813.2). They may be divided into:

- *Chelates or complexes*, which coat the gastric mucosa preferentially at sites of ulceration by forming an adherent complex with proteins. Those described in this chapter include sucralfate and tripotassium dicitratobismuthate (which also has an antibacterial role in regimens aimed at eradicating *Helicobacter pylori*)
- *Miscellaneous drugs* include liquorice and its derivatives, such as carbenoxolone, which may act by stimulating the synthesis of protective mucus

Described in this chapter are

Benexate, p. 1821.1
Carbenoxolone, p. 1825.3
Cetraxate, p. 1826.3
Dosmalfate, p. 1839.3
Ecabet, p. 1840.2
Enoxolone Aluminium, p. 1840.3
Gefarnate, p. 1844.1
Irsogladine, p. 1848.3
Liquorice, p. 1853.2
Plaunotol, p. 1879.1
Polaprezinc, p. 1879.1
Rebamipide, p. 1884.1
Sofalcone, p. 1888.2
Sucralfate, p. 1889.1
Sulglicotide, p. 1892.2
Teprenone, p. 1893.3
Tripotassium Dicitratobismuthate, p. 1822.2
Troxipide, p. 1894.3

Prokinetic drugs

Prokinetic drugs stimulate the motility of the gastrointestinal tract. Gastrointestinal smooth muscle exhibits intrinsic motor activity which is modified by autonomic innervation, local reflexes, and gastrointestinal hormones. This activity produces peristaltic waves, which move the gut contents from stomach to anus, and segmentations, which encourage digestion. Prokinetic drugs may act at various points within this complex system to enhance gastrointestinal movement. Those described in this chapter include metoclopramide, cisapride, and domperidone. Other drugs with prokinetic properties include parasympathomimetics such as bethanechol (p. 2456.2) or neostigmine (p. 687.1), and the macrolide antibacterial erythromycin (p. 291.2).

Described in this chapter are

Aclatonium Napadisilate, p. 1815.1
Acotiamide Hydrochloride, p. 1815.1
Bromopride, p. 1824.2
Cinitapride, p. 1831.3
Cisapride, p. 1831.3
Clebopride, p. 1833.1
Domperidone, p. 1838.1
Itopride, p. 1850.1
Linaclotide, p. 1853.1
Lubiprostone, p. 1856.1
Metoclopramide, p. 1862.2
Mosapride, p. 1865.2
Prucalopride, p. 1880.2
Renzapride, p. 1884.1
Tegaserod, p. 1893.1

Management of Gastrointestinal Disorders

The management of some gastrointestinal disorders is discussed below.

Aspiration syndromes

Regurgitation and aspiration of gastric contents (Mendelson's syndrome) is a potential cause of morbidity and mortality associated with anaesthesia, especially in obstetrics and in emergency surgery. Chemical pneumonitis and respiratory distress result from the acid aspiration, the risk of which is increased by the drugs given as adjuncts to anaesthesia such as opioid analgesics and atropine.

Apart from good anaesthetic technique, including a prohibition on oral intake before elective procedures, efforts to prevent or reduce the problem have focussed mainly on increasing the pH of gastric contents to above 2.5, and in reducing gastric volume. However, there is little evidence to show that reduced gastric acidity or volume is associated with decreased morbidity or mortality in patients who have aspirated gastric contents,[1] and some do not recommend the routine pre-operative use of pharmacological prophylaxis in patients undergoing elective surgery with no apparent increased risk for pulmonary aspiration.[1] Similarly there is little evidence to support the routine use of prophylactic drugs in women undergoing normal labour (particularly with the increased use of regional anaesthetic techniques).[2]

The *H_2-antagonists* decrease gastric acid secretion and may decrease gastric fluid volume. However, they do not affect the pH of fluid already in the stomach; they must therefore be given some time before anaesthesia, which limits their value in emergency procedures. Cimetidine is considered effective in most patients, although where more prolonged reduction of acidity is required H_2-antagonists with a longer duration of action such as ranitidine or famotidine may be preferred. Nizatidine has the advantage of a relatively rapid onset of action.[3] The *proton pump inhibitors* (PPIs) have also been tried, but results have been variable. A meta-analysis[4] suggested that ranitidine was more effective than a PPI in reducing the volume of gastric secretions and increasing their pH. Combination of a PPI with a prokinetic drug may produce better results.[3]

Because of the lack of effect of antisecretory drugs on the pH of existing gastric fluid H_2-antagonists may be combined with *antacids* to neutralise gastric acidity. Although magnesium trisilicate has been extensively used[6] without apparent problems particulate antacids are potentially toxic to the lung, which is why soluble antacids such as sodium citrate have been widely favoured. An effervescent formulation of sodium citrate with cimetidine has been reported to raise gastric pH above 2.5 in more than 98% of patients undergoing caesarean section.[7]

A third component of prophylactic regimens for acid aspiration may be use of a *prokinetic drug* such as metoclopramide. These increase gastric emptying and thereby decrease the volume of stomach contents, and also increase pressure at the lower oesophageal sphincter. The ability of metoclopramide to reverse the effects of opioids on gastric emptying appears to depend on the route: 10 mg given intravenously after opioid analgesia is reported to be effective in promoting gastric emptying, whereas the same dose intramuscularly is not.[8]

If aspiration occurs, pulmonary damage may result within seconds; treatment has included removal of any particulate matter, and measures to maintain the airway and ensure adequate oxygenation. Corticosteroids have been used but are no longer considered helpful.[9]

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Constipation

The pattern of normal defaecation is extremely variable, which makes constipation hard to define, and to some extent subjective. However, expert consensus considers that it occurs if 2 or more of the following features are present for at least 12 weeks in the previous year: less than 3 defaecations in a week, or hard or lumpy stool, straining, feeling of incomplete evacuation or anorectal blockage, or need for manual assistance, on at least a quarter of occasions.[1,2] New onset constipation, especially in patients over 50 years of age, or accompanying symptoms such as anaemia, abdominal pain, weight loss, or overt or occult blood in the stool should provoke urgent investigation because of the risk of malignancy or other serious bowel disorder.[3-5] Constipation can be a symptom of a range of disorders or of drug toxicity[2,3,6] and appropriate management of any underlying cause is required. It tends to be more common in the elderly, in women, and in late pregnancy.[1,2]

Certain subtypes of constipation have been identified: patients may be subdivided according to whether intestinal transit time is slow or normal, or whether there is pelvic floor dysfunction (dyssynergia; outlet obstruction; anismus).[2,3,5,7]

There is relatively little evidence to guide management. In general, stepped or graded management is favoured, beginning with advice on lifestyle (including exercise and adequate hydration), and dietary modification if appropriate.[2,4-6,8] An increase in fibre intake, preferably through a high-fibre diet, is useful in patients with normal transit times although it is less beneficial in slow-transit constipation.[5,7] In patients with pelvic floor dysfunction, biofeedback training may be instituted.[3,5,7]

Where lifestyle changes and dietary modification are insufficient, a laxative may be considered. Because of the lack of clear evidence to guide the choice of laxative, practice varies considerably. Many favour the use of either a bulk laxative or an osmotic laxative as a first choice option,[2-4,7] with stimulant laxatives tending to be reserved as a second-line option, and diphenylmethane derivatives being preferred to anthraquinones.[3,6] For the treatment of opioid-induced constipation unresponsive to usual laxative therapy opioid antagonists such as *methylnaltrexone* have been tried.

- *Bulk laxatives* include bran, ispaghula, methylcellulose and related compounds, psyllium, or sterculia. Bulk laxatives are of particular value in those with small hard stools. However, they have a delayed onset of action (up to 72 hours) and they may exacerbate symptoms of flatulence, bloating, and cramping;[6] use should be avoided where these are severe. A gradual increase in dose may help reduce such effects.[7] They may not be the first choice for elderly patients who are frail or immobile since the resulting soft faeces may result in faecal incontinence,[9] and should only be given where fluid intake is adequate, because of the risk of obstruction.[7]
- *Osmotic laxatives* include saline laxatives such as magnesium hydroxide and magnesium sulfate, poorly absorbed sugars such as lactulose or sorbitol, and macrogols (often formulated with electrolytes). Some favour the use of macrogol 3350 or 4000, for which there is reasonable evidence of benefit in chronic constipation,[5,6,10] However, in practice lactulose is widely used,[6] although it is less effective in the elderly than a combination of bulking and stimulant laxatives (see below). In the USA, a saline laxative such as magnesium hydroxide has been

recommended,[3,4,7] although saline laxatives may not be acceptable to some patients because they can cause watery stool and urgency.

- *Stimulant laxatives* in current use include diphenylmethane derivatives such as bisacodyl or sodium picosulfate, and anthraquinone-containing drugs such as senna. They have a more rapid onset of action than bulk laxatives or lactulose, and are usually given at night to help produce a bowel motion the following morning. Many traditional stimulant laxatives have fallen from use because of adverse effects, and it has been widely thought that their prolonged use or abuse may irreversibly damage colonic nerves and muscles; however, the evidence for this is poor, and appropriate stimulant laxatives used at licensed doses are unlikely to cause significant harm.[11,12] Tolerance can occur but seems to be uncommon in the majority of users.[11,12] Combined preparations are also available, and a combination of senna and fibre has been found to be more effective than the osmotic laxative lactulose in elderly patients with chronic constipation.[13]
- *Other laxatives* include the docusates, surfactants that are used as stool softeners,[7] but their efficacy used alone for constipation is not well established;[4] perhaps for this reason, they are often formulated with a stimulant or osmotic laxative. Stool softeners would have potential value for patients with haemorrhoids or anal fissures, or those in whom straining is potentially hazardous (such as the elderly or those with existing cardiovascular disease). Liquid paraffin has also been used as a lubricant for the passage of stool,[7] but should be used with caution because of its adverse effects, which include anal seepage and the risks of granulomatous disease of the gastrointestinal tract or of lipoid pneumonia on aspiration. Although it has been recommended in some countries for constipation in children,[14,15] the *UK CSM* considers it should not be used in those under 3 years of age. Prokinetic drugs have theoretical advantages in patients with slow-transit constipation, but few suitable drugs are available,[5] although the selective 5-HT_4 agonist prucalopride may be tried in chronic constipation, and tegaserod has been used in constipation-predominant irritable bowel syndrome (p. 1810.3) and in chronic constipation. The chloride-channel activator lubiprostone and the guanylate cyclase-C agonist linaclotide are also used in chronic constipation and constipation-predominant irritable bowel syndrome.

Rectal administration of laxatives using enemas or suppositories is appropriate in patients requiring rapid relief from constipation. Phosphate enemas should be used with caution because of the risks of absorption of significant amounts of phosphate.[4] Glycerol and bisacodyl may be given as suppositories to promote faecal evacuation; they should not be used regularly, as changes in the rectal epithelium have been seen with bisacodyl, and the effect of glycerol on rectal mucosa is unclear.[4]

During *pregnancy* the preferred options for management are increased fluid intake, exercise, and dietary fibre;[2] bulking agents may be given as fibre supplements, and stimulant laxatives such as senna reserved for cases where these are ineffective.[2,16]

Faecal impaction is the inability to pass a hard collection of stool, and may result in overflow diarrhoea. Faecal impaction should be treated with a laxative enema and/or a lubricant and manual disimpaction.[4,5,9] Oral laxatives should not be used because of the risk of colonic perforation.[9] When all stool has been cleared, it is important to institute measures, often including regular laxatives, to prevent constipation and recurrent impaction.[5,7,9]

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Decreased gastrointestinal motility

Decreased gastrointestinal motility may occur in any part of the gastrointestinal tract, with symptoms depending on the site. It is of varying aetiology and often secondary to some other disorder, such as infection, metabolic or electrolyte disturbance (for example in gastroparesis due to diabetic neuropathy—see also p. 465.2), or insult to the gastrointestinal tract (for example, paralytic or adynamic ileus is frequently a consequence of abdominal surgery and is a serious adverse effect of some drugs).

Acute loss of gastrointestinal motility is often self-limiting once the underlying cause has been treated. Provided the ability of gastrointestinal smooth muscle to contract has not been lost, however, prokinetic drugs such as metoclopramide or domperidone, or erythromycin, or drugs capable of stimulating functional contraction including parasympathomimetics such as neostigmine or bethanechol, may be used. The opioid μ-receptor antagonist alvimopan has recently been introduced for the treatment of postoperative ileus. Injection of botulinum toxin into the pyloric sphincter may produce temporary symptomatic improvement in patients with refractory gastroparesis. Gastric electrical stimulation may also be an option.

Drugs are less successful in chronic conditions such as chronic intestinal pseudo-obstruction where neuromuscular function of the gastrointestinal tract has some intrinsic abnormality.

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Diarrhoea

Diarrhoea is characterised by liquid stools and increased stool weight and frequency of defaecation. Although diarrhoea is commonly associated with infection (see Gastro-enteritis, p. 182.2), it may also result from the accumulation of nonabsorbed osmotically active solutes in the gastrointestinal lumen, as in lactase deficiency, or from the gastrointestinal effects of secretory stimuli other than the enterotoxins from an infection. It may also occur when intestinal motility or morphology is altered.

Acute diarrhoea may lead to excessive water and electrolyte loss and dehydration, and is potentially life-threatening in infants; frail and elderly patients are also at risk. Severe dehydration associated with acute diarrhoea (greater than 10% loss of body-weight), requires *intravenous rehydration therapy* with Ringer's lactate solution or normal saline.[1–4] Intravenous therapy is also needed for patients who are unable to drink. Otherwise, *oral rehydration therapy* to correct fluid and electrolyte depletion should form the basis of treatment for acute diarrhoea[1–6] and an oral rehydration solution containing essential electrolytes (sodium, potassium, chloride, and bicarbonate or citrate) and glucose is indicated regardless of the age of the patient or the cause of the diarrhoea. A rehydration phase, which involves the replenishment of fluid and electrolytes lost through the diarrhoea, is followed by a maintenance phase to replace continuing losses. Oral rehydration therapy does not stop diarrhoea, which usually continues for a limited period, although it can reduce stool output and vomiting. Oral rehydration therapy may need to be modified if the diarrhoea is associated with malnutrition.[7] The rationale for the composition of oral rehydration solutions is that glucose absorption is coupled to the active transport of electrolytes,[8] the absorption of which theoretically increases in efficiency as the ratio of carbohydrate to sodium approaches 1:1.

WHO originally recommended a solution containing 90 mmol/litre of sodium and 111 mmol/litre of glucose; this type of preparation has been used effectively in developing countries where diarrhoeas are commonly bacterial in origin. There is now evidence from studies and meta-analyses to suggest that solutions of reduced sodium content and osmolarity are safe and effective and may be preferable to the original standard WHO solution, even in developing countries,[9–12] and WHO and UNICEF now recommend a solution containing 75 mmol/litre of sodium and 75 mmol/litre of glucose, with a reduced total osmolarity of 245 mmol/litre.[13] Despite concerns about the possible increased risk of hyponatraemia with the use of the reduced osmolarity solutions in patients with cholera,[14–16] WHO and UNICEF have stated that hyponatraemia may also occur with the standard WHO formulation, and that there is no evidence to suggest that this transient hyponatraemia has had significant adverse clinical consequences for cholera patients.[13]

In developed countries viral diarrhoeas, which are associated with less electrolyte loss, are more common, and reduced osmolarity solutions are favoured.[2] Commercial preparations available in the UK, for example, usually provide 50 to 60 mmol/litre of sodium and 90 to 111 mmol/litre of glucose; the total osmolarity is slightly hypotonic (about 250 mmol/litre) to prevent possible induction of osmotic diarrhoea.[17] Similar preparations are available in other developed countries.[18]

Areas of debate have included the necessity for inclusion of citrate or bicarbonate,[17] and whether cereal-based rather than glucose-based rehydration solutions would be preferable. There is considerable evidence that cereal-based solutions tend to produce more rapid resolution of diarrhoea, although one study has suggested that the reduction in stool output is temporary,[19] and another found that a glucose-based solution was equally effective when combined with early re-introduction of feeding.[20] In 1994, a review of clinical studies concluded that a rice-based rehydration solution should be recommended for patients with cholera, but that there was no reason to change from WHO's glucose-based formulation for children with non-cholera diarrhoea.[21] A study in 48 patients with cholera compared the use of standard glucose-based oral rehydration therapy, standard therapy plus rice flour, and standard therapy plus amylase-resistant starch.[22] The addition of amylase-resistant starch to standard oral rehydration solution was shown to reduce stool output and to reduce the duration of diarrhoea,[22] although the methodology of this study was questioned[23] and further investigation of such solutions is required.

Home remedies[1] that have been used to prevent dehydration include coconut water, rice water, soups, unsweetened fresh fruit juice, and unsweetened weak tea; these may be of value when more conventional oral rehydration solutions are unavailable. The use of cordials and soft drinks with low pH and high osmolality, however, may exacerbate diarrhoea and dehydration.[1,18]

Oral rehydration therapy should be combined with *dietary measures*, particularly in children, to avoid malnutrition owing to low food intake during the illness, and as mentioned above, may need to be modified if the diarrhoea is associated with malnutrition. Breast feeding should be continued throughout rehydration therapy,[2,4,6,17] as such feeding may decrease stool output and shorten the duration of diarrhoea.[2] Dilution of formula feeds does not seem to be of clinical benefit and may even prolong symptoms.[4,8] Generally food should not be withheld in adults or children with diarrhoea, but for those with some signs of dehydration, food is not normally given during the initial rehydration period.[1]

To reduce the duration and severity of diarrhoea, and to prevent recurrence, zinc supplements are recommended by WHO as adjunctive therapy to oral rehydration salts for acute diarrhoea, see p. 2127.2. Children with persistent diarrhoea, lasting at least 14 days, should receive zinc as part of a multivitamin and mineral supplement.[1] Vitamin A may be important in reducing mortality, see p. 2100.1.

There is considerable interest in the potential use of *probiotic bacteria*, or *prebiotic foods* intended to stimulate the growth of beneficial species in the gastrointestinal tract, in the management of diarrhoea. Although meta-analyses have suggested that treatment with lactic-acid producing organisms may reduce stool frequency and disease duration in children with acute infectious diarrhoea,[24] and may reduce the risk of antibacterial-associated diarrhoea in children,[25] the role of probiotics and prebiotics remains to be established,[4,8] particularly since many commercial products are poorly characterised.

Oral rehydration therapy prevents dehydration, but does not necessarily shorten the duration of the diarrhoea, and patients therefore frequently desire the symptomatic relief provided by *drug therapy*. Use of such therapy should be

balanced against the risk that it may distract from the need for oral rehydration therapy and may have undesirable adverse effects. WHO considers that antidiarrhoeal drug therapy is of limited value for acute infectious diarrhoea, does not reduce fluid and electrolyte loss, may delay the expulsion of causative micro-organisms, and should never be used in children.[26] However, it has been pointed out that extrapolating results in children to adult treatment is unwarranted; there is no good evidence that antidiarrhoeal drugs prolong illness or retard expulsion of pathogens, and no reason to withhold medication in otherwise healthy adults.[27] Short courses of antidiarrhoeals are often used in practice (frequently as self medication) if symptoms are causing discomfort.[3,27,28]

The main groups of antidiarrhoeal drugs are adsorbents such as attapulgite, kaolin, and pectin, and drugs that reduce intestinal motility such as diphenoxylate, loperamide, and codeine. Oral loperamide has been recommended as the treatment of choice, particularly for self-medication,[3,27] although bismuth salicylate, which has antisecretory properties, is probably equally effective,[3] and may be preferred in some countries such as the USA.[28] Other drugs with antisecretory properties are under investigation; they include the enkephalinase inhibitor racecadotril, which unlike other antidiarrhoeal drugs is of interest as a potential adjunct in children.[4] Bulk laxatives such as methylcellulose have also been used for symptomatic treatment because of their absorptive capacity.

Antibacterial and antiprotozoal drugs have been used for infective diarrhoeas, including the prophylaxis and treatment of travellers' diarrhoea (see Gastro-enteritis, p. 182.2 and p. 921.2), but their overuse encourages the development of resistance and prophylaxis is not recommended. Vaccines are being developed for the prevention of rotaviral diarrhoeas (p. 2416.1).

Chronic diarrhoea may be associated with underlying disease and therefore symptomatic relief is less appropriate than treatment of the disease itself. For example, colestyramine will reduce the diarrhoea associated with bile acid malabsorption. Where the disease process responsible for chronic diarrhoea cannot be satisfactorily suppressed, however, symptomatic relief may be appropriate,[29] for example in diabetic diarrhoea (see p. 464.1).

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Diverticular disease

Diverticula are small hernias or pouches of mucosa that develop through the muscular wall of the gut (especially the colon) or other hollow organs; they increase in prevalence with increasing age. Diverticular disease (the presence of colonic diverticula) is usually asymptomatic, but may be associated with symptoms of abdominal pain and altered bowel habit (diverticulosis). Occasionally there may be severe life-threatening complications such as inflammation and necrosis of diverticula (diverticulitis), perforation, fistula formation, obstruction, or haemorrhage. There is some evidence that the use of NSAIDs may be associated with an increase in diverticular complications such as perforation.

In uncomplicated diverticular disease, treatment is with a high-fibre diet, gradually supplemented if necessary with a bulk laxative such as bran or ispaghula, to ease constipation, although the evidence to support such management is limited. Supplements may not relieve the other symptoms of diverticular disease. The antibacterial rifaximin may be of benefit in improving symptoms; giving rifaximin and fibre supplementation has been shown to be more effective than fibre supplementation alone. Rifaximin has also been combined with 5-aminosalicylates, chiefly mesalazine; the latter may be of benefit in maintaining remission. Use of probiotics, in the form of lactic-acid-producing organisms, after a non-absorbed antibacterial such as rifaximin has also produced some evidence of additional benefit. Antispasmodics such as antimuscarinics or mebeverine may be useful in relieving pain due to muscle spasm.

Diverticulitis requires treatment with broad-spectrum antibacterials and fluid support; analgesia may be needed for severe pain. If peritonitis or abscess develops, surgical intervention may be necessary. Surgical resection is usually considered when fistula, perforation, or obstruction are present.

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Dumping syndrome

The word dumping in this context is used to describe the unnaturally rapid transport of gastric contents to the small intestine. The dumping syndrome is an important cause of morbidity after gastrointestinal surgery, and is thought to be due to the destruction of normal regulatory mechanisms in the upper gastrointestinal tract.[1-3] Early dumping begins within 10 to 30 minutes of the ingestion of a meal (typically, symptoms are triggered by hyperosmolar, carbohydrate-rich food) and has gastrointestinal symptoms (fullness, abdominal pain, nausea and vomiting, explosive diarrhoea) and vasomotor symptoms (sweating, weakness, dizziness, flushing, and palpitations). The effects are thought to be due to fluid shifts from the intravascular space to the bowel lumen. Some patients have late dumping, 1 to 4 hours after a meal, with only the vasomotor symptoms; it appears to be due to reactive hypoglycaemia caused by high carbohydrate concentrations in the small intestine.

The mainstays of therapy are dietary modifications, taking small frequent meals low in carbohydrate, followed by liquids 30 minutes later. Attempts to slow or reduce carbohydrate absorption have involved the use of dietary fibre (guar gum or pectin) or α-glucosidase inhibitors such as acarbose; acarbose and pectin have also been tried in combination.[4] However, such agents may themselves cause gastrointestinal disturbances and they do not seem to be helpful in most patients.[2] However, beneficial results with somatostatin have led to the use of its longer-acting analogue, octreotide.[2,5] Octreotide substantially reduces the symptoms of both early and late dumping, probably by slowing gastric emptying and by inhibiting the release of gastrointestinal mediators (peptide hormones such as neurotensin), and prevents hyperinsulinaemia and subsequent reactive hypoglycaemia. It may be given up to 2 hours before a meal, or as long-acting formulation.[3]

In the minority of patients who do not respond to medical therapy surgery may be required.[1-3]

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Dyspepsia

Dyspepsia, also commonly known as indigestion or heartburn, is a frequent but ill-defined disorder primarily associated with epigastric discomfort or pain. It may be a symptom of specific diseases such as peptic ulcer disease, gastro-oesophageal reflux disease, gastric carcinoma, chronic pancreatitis, or gallstones. However, in many patients there is no identifiable systemic disease, in which case it is known as non-ulcer dyspepsia or functional dyspepsia.

Many reviews and recommendations have addressed the subject of dyspepsia,[1-7] and, in the UK, various authoritative guidelines have been issued.[8,9] The initial management of non-ulcer dyspepsia usually includes advice to avoid alcohol, caffeine, smoking, and aggravating foods, and to eat small regular meals to aid digestion. Results of studies of drugs for non-ulcer dyspepsia have been variable and difficult to evaluate since the condition tends to be self-limiting, and there is often a large placebo response.[10]

Drugs that *suppress gastric acid* such as *antacids* or antisecretory drugs are often used. Antacids may give some symptomatic relief, and are widely used for self-medication.[9] However, long-term use is inappropriate. Similarly, H_2-antagonists are often tried, especially for symptoms of reflux, and a systematic review[10] has suggested benefit, at least in a proportion of patients. Proton pump inhibitors (PPIs) are also widely used; although a systematic review had considered their relative efficacy in non-ulcer dyspepsia versus H_2-antagonists to be unclear,[11] others[5-7,12] consider them superior to H_2-antagonists. They may be useful for on-demand therapy to manage symptoms long-term.[9]

It is not clear what role *Helicobacter pylori* plays in the pathology of non-ulcer dyspepsia. One meta-analysis found eradication to be of no benefit in non-ulcer dyspepsia,[13] but another, incorporating more patients, found that a small benefit existed,[14] although it noted that most patients positive for *H. pylori* will continue to have symptoms after eradication. As a result there has been much debate about the appropriateness of so-called 'test and treat' strategies, but UK[9] and US[4,5] guidelines consider them a valid alternative to a trial of a PPI in the initial management of uninvestigated dyspepsia.

Initial management of dyspepsia in patients under 55 years of age who do not have so-called 'alarm symptoms' (such as chronic gastrointestinal bleeding, unintentional weight loss, difficulty swallowing, persistent vomiting, iron deficiency anaemia, or epigastric mass) should therefore consist of either:[4,9]

- an empirical one-month course of a PPI, *or*
- testing for *Helicobacter pylori* and appropriate eradication therapy. Those who are *H. pylori*-negative should be prescribed an empirical trial of acid suppression with a PPI for 1 to 2 months

Patients over 55 years of age, or those with alarm symptoms, should be referred for endoscopy. After endoscopy, treatment should be targeted at the underlying diagnosis.[4]

Prokinetic drugs may be given, particularly if an underlying gastrointestinal motility disorder is suspected. Meta-analysis has suggested that prokinetic therapy may be more effective than an H_2-antagonist in non-ulcer dyspepsia,[10,15] but this may be due to publication bias.[10] In addition, cisapride is no longer available in many countries and evidence for domperidone or metoclopramide is limited. Results with motilin agonists (derivatives of erythromycin) and 5-HT_3 antagonists have been disappointing to date.[3] Other approaches to drug therapy include the use of an insoluble bismuth salt, and the use of antispasmodics. Antidepressants may have a limited role in some patients,[5,7] and various herbal medications have been tried, though the quality of any studies is generally poor.[7]

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Eosinophilic oesophagitis

Eosinophilic oesophagitis is a disease of the oesophagus characterised by a marked accumulation of eosinophils in the oesophageal mucosa. Severe squamous epithelial hyperplasia generally occurs, resulting in complications such as oesophageal strictures and a narrow oesophagus. Symptoms include heartburn, chest pain, dysphagia, pain on swallowing, vomiting, food impaction, and feeding intolerance in children.

Although data on treatments are sparse, corticosteroids are considered appropriate. Systemic and topical corticosteroids are effective at relieving acute symptoms, although symptoms usually recur when treatment is stopped. Gastro-oesophageal reflux disease may coexist with eosinophilic oesophagitis; however, the symptoms and pathological features of eosinophilic oesophagitis do not respond to acid suppression treatment. Allergy has been implicated in eosinophilic oesophagitis, with many patients being atopic. Dietary therapy based on eliminating exposure to food allergens is considered an effective treatment option for children, in whom most of the research has been carried out.[1]

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Gastrointestinal spasm

Pain or discomfort of the gastrointestinal tract may be due to spasm of the smooth muscle of the gut; such pain and spasm may be associated with the irritable bowel syndrome (see p. 1810.3), dyspepsia (see p. 1806.3), or diverticular disease (see p. 1806.2). Antispasmodic drugs have traditionally been used in patients thought to have gastrointestinal spasm, and have mainly been of two types: antimuscarinics such as dicycloverine, and direct smooth muscle relaxants such as mebeverine; use of antimuscarinics, in particular, has tended to be limited by concern about their adverse effects.

Colic is a general term used to describe spasmodic or griping pain, usually of the viscera, and when not otherwise qualified is often understood to refer to pain in the gastrointestinal tract. Infant colic is common in the first few months of childhood,[1,2] and tends to be managed by nonpharmacological measures and assessment of the feeding technique. Elimination of cow's milk protein appears to be of benefit, but use of a low-lactose formula is not.[1] Tilactase has been added to feeds to aid lactose digestion but the extent of any benefit is unclear. Traditional remedies such as gripe water, which contains essential oils of dill or fennel and is mildly carminative, are of dubious efficacy. Antimuscarinic antispasmodics, although effective[1,2] may be associated with adverse effects, and are no longer considered appropriate.[3] Simeticone suspension, given before feeds, is commonly used but has been found to be no better than placebo.[3,4] It has been reported that sucrose, given as a 12% solution, improves infant colic.[5] Glucose solution may also have some benefit.[2]

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Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease results from the reflux of gastric or duodenal contents into the oesophagus. Symptoms include heartburn, acid regurgitation, and dysphagia (difficulty in swallowing); oesophageal inflammation and ulceration (reflux oesophagitis), and stricture formation may occur. Extra-oesophageal symptoms may include cough, horseness, and asthma. Some patients develop Barrett's oesophagus (below), which is a risk factor for oesophageal cancer (p. 705.3).

Lifestyle advice on weight loss, raising the head of the bed, stopping smoking, and avoidance of alcohol and aggravating foods such as chocolate and coffee is often given as part of initial **management**,[1-6] although the evidence for most of these interventions other than weight loss and bed position is lacking.[3]

Patients often manage initial mild symptoms with over-the-counter therapies, including *antacids* and antisecretory drugs. Although the placebo response is often high, meta-analysis has shown some additional symptomatic benefit from antacids, *histamine H_2-antagonists*, and in particular for combinations of an antacid with an alginate;[7] such combinations are believed to form an alkaline 'raft' above the stomach contents that impedes reflux and protects the oesophageal mucosa.

The symptoms and management of gastro-oesophageal reflux disease may overlap with those of dyspepsia (see p. 1806.3), and initial symptomatic management is likely to be similar.[4] Patients who do not have alarm symptoms that would indicate a need for prompt endoscopy should be treated with an appropriate dose of a *proton pump inhibitor* (PPI) for 1 to 2 months.[4,5] Such treatment is more effective for empirical management than an H_2-antagonist,[8] and is appropriate therapy for endoscopy-negative disease[8] as well as for patients with reflux oesophagitis.[9] There is no evidence for the superiority of any particular PPI, nor for greater benefit from doubling doses in patients with reflux oesophagitis.[8]

A significant minority of patients do not, however, respond to PPIs; reasons may include poor compliance, nocturnal acid breakthrough, non-acid reflux, and hypersensitivity to acid.[4,5] Trying an alternative PPI, increasing the dose, or adding a H_2-antagonist to PPI treatment have been suggested for patients with persistent symptoms,[4,10] although evidence of improved efficacy is generally lacking.[6,9,11] Some benefit has been reported in extensive metabolisers of rabeprazole when famotidine was added to treatment compared with an increased rabeprazole dose.[12]

Alternatively, a *prokinetic drug* such as metoclopramide may improve gastro-oesophageal sphincter function and accelerate gastric emptying. These appear to be as effective as H_2-antagonists,[1] although they are probably less effective than PPIs.[8] An H_2-antagonist used with cisapride may be more effective than either drug alone.[1] However, concern over the risk of cardiotoxicity and potential for serious interactions with cisapride has led to severe restrictions on its use.

In patients with mild disease, a trial of withdrawal of drug therapy is appropriate after successful initial treatment.[1] Short courses of therapy as and when symptoms demand (intermittent treatment) may be effective in uncomplicated disease.[13] However, most patients with oesophagitis relapse when treatment is withdrawn, and long-term **maintenance** therapy is likely to be required.[1,4,5] As in acute management, PPIs appear to be the most effective maintenance treatment, although the 'step-down' approach of reduced maintenance doses, which is widely favoured,[4,5] may produce less benefit than continuing to give full dose PPIs.[14] H_2 antagonists were found to be of marginal benefit for maintenance, although they did give some symptomatic relief, and although prokinetic drugs (cisapride) and sucralfate were also reported to be more effective than placebo their value was considered dubious.[14] Another approach is to use a combination for maintenance, and in one study omeprazole with cisapride provided more effective maintenance than ranitidine or cisapride alone or together.[15] Again, however, cisapride is now unlikely to be used in practice because of the risks.

Helicobacter pylori **eradication** does not heal or prevent relapse of gastro-oesophageal reflux disease,[1] and some epidemiological evidence has appeared to suggest that *H. pylori* infection protects against gastro-oesophageal reflux disease.[16] However, there is no clinical evidence that eradication of *H. pylori* exacerbates gastro-oesophageal reflux disease or significantly increases the risk of its development.[17,18]

In patients who have a poor response to drug therapy, or in those with complications such as oesophageal stricture or ulceration, **surgery** to re-establish gastro-oesophageal competence may be considered.[1,4,5] Submucosal implants and various other endoscopic techniques have also been investigated.[4] Although surgery is as effective as drug treatment, it carries greater associated risks, and many patients continue to require antisecretory drugs.[4]

Investigational approaches to drug therapy include the development of drugs with GABAergic actions similar to those of baclofen (but without its CNS effects), cholecystokinin antagonists such as loxiglumide, and cannabinoid CB_1 agonists; motilin receptor agonists such as alemcinal and mitemcinal do not appear to be of much benefit.[19]

A minority of patients with gastro-oesophageal reflux disease develop **Barrett's oesophagus** (columnar lined oesophagus, CLO), in which the normal oesophageal squamous lining is replaced with a metaplastic columnar epithelium. This is most common in patients with long-standing disease but may represent part of a spectrum of possible responses to acid reflux rather than a progression from less severe to more severe disease.[4] The abnormal epithelium in Barrett's oesophagus shows dysplastic changes that may progress to oesophageal adenocarcinoma. However, not all patients go on to develop cancer, and many aspects of management are controversial.

Management of acid reflux, as for other forms of gastro-oesophageal reflux disease, is the mainstay of management.[20-23] Long-term treatment with PPIs appears to be effective;[22] the use of maximal doses, perhaps with an H_2-antagonist at night, is advocated by some[23] but evidence to support twice daily (double) dosing is lacking.[22] As the altered epithelium is relatively less sensitive to acid, symptom control does not necessarily equate to suppression of reflux.[23] There is a lack of good evidence that control of acid reflux produces anything other than limited regression of the abnormal epithelium, or alters the risk of progression to malignancy,[22,23] although there are some results that suggest benefit.[24,25] Some evidence suggests that additional chemoprevention with aspirin or another NSAID might offer benefits in reducing cancer risk,[22,26] but this remains investigational. The roles of screening, surveillance, and endoscopic ablation therapy or photodynamic therapy (5-aminolaevulinic acid or porfimer) remain matters of debate.[20,22,23]

In **infants**, gastro-oesophageal reflux is common but usually resolves spontaneously with increasing age and requires no treatment. Occasionally, it may be associated with complications such as failure to thrive, oesophagitis, and pulmonary symptoms of acid regurgitation, but can be managed by upright positioning and the use of thickened foods; drug therapy is controversial,[27] and the evidence base is poor.[28] It has been suggested that where drug therapy is needed, an alginate-antacid combination may be appropriate initially;[27] PPIs are probably safe but are not well studied in infants.[28] Cisapride has been given[27,28] but the risk of cardiotoxicity makes the use of cisapride in infants extremely problematic (see p. 1832.2). Metoclopramide may have some benefit but again this must be weighed against the risk of adverse effects.[29] Evidence of benefit with domperidone is poor,[30] and it too has the potential for serious adverse effects, but restrictions on cisapride have led to its over-use.[28] Erythromycin has been investigated in infants with food intolerance, though not in gastro-oesophageal reflux itself; there is a risk of promoting bacterial resistance from such use.[28]

Gastro-oesophageal reflux is commonly encountered during normal **pregnancy**, and is generally managed by lifestyle and dietary modifications.[31] If drug therapy is required, nonsystemically absorbed antacids or sucralfate should be tried first. If these are ineffective, ranitidine may be tried. Proton pump inhibitors are reserved for women with severe or complicated reflux disease,[31] due to concerns about their safety in pregnancy, although the relative risk associated with exposure seems to be quite low (see under Precautions of Omeprazole, p. 1870.3).

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Haemorrhoids

Haemorrhoids ('piles') are venous swellings of the tissues around the anus: those above the dentate line (the point where the modified skin of the outer anal canal becomes gut epithelium), which usually protrude into the anal canal, are termed internal haemorrhoids, while those below this point are called external haemorrhoids. Due to internal pressure, internal haemorrhoids tend to congest, bleed, and eventually prolapse; with external haemorrhoids painful thrombosis may develop.[1-3]

Initial treatment of internal haemorrhoids involves a high-fibre diet and avoidance of straining at stool,[2-4] so bulk laxatives and faecal softeners may be indicated.[2] The prime objective of drug therapy is to control the acute bleeding phase so that definitive therapy can be scheduled.[1] Small bleeding haemorrhoids may be injected with a sclerosing agent such as oily phenol injection, but rubber band ligation, or perhaps a technique such as infra-red coagulation, is more effective and associated with fewer complications.[3,5,6] More severe and prolonged prolapse generally requires surgery.[2-4,7] Surgical excision to remove the clot is used for thrombosed external haemorrhoids.[8]

An enormous range of mainly topical drug treatments is available for symptomatic relief, but in many cases their value is at best unproven.

Topical preparations are usually made up in a lubricating or emollient base. Local anaesthetics may be included to relieve pain, and corticosteroids may be used where infection is not present: preparations containing either group of drugs are intended only for short-term use. Inclusion of antibacterials is thought to be of little value and may encourage the development of resistant organisms. Some preparations include heparinoids. Other agents frequently included for their soothing properties include various bismuth salts, zinc oxide, hamamelis, resorcinol, and peru balsam.[2,3] Topical nitrates have also been used.[1]

Bioflavonoids and various derivatives of aesculus may also be included in topical preparations; they have also been given systemically in some countries as have some other compounds such as calcium dobesilate and tribenoside, presumably for their supposed action on venous capillary walls. Oral micronised bioflavonoid preparations may reduce symptoms as an adjunct to surgery.[1,7,9]

Other agents that have been used in the treatment of haemorrhoids include pilewort (ficaria) and combinations of yeast extract with shark-liver oil.

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Hepatic encephalopathy

Hepatic encephalopathy (portal systemic encephalopathy) is a metabolically related dysfunction of the brain associated with abnormalities of liver function. It may be acute, as in patients with fulminant hepatic failure, or chronic, with acute episodes precipitated by some triggering factor, as in patients with cirrhosis or other chronic liver disease.

Treatment is aimed at identifying and correcting any precipitating factor, decreasing the production and absorption of ammonia in the gut, and increasing metabolism of ammonia in the tissues. Precipitating factors include infection, increased protein load due to gastrointestinal haemorrhage or high protein intake, alcohol abuse, electrolyte imbalance, and certain drugs (notably anxiolytics, hypnotics, and diuretics).

Restriction of dietary protein intake is a mainstay of short-term treatment, but in the long-term, care must be taken to provide adequate protein to avoid malnutrition. A daily protein intake of 0.5 to 1.5 g/kg has been recommended.[1-3] There is some evidence that vegetable protein is better tolerated than animal protein.[4,5] Giving branched-chain amino acids (valine, isoleucine, and leucine) by infusion or as dietary supplements may facilitate adequate protein intake in some patients.[1,3-5] Supplementation with ornithine aspartate has been used to increase metabolic conversion of ammonia to urea and glutamine.[2,4,5] Sodium benzoate has also been tried.[4,5]

Active drug treatment may begin with bowel cleansing by means of a magnesium sulfate enema, especially if the patient is constipated. Lactulose is then the treatment of choice in many cases, particularly in the elderly, the constipated, and those with renal impairment. It is usually given orally although it may be used rectally[2,5] or by nasogastric tube[2] when oral use is not feasible.[5] It reduces colonic pH and absorption of ammonia and aromatic amino acids. The lactulose analogue lactitol is also used.[6] However, a recent meta-analysis[7] was unable to find sufficient evidence to support or refute the use of nonabsorbable disaccharides, such as lactulose and lactitol, for hepatic encephalopathy. The disaccharidase inhibitor voglibose has been tried to reduce intestinal uptake of disaccharides and promote fermentation, with effects similar to lactulose.[5]

Alternatively, locally active antibacterials have been given to reduce the urease-producing bacteria.[2] Neomycin is the traditional drug but adverse effects such as ototoxicity and nephrotoxicity may be a problem, particularly if used long-term. Metronidazole[4] and rifaximin[4,8,9] are also used. A combination of lactulose and neomycin[4] or metronidazole has been tried in patients who fail to respond to single-drug therapy.

In low grade chronic recurrent encephalopathy *Lactobacillus acidophilus* or *Enterococcus faecium* SF68 have been tried orally in an attempt to produce a more favourable bowel flora. Results have been inconsistent.[3,10] *Helicobacter pylori* is a urease-producing organism, but the relevance of *H. pylori* infection to hepatic encephalopathy is unclear.[11]

Investigational therapy has also attempted to affect cerebral function directly. Flumazenil, a benzodiazepine antagonist, has been tried, on the basis of the suspected role of endogenous benzodiazepine-like agonists.[2,12] A systematic review[13] concluded that flumazenil did produce short-term improvement of hepatic encephalopathy but had no effect on recovery or survival; it might be considered for patients with chronic liver disease and hepatic encephalopathy but routine clinical use was not recommended. Similarly, although dopaminergics such as levodopa or bromocriptine have been given, on the grounds that impaired dopaminergic neurotransmission may play a role in the syndrome,[2] evidence to support their use was not forthcoming from a systematic review.[14]

Liver transplantation (p. 1936.3) is the ultimate therapy for end-stage cirrhosis, acute liver failure, or patients with severe refractory hepatic encephalopathy.[4]

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Inflammatory bowel disease

Inflammatory bowel disease (IBD) covers chronic non-specific inflammatory conditions of the gastrointestinal tract, of which the two major forms are *Crohn's disease* and *ulcerative colitis*.

Crohn's disease is characterised by thickened areas of the gastrointestinal wall, with inflammation extending through all layers, deep ulceration and fissuring of the mucosa, and the presence of granulomas; affected areas may occur in any part of the gastrointestinal tract, interspersed with areas of relatively normal tissue; the terminal ileum is frequently involved. Symptoms depend on the site of disease but may include abdominal pain, diarrhoea, fever, weight loss, and rectal bleeding. Extra-intestinal manifestations may include joint inflammation, skin lesions, mouth ulcers, and liver disorders.

In **ulcerative colitis**, disease is confined to the colon and rectum, inflammation is superficial but continuous over the affected area, and granulomas are rare. In mild disease, the rectum alone may be affected (proctitis); in severe disease, ulceration is extensive and much of the mucosa may be lost, with an increased risk of toxic dilatation of the colon, a potentially life-threatening complication. Symptoms include diarrhoea and rectal bleeding. The extra-intestinal manifestations are similar to those of Crohn's disease.

Drug treatments.

Although there are important differences between Crohn's disease and ulcerative colitis which affect their management, the broad principles of treatment, and the drugs used, are similar.[1-6] The aminosalicylate derivatives are generally the first choice in mild to moderate active disease, and are of particular value for maintenance treatment of ulcerative colitis; the role of maintenance treatment in Crohn's disease is less well established. Corticosteroids are also used in the initial treatment of active disease, dosage and route varying with disease site and severity. Immunosuppressant or biological therapy may be helpful in severe or chronic active disease. For Crohn's disease an elemental diet (see Inflammatory Bowel Disease, p. 2043.2) may have some value in active disease, but diet plays a lesser role in ulcerative colitis.

- Oral **sulfasalazine**, a **5-aminosalicylate** derivative (5-aminosalicylic acid linked to sulfapyridine), is of value in producing remission of mild ulcerative colitis;[7] results in Crohn's disease have been more equivocal.[4,8]

The discovery that 5-aminosalicylate was the active component of sulfasalazine led to the development of numerous derivatives, including mesalazine (5-amino-

salicylic acid itself, either used rectally, or orally in slow-release or enteric-coated form), olsalazine (2 molecules of 5-aminosalicylic acid joined by an azo bond), and a variety of forms, such as balsalazide, in which the active moiety was joined to inert carriers. All the above have been shown to be effective in active ulcerative colitis, and may be better tolerated than sulfasalazine, since many of the latter's adverse effects are due to its sulfonamide portion. In patients who can tolerate sulfasalazine, the newer drugs have no clinical advantage for remission induction.[7] Nevertheless, the risk of adverse effects on starting sulfasalazine therapy has led to increasing use of the newer derivatives. The 5-aminosalicylates are also recommended for the maintenance of remission in ulcerative colitis;[3,6,9] in contrast, although they are often used in practice it is unclear that they are of value for maintenance in patients with Crohn's disease.[3-5,10]

- The other major group of drugs used in the treatment of IBD is the **corticosteroids**, particularly for more severe ulcerative colitis, and in Crohn's disease. Rectal use may be appropriate in some patients with distal ulcerative colitis or proctitis; oral prednisone or prednisolone is often used in more severe and extensive disease, and in the most severe cases intravenous corticosteroids (usually hydrocortisone or methylprednisolone) may be given. Unfortunately, treatment of IBD is often prolonged, and adverse effects remain a problem, hence the interest in poorly absorbed or rapidly metabolised corticosteroids such as beclometasone, budesonide, or tixocortol. Oral budesonide is more effective than mesalazine in inducing remission in Crohn's disease and although it may be slightly less effective than conventional corticosteroids, adverse effects are reduced.[11] Corticosteroids are not suitable for maintenance of remission in IBD,[3,12] and inability to withdraw corticosteroid treatment without precipitating relapse (corticosteroid dependence) is a therapeutic challenge.
- Other drugs used in active IBD include **immunosuppressants**. The majority of studies have been with azathioprine, or its metabolite mercaptopurine. Because they have a slow onset of action (months) their use in acute disease is limited, but they are of benefit in remission induction in patients with chronically active disease, particularly corticosteroid-resistant or corticosteroid-dependent disease; they may also be used for maintenance in both ulcerative colitis and Crohn's disease, often with other drugs.[3-6,13,14] Low-dose intramuscular methotrexate also appears to be useful for induction[15] and maintenance[16] of remission in Crohn's disease, although it is often given subcutaneously in practice. Evidence for the oral route is lacking,[15,16] and it does not appear to be of value in ulcerative colitis.[5,6] Conversely, ciclosporin has not generally proved useful in chronically active inflammatory bowel disease but may have some value in the short-term treatment of acute severe ulcerative colitis.[5,17] Tacrolimus also appears to be of benefit in severe ulcerative colitis,[5] and possibly in Crohn's disease;[18] mycophenolate mofetil has been tried, although the limited evidence is equivocal.[18]
- Of increasing importance in the management of severe or refractory forms of IBD are the so-called '**biological therapies**', comprising in particular anti-tumour-necrosis factor antibodies such as infliximab, adalimumab, and certolizumab pegol. These have been shown to be effective for induction therapy and maintenance in Crohn's disease;[5,19,20] infliximab[5,20] and adalimumab[21,22] are also used for induction and maintenance of remission in ulcerative colitis.[5,20] Golimumab is another drug in this group that may be used for ulcerative colitis. The anti-integrin antibody natalizumab is effective in inducing remission in Crohn's disease.[23] Thalidomide, a tumour necrosis factor inhibitor, has also been tried in Crohn's disease with some benefit,[18,24] but another such inhibitor, pentoxifylline, was ineffective.[25]
- **Metronidazole** is useful in fistulising perineal Crohn's disease and may be used in colonic Crohn's disease. It is usually given for 3 months. Ciprofloxacin is an alternative, and has also been given with metronidazole,[26,27] although the combination may not be very well tolerated. There has been interest in the possible causal role of *Mycobacterium paratuberculosis* in Crohn's disease,[28] but a study of 2 years of antituberculous therapy with clarithromycin, rifabutin, and clofazimine in patients with Crohn's disease found no evidence of sustained benefit, suggesting that the organism probably did not play a significant role.[29] In contrast, a meta-analysis[30] of several mostly small studies suggested that long-term treatment with a nitroimidazole such as metronidazole, or with clofazimine, might have benefits in patients with Crohn's disease. Antibacterials do not have a role in ulcerative colitis, except for infection prophylaxis in severe attacks.
- **Many other drugs** are being or have been tried in IBD, including immunoglobulins, some interleukins, interferons, short-chain fatty acids, heparin, factor XIII, rosiglitazone, and aminosalicylic acid (4-aminosalicylic acid as opposed to 5-aminosalicylic acid). There have been some short-term responses to the anti-integrin antibody, vedolizumab,[31] and to the anti-interleukin-12 antibody, briakinumab.[32] There is limited evidence of improvement in disease severity from the use of the granulocyte-macrophage colony-stimulating factor sargramostim,[33] which is thought able to stimulate intestinal innate immune defence processes that may be impaired in Crohn's disease. Other biological therapies which are being investigated include the ICAM-antisense oligonucleotide alicaforsen, the T-cell costimulation blocker abatacept, the anti-CD3 antibody visilizumab, and the CCR9 chemokine receptor inhibitor CCX-282.[34] Nicotine has been tried in ulcerative colitis, based on the observation that the disease is rare in smokers. Studies have suggested that nicotine, supplied via transdermal patch, may have benefit in active disease,[35] although it is ineffective for maintenance.[36] Rectal and oral formulations of nicotine are under investigation.

Nutritional and dietary therapies.

Correction of nutritional deficiencies may be necessary in severe IBD, but dietary modification may also have therapeutic effects. In Crohn's disease, enteral feeding, often with an elemental diet is effective in inducing remission (see Inflammatory Bowel Disease, p. 2043.2), although corticosteroids are more effective;[37] there is also some evidence of benefit in maintaining remission.[38] Elemental diets are useful in children and those unable to tolerate corticosteroids. The role of omega-3 fatty acids has been investigated, but systematic reviews have concluded that they are ineffective for maintenance of remission in Crohn's[39] and ulcerative colitis.[40]

There has been some interest in manipulation of the bowel flora through use of lactobacilli and other probiotic bacteria.[41] There have been some reports of benefit in ulcerative colitis,[42,43] and probiotics may be useful in the management of pouchitis,[3,6] but there is no good evidence to date of benefit in Crohn's disease.[44] The observation that inflammatory bowel disease is uncommon in developing countries where most people carry helminths has led to preliminary studies of bowel colonisation using *Trichuris suis* ova (porcine whipworm) in active Crohn's disease[45] and ulcerative colitis.[46]

Surgery.

In patients with ulcerative colitis surgical colectomy is curative, and may avoid the risks of long-term corticosteroid therapy and the increased risk of bowel cancer to which patients with inflammatory bowel disease are subject. Formation of an ileoanal pouch, which acts as a reservoir for the ileal contents, avoids the necessity for a standard ileostomy and maintains a degree of continence in suitable patients. Curative surgery is not possible in Crohn's disease, since recurrence elsewhere in the gut is almost inevitable, but resection of the affected area becomes necessary in many patients during the course of their illness.

CHOICE OF THERAPY

Ulcerative colitis.

- ACTIVE DISEASE:
  - ***mild to moderate***

    In mild to moderate *distal* disease topical mesalazine, preferably with an oral aminosalicylate (balsalazide, mesalazine, or olsalazine), is the treatment of choice.[3,6] Selected patients may benefit from oral sulfasalazine. Patients intolerant of topical mesalazine may be given a topical corticosteroid instead, though they are less effective.[47] Suppositories are suitable for *proctitis* but foam or liquid enemas are required for more proximal disease (*proctocolitis*).[3] Patients who fail to improve on a combination of oral aminosalicylate with topical mesalazine or corticosteroid may require an oral corticosteroid (e.g. prednisone or prednisolone 40 mg daily).[3,5,48] Infliximab is an alternative.[6]

    In *left-sided* or more *extensive* ulcerative colitis the preferred therapy is an oral aminosalicylate;[3,5,6] olsalazine is best avoided in patients with *pancolitis* as it may be more likely to produce diarrhoea than mesalazine or balsalazide.[3] There is some evidence that the benefits of aminosalicylates are dose related,[5,6] and some controversy exists as to the optimum induction dose: use of higher doses initially may produce better responses,[5,6] but there is an increased risk of toxicity. Some recommend the addition of topical aminosalicylates as the combination is considered more effective than oral treatment alone.[48]

    Patients who fail to respond to aminosalicylates should be given an oral corticosteroid (as above).[3,6,48] The corticosteroid should be reduced gradually (tapered) over several weeks once response is achieved.[3,6] Since long-term treatment with corticosteroids is undesirable, patients with *chronic active disease* who are at high risk of relapse when the corticosteroid is withdrawn (corticosteroid-dependent disease) should be treated with a thiopurine (azathioprine or mercaptopurine) as a corticosteroid-sparing drug.[3,6,48] Thiopurines may also be effective in inducing remission in some patients who do not respond to oral corticosteroids, although their slow onset of action is problematic.[6] In patients with more extensive, moderate to severe disease, infliximab may be an option.[5,6] Adalimumab and golimumab are also licensed for use in such patients.
  - ***severe***

    Patients who present with severe colitis or who fail to respond to maximal oral treatment should be admitted to hospital for treatment with intravenous corticosteroids.[3,5,6,48] Patients should be given appropriate supportive therapy (including nutritional support if the patient is malnourished, intravenous antibacterials for infection, and blood transfusion if markedly anaemic).[3,6] Intravenous ciclosporin may be a useful option in patients with severe disease who cannot tolerate corticosteroids.[48] Ciclosporin should also be considered as a second-line treatment for those who fail to respond to intravenous corticosteroids within a few days.[3,5,6,48] Infliximab or tacrolimus are also options.[5,6,48] Patients who respond to intravenous ciclosporin may be given oral continuation treatment for 3 to 6 months.[3] Drug therapy is ineffective in up to 40% of patients with severe colitis,[6] and colectomy is an alternative.[3,6]
- MAINTENANCE:

  Lifelong maintenance therapy is generally recommended for patients with ulcerative colitis once remission is achieved, particularly in those with left-sided or more extensive disease, or those with distal disease who relapse more than once a year.[3] The treatment of choice is an oral aminosalicylate,[3,5,6,48] most often mesalazine,[5] although in those that can tolerate it sulfasalazine is possibly more effective.[9] A combination of oral and topical aminosalicylates has been recommended as a second-line maintenance treatment.[48] Topical aminosalicylates alone have been used for maintenance in patients with proctitis, left-sided,[48] or distal disease;[3,5] a combination of oral and rectal aminosalicylates can be used second line.[48] Corticosteroids are ineffective in maintaining remission and associated with severe adverse effects on prolonged use. Azathioprine may be used for maintenance therapy, but is best reserved for patients who relapse frequently despite aminosalicylate maintenance, or who are unable to tolerate such therapy.[3,6,48] Patients with gastrointestinal intolerance of azathioprine may be tried cautiously with mercaptopurine; alternatively, surgery may be considered.[3] Infliximab is also effective for maintenance of remission,[6] especially in patients who remain corticosteroid dependent despite alternative therapies.[5] Golimumab is also used.
- POUCHITIS.

  Ileoanal pouch anastomosis allows for surgical removal of the colon without loss of continence or the need for an ostomy, but subsequent inflammation of the pouch (pouchitis) occurs in about half of all patients.[6] On the basis of limited evidence it is considered to be best treated by a short course of antibacterials (metronidazole or ciprofloxacin).[3,6] If these are ineffective, mesalazine or corticosteroids may be considered.[3] Use of a probiotic formulation, VSL 3, containing a mixture of bacteria, may also be of benefit.[3,6]

Crohn's disease.

- ACTIVE DISEASE:
  - ***mild to moderate***

    First-line therapy in mild to moderate Crohn's disease is a matter of some debate. Oral mesalazine is of limited benefit in *ileal* or *ileocaecal* disease,[4,5] and some consider that it should not be used at all,[5] although others recommend high doses as an appropriate initial therapy.[3] Aminosalicylates may be of more benefit in *colonic* disease, particularly sulfasalazine if it can be tolerated.[3-5] Others favour the use of oral budesonide as first-line therapy for mild to moderate ileocaecal disease;[4,5] although it is somewhat less effective than conventional oral corticosteroids, which are an option in more active disease,[3,4] it produces fewer adverse effects.[11] Opinion also varies on the use of topical mesalazine in colonic disease,[3,4] although it is widely used.[4] Nutritional support (enteral feeding or the use of elemental diets) may be considered as an alternative to drug therapy or surgery in selected patients.[3]
  - ***moderate to severe***

    In outpatients with moderate to severe disease, and those who fail to respond to initial therapy with budesonide or aminosalicylates, conventional oral corticosteroids, typically in a dose corresponding to

40 mg of prednisolone daily (or up to 1 mg/kg daily), are recommended.[3-5] Once response has been achieved, dosage should be gradually tapered off.[3,4]
In patients who have relapsed, azathioprine or mercaptopurine may be added,[4] but they are not best suited to induction of remission because of the delay in onset.[3] Methotrexate may be an alternative in selected patients.[4]
In patients with severe extensive or *fulminant* disease intravenous corticosteroids should be given.[3-5] Adding intravenous metronidazole may be advisable, because of the difficulty of distinguishing active disease from a septic complication.[3] Infliximab should be considered in patients with disease *refractory* to corticosteroids;[3-5] adalimumab or certolizumab pegol may be alternatives.[5]

- ***fistulising disease***
  Simple perianal fistulae can be treated with metronidazole or ciprofloxacin.[3,5] Azathioprine or mercaptopurine are also potentially effective,[3] while infliximab is recommended in patients who do not respond to other treatment.[3,5] An alternative to infliximab is adalimumab.[5] Surgery is appropriate for complex or persistent fistulae.[3,5]
- ***chronic active and corticosteroid dependent disease***
  Azathioprine or mercaptopurine are the drugs of choice in corticosteroid dependent disease.[3] If they are ineffective or not tolerated, intramuscular methotrexate may be considered;[4] it is also considered appropriate for the management of chronic active disease.[3] Infliximab is generally reserved for patients who fail first-line therapy, as an alternative to surgical resection.[3]

- MAINTENANCE:
  The most important intervention in maintaining remission in patients with Crohn's disease is probably to persuade those who smoke to stop smoking.[3] Mesalazine appears to be of limited benefit at best for the maintenance of remission,[3,4,10,49] although it is widely used,[5] and the other aminosalicylates are considered inappropriate.[3,4] Corticosteroids are also not effective for maintenance,[3,4,12] although budesonide may delay relapse for a limited period.[4,5] In patients who required corticosteroids to achieve remission, the usual drug treatment for maintenance is a thiopurine (azathioprine or mercaptopurine).[3-5] In patients who achieved remission with intramuscular methotrexate, it may be continued for maintenance;[3] it is also an option in patients intolerant of thiopurines.[4] Thiopurine maintenance may need to be continued for several years,[4] or even indefinitely.[5] Infliximab is also an option for maintenance, particularly in patients brought to remission with the same drug,[3,4] or those who cannot maintain remission or who remain corticosteroid dependent despite the use of maintenance immunosuppression.[5] Alternatives may be adalimumab or certolizumab pegol.[5] To prevent recurrence following surgery, short-term antibacterial therapy with nitroimidazoles has been recommended in those with risk factors for early recurrence, although adverse effects limit longer-term use. Mesalazine has also shown benefit in maintaining a surgically-induced remission, as have azathioprine and mercaptopurine, although the risk of adverse effects is higher with the immunosuppressants. Promising results have been reported from early studies using postoperative infliximab.[50]

Patients with inflammatory bowel disease have an increased risk of developing colorectal cancer and chemoprevention has been investigated. The aminosalicylates have shown a preventive effect in most studies, and there is strong evidence that ursodeoxycholic acid reduces colorectal cancer in patients with ulcerative colitis who also have primary sclerosing cholangitis.[51]

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Irritable bowel syndrome

Irritable bowel syndrome is a functional gastrointestinal disorder of abdominal pain and altered bowel habit; pain is characteristically relieved by defaecation and may be associated with increase or decrease in stool frequency. There may be abdominal bloating. Women are more often affected than men. Most patients have symptoms intermittently, with flares lasting several days followed by periods of remission.[1] Patients may be classified as having different subtypes of the syndrome, depending on the nature of the main symptoms.

Given the heterogeneity of the condition, only a minority of patients will respond to any given treatment, and this together with a high placebo response rate limits the evidence base for treatment.[1-3] The mainstay of treatment is explanation and reassurance, coupled with sensible advice about lifestyle.[1,4] Dietary modification should involve increasing the amount of vegetable fibre in the diet initially (but see below); some patients respond to exclusion of particular foods but this is probably best reserved for more refractory cases, and should not be allowed to compromise proper nutrition.[1]

Formal psychological therapies may be appropriate in some patients, especially if they have other psychological problems such as marked anxiety or depression, or are unwilling to consider symptomatic drug therapy.[1] Hypnotherapy may have a role in refractory patients,[1] but a systematic review, although noting promising results, was unable to confirm benefit.[5]

Many drug treatments have been tried in irritable bowel syndrome. Short-term drug therapy may be useful in managing symptoms,[1-4,6-8] and should be directed according to which predominate:

- in patients in whom *diarrhoea* is predominant, loperamide may be considered; it is preferred to other opioid antidiarrhoeal drugs because it does not pass the blood-brain barrier. Alternatively, colestyramine may be of benefit. The 5-HT_3 antagonist alosetron is also available in some countries for use in women with severe symptoms unresponsive to conventional therapy; it was previously withdrawn due to gastrointestinal toxicity
- in *constipation-predominant* forms of the syndrome fibre supplementation is often advocated. However, insoluble fibre, such as bran, may exacerbate pain and bloating in some patients, and if fibre supplements are to be given, soluble fibre, such as ispaghula, is preferable.[1] The benefits of bulking agents in general have been questioned.[9] An osmotic laxative or stool softener may be added in patients who fail to respond to fibre, but stimulant laxatives should be avoided or used only occasionally.[1] The synthetic peptide linaclotide acts locally to activate guanylate cyclase-C receptors and reduce constipation.[10] Tegaserod, a partial agonist at 5-HT_4 receptors, has also been effective in this group of patients, although it has been withdrawn from the market in many countries due to cardiovascular ischaemic events
- in patients with *abdominal pain*, 'as-needed' antispasmodics may be tried. These should be taken before meals if abdominal pain occurs principally after eating. Examples include alverine, dicycloverine, hyoscine, mebeverine, peppermint oil, and pinaverium. Systematic reviews considered the evidence of benefit to be greatest for hyoscine and its derivatives[11] cimetropium, dicycloverine, trimebutine, and pinaverium;[9] peppermint oil was also considered effective.[9,11] Low-dose tricyclics have been suggested for second-line use in patients unresponsive to antispasmodics.[1] Reviews[9,12] found antidepressants more beneficial than placebo for treating symptoms of irritable bowel syndrome. Tricyclic antidepressants and SSRIs were considered equally effective
- patients whose symptoms are associated with mild or masked *depression* may also obtain benefit from antidepressant therapy; a depressed patient with increased bowel frequency and abdominal pain may benefit from a tricyclic antidepressant, which slows intestinal transit. It has been suggested that patients with constipation may be better treated with an SSRI

Many other drugs have been tried in irritable bowel syndrome, but results have mostly been variable.[2,3] Interest in new pharmacological approaches has included investigation of cholecystokinin antagonists (loxiglumide and dexloxiglumide); 5-HT_4-agonists such as ATI-7505 as well as compounds with mixed actions such as renzapride; κ-opioid agonists such as asimadoline and possibly μ-opioid antagonists such as alvimopan; the 2,3-benzodiazepine receptor modulator dextofisopam; chloride channel activators such as lubiprostone; melatonin; non-absorbed antibacterials such as neomycin or rifaximin, or more promisingly the use of probiotic mixtures of lactic acid-producing organisms; and recombinant human nerve growth factors.[13-15] Many herbal medicines have also been tried: a systematic review found the studies mostly to be small and of poor quality, but suggested that there was evidence of benefit for some herbal combinations including Chinese traditional medicines such as tongxie yaofang.[16]

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Microscopic colitis

Microscopic colitis covers the diseases collagenous colitis and lymphocytic colitis, which are characterised by chronic, watery, non-bloody diarrhoea with intra-epithelial lymphocytic infiltration; in collagenous colitis this is accompanied by a thickened band of collagen immediately below the surface epithelium of the colonic mucosa.[1-4] Although originally considered to be rare, more recent studies have suggested an increased incidence;[2-4] differentiating from the diarrhoea-predominant form of irritable bowel syndrome (p. 1810.3) may be difficult. It has been suggested that the disease is more common in middle-aged women,[2] but others dispute this.[3]

The evidence base for management is limited, and is complicated by the fact that the disease may remit spontaneously.[2-4] Initial measures may include dietary modification, with avoidance of caffeine[2,3] or lactose-containing foods.[2] A possible association with NSAIDs has been suggested; such drugs should be withdrawn, or their use minimised, if possible.[2,3] Drug treatment has been largely empirical, and relapse is quite common once treatment stops. Antidiarrhoeal treatment with loperamide or fibre supplements has been proposed initially.[1-3,5] Systematic review[6] has suggested that budesonide (see also p. 1626.1), and probably bismuth salicylate, are of benefit in collagenous colitis, and they may be considered for second-line therapy.[3] Data from a small study suggested that bismuth salicylate might also be beneficial for lymphocytic colitis, although no firm conclusions could be drawn.[7] In unresponsive patients, sulfasalazine or another 5-aminosalicylate may be considered;[1-3] it has been suggested that mesalazine or olsalazine may be less effective (though better tolerated) than sulfasalazine.[1,2] Other drugs that may be tried in resistant cases include colestyramine, antibacterials such as metronidazole or erythromycin, oral prednisolone, or immunosuppressants such as azathioprine, mercaptopurine, or methotrexate.[1-3,5] Octreotide and verapamil have also been reported to relieve symptoms.[3]

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Mouth ulceration

Recurrent ulceration of the oral mucosa is usually idiopathic and self-limiting and is known as recurrent aphthous stomatitis or recurrent aphthous ulceration. However, oral ulcers (canker sores) may also be caused by mechanical trauma, nutritional deficiencies (particularly iron, folic acid, or vitamin B_{12}), drug reactions, or underlying disease such as Behçet's syndrome (p. 1601.1).

Management includes identifying any underlying disease or nutritional deficiency and treating these as appropriate. Usually no underlying cause can be found, and treatment is purely symptomatic; it may include topical anti-inflammatories, local anaesthetics, antiseptics, astringents, or antihistamines. The value of many of these drugs in reducing symptoms remains anecdotal, and no treatments have yet been proven to reduce the incidence of recurrences.

Where ulceration is due to minor trauma frequent use of a warm saline or compound thymol glycerin mouthwash may be all that is required to relieve discomfort and swelling. Alternatively, pain relief may be obtained with local anaesthetics or analgesics, but their efficacy in oral ulceration is limited by their relatively short duration of action when applied topically. Salicylates are widely used, mainly as choline salicylate gel, although they themselves have the potential for local irritation and ulceration. Benzydamine spray or mouthwash may also be helpful. Lidocaine, as a gel or lozenges, may be of value in pain that has not responded to other measures. Topical corticosteroids are probably the most effective symptomatic treatment for recurrent aphthous stomatitis. Pellets or lozenges of hydrocortisone are allowed to dissolve next to an ulcer, or triamcinolone in an oral paste formulation may be used, although the paste may sometimes be difficult to apply. Mouthwashes have been employed particularly when ulceration is widespread in the mouth and a dexamethasone mouthwash has been used effectively. The healing properties of carbenoxolone have also been employed as a gel or mouthwash, and the mast-cell stabilising agent amlexanox is also used as an oral paste.

Mechanical protection may be provided by a paste or powder of carmellose sodium, although application may be difficult.

Use of an antiseptic mouthwash such as chlorhexidine or povidone-iodine may be helpful, since secondary bacterial infection can delay healing. Chlorhexidine is also available as a gel. Tetracyclines, used as mouthwashes, reportedly reduce ulcer pain and duration, but their potential for adverse effects if swallowed must be borne in mind. Use of hydrogen peroxide 3% is inadvisable, as it can cause ulceration, but application of a 1.5% solution to individual ulcers, with a topical corticosteroid, may be helpful in producing resolution.

Many other drugs have been tried in aphthous ulceration. Sucralfate may be of benefit. Drugs such as levamisole and thalidomide, although possibly beneficial, are unlikely to be suitable in most cases because of their adverse effects, although thalidomide is used, for example, for aphthous stomatitis in patients with AIDS. Pentoxifylline, which, like thalidomide, inhibits tumour necrosis factor production, has been used in patients with minor recurrent aphthous ulceration. Systemic corticosteroids are generally reserved for cases with severe underlying disease.

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Nausea and vomiting

Vomiting follows stimulation of the vomiting centre in the medulla of the brain. This may be via the chemoreceptor trigger zone, which is sensitive to many drugs and to certain metabolic disturbances, or from actions on other areas such as the vestibular apparatus of the ear (in motion sickness), the cerebral cortex (in psychogenic vomiting), and multiple peripheral receptors. In adults vomiting is almost invariably preceded by a sensation of nausea.

In situations where it can be anticipated, such as motion sickness, surgery, and cancer therapy, antiemetic drugs are given prophylactically, but if this fails they may need to be given therapeutically. Vomiting of unknown origin should ideally not be treated until the underlying cause has been found. If vomiting is prolonged, dehydration, hypokalaemia, and alkalosis may occur and replacement of fluid and electrolytes may be necessary, especially in young children and the elderly.

Cancer chemotherapy. Nausea and vomiting are common adverse effects of cancer chemotherapy and for many patients represent a major drawback to treatment. Once experienced, anticipatory vomiting may occur at the sight of medical staff or a needle and this problem may be severe enough in some cases to hinder or prevent further treatment.

Antineoplastic or cytotoxic drugs may induce vomiting by both a central action on the chemoreceptor trigger zone and a peripheral action on the gastrointestinal tract. The cerebral cortex is probably responsible for anticipatory vomiting. Mechanisms involving 5-HT_3-receptors are important in the pathogenesis of *acute cisplatin-associated vomiting*, whereas different mechanisms are probably involved in *delayed emesis*.

The emetic potential of antineoplastics varies in terms of severity and incidence. A risk classification system, based on the proportion of patients who have emesis in the absence of effective antiemetic prophylaxis, has been developed. Although there are slight variations in published lists,[1-3] examples of risk for some common drugs include:

- *high (more than 90% frequency of emesis)* and can be very severe with chlormethine, cisplatin, high-dose cyclophosphamide, dacarbazine, dactinomycin, oral procarbazine, and streptozocin
- *moderate (30 to 90% frequency of emesis)* with carboplatin, more modest doses of cyclophosphamide, daunorubicin, doxorubicin, epirubicin, oral etoposide, idarubicin, oral imatinib, irinotecan, high-dose methotrexate, oxaliplatin, oral temozolomide, and oral vinorelbine
- *low (10 to 30% frequency of emesis)* with oral capecitabine, etoposide, oral fludarabine, fluorouracil, gemcitabine, lower doses of methotrexate, mitomycin, mitoxantrone, pemetrexed, and taxanes
- *minimal (less than 10% frequency of emesis)* with bleomycin, busulfan, oral chlorambucil, cladribine, oral erlotinib, fludarabine, oral gefitinib, oral hydroxycarbamide, oral methotrexate, rituximab, oral tioguanine, and vinca alkaloids

Emetogenicity may depend to some extent on the dose, route, and schedule of chemotherapy. Some combination therapy has resulted in a higher incidence of vomiting than would be expected from the constituents.

The *onset and duration* of vomiting also varies from drug to drug. For cisplatin the onset may be between 4 and 8 hours after a dose, while the duration may be up to 48 hours or occasionally even longer; a persistent feeling of nausea, and sometimes vomiting, lasting for several days may also occur. After chlormethine, vomiting may begin within a half to 2 hours, whereas after cyclophosphamide there may be a latent interval of 9 to 18 hours, but in both cases vomiting is generally less prolonged than with cisplatin. *Acute emesis* (that occurring within 24 hours of chemotherapy) has generally been easier to control than *delayed emesis* (that occurring more than 24 hours after chemotherapy) or *anticipatory emesis*. In patients whose regimens are given over several days delayed emesis from the initial doses may overlap with acute emesis from later doses.

MANAGEMENT. Guidelines for the management of nausea and vomiting associated with chemotherapy have been produced.[1-3] It is important that effective antiemetic prophylaxis is given from the first course of chemotherapy, to avoid subsequent problems with anticipatory vomiting. With the antiemetic drugs now available it should be possible to control acute emesis; delayed emesis has proved more resistant but new treatments are becoming available. Drugs used in antiemetic regimens have included:

- dopamine antagonists such as metoclopramide, domperidone, and some phenothiazines such as prochlorperazine
- corticosteroids such as dexamethasone
- 5-HT_3 antagonists such as ondansetron

- neurokinin-1 (NK-1) receptor antagonists such as aprepitant
- cannabinoids such as nabilone
- benzodiazepines such as lorazepam
- antihistamines such as diphenhydramine

The choice depends on the emetogenicity of the cancer chemotherapy regimen, as well as factors such as the age of the patient.

- For prophylaxis of *acute emesis* associated with *highly emetogenic chemotherapy*, a 5-HT_3 antagonist with dexamethasone and aprepitant (or fosaprepitant) is recommended.[1-3] At equipotent doses, dolasetron, granisetron, ondansetron, and tropisetron are effective and equally safe.[1,2] Palonosetron, which has a prolonged action, may also be used.[2] High-dose metoclopramide was formerly used, but frequently caused extrapyramidal adverse effects, particularly in patients under 30 years of age; diphenhydramine was used to reduce these effects
- For prophylaxis of *acute emesis* associated with *moderately emetogenic chemotherapy*, dexamethasone with a 5-HT_3 antagonist is suggested.[1-3] Aprepitant (or fosaprepitant) may be added for patients given an anthracycline and cyclophosphamide or other chemotherapy drugs of moderate emetic risk
- Dexamethasone alone may be used for prophylaxis with chemotherapy of *low emetic risk*;[1-3] alternatives include prochlorperazine or metoclopramide.[2] No routine prophylactic antiemetic needs to be given for chemotherapy of *minimal emetic risk*;[1-3] however, as-needed or prophylactic use of dexamethasone, a phenothiazine, or metoclopramide is common, particularly for patients with poor emetic control during previous therapy[1]
- Lorazepam may be used for its amnestic, sedative, and anxiolytic effects as an adjunct to antiemetics when *anticipatory emesis* is a problem
- Good control of acute emesis is important in preventing *delayed emesis*. In addition, for prophylaxis of delayed emesis from highly emetogenic chemotherapy, a combination of dexamethasone with aprepitant may be used. After moderately emetogenic chemotherapy, prophylaxis with a single drug such as dexamethasone or a 5-HT_3 antagonist may be sufficient.[1,3] Aprepitant or dexamethasone alone has been suggested for patients given an anthracycline with cyclophosphamide[1,3]

Cannabinoids such as dronabinol and nabilone have been used for chemotherapy-induced nausea and vomiting, usually as second-line drugs. Although they have some advantages because of their effects on mood, their use is limited by adverse effects.[4]

If *breakthrough emesis* occurs, management is often difficult. The general principle of treatment is to add an additional antiemetic from a different class; multiple concurrent drugs, perhaps in alternating schedules or by alternating routes may need to be considered. Since oral dosage may not be feasible because of ongoing vomiting, treatment is often given by the rectal or intravenous routes.[2] More intensive prophylactic treatment should be considered in subsequent courses.

Motion sickness has been described as a normal reaction to stimuli that occur during passive transportation and to which the individual is not adapted. The term embraces all forms of travel sickness including sea sickness, car sickness, train sickness, and air sickness. It is a type of vertigo in which autonomic symptoms predominate, therefore signs and symptoms include pallor, sweating, increased salivation, yawning, malaise, and hyperventilation.

MANAGEMENT. The aim is to *prevent* motion sickness and antiemetics are more effective if given prophylactically before nausea and vomiting has developed. The principal drugs used are the antimuscarinic hyoscine and some of the centrally acting antihistamines.[5,6] In some countries dexamfetamine has been tried,[6] although its adverse effects and the risk of abuse make it an unlikely choice. Antiemetic drugs *not* effective against motion sickness include metoclopramide, domperidone, chlorpromazine, and 5-HT_3 antagonists. Ginger has been tried. Evidence for the value of wrist acupressure is equivocal.[6]

For short-term protection against motion sickness hyoscine hydrobromide has been shown to be effective.[7] It can be taken orally about 30 minutes before a journey followed by further doses every 6 hours if necessary. Transdermal hyoscine has a longer duration of action, but the patches need to be applied to the skin several hours before travelling.

There is little good evidence comparing the efficacy of antihistamines with hyoscine against motion sickness,[7] but they are often better tolerated. They are usually given orally and include cinnarizine, cyclizine, dimenhydrinate, meclozine, and promethazine; all have similar efficacy, but differ in onset and duration of action and in the extent of adverse effects such as drowsiness. Their antimuscarinic properties may contribute to their effects. Non-sedating antihistamines (e.g. astemizole and terfenadine) penetrate poorly into the CNS and do not appear to be effective against motion sickness.

Once motion sickness has developed, gastric motility is inhibited and oral antiemetics are unlikely to be effective. Where intramuscular injection is feasible, promethazine appears to be the most effective treatment. If exposure is likely to be prolonged, transdermal hyoscine may be useful, but will not provide benefit for some hours.[6]

Palliative care. Nausea and vomiting are common in terminal illness, and may be prolonged. Causes may include gastric irritation or stasis, bowel obstruction, renal failure, hypercalcaemia, raised intracranial pressure, infection, or the effects of drugs or radiation; anxiety, cough, and pain may exacerbate the condition.[8-11]

MANAGEMENT. Management will depend on the cause of the nausea and vomiting.[9,10] The evidence base for many antiemetics in terminal care is poor; it is perhaps best for metoclopramide, but evidence for many common and apparently effective interventions, such as haloperidol, cyclizine, and levomepromazine, is conflicting.[12] However, guidelines have been developed, either empirically or based on considerations of the likely causes. Recommendations include:[9]

- any correctable causes should be managed appropriately, and treatment for exacerbating conditions (such as anxiety) given
- an appropriate antiemetic should be given immediately, and repeated as often as necessary. If nausea is continuous or vomiting frequent, subcutaneous injection or continuous subcutaneous infusion may be preferred to the oral route. The usual initial choice for palliative care in the UK is between metoclopramide (preferred if the cause is gastric stasis, gastritis, or functional bowel obstruction), haloperidol (favoured in drug-induced vomiting, hypercalcaemia, and renal failure), and cyclizine (raised intracranial pressure, motion sickness, organic bowel obstruction)
- if treatment fails an alternative drug may be considered, or combination therapy may be necessary (prokinetics such as metoclopramide should not be combined with antimuscarinic drugs as their actions are antagonistic). Dexamethasone (usually added to the regimen), or levomepromazine or olanzapine (broad-spectrum antiemetics; these are usually substituted for the previous regimen) are useful where first-line drugs fail. Olanzapine is usually used if levomepromazine is too sedative. Other phenothiazines, notably prochlorperazine, and the phenothiazine antihistamine promethazine, are sometimes still used, but chlorpromazine is less effective than levomepromazine where a broad-spectrum drug is required. The role of 5-HT_3 antagonists is limited but they may be useful in nausea and vomiting secondary to chemotherapy (above) or radiotherapy (below), or sometimes in bowel obstruction or renal failure
- if there is colic or a need to reduce secretions, hyoscine butylbromide should be given, alone or with cyclizine. If this is inadequate in patients with obstruction, octreotide may be helpful

Non-drug measures may include appropriate diet and avoidance of unpleasant odours, adequate hydration, and regular mouth care.[8,10] Acupressure and acupuncture may provide some benefit.[10,13]

Postoperative nausea and vomiting (PONV) is a common and distressing adverse effect of anaesthesia and surgery;[14-18] it is seen in some 20 to 30% of patients undergoing surgery under general anaesthesia,[15,16,19] and is perceived by patients as a problem comparable to postoperative pain.[20]

Risk factors for PONV include a history of motion sickness or previous PONV, female sex, not smoking, use of opioids during or after surgery, use of volatile inhaled anaesthetics or nitrous oxide, and prolonged surgery.[15-19,21,22] It is widely considered that certain types of surgery carry an increased risk, but it is unclear whether the increase is due to the type of surgery or independent risk factors.[15,16] A study comparing various predictive models found that none was perfect, but that a simplified model based on history, sex, smoking status, and opioid use was as effective as more complex methods.[21]

MANAGEMENT. Prediction of risk is of value since much of the management of PONV focuses on prevention. It is generally agreed that prophylaxis should be reserved for patients at moderate to high risk. In these, various strategies may be adopted to *reduce risk* where possible, including the use of regional anaesthesia or total intravenous anaesthesia with propofol (but see also p. 1910.2), avoidance of nitrous oxide, minimal use of opioids, adequate hydration (especially with colloids), and possibly the use of intraoperative supplemental oxygen (although not all studies found this of benefit).[15,16] Avoidance of high-dose neostigmine (limiting the dose to a maximum of 2.5 mg in adults) has also been suggested.[16] There is evidence that some nonpharmacological interventions, such as acupuncture of the P6 point, may also be effective, especially for nausea.[23]

Many types of drugs have been tried as *prophylactic antiemetics*. These include the 5-HT_3 antagonists, phenothiazines such as prochlorperazine, butyrophenones such as droperidol, antihistamines such as promethazine, cyclizine, or dimenhydrinate, and some other drugs such as dexamethasone and hyoscine.[18,22] A large and well-designed multicentre study (IMPACT) has shown that ondansetron, droperidol, and dexamethasone are of similar efficacy;[24] it also confirmed that avoidance of volatile anaesthetics and nitrous oxide was of as much benefit in preventing PONV as use of a prophylactic antiemetic. The evidence suggests that other 5-HT_3 antagonists are of similar efficacy to ondansetron.[16] Evidence for some of the older drugs is less extensive, although benefit has often been shown in individual studies.[16] Systematic reviews have confirmed the benefit of prophylaxis with dimenhydrinate[25] and transdermal hyoscine[26] but have suggested that metoclopramide, which has been widely used, is in fact of little value in preventing PONV,[27,28] perhaps because the doses used are too low.[28] However, another systematic review[29] included metoclopramide in a list of drugs that reliably prevented PONV compared with placebo; other drugs listed were cyclizine, dexamethasone, dolasetron, droperidol, granisetron, ondansetron, and tropisetron. Ginger root has also been suggested, but again does not seem to be effective in this context,[30] although there is some evidence of benefit for intramuscular ephedrine.[31] Clonidine has also been reported to produce benefit,[32,33] possibly secondary to reduced sympathetic tone and lower use of inhalation anaesthetics and opioids. Neurokinin-1 antagonists such as aprepitant may also be effective.[22]

In patients at moderate risk of PONV, therefore, in addition to risk reduction, use of 1 or 2 prophylactic antiemetics may be considered,[15,16] such as a 5-HT_3 antagonist, droperidol (although concerns about effects on QT interval have restricted its availability), or dexamethasone; or perhaps transdermal hyoscine, dimenhydrinate, or another drug such as promethazine or a heterocyclic phenothiazine (prochlorperazine or perphenazine). In patients at higher risk, or in whom nausea and vomiting would be particularly problematic, a combination of antiemetics from different classes should be given,[15,16] since the IMPACT study has shown that the effects of such interventions are additive.[24]

If PONV develops, *treatment* will depend on whether prophylaxis was given. In patients who have received no prophylaxis, or only dexamethasone, a small dose of a 5-HT_3 antagonist has been recommended.[15,16] If PONV occurs within 6 hours of surgery despite antiemetic prophylaxis, additional doses of the same drug convey no further benefit, and treatment with drugs from another class is recommended.[15,16,18,22] Beyond this time any suitable drug may be used, but dexamethasone and transdermal hyoscine are not recommended for treatment because of their slow onset of action.[16]

Pregnancy. Nausea and vomiting or 'morning sickness' is common in the first trimester of pregnancy, but is generally mild and does not require drug therapy. Dietary modification such as eating small frequent carbohydrate meals is widely thought to be helpful.[34] A systematic review has suggested that pyridoxine, which has been shown to be of benefit, should be tried first if drug therapy is required.[34] Benefit has also been reported with ginger root,[34,35] but evidence of benefit from stimulation of the P6 acupuncture point is ambiguous.[34] Antihistamines such as buclizine, dimenhydrinate, hydroxyzine, meclozine, promethazine, and thiethylperazine have also been tried, and appear to be more effective than placebo,[34] but there are obvious concerns about potential effects on the fetus (see Pregnancy, under Precautions for Antihistamines, p. 614.2). Although no real evidence of a teratogenic effect exists,[36] therapy has tended to be reserved for severe cases, and short-term use. In some countries metoclopramide has been widely used; there is evidence for a lack of adverse effects on the fetus,[37] but younger mothers may be at increased risk of extrapyramidal effects.

Persistent vomiting and severe nausea may progress to *hyperemesis gravidarum* if adequate hydration cannot be maintained; the condition occurs in up to 1% of pregnancies.[38] Management of hyperemesis includes hospitalisation for intravenous fluid and electrolyte replacement, and this is usually sufficient. Routine thiamine supplementation, orally if tolerated, otherwise parenterally, has been recommended to reduce the risk of Wernicke's encephalopathy[38,39] (see Wernicke-Korsakoff Syndrome, p. 2103.3), although there is some dissent from this view.[40] If hyperemesis fails to respond to rehydration, antiemetics should be used; options include domperidone, phenothiazines, and antihistamines.[38] It has been suggested that hyperemesis unresponsive to conventional therapy may respond to oral prednisolone or intravenous hydrocortisone.[38] There have also been anecdotal reports of ondansetron being used successfully in life-threatening

hyperemesis gravidarum unresponsive to conventional treatment,[41] although a double-blind pilot study found it to be no more effective than promethazine.[42] A systematic review found no evidence of benefit for any intervention in hyperemesis gravidarum.[34]

After a review[43] of the data the American Gastroenterological Association Institute considered[44] that metoclopramide, prochlorperazine, promethazine, trimethobenzamide, and ondansetron were of low risk in pregnant women and could be used for nausea and vomiting and for hyperemesis gravidarum.

Radiotherapy. The risk of emesis with radiotherapy varies with the treatment given, particularly the area of the body irradiated. However, emetic risk, and recommendations for use of antiemetics, are less clearly defined than in the situation of chemotherapy-induced nausea and vomiting.[1] Use of a prophylactic 5-HT_3 antagonist with or without dexamethasone is usually recommended in patients receiving radiation to the upper abdomen or total body irradiation.[1,2] For radiotherapy of minimal emetogenic potential, treatment on an as-needed only basis has been suggested.[1]

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Oesophageal motility disorders

Oesophageal disorders, many due to disturbances in oesophageal motility, may produce non-cardiac chest pain, similar to that of angina pectoris, from which they must be differentiated.

Achalasia is obstruction caused by failure of the lower oesophageal sphincter to relax and permit passage of food into the stomach. It is accompanied by dilatation and abnormal peristalsis in the oesophagus, which becomes a reservoir for the unassimilated matter; symptoms include dysphagia and sometimes pain. The treatment of choice is mechanical dilatation of the sphincter or surgery. Laparoscopic techniques have reduced the risks associated with surgery, and this may become the preferred treatment. Taking isosorbide dinitrate or nifedipine before eating results in some improvement in achalasia, but these drugs have a role only as a temporary measure, or when other options are not suitable. Sildenafil is under investigation. More recently, injection of botulinum toxin into the lower oesophageal sphincter has been found to be effective, but remission in the long-term is better with mechanical dilatation than botulinum toxin. Therefore, it has been recommended that botulinum toxin be reserved for patients thought to be at risk from mechanical dilatation or surgery.

Oesophageal spasm, although frequently asymptomatic, can produce dysphagia and pain. Drug treatment of diffuse oesophageal spasm, or its variant 'nutcracker oesophagus' which is characterised by high amplitude peristalsis in the oesophagus, is often ineffective. Antimuscarinic antispasmodics, nitrates, and calcium-channel blockers have been tried in an attempt to relax the smooth muscle, but results are often disappointing; experience with nifedipine in patients with nutcracker oesophagus suggests that decrease in oesophageal pressure may not correlate with reduction in pain. As with achalasia, minimally invasive surgery is effective for these conditions. Sildenafil is also under investigation.

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Peptic ulcer disease

Peptic ulceration is a common condition consisting of a distinct break in the gastrointestinal mucosa, usually of the stomach or duodenum. Duodenal ulcers are rarely malignant but gastric ulcers are more commonly associated with malignancy.

The aetiology of peptic ulcer disease is probably multifactorial but the bacterium *Helicobacter pylori* plays an important role. Abnormalities of normal mucosal defence mechanisms, and, in the case of gastric ulcer, reflux of duodenal contents into the stomach or delayed gastric emptying may also be involved. Other factors include emotional stress, smoking, alcohol, and drugs such as NSAIDs or corticosteroids.

Peptic ulcer disease usually presents as dyspeptic pain, sometimes associated with nausea, vomiting, anorexia, heartburn, or bloating. Patients may develop complications such as bleeding, obstruction, or perforation.

Certain simple measures such as bed rest, dietary modification, and cessation of smoking, may accelerate ulcer healing, but these play an adjuvant role, and the basis of treatment is pharmacological. Treatment is aimed at eradicating *H. pylori* with antibacterials and neutralising or inhibiting acid activity with antisecretory drugs. Surgical treatment is used in patients with acute complications such as perforation, haemorrhage, obstruction, or pyloric stenosis, or in patients with recurrent or intractable ulcer disease, or where there is suspicion of malignancy.

Anti-Helicobacter therapy. The presence of *H. pylori* should usually be confirmed before therapy to eradicate the infection is started. The urea breath test is the most widely used method to test for *H. pylori*, but may produce false-negatives if used during or too soon after treatment with proton pump inhibitors (see Helicobacter Infection under Precautions for Omeprazole, p. 1870.2) or antibacterials. There is good evidence that eradication therapy has benefits both in healing ulcers and preventing recurrence, especially for duodenal ulcer.[1] Many different regimens have been tried, using various combinations of oral antibacterials with antisecretory drugs. Expert consensus is that any treatment regimen should achieve at least 80% eradication of *H. pylori*,[2] and the most appropriate regimen may therefore depend to some extent on local patterns of resistance.

The following recommendations have been made by an international expert group:[2]

- ***where clarithromycin resistance is below 15 to 20%***
  - **triple therapy** with a proton pump inhibitor (PPI), clarithromycin, and metronidazole (provided the prevalence of metronidazole resistance is less than 40%), for 14 days
    or
    PPI, clarithromycin, and amoxicillin, for 14 days
    or
  - **quadruple therapy** with a bismuth compound, a PPI, and two antibacterials, for 14 days. Such a regimen as used in the UK (usually for rescue therapy, see below) comprises a proton pump inhibitor with tripotassium dicitratobismuthate, tetracycline, and metronidazole.
  - Treatment for 7 days rather than 14 may be acceptable where local studies show it to be effective (in the UK, the *BNF* considers that adverse effects and poor compliance are likely to offset any therapeutic gain from 14-day regimens)
- ***in areas of high clarithromycin resistance*** it may be appropriate to consider antibacterial susceptibility testing before beginning treatment; regimens that may be considered include:
  bismuth-containing quadruple therapy as above
  or
  PPI, amoxicillin, and metronidazole (provided metronidazole resistance is low)
  or
  PPI, tetracycline, and metronidazole
- testing to confirm eradication, at least 4 weeks after treatment, is recommended; a urea breath test is the preferred method
- rescue treatments in patients with refractory disease should be based on antibacterial susceptibility testing. In the UK, the *BNF* considers that the bismuth-based quadruple therapy regimen referred to above may be effective.
- other antibacterials that have been investigated in eradication regimens (mainly as rescue treatments) include rifabutin and levofloxacin, although there might be concerns about selecting for mycobacterial resistance if the former were to be used widely, and increasing fluoroquinolone resistance may limit the value of the other

There is some evidence that a **sequential regimen** of a PPI with amoxicillin for 5 days, followed by the PPI with a nitroimidazole antibacterial (tinidazole) and clarithromycin for a further 5 days, is more effective than a standard 7- or 10-day triple therapy regimen in treatment-naive patients.[3] The potential value of such regimens remains to be more widely proven.[2,4]

The use of **dual therapy** regimens comprising a PPI and an antibacterial is no longer recommended. Similarly, although acid suppressive therapy has sometimes been continued after completing eradication therapy, the *BNF* considers this unnecessary, unless the ulcer is large or complicated by bleeding or perforation.

Before the advent of *H. pylori* eradication therapy, drug treatment of gastric and duodenal ulcers relied mainly on antisecretory therapy. Four to 8 weeks of H_2-antagonist or proton pump inhibitor therapy was required for ulcer

healing. Because of the high incidence of relapse, these drugs were then often given as maintenance therapy. Numerous other drugs were formerly used in peptic ulcer disease before the development of H_2-antagonists and proton pump inhibitors, including antacids, antimuscarinics such as pirenzepine, and mucosal protectants such as sucralfate.

NSAID-induced ulceration. The ulcerogenic effects of NSAIDs have been attributed to inhibition of prostaglandin synthesis and mucosal cell proliferation, and the ulcers they cause may differ from non-iatrogenic ulcers in their pathology and prognosis.[5,6] As many as 25% of chronic NSAID users will develop ulcers, and 2 to 4% will bleed or perforate.[7] Although considered to be independent risk factors for peptic ulcer disease, *H. pylori* infection and NSAID use may act synergistically in peptic ulceration and ulcer bleeding.[8,9] If peptic ulceration develops during treatment with an NSAID the drug should be withdrawn if possible. If this can be done, the ulcer may be treated with an antisecretory drug such as an H_2-antagonist or PPI given for 4 to 8 weeks. If NSAIDS have to be continued, *treatment* is with antisecretory drugs or the prostaglandin analogue misoprostol.[5,6] Ulcers tend to heal more slowly with H_2-antagonists if NSAIDs are continued, whereas the rate of ulcer healing with PPIs appears not to be affected. There is also some evidence that omeprazole is more effective at healing NSAID-associated ulceration than misoprostol.[10] Patients at high risk of NSAID-associated gastrointestinal complications, including those with a history of these events, should receive *prophylactic therapy* if NSAID treatment is absolutely necessary.[5-7] A systematic review[11] concluded that misoprostol, PPIs, and double-dose H_2 antagonists are effective at preventing chronic NSAID-associated gastric and duodenal ulcers. Standard doses of H_2-antagonists prevent NSAID-associated duodenal ulceration, but appear to be less effective in preventing gastric ulceration. Another systematic review also found that misoprostol, and probably PPIs, were effective in reducing the risk of symptomatic NSAID-associated ulceration, as was the use of specific inhibitors of cyclo-oxygenase-2 such as celecoxib;[12] use of a cyclo-oxygenase-2 inhibitor with a PPI may be appropriate in very high risk patients.[13] After healing of NSAID-associated ulceration, prophylaxis with a proton pump inhibitor was more effective at preventing recurrence than an H_2 antagonist,[14,15] and omeprazole was more effective and better tolerated than misoprostol.[10] Whether *H. pylori* eradication is appropriate in patients receiving long-term NSAIDs remains debatable. There is some evidence that eradication reduces the risk of bleeding in patients who have not previously taken NSAIDs,[2,16] and testing and eradication in patients taking PPIs long-term for prevention of NSAID-induced ulceration has been advocated by an expert consensus, since there is evidence that combination of *H. pylori* infection and long-term acid suppression may accelerate the development of pre-malignant changes in the stomach.[2] However, PPI maintenance is more effective than *H. pylori* eradication in preventing ulcer recurrence or bleeding in patients taking NSAIDs,[2] and there is no convincing evidence that eradication speeds ulcer healing.[16]

Stress ulceration may occur in the stomach or the duodenum after major physical trauma such as burns or surgery, or after severe sepsis or illness. H_2-antagonists and sucralfate are widely used for the prevention of stress ulceration in high-risk patients in intensive care units,[17-19] and prophylactic therapy is increasingly used, though with little evidence, in less severely ill patients.[20] Pirenzepine is used in a few countries, and some[17] prefer it in neurosurgical patients and those with head trauma. H_2-antagonists may be given orally, by nasogastric tube, or by the intravenous route (intermittent or continuous). Meta-analysis has indicated that sucralfate may be as effective as an H_2-antagonist in reducing bleeding, and is associated with lower rates of mortality and pneumonia.[21] For discussion of the possible increased risk of infections with acid suppressing drugs, see Infection, under Omeprazole, p. 1870.1. The findings of a subsequent large randomised study[22] by the same authors were at odds with those of this meta-analysis, suggesting that intravenous ranitidine was more effective than sucralfate given orally or via nasogastric tube in reducing clinically significant gastrointestinal bleeding. Moreover, there was no difference in rate of ventilator-associated mortality between ranitidine and sucralfate recipients. A further meta-analysis[23] has in turn raised doubts about the efficacy of ranitidine; no significant benefit was found for ranitidine, compared with placebo, in the prevention of bleeding. One clinical guideline suggests that, given the conflicting evidence, the choice between antacids, H_2-antagonists, and sucralfate be made on an institutional basis.[18] PPIs are also used for stress ulcer prophylaxis, although evidence for such use is lacking.[19]

Bleeding ulcer. Peptic ulceration is responsible for about 50% of all cases of upper gastrointestinal bleeding: the condition is potentially life-threatening and in severe cases prompt resuscitation with intravenous fluids and blood may be required. About 80% of patients will stop bleeding spontaneously without recurrence, but the remaining 20% are at risk of severe morbidity or death,[24] and early stratification into low- and high-risk categories on the basis of clinical and endoscopic criteria is important for proper management.[24,25] No treatment may be needed for low-risk patients, but those with a clot in an ulcer bed should undergo irrigation and appropriate treatment of the underlying lesion, and high-risk patients should be given immediate endoscopic injection therapy for haemostasis.[24]

Many different solutions have been used for endoscopic injection, including adrenaline (alone or with sclerosants such as monoethanolamine or lauromacrogol), alcohol, fibrin glue, sodium tetradecyl sulfate, thrombin, or saline (normal or hypertonic). None has been clearly shown to be superior,[24] but sclerosants and alcohol increase the risk of complications such as perforation and necrosis compared with adrenaline.[25] Adrenaline injection 1 in 10 000 is commonly used; a large volume (over 13 mL) is considered more effective at achieving sustained haemostasis than smaller volumes.[25] Thermal, laser, or multipolar (coaptive) or plasma electrocoagulative endoscopic techniques are also of benefit, and again there is no clear evidence to prefer one over another.[24] The use of mechanical clips may also be effective.[24,25] A combination of endoscopic therapies may be of greater benefit than monotherapy.[24,25] If endoscopic treatments fail to stop bleeding, or rebleeding occurs, further endoscopic therapy may be considered, but otherwise patients require surgery,[24,25] or selective arterial embolisation.[25]

There is good evidence from systematic review[26] that treatment with PPIs reduces rebleeding and surgery in patients with acute bleeding peptic ulcers; one such review did not show reduced mortality,[26] although others consider it to have been proven.[24] An intravenous bolus of a PPI followed by continuous infusion for 72 hours is recommended in patients who have undergone successful endoscopic therapy.[24,25] There is no evidence that any PPI is superior to others.[24,27] Some suggest that high-dose PPI therapy (oral or intravenous, depending on the degree of risk) should also be considered in patients awaiting endoscopy.[24]

In contrast, there is no evidence that H_2-antagonists are of benefit in the treatment of acute nonvariceal bleeding, and somatostatin, octreotide, or tranexamic acid are not recommended.[24,25,28]

Eradication of *H. pylori* is recommended in those patients positive for the organism;[24,25] eradication therapy is superior to antisecretory drugs alone in preventing rebleeding.[29]

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Zollinger-Ellison syndrome

Zollinger-Ellison syndrome is a rare disorder characterised by the presence of a gastrin-producing tumour (gastrinoma), which leads to hypersecretion of gastric acid and consequent peptic ulcer disease (often with complications such as perforation or bleeding), diarrhoea, or malabsorption. Gastrinomas usually occur in the non-beta islet cells of the pancreas or in the duodenal wall. Up to two-thirds are malignant. About 20 to 25% of cases are seen in patients with multiple endocrine neoplasia type 1 (MEN-1) syndrome.

Initial treatment is aimed at controlling the hypersecretion of gastric acid with an antisecretory drug. Giving enough medication just to control symptoms is not considered adequate, and it is important that acid secretion is reduced below 10 mmol/hour. Intravenous H_2-antagonists or proton pump inhibitors may be required initially. Once the symptoms have been controlled the tumour can be investigated for surgical removal. When complete removal is not possible then antisecretory therapy is continued indefinitely. A proton pump inhibitor is the drug of choice; it profoundly reduces acid secretion with once- or twice-daily use, although relatively high doses are required compared with those used in other conditions. An H_2-antagonist such as cimetidine or ranitidine may be used as an alternative to omeprazole, and, as with omeprazole, daily doses are higher than those used for other conditions; they are given in 3 or 4 divided doses. The somatostatin analogue octreotide can be used to reduce serum gastrin, but has to be given subcutaneously, and is not well tolerated.

Parietal cell vagotomy may be performed to reduce acid secretion if the tumour is not found, to allow lower doses of antisecretory drugs to be used.

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Aceglutamide Aluminium *(rINNM)*

Aceglutamida de aluminio; Aceglutamide Aluminum (USAN); Acéglutamide d'Aluminium; Aluminii Aceglutamidum; KW-110; Алюминий Ацеглутамид.

Pentakis (N^2-acetyl-L-glutaminato)tetrahydroxytrialuminium.

$C_{35}H_{59}Al_3N_{10}O_{24}$=1084.8

CAS — 12607-92-0.

UNII — R7QTG0PMPX.

Pharmacopoeias. In *Jpn.*

Profile

Aceglutamide aluminium, a complex of aceglutamide with aluminium hydroxide, is an antacid with general properties similar to those of aluminium hydroxide (p. 1817.2). It is given orally in a usual dose of 700 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Glumal.

Aclatonium Napadisilate (BAN, rINN)

Aclatonii Napadisilas; Aclatonium Napadisylate; Celatonium Napadisilate; Choline Naphthalene-1,5-Disulphonate (2:1) Dilactate Diacetate; Napadisilate d'Aclatonium; Napadisilato de aclatonio; SKF-100916-J; TM-723; Аклатония Нападизилат.

2-(2-Acetoxypropionyloxy)ethyltrimethylammonium naphthalene-1,5-disulphonate (2:1).

$2C_{10}H_{20}NO_4.C_{10}H_6O_6S_2$=722.8

CAS — 55077-30-0.

UNII — YX23434YHQ.

Profile

Aclatonium napadisilate is a cholinergic agonist given orally for its prokinetic properties in the management of decreased gastrointestinal motility (p. 1805.2) after gastrointestinal surgery, and to relieve symptoms of biliary dyskinesia and chronic gastritis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Abovis.

Acotiamide Hydrochloride (USAN, rINNM)

Acotiamide, Chlorhydrate d'; Acotiamidi Hydrochloridum; Hidrocloruro de acotiamida; YM-443; Z-338; Акотиамида Гидрохлорид.

N-(2-[bis(1-Methylethyl)amino]ethyl)-2-[(2-hydroxy-4,5-dimethoxybenzoyl)amino]thiazole-4-carboxamide monohydrochloride trihydrate.

$C_{21}H_{30}N_4O_5S.HCl.3H_2O$=541.1

CAS — 773092-05-0.

UNII — NMW7447A9A.

Profile

Acotiamide hydrochloride inhibits peripheral anticholinesterase activity which improves gastrointestinal motility and gastric emptying; it is used orally in the symptomatic relief of functional dyspepsia. Adverse effects have included constipation, diarrhoea, and nasopharyngitis; raised triglyceride, liver enzymes, and prolactin levels have also been reported.

References.

1. Nolan ML, Scott LJ. Acotiamide: first global approval. *Drugs* 2013; 73: 1377–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Acofide.

Albumin Tannate

Albuminitannaatti; Albúmina, tanato de; Albumini Tannas; Albumintannat; Albutannin; Tannin Albuminate; Альбумин Таннат.

CAS — 9006-52-4.

ATC — A07XA01.

ATC Vet — QA07XA01.

Pharmacopoeias. In *Jpn*.

Profile

Albumin tannate, a compound of tannin with albumin, is given orally for its astringent properties in the treatment of diarrhoea (p. 1805.2). It is stated to liberate tannic acid (p. 2625.2) in the gastrointestinal tract.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Tannalbin; *China*: Dan Na Er Bin (单那尔滨); *Ger.*: Tannalbin; *Neth.*: Entosorbine-N; *Pol.*: Taninal.

Multi-ingredient Preparations. *Austria*: Neoplex; *Belg.*: Tanalone; *Fin.*: Tannopon†; *Ger.*: Tannacomp; *Hung.*: Bolus Adstringens; *Pol.*: Salotannal†; *Spain*: Demusin†; Salitanol Estreptomicina†.

Alexitol Sodium (BAN, rINN)

Alexitol sódico; Alexitol Sodique; Alexitolum Natricum; Алекситол Натрий.

Sodium poly(hydroxyaluminium) carbonate-hexitol complex.

CAS — 66813-51-2.

Profile

Alexitol sodium is an antacid with general properties similar to those of aluminium hydroxide (p. 1817.2). It is given orally in doses of 360 to 720 mg when required, up to a maximum of sixteen 360-mg tablets in 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hong Kong*: Actal; *Malaysia*: Actal†; *Singapore*: Actal; *Thai.*: Actal†; *UK*: Actal.

Multi-ingredient Preparations. *Malaysia*: Actal Plus†.

Alicaforsen (rINN)

Alicaforsén; Alicaforsenum; Аликафорсен.

2′-Deoxy-(*R*)-*P*-thioguanylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioadenylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioadenylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioguanylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioguanylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioguanylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioadenylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioguanylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxyadenosine.

$C_{192}H_{244}N_{75}O_{98}P_{19}S_{19}$=6368.1

CAS — 185229-68-9.

Alicaforsen Sodium (USAN, rINNM)

Alicaforsen Nonadecasodium; Alicaforsén sódico; Alicaforsen Sodique; Alicaforsenum Natricum; Isis-2302; Аликафорсен Натрий.

$C_{192}H_{225}N_{75}Na_{19}O_{98}P_{19}S_{19}$=6785.8

CAS — 331257-52-4.

UNII — 4TWN6SZB8W.

Profile

Alicaforsen is an antisense oligonucleotide that inhibits the production of the cellular adhesion molecule ICAM-1, which plays a role in the inflammatory response involved in inflammatory bowel disease. It has been tried in ulcerative colitis and pouchitis, and with less success in Crohn's disease.

References.

1. Barish CF. Alicaforsen therapy in inflammatory bowel disease. *Expert Opin Biol Ther* 2005; 5: 1387–91.
2. Miner PB, *et al.* Safety and efficacy of two dose formulations of alicaforsen enema compared with mesalazine enema for treatment of mild to moderate left-sided ulcerative colitis: a randomized, double-blind, active-controlled trial. *Aliment Pharmacol Ther* 2006; 23: 1403–13. Correction. *ibid.*: 24: 1268.
3. van Deventer SJ, *et al.* A phase II dose ranging, double-blind, placebo-controlled study of alicaforsen enema in subjects with acute exacerbation of mild to moderate left-sided ulcerative colitis. *Aliment Pharmacol Ther* 2006; 23: 1415–25.
4. Miner PB, *et al.* Bioavailability and therapeutic activity of alicaforsen (ISIS 2302) administered as a rectal retention enema to subjects with active ulcerative colitis. *Aliment Pharmacol Ther* 2006; 23: 1427–34.
5. Yacyshyn B, *et al.* A randomized, double-masked, placebo-controlled study of alicaforsen, an antisense inhibitor of intercellular adhesion molecule 1, for the treatment of subjects with active Crohn's disease. *Clin Gastroenterol Hepatol* 2007; 5: 215–20.

Alizapride Hydrochloride (rINNM)

Alizaprida, hidrocloruro de; Alizapride, Chlorhydrate d'; Alizapridi Hydrochloridum; Hidrocloruro de alizaprida; Ализаприда Гидрохлорид.

N-(1-Allyl-2-pyrrolidinylmethyl)-6-methoxy-1*H*-benzotriazole-5-carboxamide hydrochloride.

$C_{16}H_{21}N_5O_2.HCl$=351.8

CAS — 59338-93-1 (alizapride); 59338-87-3 (alizapride hydrochloride).

ATC — A03FA05.

ATC Vet — QA03FA05.

UNII — 41BT72BOQ7.

Uses and Administration

Alizapride is a substituted benzamide similar to metoclopramide (p. 1862.2), which is used to control nausea and vomiting (p. 1811.3) associated with a variety of disorders. It is given as the hydrochloride but doses are expressed in terms of the base. Alizapride 50 mg is equivalent to about 55.8 mg of alizapride hydrochloride.

Alizapride hydrochloride is given in usual oral doses equivalent to 75 to 300 mg of alizapride daily in divided doses. For children's doses, see below. It is also given by intravenous or intramuscular injection in doses equivalent to 50 to 200 mg of alizapride daily.

For patients receiving cancer chemotherapy usual daily doses equivalent to alizapride 2 to 5 mg/kg have been given intravenously or intramuscularly in 2 divided doses, one 30 minutes before and one 4 to 8 hours after the cytotoxic regimen. For highly emetic regimens requiring doses above 5 mg/kg it may be given by intravenous infusion over 15 minutes every 2 hours for 5 doses, starting 30 minutes before the cytotoxic. It has been recommended that the total dose given with a course of chemotherapy does not exceed 4.5 g.

Administration in children. Alizapride hydrochloride has been given to children for the symptomatic treatment of nausea and vomiting in oral doses equivalent to 5 mg/kg of alizapride daily.

Adverse Effects and Precautions

As for Metoclopramide, (see p. 1863.2).

Pharmacokinetics

Alizapride is well absorbed from the gastrointestinal tract. It is mainly excreted unchanged in the urine and has an elimination half-life of about 3 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Gastriveran; *Belg.*: Litican; *Braz.*: Superan; *Fr.*: Plitican; *Ger.*: Vergentan; *Gr.*: Lyostene; *Ital.*: Limican; *Neth.*: Litican.

Almagate (BAN, USAN, rINN)

Almagaatti; Almagat; Almagát; Almagatas; Almagato; Almagatum; LAS-3876; Альмагат.

Aluminium trimagnesium carbonate heptahydroxide dihydrate.

$AlMg_3(CO_3)(OH)_7.2H_2O$=315.0

CAS — 66827-12-1 (almagate); 72526-11-5 (anhydrous almagate).

ATC — A02AD03.

ATC Vet — QA02AD03.

UNII — 568Z59H7ZJ.

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

Ph. Eur. 8: (Almagate). A white or almost white, fine crystalline powder. It contains 15.0 to 17.0% aluminium calculated as aluminium oxide, 36.0 to 40.0% magnesium calculated as magnesium oxide, and 12.5 to 14.5% carbonic acid calculated as carbon dioxide. Practically insoluble in water, in alcohol, and in dichloromethane. It dissolves with effervescence and heating in dilute mineral acids. The filtrate of a 4% suspension in water has a pH of 9.1 to 9.7. Store in airtight containers.

Profile

Almagate is a hydrated aluminium-magnesium hydroxycarbonate. It is an antacid with general properties similar to those of aluminium hydroxide (p. 1817.2) and magnesium carbonate (p. 1856.2). It has been given orally in doses of 1 to 1.5 g.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mex.*: Almax; *Spain*: Almax.

Almasilate (BAN, rINN)

Almasilato; Almasilatum; Aluminium Magnesium Silicate Hydrate; Magnesium Aluminosilicate Hydrate; Magnesium Aluminum Silicate Hydrate; Алмазилат.

$Al_2O_3.MgO.2SiO_2.xH_2O$=262.4 (anhydrous)

CAS — 71205-22-6; 50958-44-6.

ATC — A02AD05.

ATC Vet — QA02AD05.

UNII — 7TO1453R7L (anhydrous almasilate); OZQ8O62H53 (almasilate monohydrate).

Profile

Almasilate is an artificial form of aluminium magnesium silicate hydrate. It is an antacid (p. 1803.1) that is given orally in doses of up to about 1 g.

A hydrated native aluminium magnesium silicate (p. 2168.2) is used as a suspending, thickening, and stabilising agent in pharmaceutical preparations. Attapulgite (p. 1820.1) is another native form.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Gelusil; Megalac; Simagel; *Rus.*: Simagel (Симагель); *Spain*: Alubifar†.

Multi-ingredient Preparations. *Ger.*: Gelusil-Lac; Neo-Pyodron N†; Ultilac N; *India*: Entasid; Intacid-MPS; *Jpn*: Eki Cabe U; *Spain*: Dolcopin; *Switz.*: Gelusil N†.

Aloes

Aclbar; Alavijų sultys, koncentruotos ir išdžiovintos (Cape aloes); Aloe, aclbar; Aloe barbadensis (Barbados aloes); Aloe, Barbados (Barbados aloes); Aloe barbadoská (Barbados aloes); Aloe capensis (Cape aloes); Aloe, Kap (Cape aloes); Aloe kapská (Cape aloes); Aloès des Barbades (Barbados aloes); Aloès du Cap (Cape aloes); Alona barbadoska (Barbados aloes); Alona przylądkowa (Cape aloes); Barbadosi áloé (Barbados aloes); Barbadosin aloe (Barbados aloes); Kapáloé (Cape aloes); Kapin aloe (Cape aloes); Tikrųjų alavijų sultys, koncentruotos ir išdžiovintos (Barbados aloes); Алоэ барбадосское (Barbados aloes); Алоэ Капское (Cape aloes).

CAS — 8001-97-6; 67479-27-0 (aloe gum).

ATC Herb — HA06AB5001 (Aloe ferox: dry leaf juice).

UNII — 0D145J8EME (Aloe ferox leaf); VSVD430YW9 (socotrine aloe).

NOTE. Do not confuse with Aloe vera (p. 1693.2).

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

Ph. Eur. 8: (Aloes, Barbados; Aloe barbadensis). The concentrated and dried juice of the leaves of *Aloe barbadensis*. It contains not less than 28% of hydroxyanthracene derivatives expressed as barbaloin and calculated with reference to the dried drug. Dark brown masses, slightly shiny or opaque with a conchoidal fracture, or a brown powder. Partly soluble in boiling water; soluble in hot alcohol. Store in airtight containers. Protect from light.

The BP 2014 lists Curaçao Aloes as an approved synonym.

Ph. Eur. 8: (Aloes, Cape; Aloe capensis). The concentrated and dried juice of the leaves of various species of *Aloe*, mainly *Aloe ferox* and its hybrids. It contains not less than 18% of hydroxyanthracene derivatives expressed as barbaloin and calculated with reference to the dried drug. Dark brown masses tinged with green and having a shiny conchoidal fracture, or a greenish-brown powder. Partly soluble in boiling water; soluble in hot alcohol; practically insoluble in ether. Store in airtight containers. Protect from light.

USP 36: (Aloe). The dried latex of the leaves of *Aloe barbadensis* (*A. vera*) known in commerce as Curaçao Aloe, or of *A. ferox* and its hybrids, known in commerce as Cape Aloe (Liliaceae). It yields not less than 50% of water-soluble extractive. It has a characteristic, somewhat sour and disagreeable, odour. Curaçao Aloe is brownish-black, opaque masses with a fractured, uneven, waxy, and somewhat resinous surface. Cape Aloe is dusty to dark brown irregular masses, the surfaces of which are often covered with a yellowish powder. Its fracture is smooth and glassy.

Uses and Administration

Aloes is an anthraquinone stimulant laxative (p. 1804.1) but other less toxic drugs are generally preferred.

Homoeopathy

Aloes have been used in homoeopathic medicines under the following names: Aloe; Cape aloes; Aloe capensis; Aloe socotrina; Alo. soc.

Adverse Effects and Precautions

As for Senna, p. 1885.3, although aloes has a more drastic and irritant action.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Contre-Coups de l'Abbe Perdrigeon; Vulcase; *Ger.*: HemoClin†; Krauterlax; *Pol.*: Biostymina; *Switz.*: HemoClin†.

Multi-ingredient Preparations. *Arg.*: Genolaxante; *Austral.*: Peritone; *Austria*: Artin†; Waldheim Abfuhrdragees forte†; *Braz.*: Camomila; Paratonico†; Vitonico; *Canad.*: Friar's Balsam; Laxatil; Laxolax; Traditional Herbal Laxative†; Traditional Laxative; *Chile*: Aloelax; Bulgarolax†; *Cz.*: Dr Theiss Schweden Krauter†; Dr Theiss Schwedenbitter†; *Fr.*: Alco-Aloe†; Dolores; Elusanes Algues brunes/aloes†; Ideolaxyl; Laxilo†; Opobyl†; Petites Pilules Carters†; Tisane D'Ars†; Tonilax; *Ger.*: Chol-Kugeletten Neu†; Cholhepan N; *Hung.*: Bano Svedkeseru; *India*: Aloederm-B; Aloederm-G; Aloederm; Alorex; Calkem; Clarina; Climdan; Climdan; Clin-3; Cytozen; Danclear; Garlill; Koiz; Livomyn; Lunarex; Marc Free; Paedritone; *Israel*: Laxative Compound; *Ital.*: Emoform Alifresh; Grani di Vals†; Lassativi Vetegali†; *Pol.*: Alax; Apinorm†; Bioaron C; Boldaloin; Boldovera; Tabulettae Laxantes; *Rus.*: Alorom (Алором); Bioaron C (Биоарон С); Doktor Mom (Доктор Мом); *S.Afr.*: Helmontskruie†; Lewensessens; Moultons Herbal Extract†; Turulington Tincture†; Wonderkroonessens; *Singapore*: Nu-Derm Toner; Sankaijo; *Spain*: Alofedina; Crislaxo; Cynaro Bilina†; Laxadinas†; Laxante Sanatorium†; Nico Hepatocyn; Opobyl; Pildoras Zeninas; *Switz.*: Padma-Lax; Padmed Laxan; Schweden-Mixtur B; *UK*: Cassilax; Dual-Lax Normal Strength; Laxative Tablets; Natural Herb Tablets; Out-of-Sorts; Senokot Dual Relief; Sure-Lax (Herbal); *Ukr.*: Bioaron C (Биоарон С); Doktor Mom (Доктор Мом сироп); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; *USA*: Diaparene Corn Starch; Vagisil.

Homoeopathic Preparations. *Austria*: Haemex; *Canad.*: Cynara Complex†; *Fr.*: Aesculus Complexe No 103; Aloe Compose; Ferrum Complexe No 29; Grindelia Complexe No 58; Homeogene 22†; L 25; Poconeol no 82†; Sepia Compose; Yucca Complexe No 110; *Switz.*: Hemolingual; Regenaplex Nr. 12; Regenaplex Nr. 25b; Regenaplex Nr. 31c; Regenaplex Nr. 3; Regenaplex Nr. 50b; Regenaplex Nr. 59b; Regenaplex Nr. 71b; Regenaplex Nr. 80aN.

Pharmacopoeial Preparations

BP 2014: Compound Benzoin Tincture;
Ph. Eur.: Aloes Dry Extract, Standardised;
USP 36: Compound Benzoin Tincture.

Aloglutamol

Trometamol Glucaldrate; Алоглутамол.

2-Amino-2-hydroxymethylpropane-1,3-diol gluconate dihydroxyaluminate.

$C_{10}H_{24}AlNO_{12}$=377.3

CAS — 13755-41-4.

ATC — A02AB06.

ATC Vet — QA02AB06.

Profile

Aloglutamol has been used as an antacid (p. 1803.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mex.*: Sabro.

Aloin *(BAN)*

Alloin; Aloína; Алоин.

CAS — 5133-19-7; 8015-61-0; 1415-73-2 (barbaloin).

UNII — W41H6S09F4.

Profile

Aloin is a crystalline substance obtained from aloes (see above). It consists of *C*-glycosides such as barbaloin. Aloin is an anthraquinone stimulant laxative. Like aloes it is very irritant and other less toxic laxatives are generally preferred. Aloin is used as a flavouring agent.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Calsalettes.

Multi-ingredient Preparations. *Austral.*: Ford Pills†; *Braz.*: Pilulas Ross; *Canad.*: Bicholate†; *Israel*: Laxative Compound; *Ital.*: Boldina He; Cuscutine†; Grani di Vals†; *Mex.*: Redotex NF; Redotex; *S.Afr.*: Brooklax Pills†; Doans Backache Pills†; SB 3 Triple Action Pills†; *Spain*: Laxante Bescansa Aloico†; *UK*: Dual-Lax Extra Strong; Modern Herbals Laxative.

Alosetron Hydrochloride

(BANM, USAN, rINNM)

Alosétron, Chlorhydrate d'; Alosetrón, hidrocloruro de; Alosetroni Hydrochloridum; GR-68755C; Hidrocloruro de alosetrón; Алосетрона Гидрохлорид.

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-imidazol-4-yl)methyl]-1*H*-pyrido[4,3-*b*]indol-1-one hydrochloride.

$C_{17}H_{18}N_4O$,HCl=330.8

CAS — 122852-42-0 (alosetron); 122852-69-1 (alosetron hydrochloride).

ATC — A03AE01.

ATC Vet — QA03AE01.

UNII — 2F5R1A46YW.

Uses and Administration

Alosetron is a 5-HT$_3$ antagonist used in the treatment of severe diarrhoea-predominant irritable bowel syndrome (p. 1810.3) in women who have not responded to conventional therapy; efficacy in men has not been established. It is given orally as the hydrochloride but doses are expressed in terms of the base; alosetron hydrochloride 1.12 mg is equivalent to about 1 mg of alosetron.

The initial dose is the equivalent of alosetron 500 micrograms twice daily. Patients who become constipated on this dose should stop alosetron until the constipation resolves; they may then be restarted on 500 micrograms once daily. If constipation recurs at the lower dose, alosetron treatment should be stopped. Patients who tolerate 500 micrograms once or twice daily may continue this dose for 4 weeks. If symptom control is still inadequate after this time, the dose may then be increased up to 1 mg twice daily. If symptoms are not adequately controlled after 4 weeks of treatment with the higher dose, alosetron should be stopped.

References.

1. Lembo A, *et al.* Alosetron in irritable bowel syndrome: strategies for its use in a common gastrointestinal disorder. *Drugs* 2003; 63: 1895–1905.
2. Mayer EA, Bradesi S. Alosetron and irritable bowel syndrome. *Expert Opin Pharmacother* 2003; 4: 2089–98.
3. Cremonini F, *et al.* Efficacy of alosetron in irritable bowel syndrome: a meta-analysis of randomized controlled trials. *Neurogastroenterol Motil* 2003; 15: 79–86.
4. Andresen V, Hollerbach S. Reassessing the benefits and risks of alosetron: what is its place in the treatment of irritable bowel syndrome? *Drug Safety* 2004; 27: 283–92.
5. Lembo AJ, *et al.* Effect of alosetron on bowel urgency and global symptoms in women with severe, diarrhea-predominant irritable bowel syndrome: analysis of two controlled trials. *Clin Gastroenterol Hepatol* 2004; 2: 675–82.
6. Chey WD, *et al.* Long-term safety and efficacy of alosetron in women with severe diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol* 2004; 99: 2195–2203.
7. Chang L, *et al.* A dose-ranging, phase II study of the efficacy and safety of alosetron in men with diarrhea-predominant IBS. *Am J Gastroenterol* 2005; 100: 115–23.
8. Rahimi R, *et al.* Efficacy and tolerability of alosetron for the treatment of irritable bowel syndrome in women and men: a meta-analysis of eight randomized, placebo-controlled, 12-week trials. *Clin Ther* 2008; 30: 884–901.
9. Lewis JH. Alosetron for severe diarrhea-predominant irritable bowel syndrome: safety and efficacy in perspective. *Expert Rev Gastroenterol Hepatol* 2010; 4: 13–29.

Adverse Effects

Serious gastrointestinal adverse effects have occurred with alosetron, and as a result, it was withdrawn from the market in the USA and subsequently reintroduced with more restricted indications. These adverse effects include severe constipation leading to obstruction, ileus, perforation, impaction, toxic megacolon, and secondary ischaemia, as well as ischaemic colitis. Fatalities have been reported.

Other gastrointestinal effects reported include abdominal distension and pain, nausea, reflux, and haemorrhoids. Adverse effects reported rarely include cardiac arrhythmias, cholecystitis, altered bilirubin levels, tremor, headache, myalgia, malaise, fatigue, and CNS effects such as confusion, anxiety, depression, and sedation. Urticaria, skin reactions, nail disorders, and alopecia can occur. Hyperglycaemia, hypoglycaemia, and disorders of calcium and phosphate metabolism have been reported.

Incidence of adverse effects. The incidence of serious gastrointestinal adverse effects with alosetron has been reviewed.[1,2] Pooled data from clinical studies suggested that the rate of ischaemic colitis in patients taking alosetron was about 0.15%, or 6.4 cases per 1000 patient-years. Results from postmarketing surveillance (before and after its temporary withdrawal from the US market) were estimated to represent a rate of 1 case per 1000 patient-years. Serious complications of constipation are less markedly increased in the population of alosetron users. A meta-analysis of 8 studies[3] reported that the incidence of serious complications of constipation was 0.08% in alosetron users; the incidence of ischaemic colitis was 0.16%. Overall, constipation and abdominal discomfort were the only adverse effects significantly associated with alosetron use, the relative risks being 4.35 and 1.96 respectively.

1. Chang L, *et al.* Incidence of ischemic colitis and serious complications of constipation among patients using alosetron: systematic review of clinical trials and post-marketing surveillance data. *Am J Gastroenterol* 2006; 101: 1069–79.
2. Chang L, *et al.* Ischemic colitis and complications of constipation associated with the use of alosetron under a risk management plan: clinical characteristics, outcomes, and incidences. *Am J Gastroenterol* 2010; 105: 866–75.
3. Rahimi R, *et al.* Efficacy and tolerability of alosetron for the treatment of irritable bowel syndrome in women and men: a meta-analysis of eight randomized, placebo-controlled, 12-week trials. *Clin Ther* 2008; 30: 884–901.

Precautions

Alosetron should be stopped immediately in patients who develop constipation or symptoms of ischaemic colitis such as new or worsening abdominal pain or blood in the stool. Treatment with alosetron should not be resumed in patients who develop ischaemic colitis.

Alosetron should not be used in patients with a history of severe or chronic constipation, intestinal obstruction or stricture, toxic megacolon, or gastrointestinal perforation or adhesions. It is also contra-indicated in patients with a history of ischaemic colitis, impaired intestinal circulation,

thrombophlebitis, or hypercoagulable state, and those with current or previous inflammatory bowel disease or diverticulitis.

Alosetron should not be used in those with severe hepatic impairment or a history thereof; it should be used with caution in patients with mild to moderate hepatic impairment. Elderly patients may be at increased risk of severe complications if constipation develops.

Interactions

Plasma concentrations of alosetron are markedly increased, and its half-life prolonged roughly threefold, when given with fluvoxamine; such a combination should be avoided. Licensed product information recommends that use with other more moderate inhibitors of cytochrome P450 isoenzyme CYP1A2 (such as quinolone antibacterials and cimetidine) should be avoided unless clinically necessary, because of the risk of similar interactions. Ketoconazole also increases plasma alosetron concentrations; care should be taken if alosetron is used with this or other potent inhibitors of the CYP3A4 isoenzyme (including clarithromycin, telithromycin, HIV-protease inhibitors, voriconazole, and itraconazole).

Pharmacokinetics

Alosetron is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations occur about 1 hour after an oral dose. Plasma concentrations are 30 to 50% lower in men than in women given the same oral dose; clearance is lower in women. Bioavailability is about 60%; the extent and rate of absorption are slightly reduced by food. Plasma protein binding is about 82%. Alosetron is extensively metabolised via cytochrome P450 isoenzymes, particularly CYP1A2, although CYP2C9 and CYP3A4 also play a role. Numerous metabolites are excreted in the urine and faeces; only 6% of a dose is recovered unchanged from the urine. The terminal elimination half-life of alosetron is reported to be about 1.5 hours.

References.
1. Koch KM, *et al.* Sex and age differences in the pharmacokinetics of alosetron. *Br J Clin Pharmacol* 2002; 53: 238–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Lotronex.

Basic Aluminium Carbonate

Aluminium Hydroxycarbonate; Aluminum Carbonate, Basic (USAN); Basic Aluminum Carbonate; Carbonato básico de aluminio; Основный Углекислый Алюминий.

UNII — 1GA689N629.

Profile

Basic aluminium carbonate is a combination of aluminium hydroxide and aluminium carbonate. It is an antacid with general properties similar to those of aluminium hydroxide (below).

Basic aluminium carbonate has also been given orally as a phosphate binder in the treatment of hyperphosphataemia. For a discussion of the choice of phosphate binders, see Renal Osteodystrophy, p. 1170.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Lithiagel.

Multi-ingredient Preparations. *Port.*: Gastropensan†.

Aluminium Formate

Aluminium Triformate; Aluminum Formate; Муравьиноки-слый Алюминий; Формиат Алюминия.

$Al(CHO_2)_3.3H_2O$=216.1

CAS — 7360-53-4 (anhydrous aluminium formate).

UNII — 0D34KG724V.

Profile

Aluminium formate has astringent properties and has been used in topical preparations for mouth disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Dynexan Zahnfleischtropfen.

Multi-ingredient Preparations. *Austria*: Cional; Dynexan; *S.Afr.*: Dynexan; *Switz.*: Mucosan†.

Aluminium Glycinate

Alluminio, glicinato de; Aluminum Glycinate; Basic Aluminium Aminoacetate; Dihydroxyaluminum Aminoacetate; Алюминия Гликинат.

(Glycinato-*N,O*)dihydroxyaluminium hydrate.

$C_2H_6AlNO_4(+xH_2O)$=135.1 (anhydrous)

CAS — 13682-92-3 (anhydrous aluminium glycinate); 41354-48-7 (aluminium glycinate hydrate).

ATC — A02AB07.

ATC Vet — QA02AB07.

UNII — DQ250MG0W6 (aluminium glycinate hydrate); 1K713C615K (anhydrous aluminium glycinate).

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Aluminium Glycinate). A white or almost white, odourless or almost odourless, powder. It contains 34.5 to 38.5% of Al_2O_3 calculated on the dried substance, and not more than 12% loss of weight on drying. Practically insoluble in water and in organic solvents; it dissolves in dilute mineral acids and in aqueous solutions of alkali hydroxides. A 4% suspension in water has a pH of 6.5 to 7.5.

USP 36: (Dihydroxyaluminum Aminoacetate). A white, odourless, powder. It may contain small amounts of aluminium oxide and aminoacetic acid. It loses not more than 14.5% of its weight on drying. Insoluble in water and in organic solvents; soluble in dilute mineral acids and in solutions of fixed alkalis. A 4% suspension in water has a pH of 6.5 to 7.5.

Profile

Aluminium glycinate is an antacid with general properties similar to those of aluminium hydroxide (below). It has been given in oral doses of up to 1.5 g.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Dafne; *Austria*: Acidrine; *Belg.*: Alucid; *Chile*: Sinacid†; *Denm.*: Alminox; *Fr.*: Acidrine; *Gr.*: Novalox; *Indon.*: Acidrine; *Ital.*: Acidrine; *Pol.*: Proacid†; *Spain*: Meteoril; Secrepat; *Thai.*: New Gel; *Turk.*: Acidrine; Alma; *Ukr.*: Secrepat Forte (Секрепат Форте).

Used as an adjunct in: *Austria*: Indobene; *Braz.*: Somalgin; *Chile*: Butartrol; Flexono; *Ital.*: Aspirina 03; *Switz.*: Bonidon†; *USA*: Buffex.

Pharmacopoeial Preparations

USP 36: Dihydroxyaluminum Aminoacetate Magma.

Aluminium Hydroxide

Alluminio hidroksidas; Alumiinihydroksidi; Aluminii Hydroxidum; Aluminii oxidum hydricum; Aluminium Oxidum Hydricum; Aluminium (oxyde d') hydraté; Aluminiumhydroxid; Aluminum Hydroxide; Alūminyum Hidroksit; Glinu wodorotlenek; Hidróxido de aluminio; Hydroxid hlinitý; Wasserhaltiges Aluminiumoxid; Алюминий Гидроксид.

CAS — 21645-51-2 [$Al(OH)_3$].

ATC — A02AB01.

ATC Vet — QA02AB01.

UNII — 5QB0T2IUN0.

NOTE. Algeldrate (*USAN, pINN*) is defined as a hydrated aluminium hydroxide with the general formula of $Al(OH)_3$.xH_2O.

Compounded preparations of aluminium hydroxide may be represented by the following names:

- Co-magaldrox *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of magnesium hydroxide and aluminium hydroxide respectively.

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

Ph. Eur. 8: (Aluminium Oxide, Hydrated; Dried Aluminium Hydroxide BP 2014). It contains the equivalent of 47 to 60% Al_2O_3. It is a white or almost white, amorphous powder. Practically insoluble in water; it dissolves in dilute mineral acids and in solutions of alkali hydroxides. Store in airtight containers at a temperature not exceeding 30 degrees.

Ph. Eur. 8: (Aluminium Hydroxide, Hydrated, for Adsorption; Aluminii Hydroxidum Hydricum ad Adsorptionem). A white or almost white, translucent, viscous, colloidal gel. A supernatant may be formed upon standing. A clear or almost clear solution is obtained with alkali hydroxide solutions and with mineral acids. pH 5.5 to 8.5. Store at a temperature not exceeding 30 degrees. Do not allow to freeze.

USP 36: (Aluminum Hydroxide Gel). A suspension of amorphous aluminium hydroxide in which there is a partial substitution of carbonate for hydroxide. It is a white viscous suspension from which small amounts of clear liquid may separate on standing. It has a pH of between 5.5 and 8.0. Store in airtight containers. Avoid freezing.

USP 36: (Dried Aluminum Hydroxide Gel). An amorphous form of aluminium hydroxide in which there is a partial substitution of carbonate for hydroxide. It contains the equivalent of not less than 76.5% of $Al(OH)_3$ and may contain varying quantities of basic aluminium carbonate and bicarbonate. The labelling requirements states that 1 g of dried aluminium hydroxide gel is equivalent to 765 mg of $Al(OH)_3$. It is a white, odourless, tasteless, amorphous powder. Insoluble in water and in alcohol; soluble in dilute mineral acids and in solutions of fixed alkali hydroxides. A 4% aqueous dispersion has a pH of not more than 10.0. Store in airtight containers.

Uses and Administration

Aluminium hydroxide is used as an antacid (p. 1803.1). It is given orally in doses of up to about 1 g, between meals and at bedtime. In order to reduce the constipating effects, aluminium hydroxide is often given with a magnesium-containing antacid, such as magnesium oxide or magnesium hydroxide.

Aluminium hydroxide binds phosphate in the gastrointestinal tract to form insoluble complexes and reduces phosphate absorption. It may thus be used to treat hyperphosphataemia in patients with chronic renal failure (although aluminium accumulation may be a problem—see Renal Osteodystrophy, p. 1170.1) or associated secondary hyperparathyroidism (p. 1170.3). With this use the dose must be adjusted to the individual patient's requirement but up to about 10 g daily may be given orally in divided doses with meals.

Aluminium hydroxide is also used as an adjuvant in adsorbed vaccines.

Polymyositis and dermatomyositis. Corticosteroids form the basis of the management of polymyositis (p. 1611.1) but the calcinosis that may occur in dermatomyositis does not always respond well. Aluminium hydroxide 1.68 to 2.24 g daily produced clinical improvement with complete clearing of most calcified nodules after 1 year in a patient with calcinosis cutis complicating juvenile dermatomyositis.[1] The calcified masses are made up of hydroxyapatite and amorphous calcium phosphate and reduction in phosphate absorption by aluminium hydroxide probably helped to reverse their formation. Subsequent cases[2,3] have also reported benefit from aluminium hydroxide treatment in the management of calcinosis.

1. Wang W-J, *et al.* Calcinosis cutis in juvenile dermatomyositis: remarkable response to aluminium hydroxide therapy. *Arch Dermatol* 1988; 124: 1721–2.
2. Nakagawa T, Takaiwa T. Calcinosis cutis in juvenile dermatomyositis responsive to aluminium hydroxide treatment. *J Dermatol* 1993; 20: 558–60.
3. Wananukul S, *et al.* Calcinosis cutis presenting years before other clinical manifestations of juvenile dermatomyositis: report of two cases. *Australas J Dermatol* 1997; 38: 202–5.

Adverse Effects and Precautions

Aluminium hydroxide, like other aluminium compounds, is astringent and may cause constipation; large doses can cause intestinal obstruction.

Excessive doses, or even normal doses in patients with low-phosphate diets, may lead to phosphate depletion accompanied by increased bone resorption and hypercalciuria with the risk of osteomalacia.

Aluminium salts are not, in general, well absorbed from the gastrointestinal tract, and systemic effects are therefore rare in patients with normal renal function. However, care is necessary in patients with chronic renal impairment: osteomalacia or adynamic bone disease, encephalopathy, dementia, and microcytic hypochromic anaemia have been associated with aluminium accumulation in such patients given large doses of aluminium hydroxide as a phosphate-binding agent. Similar adverse effects have also been associated with the aluminium content of dialysis fluids.

Aluminium hydroxide used as an adjuvant in adsorbed vaccines has been associated with the formation of granulomas.

Children. For the suggestion that aluminium-containing antacids should not be used in infants, see Toxicity, below.

Porphyria. UK licensed product information states that aluminium hydroxide may be unsafe in patients with porphyria undergoing haemodialysis. However, the Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, has not classified aluminium hydroxide.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Toxicity. References to aluminium toxicity in dialysis patients and the possible association between aluminium

ingestion and Alzheimer's disease are included under Aluminium (see p. 2440.1).

Aluminium accumulation does not generally appear to be significant in patients with normal renal function taking therapeutic doses of aluminium-containing antacids, and there is little evidence that such antacids are a risk factor for Alzheimer's disease.[1] Elevated plasma-aluminium concentrations have been reported in infants with normal renal function given aluminium-containing antacids but there were no obvious signs of toxicity.[2] There have, however, been reports of phosphate depletion and rickets in a few infants caused by the use of antacids containing magnesium and aluminium hydroxides. In these cases the antacid had been started within a few months of birth and continued for up to 8 months. In reports that described a total of 3 infants,[3,4] the authors suggested that the use of soya-based infant feeding formulas, the phytates of which can interfere with mineral absorption, may have exacerbated the phosphate-binding effect of the antacid. In another case[5] a dosing error resulted in the infant receiving an excessive dose of antacid for 6 months. The *BNFC* advises against the use of any aluminium-containing antacid in neonates and infants.

Aluminium accumulation resulting in osteomalacia or encephalopathy with seizures and dementia has been reported in children with renal failure (but not on dialysis) treated with aluminium-containing phosphate binders.[6-10] In an adult male patient with severe chronic renal failure who was not on dialysis, self-medication with antacids for at least 3 years resulted in aluminium toxicity associated with encephalopathy, bone disease, and microcytic anaemia.[11] Aluminium-containing antacids should therefore be used with caution in patients with chronic renal failure, especially children.

Oral citrate salts increase the absorption of aluminium from the gastrointestinal tract[12] and patients with renal failure taking aluminium compounds should avoid citrate-containing preparations, which include many effervescent or dispersible tablets.[13,14] Ascorbic acid has also been reported to enhance aluminium absorption.[15]

1. Platen TP, *et al.* Mortality from dementia among gastroduodenal ulcer patients. *J Epidemiol Community Health* 1991; 45: 203–6.
2. Tsou VM, *et al.* Elevated plasma aluminum levels in normal infants receiving antacids containing aluminum. *Pediatrics* 1991; 87: 148–51.
3. Pivnick EK, *et al.* Rickets secondary to phosphate depletion: a sequela of antacid use in infancy. *Clin Pediatr (Phila)* 1995; 34: 73–8.
4. Shetty AK, *et al.* Rickets and secondary craniosynostosis associated with long-term antacid use in an infant. *Arch Pediatr Adolesc Med* 1998; 152: 1243–5.
5. Robinson RF, *et al.* Metabolic bone disease after chronic antacid administration in an infant. *Ann Pharmacother* 2004; 38: 265–8.
6. Pedersen S, Nathan E. Water treatment and dialysis dementia. *Lancet* 1982; ii: 1107.
7. Griswold WR, *et al.* Accumulation of aluminum in a nondialyzed uremic child receiving aluminum hydroxide. *Pediatrics* 1983; 71: 56–8.
8. Randall ME. Aluminium toxicity in an infant not on dialysis. *Lancet* 1983; i: 1327–8.
9. Sedman AB, *et al.* Encephalopathy in childhood secondary to aluminum toxicity. *J Pediatr* 1984; 105: 836–8.
10. Andreoli SP, *et al.* Aluminum intoxication from aluminum-containing phosphate binders in children with azotemia not undergoing dialysis. *N Engl J Med* 1984; 310: 1079–84.
11. Zatta P, *et al.* A fatal case of aluminium encephalopathy in a patient with severe chronic renal failure not on dialysis. *Nephrol Dial Transplant* 2004; 19: 2929–31.
12. Walker JA, *et al.* The effect of oral bases on enteral aluminum absorption. *Arch Intern Med* 1990; 150: 2037–9.
13. Mees EJD, Başçi A. Citric acid in calcium effervescent tablets may favour aluminium intoxication. *Nephron* 1991; 59: 322.
14. Main J, Ward MK. Potentiation of aluminium absorption by effervescent analgesic tablets in a haemodialysis patient. *BMJ* 1992; 304: 1686.
15. Domingo JL, *et al.* Effect of ascorbic acid on gastrointestinal aluminium absorption. *Lancet* 1992; 338: 1467.

Interactions

As outlined on p. 1803.1, aluminium compounds used as antacids interact with many other drugs, both by alterations in gastric pH and emptying, and by direct adsorption and formation of complexes that are not absorbed. Interactions can be minimised by giving the aluminium compound and any other medication 2 to 3 hours apart. The absorption of aluminium from the gastrointestinal tract may be enhanced if aluminium compounds are taken with citrates or ascorbic acid (see Toxicity, p. 1817.3).

Pharmacokinetics

Aluminium hydroxide, given orally, slowly reacts with the hydrochloric acid in the stomach to form soluble aluminium chloride, some of which is absorbed. The presence of food or other factors that decrease gastric emptying prolongs the availability of aluminium hydroxide to react and may increase the amount of aluminium chloride formed. About 100 to 500 micrograms of the cation is reported to be absorbed from standard daily doses of an aluminium-containing antacid, leading to about a doubling of usual aluminium concentrations in the plasma of patients with normal renal function.

Absorbed aluminium is eliminated in the urine, and patients with renal failure are therefore at particular risk of accumulation (especially in bone and the CNS), and aluminium toxicity (see p. 1817.3).

The aluminium compounds remaining in the gastrointestinal tract, which account for most of a dose, form insoluble, poorly absorbed aluminium salts in the intestines including hydroxides, carbonates, phosphates and fatty acid derivatives, which are excreted in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Pepsamar; *Austral.*: Alu-Tab†; *Austria*: Anti-Phosphat; *Braz.*: Aludroxil; Aziram; Ductogel; Gastromax; Gastrox; Mylanta Plus; Pepgastrin†; Pepsamar; Peptgel; *Canad.*: Amphojel; *Ger.*: Aludrox†; Antiphosphat; *Gr.*: Alu-Cap; Pepsamar; *Hong Kong*: Alu-Tab; Gasteel; *India*: Aludrox; Dizicum; Tricaine-MPS; *Indon.*: Actal; *Irl.*: Aludrox†; *Malaysia*: Alu-Tab; *Mex.*: Domigel†; *NZ*: Alu-Tab; *Philipp.*: Alu-Tab; *Pol.*: Alusal; *Port.*: Almigastrico; Pepsamar; *S.Afr.*: Acidex†; Alukon†; Amphojel; *Singapore*: Alu-Tab†; Alutacid; *Spain*: Aluget†; Pepsamar†; *Switz.*: Anti-phosphate†; *Thai.*: Alumina-Magnesia; New Gel; *UK*: Alu-Cap; *USA*: ALternaGEL; Amphojel; Dialumen†; Nephrox.

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

Used as an adjunct in:. *Arg.*: Dristan Compuesto; *Braz.*: Engov; Enjoy; Posdrink†; Respray†; *Gr.*: Ascriptin; *Indon.*: Naspro; *Ital.*: Ascriptin; *Mex.*: Ascriptin; Meprosona-F; *Switz.*: Alcacyl; Contre-Douleurs plus; *USA*: Arthritis Pain Formula; Ascriptin; Cama Arthritis Pain Reliever; Cope; Vanquish; *Venez.*: Ascriptin.

Homoeopathic Preparations. *Chile*: Ikoplex No 19; *Cz.*: Lamioflur†.

Pharmacopoeial Preparations

BP 2014: Aluminium Hydroxide Oral Suspension; Chewable Aluminium Hydroxide Tablets; Chewable Compound Magnesium Trisilicate Tablets; Co-magaldrox Oral Suspension; Co-magaldrox Tablets;

USP 36: Alumina and Magnesia Oral Suspension; Alumina and Magnesia Tablets; Alumina and Magnesium Carbonate Oral Suspension; Alumina and Magnesium Carbonate Tablets; Alumina and Magnesium Trisilicate Oral Suspension; Alumina and Magnesium Trisilicate Tablets; Alumina, Magnesia, and Calcium Carbonate Oral Suspension; Alumina, Magnesia, and Calcium Carbonate Tablets; Alumina, Magnesia, and Simethicone Oral Suspension; Alumina, Magnesia, and Simethicone Tablets; Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets; Alumina, Magnesium Carbonate, and Magnesium Oxide Tablets; Aluminum Hydroxide Gel; Aspirin, Alumina, and Magnesia Tablets; Aspirin, Alumina, and Magnesium Oxide Tablets; Dried Aluminum Hydroxide Gel Capsules; Dried Aluminum Hydroxide Gel Tablets; Dried Aluminum Hydroxide Gel.

Aluminium Hydroxide-Magnesium Carbonate Co-dried Gel

Aluminum Hydroxide-Magnesium Carbonate Co-dried Gel; F-MA 11; Hidróxido de aluminio y carbonato de magnesio desecado, gel de.

Profile

Aluminium hydroxide-magnesium carbonate co-dried gel is a co-precipitate of aluminium hydroxide and magnesium carbonate dried to contain a proportion of water for antacid activity. It is an antacid with general properties similar to those of aluminium hydroxide (p. 1817.2) and magnesium carbonate (p. 1856.2). It has been given in oral doses of about 450 to 900 mg, usually 3 times daily after meals and before bedtime.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies combinations and complexes of aluminium, calcium, and magnesium compounds for acid related disorders as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Link; *Fin.*: Link; *Gr.*: Regla pH; *Indon.*: Stomacain; Veragel†; *Mex.*: Gelasim; *Neth.*: Regla pH; Remegel; *Norw.*: Link; *Swed.*: Link†.

Multi-ingredient Preparations. *Belg.*: Barexal; Regla pH Forte; Syngel; *Braz.*: Andursil; *Canad.*: Diovol Plus; Diovol; Gastrocalm; *Chile*: Algicote†; Disfrutab†; Ditopax; Reflumox; *Fr.*: Gastropulgite; *Ger.*: Colina Spezial; Duoventrinetten N; *Hong Kong*: Diovol Plus; Veragel; *Indon.*: Aludonna; Di-Gel; Farmacrol; Gastran†; Oskamag†; Polycrol; Simeco†; *Irl.*: Smecta; *Mex.*: Ditopax-P†; Ditopax†; *Neth.*: Algicon; Algicon; Rigoletten; *Port.*: Di-Gel†; *Singapore*: Meclosil; Veragel; *Switz.*: Andursil; *Thai.*: Defomil; Diovol†; Kremil-S; Kremil; Machto; Simeco†; Tocid; Veragel; *UK*: Simeco; *Ukr.*: Gastal (Гастал); *Venez.*: Ditosil Plus; Ditosil.

Used as an adjunct in:. *Indon.*: Rheumapill†.

Aluminium Phosphate

Aluminio fosfatas; Alumiinifosfaatti; Aluminii phosphas; Aluminio, fosfato de; Aluminium, phosphate d'; Aluminium-fosfat; Alumínium-foszfát; Aluminum Phosphate; Fosfato de aluminio; Fosforečnan hlinitý; Glinu fosforan; Glinu fosforanu; Алюминия Фосфат.

CAS — 7784-30-7 ($AlPO_4$).

ATC — A02AB03.

ATC Vet — QA02AB03.

UNII — F92V3S521O.

Pharmacopoeias. In *Viet.*

Eur. (see p. vii) includes hydrated aluminium phosphate and also a gel. *US* includes as a gel.

Ph. Eur. 8: (Aluminium Phosphate, Hydrated; Aluminii Phosphas Hydricus; Dried Aluminium Phosphate BP 2014). A white or almost white powder. Very slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute solutions of alkali hydroxides and mineral acids. A 4% suspension in water has a pH of 5.5 to 7.2. Store in airtight containers.

Ph. Eur. 8: (Aluminium Phosphate Gel; Aluminii Phosphatis Liquamen). It is aluminium phosphate in gel form containing 19 to 21% of $AlPO_4$. Practically insoluble in water, in alcohol, and in dichloromethane. It dissolves in dilute solutions of mineral acids. pH 6.0 to 8.0. Store in airtight containers.

USP 36: (Aluminum Phosphate Gel). A 4 to 5% suspension of aluminium phosphate ($AlPO_4$) in water and has a pH of 6.0 to 7.2. It is a white viscous suspension from which small amounts of water separate on standing. Store in airtight containers.

Profile

Aluminium phosphate is an antacid with general properties similar to those of aluminium hydroxide (p. 1817.2), but it does not produce phosphate depletion.

Aluminium phosphate is also used as an adjuvant in adsorbed vaccines.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Colphos (吉福士); Gui Ding Kang (贵鼎康); Phosgel (洁维乐); Yu Er (裕尔); *Fr.*: Phosphalugel; *Ger.*: Phosphalugel; *Ital.*: Fosfalugel; *Port.*: Phosphalugel; *Rus.*: Phosphalugel (Фосфалюгель); *Ukr.*: Phosphalugel (Фосфалюгель).

Multi-ingredient Preparations. *Fr.*: Isudrine†; Moxydar; Seroxydar†.

Pharmacopoeial Preparations

USP 36: Aluminum Phosphate Gel.

Aluminium Sodium Silicate

Aluminium-Natrium-Silicat; Aluminum Sodium Silicate; E554; Natrii aluminii silicas; Silicato de sodio y de aluminio; Sodium Aluminium Silicate; Sodium Aluminosilicate; Sodium et aluminium, silicate de; Sodium Silicoaluminate; Алюмосиликат Натрия.

CAS — 1344-00-9.

UNII — 0587S43PSM.

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

Ph. Eur. 8: (Aluminium Sodium Silicate). It is a silicic acid aluminium sodium salt of synthetic origin. It contains 2.7 to 7.9% aluminium and 3.7 to 6.3% sodium, both calculated with reference to the dried substance. A white or almost white, fine, light, amorphous powder. Practically insoluble in water and in organic solvents. A 5% dispersion in water has a pH of 9.5 to 11.5.

Profile

Aluminium sodium silicate is an antacid with general properties similar to those of aluminium hydroxide (p. 1817.2). Aluminium silicate has been used similarly. They are also used as food additives.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Sulfuryl†; *Indon.*: Cerplast *Port.*: Acnoil Free†.

Multi-ingredient Preparations. *Arg.*: Gastranil; *Fr.*: Cerat Inalterable†; Sulfuryl; *Ger.*: Enelbin-Paste N†; Enelbin-Paste†; *Hong Kong*: Epilon; *India*: Acnil; *Thai.*: Ulgastrin.

Homoeopathic Preparations. *Neth.*: Phonix Solidago comp.

Alverine Citrate *(BANM, USAN, rINNM)*

Alverina, citrato de; Alverincitrat; Alverine, Citrate d'; Alverini Citras; Citrato de alverina; Dipropylline Citrate; Phenpropamine Citrate; Альверина Цитрат.

N-Ethyl-3,3'-diphenyldipropylamine citrate.

$C_{20}H_{27}N,C_6H_8O_7$=473.6

CAS — 150-59-4 (alverine); 5560-59-8 (alverine citrate).

ATC — A03AX08.

ATC Vet — QA03AX08.

UNII — 9JFB58YK1E.

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

Ph. Eur. 8: (Alverine Citrate). A white or almost white crystalline powder. Slightly soluble in water and in dichloromethane; sparingly soluble in alcohol. A 0.5% solution in water has a pH of 3.5 to 4.5. Protect from light.

Uses and Administration

Alverine is an antispasmodic that acts directly on intestinal and uterine smooth muscle. It is used for the relief of smooth muscle spasm in the treatment of gastrointestinal disorders such as irritable bowel syndrome (p. 1810.3). It is also used in the treatment of dysmenorrhoea (p. 8.2).

Alverine citrate is given in oral doses of 60 to 120 mg one to three times daily. Alverine has also been given by suppository as the base.

Administration in children. Alverine citrate may be given to adolescents from the age of 12 years in the same doses as adults, see above.

Irritable bowel syndrome. Alverine citrate is widely used as an antispasmodic in the management of irritable bowel syndrome. However, a 12-week study[1] in 107 patients found that alverine citrate was no better than placebo for the relief of symptoms and improvement in general well-being. A marked placebo effect occurred and symptomatic improvement was reported by at least half the placebo group.

1. Mitchell SA, *et al.* Alverine citrate fails to relieve the symptoms of irritable bowel syndrome: results of a double-blind, randomized, placebo-controlled trial. *Aliment Pharmacol Ther* 2002; 16: 1187–95.

Adverse Effects and Precautions

Nausea, headache, pruritus, rash, and dizziness have been reported. Allergic reactions, including anaphylaxis, have also occurred. Alverine is contra-indicated in patients with intestinal obstruction or paralytic ileus.

Effects on the liver. Acute hepatitis was attributed to alverine citrate in 2 separate cases.[1,2] Evidence of an immune reaction, including antinuclear antibodies, was found in 1 case.[1]

1. Malka D, *et al.* Acute hepatitis caused by alverine associated with anti-lamin A and C autoantibodies. *J Hepatol* 1997; 27: 399–403.
2. Arhan M, *et al.* Alverine citrate induced acute hepatitis. *World J Gastroenterol* 2004; 10: 2303–4.

Pharmacokinetics

Alverine is absorbed from the gastrointestinal tract after oral doses and is rapidly metabolised to an active metabolite, peak plasma concentrations of which occur 1 to 1.5 hours after an oral dose. Further metabolism to inactive metabolites occurs; metabolites are excreted in the urine by active renal secretion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Spasmine; *China*: Spasmonal (斯莫纳); *Hong Kong*: Profenil; Spasmonal†; *Irl.*: Spasmonal; *Pol.*: Spasmolina; *Singapore*: Spasmonal; *Thai.*: Spasmonal†; *UK*: Audmonal; Spasmonal.

Multi-ingredient Preparations. *Arg.*: Meteospasmyl; *China*: Meteospasmyl (乐健素); *Cz.*: Meteospasmyl; *Fr.*: Hepatoum; Meteospasmyl; Schoum; *Hung.*: Meteospasmyl; *Indon.*: Spasmium; *Malaysia*: Meteospasmyl; *Mex.*: Meteospasmyl; *Pol.*: Meteospasmyl; *Rus.*: Meteospasmyl (Метеоспазмил); *Singapore*: Meteospasmyl; *Thai.*: Avarin; Meteospasmyl†; *Turk.*: Meteospasmyl; *Ukr.*: Meteospasmyl (Метеоспазмил).

Pharmacopoeial Preparations
BP 2014: Alverine Capsules.

Alvimopan *(BAN, USAN, rINN)*

ADL-8-2698; Alvimopán; Alvimopanum; LY-246736; Альвимопан.

[((2*S*)-2-[((3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl]-3-phenylpropanoyl)amino]acetic acid.

$C_{25}H_{32}N_2O_4$=424.5

CAS — 156053-89-3 (anhydrous alvimopan); 170098-38-1 (alvimopan dihydrate).

ATC — A06AH02.

ATC Vet — QA06AH02.

UNII — 677C126AET (alvimopan); Q153V49P3Z (anhydrous alvimopan).

Uses and Administration

Alvimopan is a peripherally acting selective antagonist of opioid μ-receptors that is used in the treatment of postoperative ileus after partial large or small bowel resection surgery with primary anastomosis. It is given in a 12-mg oral dose between 30 minutes and up to 5 hours before surgery followed by 12 mg twice daily beginning the day after surgery for a maximum of 7 days or until discharge. A maximum of 15 doses of alvimopan should be given.

References.

1. Herzog TJ, *et al.* A double-blind, randomized, placebo-controlled phase III study of the safety of alvimopan in patients who undergo simple total abdominal hysterectomy. *Am J Obstet Gynecol* 2006; 195: 445–53.
2. Tan EK, *et al.* Meta-analysis: Alvimopan vs. placebo in the treatment of post-operative ileus. *Aliment Pharmacol Ther* 2007; 25: 47–57.
3. Curran MP, *et al.* Alvimopan. *Drugs* 2008; 68: 2011–19. Correction. *ibid.*: 2324.
4. Becker G, Blum HE. Novel opioid antagonists for opioid-induced bowel dysfunction and postoperative ileus. *Lancet* 2009; 373: 1198–1206.
5. Bream-Rouwenhorst HR, Cantrell MA. Alvimopan for postoperative ileus. *Am J Health-Syst Pharm* 2009; 66: 1267–77.

Adverse Effects and Precautions

Gastrointestinal disorders such as constipation, dyspepsia, and flatulence have been reported after use of alvimopan. Anaemia, back pain, hypokalaemia, and urinary retention have also occurred.

Alvimopan should not be used in patients who have taken therapeutic doses of opioids for more than 7 consecutive days, as they are expected to be more sensitive to its effects. Use in patients with severe hepatic impairment or end-stage renal disease is not recommended due to a lack of data. Alvimopan is also not recommended in patients undergoing surgery for complete bowel obstruction.

Pharmacokinetics

Plasma-alvimopan concentrations peak about 2 hours after an oral dose. High-fat meals decrease the extent and rate of absorption. Alvimopan binds to albumin, with an average plasma protein binding of 80%. Biliary secretion is considered the primary pathway for elimination of alvimopan, but renal excretion also contributes. Unabsorbed alvimopan is metabolised by gut microflora to an amide hydrolysis compound which is also an antagonist of opioid μ-receptors. This metabolite is then excreted in the faeces and urine. The mean terminal half-life of alvimopan after multiple oral doses ranged from 10 to 17 hours.

References.

1. Foss JF, *et al.* Pharmacokinetics of alvimopan and its metabolite in healthy volunteers and patients in postoperative ileus trials. *Clin Pharmacol Ther* 2008; 83: 770–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Entereg.

Aprepitant *(USAN, rINN)*

Aprépitant; Aprepitantum; L-754030; MK-0869; MK-869; Апрепитант.

3-[((2*R*,3*S*)-3-(*p*-Fluorophenyl)-2-[[(*αR*)-α-methyl-3,5-bis(trifluoromethyl)benzyl]oxy]morpholino)methyl]-Δ^2-1,2,4-triazolin-5-one.

$C_{23}H_{21}F_7N_4O_3$=534.4

CAS — 170729-80-3.

ATC — A04AD12.

ATC Vet — QA04AD12.

UNII — 1NF15YR6UY.

Uses and Administration

Aprepitant is a neurokinin-1 (NK_1) receptor antagonist used in the management of nausea and vomiting (p. 1811.3). It is given orally in doses up to 125 mg, with a corticosteroid and a 5-HT_3 antagonist, in the prevention of acute and delayed nausea and vomiting associated with highly emetogenic or moderately emetogenic cancer chemotherapy (for details, see Administration, below).

For the prevention of postoperative nausea and vomiting a single oral dose of aprepitant 40 mg may be given within the 3 hours before induction of anaesthesia.

Where the intravenous route is preferred, it may be given as its prodrug, fosaprepitant (for details of regimens, see Uses and Administration, under Fosaprepitant, p. 1843.3).

References.

1. Diemunsch P, *et al.* Preventing postoperative nausea and vomiting: post hoc analysis of pooled data from two randomized active-controlled trials of aprepitant. *Curr Med Res Opin* 2007; 23: 2559–65.
2. Dando TM, Perry CM. Aprepitant: a review of its use in the prevention of chemotherapy-induced nausea and vomiting. *Drugs* 2004; 64: 777–94.
3. Massaro AM, Lenz KL. Aprepitant: a novel antiemetic for chemotherapy-induced nausea and vomiting. *Ann Pharmacother* 2005; 39: 77–85.
4. Warr D. The neurokinin1 receptor antagonist aprepitant as an antiemetic for moderately emetogenic chemotherapy. *Expert Opin Pharmacother* 2006; 7: 1653–8.
5. Curran MP, Robinson DM. Aprepitant: a review of its use in the prevention of nausea and vomiting. *Drugs* 2009; 69: 1853–78.

Administration. Licensed product information for aprepitant suggests the following 4-day regimen for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy:

- day 1: oral aprepitant 125 mg (given 1 hour before chemotherapy) with oral dexamethasone 12 mg and intravenous ondansetron 32 mg (both 30 minutes before chemotherapy)
- days 2 and 3: oral aprepitant 80 mg with oral dexamethasone 8 mg in the morning
- day 4: oral dexamethasone 8 mg in the morning.

In patients receiving moderately emetogenic chemotherapy, a 3-day regimen has been suggested as follows:

- day 1: oral aprepitant 125 mg (given 1 hour before chemotherapy) with oral dexamethasone 12 mg (30 minutes before chemotherapy); ondansetron is given in 2 oral doses of 8 mg, one taken 30 to 60 minutes before chemotherapy, and one taken 8 hours after the first dose
- days 2 and 3: oral aprepitant 80 mg in the morning.

Administration in renal impairment. A study in 8 patients with severe renal impairment (24-hour creatinine clearance less than 30 mL/minute per 1.73 m^2) and 8 patients with end-stage renal disease requiring haemodialysis found that pharmacokinetic parameters of aprepitant were not sufficiently different from those in 16 matched controls to warrant dosage adjustment in renal impairment.[1] Licensed product information concurs with this.

1. Bergman AJ, *et al.* Effect of impaired renal function and haemodialysis on the pharmacokinetics of aprepitant. *Clin Pharmacokinet* 2005; 44: 637–47.

Pruritus. An improvement in pruritus was reported after oral aprepitant 80 mg daily was started in 3 patients with the Sézary syndrome. Topical corticosteroid treatment had previously been unsuccessful, but improvements were noted within 2 days of starting aprepitant.[1] Beneficial results were also reported[2] in 16 of 20 patients with refractory chronic pruritus of various causes who were given 80 mg daily for 3 to 13 days; 4 patients had complete or nearly complete cessation of itch and 12 had lesser degrees of reduction. Patients with atopic dermatitis or prurigo appeared to respond better than those in whom pruritus was associated with chronic kidney disease. Aprepitant is an antagonist of the neurokinin-1 receptor, a receptor for substance P which is a mediator in the itch sensation.[1,2]

For reference to aprepitant's efficacy in managing erlotinib-induced pruritus, see Effects on the Skin, Hair, and Nails, under Erlotinib, p. 789.2.

1. Duval A, Dubertret L. Aprepitant as an antipruritic agent? *N Engl J Med* 2009; 361: 1415–16.
2. Ständer S, *et al.* Targeting the neurokinin receptor 1 with aprepitant: a novel antipruritic strategy. *PLoS One* 2010; 5: e10968.

Adverse Effects and Precautions

The most common adverse effects associated with aprepitant are headache, constipation, diarrhoea, dyspepsia, anorexia, fatigue, hiccups, eructation, and dizziness. Increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) concentrations are common. Other reported effects have included abdominal pain, oedema, tinnitus, neutropenic colitis, chills, gait disturbances, and flushing. Epigastric discomfort, dysgeusia, dry mouth, and stomatitis have also occurred. Thirst, polyuria, dysuria, haematuria, urinary frequency, arthralgia, myalgia, muscular weakness, hyperglycaemia, disorientation, euphoria, anxiety, photosensitivity, and skin disorders such as rash and pruritus have been reported. Anaemia and febrile neutropenia have occurred with aprepitant, as have cardiovascular disorders including hypertension or hypotension, palpitations, and bradycardia. Other adverse effects reported include hyponatraemia, hypokalaemia, insomnia, drowsiness, miosis, reduced visual acuity, weight changes, sensory disturbances, throat irritation, sneezing, abnormal bowel sounds, acid reflux, perforating duodenal ulcer,

dyspnoea, cough, wheezing, and hyperhidrosis. Conjunctivitis, pharyngitis, respiratory-tract infections, urinary-tract infections, candidiasis, and herpes simplex can occur. Hypersensitivity reactions including anaphylaxis, Stevens-Johnson syndrome, and angioedema with urticaria have been reported.

Licensed product information recommends caution in patients with severe hepatic impairment as clinical data are lacking in this patient group.

Interactions

During its use for 3 or 4 days in the prevention of nausea and vomiting associated with cancer chemotherapy, aprepitant produces moderate inhibition of the cytochrome P450 isoenzyme CYP3A4. Exposure to oral CYP3A4 substrates may increase substantially; the effect of aprepitant on intravenous CYP3A4 substrates is expected to be less. However, on cessation of aprepitant a transient mild induction of CYP3A4 may become apparent with a maximum effect reached 3 to 5 days later; this effect is maintained for a few days then slowly declines and is clinically insignificant about 2 weeks after stopping aprepitant. Caution is therefore required when using it with drugs that are primarily metabolised by this isoenzyme. Aprepitant should not be given with astemizole, cisapride, pimozide, terfenadine, or tolvaptan as increased plasma concentrations of these drugs could cause serious life-threatening reactions. As aprepitant is also a substrate for CYP3A4, other drugs that inhibit or induce this isoenzyme may in turn increase or decrease plasma concentrations of aprepitant.

When aprepitant is used to prevent postoperative nausea and vomiting, in a single lower dose than that used with cancer chemotherapy, the effect of aprepitant on CYP3A4 is not expected to be clinically significant.

Aprepitant also causes a delayed induction of CYP2C9 and may lower plasma concentrations of drugs metabolised by this isoenzyme, such as warfarin, phenytoin, or tolbutamide.

Aprepitant may increase systemic exposure to corticosteroids; when given together it is recommended that the usual dose of oral dexamethasone be reduced by 50%, and the dose of methylprednisolone by about 25% when given intravenously, and by 50% when given orally. It should be noted that the dose of dexamethasone in the regimens recommended for nausea and vomiting associated with cancer chemotherapy already accounts for this interaction (see Administration, p. 1819.3).

The efficacy of oral contraceptives might be reduced by aprepitant. Licensed product information suggests that alternative methods of contraception should be used during and for 1 to 2 months after stopping any dose of aprepitant.

Pharmacokinetics

Aprepitant is absorbed from the gastrointestinal tract with peak plasma concentrations occurring after about 4 hours. Bioavailability is about 60% at usual doses. It crosses the blood-brain barrier; plasma protein binding is reported to be more than 95%. Aprepitant undergoes extensive hepatic metabolism, mainly via oxidation by the cytochrome P450 isoenzyme CYP3A4; the isoenzymes CYP1A2 and CYP2C19 mediate minor metabolic pathways. The resultant metabolites have weak activity and are excreted in the urine and in the faeces. Aprepitant is not excreted unchanged in the urine. The terminal half-life is about 9 to 13 hours.

References.

1. Majumdar AK, *et al.* Pharmacokinetics of aprepitant after single and multiple oral doses in healthy volunteers. *J Clin Pharmacol* 2006; **46**: 291–300.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Emend; ***Austral.***: Emend; ***Austria***: Emend; ***Belg.***: Emend; ***Braz.***: Emend; ***Canad.***: Emend; ***Chile***: Emend; ***Cz.***: Emend; ***Denm.***: Emend; ***Fin.***: Emend; ***Fr.***: Emend; ***Ger.***: Emend; ***Gr.***: Emend; ***Hong Kong***: Emend; ***Hung.***: Emend; ***India***: Aprecap; ***Irl.***: Emend; ***Israel***: Emend; ***Ital.***: Emend; ***Jpn***: Emend; ***Malaysia***: Emend; ***Neth.***: Emend; ***Norw.***: Emend; ***NZ***: Emend; ***Pol.***: Emend; ***Port.***: Emend; ***Rus.***: Emend (Эмэпэ); ***S.Afr.***: Emend; ***Singapore***: Emend; ***Spain***: Emend; ***Swed.***: Emend; ***Switz.***: Emend; ***Thai.***: Emend; ***Turk.***: Emend; ***UK***: Emend; ***Ukr.***: Emend (Эмепэ); ***USA***: Emend; ***Venez.***: Emend.

Attapulgite

Atapulgit; Atapulgita; Аттапульгит.

CAS — 1337-76-4; 12174-11-7.

ATC — A07BC04.

ATC Vet — QA07BC04.

UNII — U6V729APAM.

Pharmacopoeias. In *Br.*

Activated attapulgite is included in *Br., It.,* and *US.* Colloidal activated attapulgite is included in *US.*

BP 2014: (Attapulgite). A purified native hydrated aluminium magnesium silicate essentially consisting of the clay mineral palygorskite. A light, cream or buff, very fine powder, free or almost free from gritty particles. A 5% suspension in water has a pH of 7.0 to 9.5.

BP 2014: (Activated Attapulgite). Attapulgite that has been carefully heated to increase its adsorptive capacity.

USP 36: (Activated Attapulgite). Processed native aluminium magnesium silicate which has been carefully heated. It is a cream-coloured, micronised, nonswelling powder, free from gritty particles. Insoluble in water.

USP 36: (Colloidal Activated Attapulgite). A native aluminium magnesium silicate that has been purified. It is a cream-coloured, micronised, nonswelling powder, free from gritty particles. Insoluble in water. A 10% suspension in water has a pH of 7.0 to 9.5.

NOTE. Another native aluminium magnesium silicate is described on p. 2168.2.

Profile

Attapulgite is highly adsorbent and is used in a wide range of products including fertilisers, pesticides, and pharmaceuticals. Activated attapulgite is an adsorbent antidiarrhoeal used as an adjunct in the management of diarrhoea (p. 1805.2) in a daily dose of up to 9 g orally in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Actapulgite; ***Canad.***: Kaopectate; ***Fr.***: Actapulgite; ***Hong Kong***: Gastrosorb†; ***Indon.***: Biodiar; Enterogit†; Kaotate†; New Diatabs; Teradi; ***Philipp.***: Polymagma†; ***Rus.***: Neointestopan (Неоинтестопан); ***Singapore***: Gastrosorb; ***Switz.***: Actapulgite†; ***Thai.***: Entox-P; ***Turk.***: Diasorb; Diyasorb†; ***UAE***: Kaptin II; ***USA***: Diasorb; Kaopectate Maximum Strength; ***Venez.***: Streptomagma.

Multi-ingredient Preparations. ***Arg.***: Enterobacticel; ***Austral.***: Diarezet†; ***Braz.***: Diazol; Dispeptrin†; ***Chile***: Diaren; Entero Micinovo; Enterol†; Liracol; Nifurat; ***Fr.***: Gastropulgite; Mucipulgite†; ***Hong Kong***: Enterocin Compound†; ***Indon.***: Andikap†; Arcapec Diagit; Entrogard; Fitodiar; Licopec Molagit; Neo Diastop; Neo Entrostop; Neo Koniform†; ***S.Afr.***: Kantrexil; ***Switz.***: Mucipulgite†; ***Turk.***: Streptomagma; ***UK***: Diocalm Dual Action; ***Venez.***: Micyn-2; Streptomagma.

Azasetron Hydrochloride *(INNM)*

Azasétron, Chlorhydrate d'; Azasetrón, hidrocloruro de; Azasetroni Hydrochloridum; Hidrocloruro de azasetrón; Nazasetron Hydrochloride; Y-25130; Азасетрона Гидрохлорид.

(±)-6-Chloro-3,4-dihydro-4-methyl-3-oxo-*N*-3-quinuclidinyl-2*H*-1,4-benzoxazine-8-carboxamide hydrochloride.

$C_{17}H_{20}ClN_3O_3,HCl$=386.3

CAS — 123040-69-7 (azasetron); 141922-90-9 (azasetron hydrochloride).

UNII — 2BSS7XL60S.

Profile

Azasetron is a 5-HT_3 antagonist with general properties similar to those of ondansetron (p. 1872.1). It is used as an antiemetic in the management of nausea and vomiting induced by cytotoxic therapy. Azasetron hydrochloride is given in a usual dose of 10 mg once daily by mouth or intravenously.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: An Shi Tong (安世通); Ding Yue (丁悦); Gan Su (感苏); Ou Li Kang Ding (欧立康定); Ou Ting (欧亭); Ri An (日安); Rui Di Su (瑞帝苏); Tan Si Ke (坦斯克); Wan Wei (万唯); Yi Qiong (依琼); Yi Su Lin (怡苏林); ***Jpn***: Serotone.

Balsalazide Sodium *(BANM, rINNM)*

Balsalazida sódica; Balsalazide Disodium (USAN); Balsalazide Sodique; Balsalazine Disodium; BX-661A; Natrii Balsalazidum; Натрий Балсалазид.

5-[4-(2-Carboxyethylcarbamoyl)phenylazo]salicylic acid, disodium salt, dihydrate.

$C_{17}H_{13}N_3Na_2O_6,2H_2O$=437.3

CAS — 80573-04-2 (balsalazide); 150399-21-6 (balsalazide disodium dihydrate).

ATC — A07EC04.

ATC Vet — QA07EC04.

UNII — 1XL6BJI034 (balsalazide disodium dihydrate); 15ASW03C9S (anhydrous balsalazide sodium).

Pharmacopoeias. In *US.*

USP 36: (Balsalazide Disodium). An orange to yellow powder. Freely soluble in water and in isotonic saline; sparingly soluble in alcohol and in methyl alcohol; practically insoluble in all other organic solvents. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Balsalazide consists of mesalazine linked to 4-aminobenzoylalanine via an azo bond. This bond is broken by colonic bacteria, releasing the active mesalazine (p. 1859.2). Balsalazide sodium is given in the treatment of mild to moderate active ulcerative colitis (p. 1808.3), in an oral dose of 2.25 g three times daily until remission or for up to 12 weeks. For maintenance of remission of ulcerative colitis a dose of 1.5 g twice daily is recommended, adjusted as necessary up to 6 g daily. For doses in children, see below.

Reviews.

1. Muijsers RBR, Goa KL. Balsalazide: a review of its therapeutic use in mild-to-moderate ulcerative colitis. *Drugs* 2002; **62**: 1689–705.
2. Patil SA, Muss AC. Balsalazide disodium for the treatment of ulcerative colitis. *Expert Rev Gastroenterol Hepatol* 2008; **2**: 177–84.
3. Rahimi R, *et al.* Comparison of mesalazine and balsalazide in induction and maintenance of remission in patients with ulcerative colitis: a meta-analysis. *Dig Dis Sci* 2009; **54**: 712–21.

Administration in children. Balsalazide sodium is not licensed in the UK for use in children under 18 years of age. However, the *BNFC* recommends that, in those aged 12 years and over, 2.25 g may be given orally three times daily for an acute attack of mild to moderate ulcerative colitis, until remission occurs, or for up to 12 weeks. For maintenance, 1.5 g twice daily is recommended, adjusted according to response up to a maximum of 6 g daily.

In the USA, licensed doses in children aged 5 to 17 years are 750 mg three times daily by mouth, or 2.25 g three times daily; treatment may be continued for up to 8 weeks.

Adverse Effects and Precautions

As for Mesalazine, p. 1860.1. If a blood dyscrasia is suspected treatment should be stopped immediately and a blood count performed. Patients or their carers should be told how to recognise signs of haematotoxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop. Balsalazide should not be used in patients with severe hepatic impairment or moderate or severe renal impairment; care is required in those with lesser degrees of hepatic or renal impairment, and in asthma, bleeding disorders, or active peptic ulcer disease.

Reviews.

1. Baker DE. Safety of balsalazide therapy in the treatment of inflammatory bowel disease. *Rev Gastroenterol Disord* 2005; **5**: 135–41.

Effects on the cardiovascular system. Myocarditis similar to that seen with mesalazine (see p. 1860.2) has been described in a patient some days after his treatment was altered from mesalazine to balsalazide; the condition resolved once balsalazide was withdrawn.[1]

See also Hypersensitivity, below.

1. Robertson E, *et al.* Balsalazide-induced myocarditis. *Int J Cardiol* 2008; **130**: e121–e122.

Hypersensitivity. A case of acute pericarditis, cholestasis, and vasculitis resulting from hypersensitivity to balsalazide has been reported.[1] The authors noted similarities to mesalazine-associated pericarditis and lupus-like syndrome (see Effects on the Cardiovascular System, p. 1860.2).

1. Adhiyaman V, *et al.* Hypersensitivity reaction to balsalazide. *BMJ* 2000; **320**: 613.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies balsalazide 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 03/10/11)

Pharmacokinetics

Very little of an oral dose of balsalazide is absorbed via the upper gastrointestinal tract, and almost the entire dose reaches its site of action in the colon intact. It is broken down by the colonic bacterial flora into 5-aminosalicylic acid (mesalazine), which is active, and 4-aminobenzoylalanine, which is considered to be an inert carrier. About 25% of the released mesalazine is absorbed and acetylated, as described under mesalazine (p. 1861.2). A small proportion of 4-aminobenzoylalanine is absorbed and

acetylated by first-pass metabolism through the liver. The acetylated metabolites are excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Benoquin; *Austral.*: Colazide; *China*: Ao Rui Xin (奥瑞欣); Bei Le Si (贝乐司); Sai Lai De (塞莱得); *Denm.*: Premid; *India*: Balacol; Colorex; Cozabal; Intazide; *Ital.*: Balzide; *Norw.*: Colazid; *UK*: Colazide; *USA*: Colazal.

Multi-ingredient Preparations. *Swed.*: Colazid.

Pharmacopoeial Preparations
USP 36: Balsalazide Disodium Capsules.

Benexate Hydrochloride *(rINNM)*

Benexate, Chlorhydrate de; Benexati Hydrochloridum; Hidrocloruro de benexato; Бенексата Гидрохлорид.
Benzyl salicylate *trans*-4-(guanidinomethyl)cyclohexanecarboxylate hydrochloride.
$C_{23}H_{27}N_3O_4$,HCl=445.9
CAS — 78718-52-2 (benexate); 78718-25-9 (benexate hydrochloride); 91574-91-3 (benexate hydrochloride betadex).
UNII — QVN4YYK2C6.

Profile

Benexate hydrochloride is a mucosal protectant that has been used in the management of peptic ulcer disease. The β-cyclodextrin clathrate, benexate hydrochloride betadex, has been given in an oral dose of 400 mg twice daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Ulgut.

Bisacodyl *(BAN, rINN)*

Bisacodilo; Bisacodylum; Bisakodil; Bisakodilis; Bisakodyl; Bisakodyyli; Biszakodil; Бисакодил.
4,4′-(2-Pyridylmethylene)di(phenyl acetate).
$C_{22}H_{19}NO_4$=361.4
CAS — 603-50-9.
ATC — A06AB02; A06AG02.
ATC Vet — QA06AB02; QA06AG02.
UNII — 10X0709Y6I.

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

Ph. Eur. 8: (Bisacodyl). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone. It dissolves in dilute mineral acids. Protect from light.

USP 36: (Bisacodyl). A white to off-white crystalline powder. Practically insoluble in water; soluble in benzene; soluble 1 in 210 of alcohol, 1 in 2.5 of chloroform, and 1 in 275 of ether; sparingly soluble in methyl alcohol.

Bisacodyl Tannex *(BANM, USAN, rINNM)*

CAS — 1336-29-4.
ATC — A06AB02; A06AG02.
ATC Vet — QA06AB02; QA06AG02.

Uses and Administration

Bisacodyl is a diphenylmethane stimulant laxative (p. 1804.1) used for the treatment of constipation (p. 1804.3) and for bowel evacuation before investigational procedures or surgery. Its action is mainly in the large intestine and it is usually effective within 6 to 12 hours after oral doses, within 15 to 60 minutes after rectal use by suppository, and within 5 to 20 minutes when given as an enema. Bisacodyl tablets should be swallowed whole and should not be taken within 1 hour of milk or antacids.

For constipation, bisacodyl is given in usual doses of 5 to 10 mg daily as enteric-coated tablets given at night; up to 20 mg may be given if necessary. Alternatively a dose of 10 mg as a suppository or enema may be given in the morning. For complete bowel evacuation, an oral dose of 10 to 20 mg may be given the night before the procedure, followed by 10 mg as a suppository the next morning. Alternatively, an oral dose of 10 mg may be given on each of the 2 nights before the procedure. For doses in children, see below.

A complex of bisacodyl with tannic acid (bisacodyl tannex) has been given with a barium sulfate enema before radiographic examination of the colon.

Administration in children. For **constipation**, the following oral doses of bisacodyl are recommended for children, to be taken at night:
- 4 to 10 years: 5 mg
- over 10 years: 5 to 10 mg, increased if necessary to a maximum of 20 mg

Alternatively, the following rectal doses are recommended, to be inserted in the morning:
- up to 10 years: 5 mg
- over 10 years: 10 mg

The *BNFC* gives similar doses, but limits the use of suppositories in children to those aged over 2 years.

For **bowel clearance before surgery or radiological investigation**, the following doses are recommended:
- 4 to 10 years: 5 mg orally the night before, followed by 5 mg as a suppository the next morning
- over 10 years: 10 to 20 mg orally the night before, followed by 10 mg as a suppository the next morning

The *BNFC* gives similar doses but allows for the use of oral doses for 2 nights before the procedure, followed, if necessary, by the rectal dose 1 hour before the procedure.

Adverse Effects

Bisacodyl and other stimulant laxatives may cause abdominal discomfort such as colic or cramps. Prolonged use or overdosage can result in diarrhoea with excessive loss of water and electrolytes, particularly potassium; there is also the possibility of developing an atonic non-functioning colon. Haematochezia (blood in the stool) may be seen but is usually mild and self-limiting; more severe bloody diarrhoea may be associated with colonic mucosal ischaemia. Hypersensitivity reactions, including angioedema and anaphylactoid reactions, have been reported rarely. When given rectally, bisacodyl sometimes causes irritation and may cause proctitis or sloughing of the epithelium. To avoid gastric irritation bisacodyl tablets are enteric-coated.

Precautions

As with other laxatives, prolonged use should be avoided. Bisacodyl should not be given to patients with intestinal obstruction or acute abdominal conditions such as appendicitis; care should also be taken in patients with inflammatory bowel disease. It should not be used in patients with severe dehydration. The suppositories should preferably be avoided in patients with anal fissures, proctitis, or ulcerated haemorrhoids.

Handling. Inhalation of bisacodyl powder and contact with eyes, skin, and mucous membranes should be avoided.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bisacodyl as probably not porphyrinogenic when given as tablets or suppositories, and not porphyrinogenic as an enema; 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 10/11/11)

Pharmacokinetics

On oral or rectal use bisacodyl is converted to the active desacetyl metabolite bis(*p*-hydroxyphenyl)pyridyl-2-methane by intestinal and bacterial enzymes. Absorption from the gastrointestinal tract is minimal with enteric-coated tablets or suppositories; the small amount absorbed is excreted in the urine as the glucuronide. Bisacodyl is mainly excreted in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dulcolax; Laxamin; Modaton; Tractoduo; *Austral.*: Bisalax; Dulcolax; Lax-Tab; *Austria*: Dulcolax; Laxbene; *Belg.*: Bisolax; Carters; Dulcolax; Henafurinet†; Mucinum; Purgo-Pil; *Braz.*: Bisalax; Cronoplex†; Deltalax; Dulcolax; Fideine; Isilax; Plesonax; *Canad.*: Alophen†; Bisacolax; Carters Little Pills; Codulax; Correctol; Dulcolax; Silver Bullet; Soflax EX; The Magic Bullet; Woman's Laxative; *Chile*: Alsylax; *China*: Dulcolax (乐可舒); Jie Tai (解泰); Longshutong (隆舒通); *Cz.*: Dulcolax; Fenolax; Stadalax; *Denm.*: Dulcolax; Perilax; Toilax; *Fin.*: Metalax; Toilax; *Fr.*: Contalax; Dulcolax; *Ger.*: Bekunis Bisacodyl; Bisco-Zitron; Drix Bisacodyl; Dulcolax; Florisan N†; Laxagetten; Laxans-ratiopharm; Laxans; Laxysat Burger†; Mediolax; Pyrilax; Tempolax†; Tirgon; *Gr.*: Dulcolax; Florisan N; *Hong Kong*: Bicolax†; Bisedyl†; Dulax†; Dulcolax; Marcholax†; Monolax†; *Hung.*: Dulcolax; Stadalax; *India*: Bidlax; Bisariv; Bo-Lax; Conlax; Dulcolax; JuLax; Junifree; Laxodyl; *Indon.*: Bicolax; Custodiol; Dulcolax; Laxacod†; Laxamex†; Laxana; Stolax; *Irl.*: Dulcolax; Toilax; *Israel*: Atzirut X; Contalax; Laxadin; *Ital.*: Alaxa; Confetto CM; Dulcolax; Normalene; Sacodil; Stixenil; Verecolene CM; *Malaysia*: Dulcolax; *Mex.*: Dulcolan; Dulcolax; *Neth.*: Dulcolax; Kruidvat Laxeertabletten; Laxeerdrageest†; Laxeertabletten; Laxeerzetpillen†; Nourilax; Trekpleister Laxeertabletten; *Norw.*: Dulcolax; Toilax; *NZ*: Dulcolax; Fleet Laxative†; Lax-Tab; *Philipp.*: Bisalax; Dulcolax; Vesilac; *Port.*: Bekunis Laxante Bisacodil; Dulcolax; Moderlax; *Rus.*: Dulcolax (Дульколакс); *S.Afr.*: Dulcolax; Megalax; Perilax†; *Singapore*: Bicolax; Biolax; Dilax; Dulcolax; Ebolin; Laxodyl; SL Laxative; Sunny Laxative; Unilax; *Spain*: Dulcolaxo; Laxabixal; *Swed.*: Dulcolax; Toilax; *Switz.*: Bekunis Dragees; Demolaxin†; Dulcolax; Muxol; Prontolax; Softala-X; Tavolax; *Thai.*: Bisacod; Bisacodylcoated; Conlax; Dulcolax; Emulax; Gencolax; Kadolax; KB Biscod; Laxadryl; Laxcodyl; Laxitab†; Monolax; Vacolax†; *Turk.*: Bisakol; Laksotek; Sekolaks; *UAE*: Laxocodyl; *UK*: Biolax; Boots Constipation Relief; Dulcolax; Entrolax; *USA*: Alophen; Bisa-Lax; Correctol; Doxidan†; Dulcolax; Evac-Q-Tabs; Ex-Lax Ultra; Feen-A-Mint; Fleet Bisacodyl; Fleet Laxative; Gentlax; Modane; *Venez.*: Dulcolan.

Multi-ingredient Preparations. *Arg.*: En-Ga-Lax; Fosfo-Dom Kit; Laxicona; Nigalax; Nigalax; *Austral.*: Coloxyl; Go Kit Plus; Go Kit; *Austria*: Laxbene; Prepacol; Purgazen†; *Belg.*: Prepacol; Softene; *Braz.*: Belpidex; *Canad.*: Bekunis†; Bi-PegLyte; Bichotate†; Gentlax S†; Roycac Kit†; *Chile*: Laxogeno; *Cz.*: Prepacol; *Fr.*: Prepacol; *Ger.*: Prepacol; *Gr.*: Florisan; *Hung.*: Laxbene; *NZ*: Coloxyl†; *Port.*: Bekunis; *Spain*: Bekunis Complex; *Thai.*: Bisolax; Chinta-lax; T Man Lax; *Turk.*: Bekunis; *USA*: Dulcolax Bowel Prep Kit; Fleet Prep Kit No. 1†; Fleet Prep Kit No. 2†; Fleet Prep Kit No. 3; HalfLytely and Bisacodyl Bowel Prep Kit; X-Prep Bowel Evacuant Kit-1†.

Pharmacopoeial Preparations
BP 2014: Bisacodyl Suppositories; Gastro-resistant Bisacodyl Tablets;
USP 36: Bisacodyl Delayed-release Tablets; Bisacodyl Rectal Suspension; Bisacodyl Suppositories.

Bismuth Compounds

Bismuto, compuestos de; Висмут Соединения.

Profile

Bismuth compounds have been used for their astringent and antidiarrhoeal properties in a variety of gastrointestinal disorders, and have been applied topically in skin disorders and anorectal disorders such as haemorrhoids. Certain salts are active against *Helicobacter pylori* and are used in the treatment of peptic ulcer disease.

Bismuth Aluminate *(USAN)*

Aluminato de bismuto; Aluminum Bismuth Oxide; Алюминат Висмута.
$Bi_2(Al_2O_4)_3$,10H_2O=952.0
CAS — 12284-76-3 (anhydrous bismuth aluminate).
UNII — JB5Y63JDHJ.

Pharmacopoeias. In *Chin.* and *Fr.*

Bismuth Citrate

Citrato de bismuto; Цитрат Висмута.
$BiC_6H_5O_7$=398.1
CAS — 813-93-4.
UNII — N04867Y76N.

NOTE. Do not confuse with bismuth subcitrate potassium (p. 1822.1) or tripotassium dicitratobismuthate (colloidal bismuth subcitrate, p. 1822.2).

Pharmacopoeias. In *US*.

USP 36: (Bismuth Citrate). A white, amorphous or crystalline powder. Insoluble in water and in alcohol; soluble in dilute ammonia solution and in solutions of alkali citrates. Store in airtight containers. Protect from light. Prevent exposure to temperatures above 40 degrees.

Bismuth Oxide

Bismuth Trioxide; Óxido de bismuto; Оксид Висмута.
Bi_2O_3=466.0
CAS — 1304-76-3.
UNII — A614E79QF1.

Bismuth Salicylate

Basic Bismuth Salicylate; Bázisos bizmut-szalicilát; Bismuth Oxysalicylate; Bismuth, sous-salicylate de; Bismuth Subsalicylate (USAN); Bismuthi subsalicylas; Bismuto subsalicilatas; Bismutsalicylat, Basisches; Salicilato de bismuto; Salicylan bismutitý zásaditý; Vismutsubsalicylat; Vismuttisubsalisylaatti; Салицилат Висмута.
$C_7H_5BiO_4$=362.1
CAS — 14882-18-9.
UNII — 62TEY51RR1.

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

Ph. Eur. 8: (Bismuth Subsalicylate). A complex of bismuth and salicylic acid. It contains not less than 56% and not

more than 59.4% of Bi, calculated with reference to the dried substance. A white or almost white powder. Practically insoluble in water and in alcohol; dissolves in mineral acids with decomposition. Protect from light.

USP 36: (Bismuth Subsalicylate). A basic salt corresponding to $C_7H_5BiO_4$ and containing not less than 56.0% and not more than 59.4% of Bi and not less than 36.5% and not more than 39.3% of total salicylates. It is a fine, odourless, white to off-white microcrystalline powder. Practically insoluble in water, in alcohol, and in ether. It reacts with alkalis and mineral acids. Store in airtight containers. Protect from light.

Bismuth Subcarbonate *(USAN)*

Basic Bismuth Carbonate; Basisches Wismutkarbonat; Bázisos bizmutkarbonát; Bism. Carb.; Bismutcarbonat, Basisches; Bismuth Carbonate; Bismuth Oxycarbonate; Bismuth, sous-carbonate de; Bismuthi Subcarbonas; Bismuto subkarbonatas; Bismutylum Carbonicum; Carbonato de Bismutila; Subcarbonato de bismuto; Uhličitan bismutitý zásaditý; Vismutsubkarbonat; Vismuttisubkarbonaatti; Основный Углекислый Висмут.

CBi_2O_5=510.0

CAS — 5892-10-4 (anhydrous bismuth subcarbonate); 5798-45-8 (bismuth subcarbonate hemihydrate).

UNII — M41L2IN55T (bismuth subcarbonate); NJT50MK51G (bismuth subcarbonate hemihydrate).

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

Ph. Eur. 8: (Bismuth Subcarbonate). A white or almost white powder. Practically insoluble in water and in alcohol. It dissolves in mineral acids with effervescence. Protect from light.

USP 36: (Bismuth Subcarbonate). A white or almost white powder. Practically insoluble in water, in alcohol, and in ether; dissolves in dilute acids with effervescence. Protect from light.

Bismuth Subcitrate Potassium *(USAN)*

1001277; Biskalcitrate potassium; Bismuth Biscalcitrate; Bismuth biskalcitrate; Основный Калиевый Цитрат Висмута. Bismuth pentapotassium dihydroxide bis(2-hydroxypropane-1,2,3-tricarboxylate hydrate).

$C_{12}H_{14}BiK_5O_{17}$=834.7

CAS — 880149-29-1.

UNII — R3O80H60KX.

NOTE. Do not confuse with bismuth citrate (p. 1821.3) or tripotassium dicitratobismuthate (colloidal bismuth subcitrate, below).

Bismuth Subgallate *(USAN)*

Basic Bismuth Gallate; Basisches Wismutgallat; Bázisos bizmut-gallát; Bism. Subgall.; Bismutgallat, Basisches; Bismuth Oxygallate; Bismuth, sous-gallate de; Bismuthi Subgallas; Bismuto subgalatas; Bizmut Subgalat; Bizmutu galusan zasadowy; Gallan bismutitý zásaditý; Subgalato de bismuto; Vismutsubgallat; Vismuttisubgallaatti; Основный Галловокислый Висмут.

$C_7H_5BiO_6$=394.1

CAS — 99-26-3.

UNII — YIW503MI7V.

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

Ph. Eur. 8: (Bismuth Subgallate). A complex of bismuth and gallic acid. It contains not less than 48% and not more than 51% of Bi, calculated with reference to the dried substance. A yellow powder. Practically insoluble in water and in alcohol; dissolves in mineral acids with decomposition and in alkali hydroxides, producing a reddish-brown liquid. Protect from light.

USP 36: (Bismuth Subgallate). A basic salt containing 52 to 57% of Bi_2O_3 when dried at 105 degrees for 3 hours. It is an odourless amorphous bright yellow powder. Practically insoluble in water, in alcohol, in chloroform, and in ether; insoluble in very dilute mineral acids; dissolves readily with decomposition in warm, moderately dilute hydrochloric, nitric, or sulfuric acids; readily dissolves in solutions of alkali hydroxides to form a clear yellow liquid which rapidly becomes deep red. Store in airtight containers. Protect from light.

Bismuth Subnitrate

Subazotato de Bismuto; Basic Bismuth Nitrate; Basisches Wismutnitrat; Bázisos bizmut-nitrát; Bism. Subnit.; Bismuth Hydroxide Nitrate Oxide; Bismuth Nitrate, Heavy; Bismuth Oxynitrate; Bismuth (Sous-Nitrate de) Lourd; Bismuth, sous-nitrate de; Bismuthi Subnitras; Bismuthyl Nitrate; Bismuto subnitratas; Bismuto subnitratas sunkusis; Bizmut Subnitrat; Bizmutu azotan zasadowy; Bizmutu(III) azotan zasadowy; Magistery of Bismuth; Nitrato de Bismutilo; Subnitrato de bismuto; Vismutsubnitrat; Vismuttisubnitraatti; White Bismuth; Основный Азотнокислый Висмут.

$Bi_5O(OH)_9(NO_3)_4$=1462.0

CAS — 1304-85-4.

ATC — A02BX12.

ATC Vet — QA02BX12.

UNII — H19J064BA5.

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

Fr. also includes Bismuth (Sous-Nitrate de) Léger (Bismuthi Subnitras Levis) which is described as a variable mixture of bismuth hydroxide, carbonate, and subnitrate.

Ph. Eur. 8: (Bismuth Subnitrate, Heavy). It contains not less than 71% and not more than 74% of Bi, calculated with reference to the dried substance. A white or almost white powder. Practically insoluble in water and in alcohol; dissolves in mineral acids with decomposition.

USP 36: (Bismuth Subnitrate). A basic salt containing not less than 79% of Bi_2O_3 calculated on the dried basis. It is a white, slightly hygroscopic powder. Practically insoluble in water and in alcohol; readily dissolves in nitric and hydrochloric acids.

Tripotassium Dicitratobismuthate

Bizmut Subsitrat; Colloidal Bismuth Subcitrate; Dicitratobismutato tripotásico; Tripotasyum Disitratobizmutat; Висмут Трикалия Дицитрат.

CAS — 57644-54-9.

ATC — A02BX05.

ATC Vet — QA02BX05.

NOTE. Do not confuse with bismuth citrate (p. 1821.3) or bismuth subcitrate potassium (above).

Uses and Administration

Some insoluble salts of bismuth are given orally for their supposed antacid action and for their mildly astringent action in various gastrointestinal disorders, including diarrhoea (p. 1805.2) and dyspepsia (p. 1806.3). Such salts include the aluminate, salicylate, subcarbonate, and subnitrate. Bismuth salicylate, which is given as an antidiarrhoeal and weak antacid in doses up to about 4 g daily in divided doses, possesses in addition the properties of the salicylates.

Tripotassium dicitratobismuthate is active against *Helicobacter pylori* and has been used as triple therapy (with metronidazole and either tetracycline or amoxicillin) to eradicate this organism and thereby prevent relapse of duodenal ulcer. It is also used as a mucosal protectant for the treatment of peptic ulcer disease (p. 1813.2). Bismuth subcitrate potassium and bismuth salicylate are also active against *H. pylori* and have been used similarly in eradication regimens.

The usual oral dose of tripotassium dicitratobismuthate in benign gastric and duodenal ulceration is 240 mg twice daily, or 120 mg four times daily before food. Treatment is for a period of 4 weeks, extended to 8 weeks if necessary. Maintenance therapy with tripotassium dicitratobismuthate is not recommended although treatment may be repeated after a drug-free interval of one month. When used as part of triple therapy the usual dose of tripotassium dicitratobismuthate has been 120 mg four times daily for 2 weeks. The usual dose of bismuth salicylate as part of triple therapy is 525 mg four times daily for 2 weeks. Appropriate antisecretory treatment with a histamine H_2-antagonist or a proton pump inhibitor is usually added to these regimens.

A complex of bismuth citrate with ranitidine, ranitidine bismuth citrate (p. 1883.3), has also been used in the treatment of peptic ulcer disease. Colloidal bismuth pectin, a complex salt of bismuth, potassium, and *d*-polygalacturonic acid, has also been used.

Some insoluble salts of bismuth have been used topically in the treatment of skin disorders, wounds, and burns. Some have been used as ingredients of ointments or suppositories (sometimes containing more than one bismuth salt) in the treatment of haemorrhoids and other anorectal disorders (p. 1808.1). Bismuth compounds that have been used topically and/or rectally include the oxide, subgallate, and subnitrate; bismuth resorcinol compounds have also been used. For the use of bismuth subnitrate and iodoform paste as a wound dressing, see Iodoform, p. 1758.2.

Numerous other salts and compounds of bismuth have been promoted for various therapeutic purposes. Glycobiarsol was formerly given orally as an amoebicide.

Homoeopathy

Bismuth has been used in homoeopathic medicines under the following names: Bismuthum; Bismutum metallicum; Bismuthum metallicum; Bismuth met.

Bismuth oxide has been used in homoeopathic medicines under the following names: Bismuthum oxydatum; Bismuth oxyd; Bis. ox.

Bismuth subnitrate has been used in homoeopathic medicines under the following names: Heavy bismuth subnitrate; Bismuthi subnitras ponderosus; Bismuthum subnitricum; Bismuth sub; Bismutum subnitricum; Bism sub.

Adverse Effects, Treatment, and Precautions

The bismuth compounds listed above are insoluble or very poorly soluble, and bismuth toxicity does not appear to be common if they are used for limited periods. However excessive or prolonged dosage may produce symptoms of bismuth poisoning, and for this reason long-term systemic therapy is not recommended. Reversible encephalopathy (see below) was once a problem in some countries, notably France and Australia; bone and joint toxicity had also occurred, sometimes associated with the encephalopathy. This led to restrictions on the use of bismuth salts and a virtual disappearance of these toxic effects.

Nausea and vomiting have been reported. Darkening or blackening of the faeces and tongue may occur due to conversion to bismuth sulfide in the gastrointestinal tract.

The effects of *acute bismuth intoxication* include gastrointestinal disturbances, skin reactions, stomatitis, and discoloration of mucous membranes; a characteristic blue line may appear on the gums. There may be renal failure and liver damage.

Other adverse effects may not be related to the bismuth content. With bismuth subnitrate given orally there is a risk of the nitrate being reduced in the intestines to nitrite and the development of methaemoglobinaemia. Absorption of salicylate occurs from oral bismuth salicylate and therefore the adverse effects, treatment of adverse effects, and precautions of aspirin (p. 24.2) should be considered.

Gastric lavage should be considered in overdosage; oral activated charcoal and the use of a chelating agent such as dimercaprol, succimer, or unithiol have been recommended (see also Overdosage, below). Renal function should be monitored for 10 days after acute overdosage.

Bismuth compounds should not be given to patients with moderate to severe renal impairment.

Encephalopathy. Reviews[1,2] and reports[3-11] of reversible bismuth encephalopathy. Many of the original reports implicated bismuth subgallate or subnitrate, in most but not all cases at high doses or for prolonged periods; toxicity has also occurred with other salts.[6-9] Patients receiving the subcitrate (480 mg daily) or the subnitrate (1.8 g daily) for 8 weeks in the treatment of *Helicobacter pylori* infection, showed no evidence of neurological changes compared with a control group.[12]

1. Winship KA. Toxicity of bismuth salts. *Adverse Drug React Acute Poisoning Rev* 1983; 2: 103–21.
2. Slikkerveer A, de Wolff FA. Pharmacokinetics and toxicity of bismuth compounds. *Med Toxicol Adverse Drug Exp* 1989; 4: 303–23.
3. Morrow AW. Request for reports: adverse reactions with bismuth subgallate. *Med J Aust* 1973; 1: 912.
4. Martin-Bouyer G. Intoxications par les sels de bismuth administrés par voie orale: enquête épidémiologique. *Therapie* 1976; 31: 683–702.
5. Stahl JP, *et al.* Encéphalites au sel insoluble de bismuth: toujours d'actualité. *Nouv Presse Med* 1982; 11: 3856.
6. Hasking GJ, Duggan JM. Encephalopathy from bismuth subsalicylate. *Med J Aust* 1982; 2: 167.
7. Weller MPI. Neuropsychiatric symptoms following bismuth intoxication. *Postgrad Med J* 1988; 64: 308–10.
8. Mendelowitz PC, *et al.* Bismuth absorption and myoclonic encephalopathy during bismuth subsalicylate therapy. *Ann Intern Med* 1990; 112: 140–1.
9. Playford RJ, *et al.* Bismuth induced encephalopathy caused by tripotassium dicitrato bismuthate in a patient with chronic renal failure. *Gut* 1990; 31: 359–60.
10. Von Bose MJ, Zaudig M. Encephalopathy resembling Creutzfeldt-Jakob disease following oral prescribed doses of bismuth nitrate. *Br J Psychiatry* 1991; 158: 278–80.
11. Teepker M, *et al.* Myoclonic encephalopathy caused by chronic bismuth abuse. *Epileptic Disord* 2002; 4: 229–33.
12. Noach LA, *et al.* Bismuth salts and neurotoxicity: a randomised, single-blind and controlled study. *Hum Exp Toxicol* 1995; 14: 349–55.

TOPICAL APPLICATION. Encephalopathy has been associated with the use of bismuth iodoform paraffin paste (BIPP) for the packing of wound cavities after surgery to the head and neck, although there is some debate as to whether the bismuth or the iodoform component is responsible—see p. 1758.2.

Overdosage. Bismuth salicylate or tripotassium dicitratobismuthate in recommended doses are rarely associated with serious adverse effects but there are reports of renal failure,[1-7] encephalopathy,[8-10] and neurotoxicity[1] in acute[1-6,9] or chronic[8,10] overdose. Bismuth has been detected in the blood, urine, stools, and kidneys of these patients; a blood concentration of 1.6 micrograms/mL was found[2] 4 hours after an oral dose of 9.6 g.

The optimal treatment of bismuth overdosage is unknown. Gastric lavage, purgation, and hydration should be considered, even if the patient presents late, as bismuth may be absorbed from the colon.[1,2] Chelating agents may be effective; unithiol has been reported to increase the renal clearance of bismuth with a reduction in the blood concentration.[8] *Haemodialysis* may be necessary[1-3] but

whether this hastens tissue clearance is uncertain. Haemodialysis plus unithiol treatment has been reported to successfully eliminate bismuth.[6] Peritoneal dialysis has also been effectively used in a paediatric patient.[5]

Prolonged ingestion of bismuth salicylate in excessive doses by an elderly diabetic was associated with hearing disturbances, vertigo, acid–base abnormalities and mild clotting disturbances.[11] The toxicity was thought to be due to the salicylate component.

1. Hudson M, Mowat NAG. Reversible toxicity in poisoning with colloidal bismuth subcitrate. *BMJ* 1989; 299: 159.
2. Taylor BG, Klenerman P. Acute renal failure after colloidal bismuth subcitrate overdose. *Lancet* 1990; 335: 670–1.
3. Huwez F, *et al.* Acute renal failure after overdose of colloidal bismuth subcitrate. *Lancet* 1992; 340: 1298.
4. Akpolat I, *et al.* Acute renal failure due to overdose of colloidal bismuth. *Nephrol Dial Transplant* 1996; 11: 1890–8.
5. İ. şlek İ, *et al.* Reversible nephrotoxicity after overdose of colloidal bismuth subcitrate. *Pediatr Nephrol* 2001; 16: 510–14.
6. Eruz P, *et al.* Fanconi's syndrome, acute renal failure, and tonsil ulcerations after colloidal bismuth subcitrate intoxication. *Am J Kidney Dis* 2002; 39: E18.
7. Cengiz N, *et al.* Acute renal failure after overdose of colloidal bismuth subcitrate. *Pediatr Nephrol* 2005; 20: 1355–8.
8. Playford RJ, *et al.* Bismuth induced encephalopathy caused by tri potassium dicitrato bismuthate in a patient with chronic renal failure. *Gut* 1990; 31: 359–60.
9. Hasking GJ, Duggan JM. Encephalopathy from bismuth subsalicylate. *Med J Aust* 1982; 2: 167.
10. Mendelowitz PC, *et al.* Bismuth absorption and myoclonic encephalopathy during bismuth subsalicylate therapy. *Ann Intern Med* 1990; 112: 140–1.
11. Vernace MA, *et al.* Chronic salicylate toxicity due to consumption of over-the-counter bismuth subsalicylate. *Am J Med* 1994; 97: 308–9.

Toxicity from non-conventional use. The FDA has warned against use of an injectable product called bismacine or chromacine, which contains large amounts of bismuth. There are reports of death or serious adverse effects associated with its use. Although unlicensed for any use, bismacine has apparently been used in alternative medicine to treat Lyme disease.[1]

1. FDA. FDA warns consumers and health care providers not to use bismacine, also known as chromacine (Issued 21st July 2006). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108696.htm (accessed 15/07/10)

Interactions

Bismuth salts given orally reduce the absorption of tetracyclines, possibly by chelation or by reducing tetracycline solubility as a result of increasing the gastric pH. This interaction can be minimised by separating doses of the two drugs by a couple of hours. The clinical significance of this interaction to the use of bismuth salts for peptic ulcer disease is unclear; tripotassium dicitratobismuthate or bismuth salicylate have been given at the same time as tetracycline as part of triple therapy for the eradication of *Helicobacter pylori*.

Antisecretory drugs. Pretreatment with *omeprazole* resulted in about a threefold increase in absorption of bismuth from tripotassium dicitratobismuthate in 6 healthy subjects.[1] The mean peak plasma concentration of bismuth after a single dose of 240 mg of tripotassium dicitratobismuthate was increased from 36.7 to 86.7 nanograms/mL after omeprazole suggesting an increased risk of toxicity from combined therapy. The mechanism was thought to be the increase in gastric pH produced by the antisecretory drug as similar results had been reported with *ranitidine*.[2] However, the clinical significance of these interactions to the use of antisecretory drugs with bismuth compounds for eradication of *Helicobacter pylori* is unclear; bismuth compounds have been combined with proton pump inhibitors or H_2 antagonists in short-term regimens as part of triple or quadruple therapy.

1. Treiber G, *et al.* Omeprazole-induced increase in the absorption of bismuth from tripotassium dicitrato bismuthate. *Clin Pharmacol Ther* 1994; 55: 486–91.
2. Nwokolo CU, *et al.* The effect of histamine H_2-receptor blockade on bismuth absorption from three ulcer-healing compounds. *Gastroenterology* 1991; 101: 889–94.

Pharmacokinetics

Poorly soluble bismuth compounds are largely converted to insoluble bismuth oxide, hydroxide, and oxychloride in the acidic environment of the stomach. Most of the bismuth compounds included in this monograph are thus only slightly absorbed. Increased gastric pH may increase bismuth absorption—see Antisecretory Drugs, above. Unabsorbed bismuth is excreted in the faeces. Absorbed bismuth is distributed throughout body tissues, including bone, and is slowly excreted in the urine and bile. It has a plasma half-life of about 5 days and continues to be excreted for about 12 weeks after stopping therapy.

References.

1. Nwokolo CU, *et al.* The absorption of bismuth from oral doses of tripotassium dicitrato bismuthate. *Aliment Pharmacol Ther* 1989; 3: 29–39.
2. Froomes PRA, *et al.* Absorption and elimination of bismuth from oral doses of tripotassium dicitrato bismuthate. *Eur J Clin Pharmacol* 1989; 37: 533–6.
3. Lacey LF, *et al.* Comparative pharmacokinetics of bismuth from ranitidine bismuth citrate (GR122311X), a novel anti-ulcerant and tripotassium dicitrato bismuthate (TDB). *Eur J Clin Pharmacol* 1994; 47: 177–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Re-Dux; Sesamoil; *Braz.*: Pepto-Bismol†; Peptozil; Peptulan; *Canad.*: Devrom; Maalox Multi-action†; Neo-Laryngobis; Pepto-Bismol; Stomak-Care; Xeroform; *China*: Ai Xi (艾悉); De Bi Tai (得必泰); De-Nol (德诺); Li Bi De (力比得); Wei Di Ya (唯迪亚); Xi Xin (悉欣); *Ger.*: Haemo-Exhirud Bufexamac†; Stryphnasal N; *Gr.*: De-Nol; *Hong Kong*: De-Nol; Pepto-Bismol†; *India*: Denol; Trymo; *Indon.*: Scantoma; Stobiol; *Israel*: BITNI X; Kalbeten; Peptolite; Pink Bismuth; *Ital.*: De-Nol; *Mex.*: Bismed; Bismofarma; Bisval†; Facidmol; Itamol; Pepto-Bismol; Siparox; Sucrato; *Neth.*: De-Nol; *NZ*: De-Nol; *Rus.*: De-Nol (Де-Нол); *S.Afr.*: De-Nol; *Singapore*: De-Nol; *Spain*: Gastrodenol; Rectamigdol†; *Switz.*: Amygdorectol; *Thai.*: Besmal; De-Nol; Gastro-Bismol; *Turk.*: De-Nol; Dermatol; *UK*: De-Noltab; Pepto-Bismol; *Ukr.*: De-Nol (Де-Нол); Gastro-Norm (Гастро-Норм); Vis-nol (Вис-Нол); *USA*: Bismatrol; Children's Kaopectate; Devrom; Kao-Tin; Kaopectate; Kapectolin†; Maalox Total Relief; Peptic Relief; Pepto-Bismol.

Multi-ingredient Preparations. *Arg.*: Anusol Duo S; Anusol-HC; Anusol†; Benitol; Colistop; Crema De Bismuto; Gastop; Gastranil; Gastricur; Lemil; Mabis†; Macoderm; Neoastrin; *Austral.*: BIP; *Belg.*: Procto-Synalar; Rectovasol; *Braz.*: Aftine; Anusol-HC; Bismu-Jet; Claudemor; Colutoide; Cutisanol; Cutisanol; Hemodase; Magnesia Bisurada; *Canad.*: Bismutal; Bismuth + Antacid; Onrectal†; Pepto-Bismol; Watkins Settelz†; *China*: Chanyanling (肠炎灵); Ge Lai Shi (格来士); Pepto-Bismol (佩普); Qiyu (奇钰); Yi Shuang Bi (易双必); Yilishu (宜立舒); *Cz.*: Carbocit; Mastu S†; Spofax; Suspensio Visnevski cum Pice Liquida HBP; *Fin.*: Tannopon†; *Fr.*: Anusol†; Bi-Qui-Nol; Cutiphile†; Paps†; Pholcones Bismuth; *Ger.*: Anaesthesin akut†; Angass†; Bismolan H Corti; Eulatin NH; Eulatin NH; Faktu akut†; Hamo-ratiopharm N†; Hamoagil plus†; Hexamon Bufexamac†; Mastu akut†; Mastu; Ventricon N†; *Gr.*: Hemorroidal; *Hong Kong*: Anusol; Anuzinc†; Haemoral†; Mastu S†; Rowatanal; *Hung.*: Bolus Adstringens; Gastritec; Mastu S†; Nilacid; *Indon.*: Anusol-HC†; Anusol†; *Irl.*: Anugesic-HC; Anugesic-HC; Anusol-HC; Anusol; Anusol; Hemocane; Pylera; Rowatanal; *Israel*: Hemo; Hemo; Rectozorin; Rectozorin; Rekiv†; *Ital.*: Antiemorroidali†; *Malaysia*: Rowatanal; *Mex.*: Estomacurol†; Heliton; Pepti-Max; *Neth.*: Anaesthetica†; Roteroblong Maagtabletten; Suppositoria contra haemorrhoides; Theranal; *Pol.*: Gastro†; Hemorectal; *Port.*: Synalar Rectal; *Rus.*: Anaesthesol (Анестезол); Anusol (Анузол); Neo-Anusol (Неоанузол); Proctosan (Проктозан); Simetrid (Симетрид); Vicair (Викаир); Vicalin (Викалин); *S.Afr.*: Adco-Biskapect†; Anugesic†; Anusol; Arola Rosebalm†; Chloropect; Enterodyne†; Kantrexil; Sentinel Ulcer Mixture†; *Singapore*: Rowatanal†; *Spain*: Grietalgen; Nasopomada†; Synalar Rectal; *Switz.*: Bismorectal†; Cicafissan; Furodermal†; Haemocortin†; Haemolan†; La pommade du Dr Brand; Rectoseptal-Neo bismuthe; *Thai.*: Antidiarrhoeals for children; Anusol†; Biodan; Bismocane; Mastu S†; Ulgastrin; *Turk.*: Deriseptol; Derivit; Dermikolin; Dervanol; Hemoralgine; Kortos; Metamorfoz; *UK*: Anugesic-HC†; Anugesic-HC; Anusol-HC, Plus HC; Anusol; Anusol; Bisma-Rex; Hemocane; Moorland; OxBipp; Stomach Mixture; *Ukr.*: Proctosan (Проктозан); Vicair (Викаир); Vicalin (Викалин); *USA*: Anumed HC; Anumed; BFI; Calmol; Helidac; Hem-Prep; Hemril; K-C; Kao-Paverin; Kaodene Non-Narcotic; Mammol; Pylera; Rectagene Medicated Rectal Balm; *Venez.*: Klincosal; Polantac.

Homoeopathic Preparations. *Austria*: Astomera; *Fr.*: Argentum Complexe no 98; *Ger.*: Gastritis Complex; Gastro Magentabletten; Nuxal comp.

Pharmacopoeial Preparations

BPC 1954: Bismuth Subnitrate and Iodoform Paste;
USP 36: Bismuth Subsalicylate Magma; Bismuth Subsalicylate Oral Suspension; Bismuth Subsalicylate Tablets; Compound Resorcinol Ointment; Milk of Bismuth.

Bisoxatin Acetate (BANM, USAN, rINNM)

Acetato de bisoxatina; Bisoxatin Diacetate; Bisoxatina, acetato de; Bisoxatine, Acétate de; Bisoxatini Acetas; Wy-8138; Бизоксатина Ацетат.

2,2-Bis(4-hydroxyphenyl)-1,4-benzoxazin-3(2*H*,4*H*)-one diacetate.

$C_{24}H_{19}NO_6$=417.4

CAS — 17692-24-9 (bisoxatin); 14008-48-1 (bisoxatin acetate).

ATC — A06AB09.

ATC Vet — QA06AB09.

UNII — 79WSLFS83K.

Profile

Bisoxatin acetate is a stimulant laxative that has been used in a usual oral dose of 120 mg at night in the treatment of constipation (p. 1804.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Wylaxine; *Venez.*: Regoxal.

Bran

Crusca; Farelo; Kleie; Salvado; Son; Отруби.

UNII — 1L922R9NG2 (bran, fibre); KQX236OK4U (oat bran); R60QEP13IC (rice bran); 6L966A1IMR (wheat bran).

Description. Bran consists of the fibrous outer layers of cereal grains. It contains celluloses, polysaccharides or hemicelluloses, protein, fat, minerals, and moisture and may contain part of the germ or embryo. Bran provides water-insoluble fibre and, depending on the source, may also provide water-soluble fibre (see also Dietary Role, below). It comprises about 12% of the weight of the grain and is a byproduct of flour milling. It is available in various grades.

Pharmacopoeias. *US* includes wheat bran.

USP 36: (Wheat Bran). The outer fraction of the cereal grain (comprising the pericarp, seed coat (testa), nucellar tissue, and aleurone layer) derived from *Triticum aestivum, T. compactum, T. durum*, or other common einkorn and emmer wheat cultivars. It is obtained by milling and processing the whole wheat grain, and is available in a variety of particle sizes depending on the degree of milling. It contains not less than 36% of dietary fibre. It is a light tan powder having a characteristic aroma. Practically insoluble in cold water and in alcohol.

Uses and Administration

The main use of bran is as a bulk laxative and source of dietary fibre in the management of disorders of the gastrointestinal tract such as constipation (p. 1804.3), especially in diverticular disease (p. 1806.2); it is also widely used in irritable bowel syndrome, although its value has been questioned (see p. 1810.3). It should always be taken with plenty of fluid.

Bran is used as the basis for some breakfast cereals.

Dietary role. There is no precise definition for the complex mixture of substances known as dietary fibre. It has been defined as *plant* polysaccharides and lignin resistant to hydrolysis by the digestive enzymes of humans but this covers many substances other than cell-wall and related polysaccharides. Non-starch polysaccharides are the major component of the plant cell wall and are used as an index of dietary fibre. They comprise water-soluble fibres such as pectins, gums, and mucilages and water-insoluble fibres such as cellulose. Wheat, maize, and rice contain mainly insoluble non-starch polysaccharides whereas oats, barley, and rye have a significant proportion of soluble fibres.[1] Because the USA originally included nondigestible *animal* carbohydrates in the definition of fibre, the Food and Nutrition Board in the USA proposed a new definition of fibre, whereby dietary fibre consists of nondigestible carbohydrates and lignin that are intrinsic and intact in plants, and functional fibre consists of isolated, nondigestible plant or animal carbohydrates that have beneficial physiological effects in humans. Total fibre is the sum of dietary and functional fibre.[2]

In the UK, dietary reference values (DRV) have been published for non-starch polysaccharides.[1] It has been proposed[1] that adult diets should contain an average for the population of 18 g daily (individual range 12 to 24 g daily) non-starch polysaccharide from a variety of foods whose constituents contain it as a naturally integrated component. Children should receive proportionately less non-starch polysaccharide according to body size. No evidence exists for benefit of intakes of non-starch polysaccharide in excess of 32 g daily, and therefore there is no advantage in exceeding this amount.

In the USA, a total dietary fibre intake of 14 g of fibre per 1000 calories consumed has been suggested for adults and children aged from 1 year.[3]

1. DOH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids*. Washington DC: National Academy Press, 2002/2005. Also available at: http://www.nap.edu/openbook.php?record_id=10490 (accessed 04/04/08)
3. Slavin JL. Position of the American Dietetic Association: health implications of dietary fiber. *J Am Diet Assoc* 2008; 108: 1716–31. Correction. *ibid.* 2009; 109: 350. Also available at: http://www.eatright.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=8442 (accessed 15/07/10)

Disease prevention. Diseases such as colorectal cancer, ischaemic heart disease, diabetes mellitus, and obesity are common in affluent developed countries but occur rarely

in rural Africa. This difference in disease patterns has been linked to the low fibre intake in developed countries compared with rural Africans. However, there are many other differences in diet and lifestyle, such as a lower intake of fat, protein, and sugar in rural Africans and less exposure to toxins and pollutants, any of which could contribute to the difference. The excessive consumption of energy-rich foods may be more to blame for diseases of affluence than is deficiency of dietary fibre.[1]

Results from large prospective cohort studies have been conflicting as to whether there is any *reduction in risk* of **colorectal cancer** associated with a high intake of dietary fibre, and have mostly failed to show a reduction in the *recurrence rate* of colorectal adenomas (although most adenomas do not develop into cancer, and so the relevance of these results is unclear[2]). A pooled analysis of 13 prospective cohort studies found a significant inverse association between dietary fibre intake and colorectal cancer. However, after adjusting for other risk-factors, this association was attenuated and no longer statistically significant. There was some suggestion that intake of dietary fibre from cereals and from whole-grain foods were both associated with a weak reduction in the risk of rectal cancer.[3] Some have commented[4] that fibre is a broad term encompassing a wide range of organic material, which may have a large number of actions on digestive physiology. Furthermore, there is some concern that the use of fibre supplements is not entirely without harmful effects: it has been pointed out that fermentable fibre substrates can stimulate cell proliferation in the colon.[5] However, the role of cell proliferation as a marker for the development of colonic cancer is questioned by some authors.[6]

A small randomised crossover study[7] in patients with type 2 **diabetes mellitus** suggested that an increased intake of dietary fibre was associated with improved glycaemic control, decreased hyperinsulinaemia, and lower plasma lipid concentrations. In prospective cohort studies, inverse associations were found between whole-grain intake and the risk of type 2 diabetes mellitus;[8-11] in some studies, this inverse association persisted for cereal fibre intake,[9-11] but in one the protective effect of whole grain could not entirely be explained by fibre content.[8]

Fibre may act as an obstacle to energy intake by displacing available calories and nutrients from the diet, by increasing satiety, and by decreasing the absorption efficiency of the small intestine. Epidemiological studies support the hypothesis that a higher dietary fibre intake prevents **obesity**; populations that report higher fibre consumption also demonstrate lower obesity rates.[12] Weight gain was inversely associated with increases in the intake of whole grains but positively associated with increases in the intake of refined grains, emphasising the importance of distinguishing whole-grain from refined-grain products.[13]

A large prospective cohort study in men found an inverse association between whole-grain intake and the incidence of **coronary heart disease**; the finding was even stronger for bran intake. These associations were attenuated, but not eliminated, by adjustment for other risk factors for coronary heart disease.[14] There is some suggestion that diets high in fibre may have a moderate effect on blood pressure reduction.[15]

1. Anonymous. The bran wagon. *Lancet* 1987; **i**: 782–3.
2. Byers T. Diet, colorectal adenomas, and colorectal cancer. *N Engl J Med* 2000; **342**: 1206–7.
3. Park Y, *et al.* Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. *JAMA* 2005; **294**: 2849–57.
4. Goodlad RA. Dietary fibre and the risk of colorectal cancer. *Gut* 2001; **48**: 587–9.
5. Wasan HS, Goodlad RA. Fibre-supplemented foods may damage your health. *Lancet* 1996; **348**: 319–20.
6. Hill MJ, Leeds AR. Fibre and colorectal cancer. *Lancet* 1996; **348**: 957.
7. Chandalia M, *et al.* Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. *N Engl J Med* 2000; **342**: 1392–8.
8. Liu S, *et al.* A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. *Am J Public Health* 2000; **90**: 1409–15.
9. Meyer KA, *et al.* Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr* 2000; **71**: 921–30.
10. Fung TT, *et al.* Whole-grain intake and the risk of type 2 diabetes: a prospective study in men. *Am J Clin Nutr* 2002; **76**: 535–40.
11. Montonen J, *et al.* Whole-grain and fiber intake and the incidence of type 2 diabetes. *Am J Clin Nutr* 2003; **77**: 622–9.
12. Slavin JL. Dietary fiber and body weight. *Nutrition* 2005; **21**: 411–18.
13. Liu S, *et al.* Relation between changes in intakes of dietary fiber and grain products and changes in weight and development of obesity among middle-aged women. *Am J Clin Nutr* 2003; **78**: 920–7.
14. Jensen MK, *et al.* Intakes of whole grains, bran, and germ and the risk of coronary heart disease in men. *Am J Clin Nutr* 2004; **80**: 1492–9.
15. He J, *et al.* Effect of dietary fiber intake on blood pressure: a randomized, double-blind, placebo-controlled trial. *J Hypertens* 2004; **22**: 73–80.

Adverse Effects

Large quantities of bran may temporarily increase flatulence and abdominal distension, and intestinal obstruction may occur rarely.

Colonic atony. Colonic atony has been reported in patients who had increased their intake of dietary fibre to relieve constipation associated with systemic sclerosis.[1]

1. Gough A, *et al.* Dietary advice in systemic sclerosis: the dangers of a high fibre diet. *Ann Rheum Dis* 1998; **57**: 641–2.

Diarrhoea. A report of diarrhoea induced by a dramatic increase in fibre intake. Reduction of dietary fibre led to a return to normal bowel habit in 2 to 3 days.[1]

1. Saifbl P. Diarrhea due to fiber overload. *N Engl J Med* 1989; **320**: 599.

Intestinal obstruction. Intestinal obstruction associated with excessive bran intake has been reported.[1-3]

1. Allen-Mersh T, De Jode LR. Is bran useful in diverticular disease? *BMJ* 1982; **284**: 740.
2. Cooper SG, Tracey BJ. Small-bowel obstruction caused by oat-bran bezoar. *N Engl J Med* 1989; **320**: 1148–9.
3. Miller DL, *et al.* Small-bowel obstruction from bran cereal. *JAMA* 1990; **263**: 813–14.

Precautions

Bran is contra-indicated in patients with intestinal obstruction or with undiagnosed abdominal symptoms. There is a particular risk of intestinal or oesophageal obstruction if bulk laxatives are swallowed dry; they should be taken with sufficient fluid and should not be taken immediately before going to bed. Wheat bran should be avoided in gluten enteropathies and coeliac disease.

Interactions

Bran may reduce the absorption of some drugs when given together orally. Interference with iron, zinc, and calcium absorption has been reported; calcium phosphate may be added to bran to neutralise fytic acid, which can contribute to such interference.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Trifibra Mix; *China*: Fiberform (非比获); *Fr.*: Doses-O-Son; Infibran†; *India*: Imbran; *Neth.*: Fiberform; *Port.*: Infibran†; *Swed.*: Fiberform Mix†; Fiberform†.

Multi-ingredient Preparations. *Arg.*: Adelgacin; Gelax; *Chile*: Naticare; *Mex.*: Psilumax†; *Pol.*: Magnezytki†; Otrebuski†.

Bromopride *(rINN)*

Bromoprida; Bromopridum; CM-8252; VAL-13081; Бромоприд.

4-Amino-5-bromo-*N*-(2-diethylaminoethyl)-*o*-anisamide.

$C_{14}H_{22}BrN_3O_2$=344.3

CAS — 4093-35-0.

ATC — A03FA04.

ATC Vet — QA03FA04.

UNII — 75473V2YZK.

Profile

Bromopride is a substituted benzamide similar to metoclopramide (p. 1862.2), used in a variety of gastrointestinal disorders including nausea and vomiting (p. 1811.3) and motility disorders. It is given in a usual oral dose of 20 to 60 mg daily in divided doses, or 10 to 20 mg daily by intramuscular or intravenous injection. The hydrochloride is also used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Bilenzima†; Bromogex; Bromopan; Digerex†; Digesan; Digesprid; Digestil; Digestina; Pangest; Plamet; Pridecil; *Ital.*: Procirex; Valopride.

Multi-ingredient Preparations. *Braz.*: Digecap-Zimatico; Lansoprid†; Primeral; *Port.*: Modulanzime.

Buckthorn

Bacca Spinae Cervinae; Espino Cerval; Kreuzdorn; Nerprun; Крушина Слабительная; Жостер Слабительный.

UNII — B4R1EZ1R1D (buckthorn extract).

NOTE. Distinguish from Alder Buckthorn Bark (see Frangula Bark, p. 1843.3) and from Sea Buckthorn (p. 2611.3).

Pharmacopoeias. In *Ger.*

Profile

Buckthorn is the dried ripe fruit of *Rhamnus cathartica* (Rhamnaceae); the bark is also occasionally used. Buckthorn is an anthraquinone stimulant laxative.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Colon Care; Detox Pro gram; Neo-Cleanse; *Rus.*: Laxantis Species No 1 (Слабительный Сбор 1); Proctophytol (Проктофитол); Vicalin (Викалин); *UK* Cleansing Herbs; Lion Cleansing Herbs; *USA*: Detox.

Butropium Bromide *(rINN)*

Bromuro de butropio; Butropii Bromidum; Butropio, bromuro de; Butropium, Bromure de; Бутропия Бромид.

(-)-(1*R*,3*r*,5*S*)-8-(4-Butoxybenzyl)-3-[(*S*)-tropoyloxy]tropanium bromide.

$C_{28}H_{38}BrNO_4$=532.5

CAS — 29025-14-7.

UNII — R3K4503MV7.

Pharmacopoeias. In *Jpn.*

Profile

Butropium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been used in the symptomatic treatment of visceral spasms in an oral dose of 30 mg daily in 3 divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Coliopan†; *Jpn*: Coliopan; *Malaysia*: Coliopan.

Calcium Carbonate

Calcii carbonas; Calcii Carbonas Praecipitatus (precipitated calcium carbonate); Calcium, carbonate de; Calciumcarbonat; Carbonato de calcio; Creta Preparada; E170; Kalcio karbonatas; Kalciumkarbonat; Kalcium-karbonát; Kalsiumkarbonaatti; Kalsiyum Karbonat; Precipitated Calcium Carbonate; Precipitated Chalk; Uhličitan vápenatý; Wapnia węglan; Wapnia węglan strącony (precipitated calcium carbonate); Кальция Карбонат.

$CaCO_3$=100.1

CAS — 471-34-1.

ATC — A02AC01; A12AA04.

ATC Vet — QA02AC01; QA12AA04.

UNII — H0G9379FGK.

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

US includes Ground Limestone.

Ph. Eur. 5: (Calcium Carbonate). A white or almost white powder. Practically insoluble in water.

USP 36: (Calcium Carbonate). A fine, white, odourless microcrystalline powder. Practically insoluble in water; its solubility in water is increased by the presence of carbon dioxide or ammonium salts although the presence of any alkali hydroxide reduces its solubility; insoluble in alcohol; dissolves with effervescence in acetic acid, in hydrochloric acid, and in nitric acid.

USP 36: (Ground Limestone). A white to off-white, fine microcrystalline powder mostly consisting of calcium carbonate.

Uses and Administration

Calcium carbonate is used as an antacid (p. 1803.1), usually in oral doses of up to about 1.5 g. It is often given with other antacids, especially magnesium-containing antacids.

Calcium carbonate is also used as a calcium supplement in deficiency states and as an adjunct in the management of osteoporosis, as described under Calcium, p. 1784.3.

Calcium carbonate binds phosphate in the gastrointestinal tract to form insoluble complexes and reduces phosphate absorption. It is used to treat hyperphosphataemia in patients with chronic renal failure (see Renal Osteodystrophy, p. 1170.1) or associated secondary hyperparathyroidism (p. 1170.3). Doses are adjusted according to serum phosphate concentrations. Typical oral doses of calcium carbonate range from about 3 to 7 g (1.2 to 2.8 g calcium) daily in divided doses, although the US National Kidney Foundation suggests that the total dose of elemental calcium provided by the calcium-based phosphate binder should not exceed 1.5 g daily in those with kidney failure. For doses in children, see p. 1825.1.

Calcium carbonate is also used as a food additive.

Homoeopathy

Native forms of calcium carbonate have been used in homoeopathic medicines under the following names: Calcarea Carbonica; Calc. Carb.; Calcium carbonicum

Hahnemanni; Conchae; Calcium Carbonate of Hahnemann; Cal. carb.

Administration in children. Calcium carbonate can be used as a phosphate binder in children with renal failure and hyperphosphataemia. The *BNFC* suggests the following oral doses of calcium carbonate, given 3 or 4 times daily with or before meals, and adjusted as necessary:

- 1 month to 1 year of age: 120 mg
- 1 to 6 years: 300 mg
- 6 to 12 years: 600 mg
- 12 to 18 years: 1.25 g

Adverse Effects, Treatment, and Precautions

Calcium carbonate may occasionally cause constipation. Flatulence from released carbon dioxide may occur in some patients. High doses or prolonged use may lead to gastric hypersecretion and acid rebound. Like other calcium salts (see p. 1786.1), calcium carbonate can cause hypercalcaemia, particularly in patients with renal impairment or after high doses. Alkalosis (p. 1775.3) may also occur as a result of the carbonate anion. There have been rare reports of the milk-alkali syndrome, see below, and tissue calcification. The possibility of an increased risk of myocardial infarction associated with the use of calcium supplements has been raised (see Effects on the Cardiovascular System, p. 1786.1).

For precautions to be observed with the use of calcium carbonate, see Calcium, p. 1786.1.

Milk-alkali syndrome. The milk-alkali syndrome of hypercalcaemia, alkalosis and renal impairment was first identified in the 1920s and may still occur in patients who take large amounts of calcium and absorbable alkali.[1-3] With chronic ingestion, abnormal calcification can develop.[3]

Calcium carbonate is a common source of calcium and alkali, and milk-alkali syndrome can be seen in patients being treated for osteoporosis and after high intake of antacids.[3] Although an elemental calcium intake of up to 2 g daily is considered safe, milk-alkali syndrome has been reported with even lower daily doses.[1,3] Some patients may be more susceptible; predisposing factors include the chronic vomiting associated with bulimia or hyperemesis of pregnancy,[3] pre-existing renal failure, and concomitant use of other medicines which alter calcium homoeostasis.[1,3]

For reference to thiazide diuretics increasing the risk of the milk-alkali syndrome in patients taking moderately large doses of calcium carbonate, see p. 1406.2.

1. Picolos MK, *et al.* Milk-alkali syndrome is a major cause of hypercalcaemia among non-end-stage renal disease (non-ESRD) inpatients. *Clin Endocrinol (Oxf)* 2005; 63: 566–76.
2. Felsenfeld AJ, Levine BS. Milk alkali syndrome and the dynamics of calcium homeostasis. *Clin J Am Soc Nephrol* 2006; 1: 641–54.
3. Medarov BI. Milk-alkali syndrome. *Mayo Clin Proc* 2009; 84: 261–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies calcium carbonate 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 06/10/11)

Interactions

As for other calcium salts, p. 1786.1.

As outlined on p. 1803.1, antacids, including calcium salts, interact with many other drugs both by alterations in gastric pH and emptying, and by formation of complexes that are not absorbed. Interactions can be minimised by giving calcium carbonate and any other medication 2 to 3 hours apart.

Omeprazole. In a study[1] of 18 women over the age of 65, the use of omeprazole for a week significantly reduced the absorption of calcium from a calcium carbonate supplement given on an empty stomach. Fractional calcium absorption was reduced from 9.1% with placebo to 3.5% with omeprazole.

1. O'Connell MB, *et al.* Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. *Am J Med* 2005; 118: 778–81.

Pharmacokinetics

Calcium carbonate is converted to calcium chloride by gastric acid. Some of the calcium is absorbed from the intestines and the unabsorbed portion is excreted in the faeces, as described for other calcium salts, p. 1786.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acomplex P; Calcio Acido; Calcional; Calcium-Sandoz; Pluscal; Renacalcio; Ultracalcium; Uvasal Tums; ***Austral.***: Andrews Tums; Cal-Sup; Caltrate; Sandocal†; Titralac; ***Austria***: Calcium-Sandoz; Dreisacarb; ***Belg.***: Cacit; Calci-Chew; Sandoz Calcium; Steocar; ***Braz.***: Calcium-Sandoz F; Calsan; Fontical; Maxicalc; Os-Cal; Osseopor; Rhamical; ***Canad.***: Apo-Cal; Cal-500; Calciforte†; Calcium Oyster Shell†; Calcium-Sandoz; Calsan; Caltrate; Hi Potency Cal†; Neo Cal†; Nu-Cal; Os-Cal†; Trial Antacid†; Tums; ***Chile***: Calcefor; Calcio†; Calcium Factor†; Calcium-Sandoz†; Calcivorin; Caprimida; Elcal; Kaplus; Levucal; Natecal; Sanidecal; ***China***: Calcichew (凯思立); Gu Yuan (固元); Kaifang (凯方); Mylanta (兰达); Na Nuo Ka (纳诺卡); Xie Da Li (协达利); ***Cz.***: Maxi-Kalz; Vitacalcin; ***Denm.***: Calcium-Sandoz; ***Fin.***: Calcichew; Calcium-Sandoz†; Kalcidon†; Kalcipos; ***Fr.***: Cacit; Calcidia; Calcidose; Calciprat; Calcium-Sandoz; Calperos; Calprimum; Caltrate; Densical; Bucalcic†; Fixical; Osteocal†; Perical†; ***Ger.***: Calci-Gry†; Calcimagon; Calcimed; Calcium AL†; Calcium beta; Calcium Stada†; Calcium Verla; Calcium-CT†; Calcium-Sandoz†; CC-Nefro; Dreisacarb; Loscalcon†; Ospur Ca; ***Gr.***: Alcamex; Body-Calcin; Calciform; Calciforte; Calcioral; Frubiose-N; ***Hong Kong***: Apo-Cal; Calcium-Sandoz; Caltrate; Doctor's Choice Calcium†; Os-Cal; Scott's Hi-Calcium†; Titralac†; ***Hung.***: Beres Calcium; Calcicarb; Calcichew; Calcium-Sandoz; Remegel; ***India***: Bonycal; Calcicip; Calcium-Sandoz; Calibon-Z; Oscal; Sandocal; ***Indon.***: Calcium-Sandoz Junior Strength; Calnat; Calos; Calsan†; Osteocal; Stomacain; ***Irl.***: Cacit; Calcichew; Remegel; Rennie Chewable Tablets; Rowarolan; Sandocal; ***Israel***: Calci-Rav; Calcimore; Calcium-Sandoz; Caltrate†; Fast; Kal Zarevet†; N-Zarevet; Tums; Tzarevet X; ***Ital.***: Adiecal; Biocalcium†; Cacit; Cal-Car; Calciodie; Calcioplus†; Calcium-Sandoz; Calma; Carbosint; Idracal; Lubical; Metocal; Recal; Savecal†; Top Calcium†; ***Malaysia***: Cal-Sup†; Caltrate; ***Mex.***: Bexacal; Calcidef; Calcifar; Calcium-Sandoz; Calsan; Caltrate; Ciocar†; Mubonet; Osteomin; Solibone†; Tums; ***Mon.***: Orocal; ***Neth.***: Cacit; Calci-Chew; Calcium-Sandoz; ***Norw.***: Calcium-Sandoz; Titralac; ***NZ***: Calcium-Sandoz†; Caltrate; Osteo; Titralac; ***Philipp.***: Calbone; Calci-Aid; Calcium-Sandoz†; Calmate†; Calsan; Tums; ***Pol.***: Additiva Calcium†; Calcium-Sandoz Forte; Calperos; FrutiCal†; Ostical†; Vicalvit†; ***Port.***: Calcior; Calcioral; Calcitab; Calcium-Sandoz; Natecal; Sandocal†; Tums; ***Rus.***: Calcium-Sandoz Forte (Кальций-Сандоз Форте); ***S.Afr.***: B-Cal; Calcichew; Calcium-Sandoz; Calsuba†; Caltrate; Fizzical; Titralac†; Tums†; ***Singapore***: Apo-Cal; Bonacal; Cal-Sup†; Calcium-Sandoz Forte; Calperos; Caltrate; Remegel; ***Spain***: Calcium-Sandoz Forte†; Caosina; Carbocal; Cimascal; Densical†; Mastical; Natecal; Osteocal†; ***Swed.***: Calcitugg; Calcium-Sandoz; Kalcidon; Kalcipos; Kalcitena†; ***Switz.***: Calcium-Sandoz; Calperos; Fixateur phospho-calcique; Natecal D; ***Thai.***: BayCal; Bo-Ne-Ca; Bonetec; Cal-Os; Cal-ups; Calbone†; Calcanate; Calcap; Calcar; Calcarbonate†; Calcium Central Poly; Calcium TO; Calcium-Sandoz Bonacal; Calcium-Sandoz; Calhof; Calmate; Calsum; Caltab Forte†; Caltab; Caltrate; Caltrex; Carbocal; Carbocalc†; Chalkcap; Chalktab; GPO Cal; Kal-Forte; OB Cal; Patar Kal; Pharcal; Prima-Cal; T-Bon; V-Calcium; Weifa-Calcium†; ***Turk.***: Anti-Fosfat Cc; Calcimed; Calcium-Sandoz; Ostram; ***UK***: Adcal; Cacit; Calchew; Rap-eze; Remegel; Rennie Soft Chews; Sandocal; Sea-Cal; Setlers; Tums; ***USA***: Alka-Mints; Antacid; Caici-Chew; Caici-Mix; Calcium-600; Caltrate; Chooz; Maalox Antacid Barrier; Maalox Childrens; Mallamint; Mylanta†; Nephro-Calci; Os-Cal; Oysco; Oyst-Cal; Pepto Children's; Rolaids Extra Strength Softchews; Surpass; Titralac Extra Strength; Trial Antacid; Tums; ***Venez.***: Calcion; Calcium-Sandoz; Foscalvit; Frutacid; Sandocal; Titralac; Tums.

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

Used as an adjunct in:. *Arg.*: Aspirina; ***Braz.***: Bufferin; ***Canad.***: Aspirin with Stomach Guard; Bufferin; Tri-Buffered ASA†; ***Mex.***: Reumophan Alka; ***Pol.***: Calcipiryna†; Polopiryna S; ***USA***: Adprin-B; Ascriptin; Bufferin; Extra Strength Bayer Plus.

Homoeopathic Preparations. ***Austral.***: Allergy Relief; Elimitona Slim & Detox; ***Austria***: Osanit Zahnungskugelchen; Osteopiex; Steiroplex; Zahnkugelchen; ***Canad.***: Bioactiv E†; Bioactiv R†; Earache; Formula DE 226†; Hea Complex†; Hepar Compositum; Homeo-Form P†; Hylands Formula S; Hylands Sinus†; Minerals+; Phyto-Cal; Rexorubia†; Sinus Ease; Sinus; Sinuspax†; Sorinoheel; Tee Complex†; Ubicoenzyme; Ursical Formula†; Urticalcin; Viburcol; ***Chile***: Bioactiv D; Bioactiv E; Bioactiv R; ***Cz.***: Hormeel S; Viburcol; ***Fr.***: Abbe Chaupitre no 44†; Abbe Chaupitre no 48†; Calcarea Compose; Dolitravel†; Jenoverine†; Osteocynesine; Rexorubia; Sels Calcaires Nutritifs; Sepia Complexe No 20; Sinuspax; Slimum†; Veino-Drainol†; ***Ger.***: Agaricus comp Phosphorus; Araniforce rheuma†; Calciurell; Chirofossat; Feminon N; Hepar comp; Hewelymphon N†; Infi-Symphytum; Infifer N; Infihepan; Osanit; Osteoplex; Otio-cyl Ho-Len-Complex; Oto-cyl Ho-Len-Complex; Pflugerplex Lemna; Ranocalcin HM; Sepia comp; Steirocall; Steiroplex†; Viburcol N; ***Hung.***: Hormeel S; Viburcol; ***Neth.***: Auriculite; Dermafleur; Jenoverine†; Kind 0-6 Caltrivat; Lergilite; Myamolite; Osteocynesine†; Prurilite; Urtizon complex; Venafleur; Viburcol H; ***Port.***: Osteocynesine; ***Rus.***: Berberis-Plus (Берберис-Плюс); Hormeel SN (Гормель СН); Urtica-Plus (Уртика-Плюс); ***S.Afr.***: Aufbaukalk II†; Viburcol; ***Switz.***: Regenaplex Nr. 51c; Regenaplex Nr. 88b; Urticalcin; Viburcol N; ***UK***: Conchae comp.; Fragador; ***Ukr.***: Immunokind (Иммунокинд).

Pharmacopoeial Preparations

BP 2014: Alginate Raft-forming Oral Suspension; Calcium and Colecalciferol Tablets; Chewable Calcium and Colecalciferol Tablets; Chewable Calcium Carbonate and Heavy Magnesium Carbonate Tablets; Chewable Calcium Carbonate Tablets;

USP 36: Alumina, Magnesia, and Calcium Carbonate Oral Suspension; Alumina, Magnesia, and Calcium Carbonate Tablets; Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets; Aluminum Subacetate Topical Solution; Calcium and Magnesium Carbonates Oral Suspension; Calcium and Magnesium Carbonates Tablets; Calcium Carbonate and Magnesia Tablets; Calcium Carbonate Lozenges; Calcium Carbonate Oral Suspension; Calcium Carbonate Tablets; Calcium Carbonate, Magnesia, and Simethicone Tablets.

Carbenoxolone Sodium *(BANM, USAN, rINNM)*

Carbenoxolona sódica; Carbénoxolone Sodique; Disodium Enoxolone Succinate; Karbenoksolon Sodyum; Natrii Carbenoxolonum; Натрий Карбеноксолон.

3β-(3-Carboxypropionyloxy)-11-oxo-olean-12-en-30-oic acid, Disodium Salt.

$C_{34}H_{48}Na_2O_7$=614.7

CAS — 5697-56-3 (carbenoxolone); 7421-40-1 (carbenoxolone disodium).

ATC — A02BX01.

ATC Vet — QA02BX01.

UNII — F1MP7242Z5.

Pharmacopoeias. In *Br.*

BP 2014: (Carbenoxolone Sodium). A white or pale cream-coloured, hygroscopic powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform and in ether. A 10% solution in water has a pH of 8.0 to 9.2.

Profile

Carbenoxolone sodium is a synthetic derivative of glycyrrhizic acid (p. 2520.2) that is one of many topical treatments for the symptomatic management of mouth ulceration (p. 1811.2). It is usually used as a 2% gel; a 1% mouthwash has been used. It was formerly also used as a mucosal protectant in peptic ulcer disease and has been given with antacids and alginic acid in gastro-oesophageal reflux disease.

Adverse effects. Carbenoxolone has mineralocorticoid-like effects and ingestion has been associated with sodium and water retention and hypokalaemia. Muscle weakness,[1-5] muscle necrosis,[4] myopathy,[1] hypertension,[2] headache,[2] cardiac failure,[2] mental confusion,[4] areflexia,[3] renal tubular dysfunction,[5] and acute tubular necrosis[4] have all been associated with carbenoxolone-induced hypokalaemia. Carbenoxolone-induced hypertension may have precipitated the onset of fatal polyarteritis in a patient predisposed to this condition.[6]

1. Fyfe T, *et al.* Myopathy and hypokalaemia in carbenoxolone therapy. *BMJ* 1969; 3: 476.
2. Davies GJ, *et al.* Complications of carbenoxolone therapy. *BMJ* 1974; 3: 400–2.
3. Royston A, Prout BJ. Carbenoxolone-induced hypokalaemia simulating Guillain-Barré syndrome. *BMJ* 1976; 2: 150–1.
4. Descamps C, *et al.* Rhabdomyolysis and acute tubular necrosis associated with carbenoxolone and diuretic treatment. *BMJ* 1977; 1: 272.
5. Dickinson RJ, Swaminathan R. Total body potassium depletion and renal tubular dysfunction following carbenoxolone therapy. *Postgrad Med J* 1978; 54: 836–7.
6. Sloan J, Weaver JA. A case of polyarteritis developing after carbenoxolone therapy. *Ir Med J* 1968; 1: 505–7.

Handling. Carbenoxolone sodium powder is irritant to nasal membranes.

Mental function. High cortisol concentrations have been associated with poorer memory and neuronal loss in some patients. Carbenoxolone inhibits 11-β-hydroxysteroid dehydrogenase type 1, and thus may selectively lower intracellular cortisol. In a small crossover study[1] in 10 healthy elderly men, oral carbenoxolone 100 mg three times daily for 4 weeks significantly improved verbal fluency compared with placebo, but did not influence visual or verbal memory, nonverbal reasoning, or processing speed. Twelve patients with stable type 2 diabetes were given carbenoxolone at the same dose for 6 weeks. Verbal memory was significantly improved compared with placebo, but verbal fluency and other scores were unaltered. All subjects were given amiloride 10 mg daily to prevent mineralocorticoid adverse effects[1] (although this has been reported to reduce the efficacy of carbenoxolone).

1. Sandeep TC, *et al.* 11β-Hydroxysteroid dehydrogenase inhibition improves cognitive function in healthy elderly men and type 2 diabetics. *Proc Natl Acad Sci U S A* 2004; 101: 6734–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Bioral†; ***Austria***: Rowadermat; ***Hong Kong***: Herpesan; ***Hung.***: Carbosan; ***Irl.***: Carbosan; ***Malaysia***: Herpesan; ***Philipp.***: Rowagel; ***Singapore***: Herpesan†; ***Spain***: Sanodin.

Multi-ingredient Preparations. ***Irl.***: Pyrogastrone†.

Casanthranol *(USAN)*

Casantranol; Казантранол.
CAS — 8024-48-4.
UNII — 3SJ3U7J6V2.

Pharmacopoeias. In *US*.

USP 36: (Casanthranol). It is obtained from cascara. It contains not less than 20% of total hydroxyanthracene derivatives calculated on the dried basis, of which not less than 80% consists of cascarosides, both calculated as cascaroside A ($C_{27}H_{32}O_{14}$=580.5).

It is a light tan to brown, amorphous, hygroscopic powder. Freely soluble in water with some residue; partially soluble in methyl alcohol and in hot isopropyl alcohol; practically insoluble in acetone. Store in airtight containers at a temperature not exceeding 30 degrees. Protect from light.

Profile

Casanthranol is an anthraquinone stimulant laxative with general properties similar to those of senna (p. 1885.1). It is given in usual oral doses of 30 to 60 mg daily with a faecal softener. In severe cases a dose of 90 mg daily, or 60 mg twice daily, may be given.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Neth.*: Cascalax†.

Multi-ingredient Preparations. *Arg.*: Bil 13; En-Ga-Lax; *Canad.*: Laxolax Phyto†; *Spain*: Laxvital†; *USA*: Black-Draught; Docusoft Plus; Laxative & Stool Softener.

Cascara

Amerikinių šaltekšnių žievė; Cáscara sagrada; Cascararinde; Chittem Bark; Kaszkarabokor kéreg; Kůra řešetláku Purshova; Rhamni Purshianae Cortex; Rhamni Purshiani Cortex; Sacred Bark; Sagradabark; Sagradankuori; Крушина Пурша; Жостер Пурша.
CAS — 8047-27-6; 8015-89-2 (cascara sagrada extract).
ATC — A06AB07.
ATC Vet — QA06AB07.
ATC Herb — HA06AB5014 (Rhamnus purshiana: bark).
UNII — 4VBP01X99F.

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

Ph. Eur. 8: (Cascara). The dried, whole or fragmented bark of *Rhamnus purshianus* (=*Frangula purshiana*). It contains not less than 8.0% of hydroxyanthracene glycosides of which not less than 60% consists of cascarosides, both expressed as cascaroside A ($C_{27}H_{32}O_{14}$=580.5). and calculated with reference to the dried drug. Protect from light.

USP 36: (Cascara Sagrada). The dried bark of *Rhamnus purshianus* (Rhamnaceae). It contains not less than 7% of total hydroxyanthracene derivatives calculated on the dried basis, of which not less than 60% consists of cascarosides, both calculated as cascaroside A. It has a distinct odour.

Profile

Cascara is an anthraquinone stimulant laxative with general properties similar to those of senna (p. 1885.1). It has been used in the treatment of constipation in oral doses equivalent to about 20 to 30 mg of total hydroxyanthracene derivatives daily.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving cascara, 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 08/11/06)**

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Natulax†; *Belg.*: Laxafytol; *Braz.*: Laxsotrin†; Verilax; *Fr.*: Peristaltine†; *Ger.*: Legapas.

Multi-ingredient Preparations. *Arg.*: Bilidren; Cascara Sagrada Bouzen; Cascara Sagrada Oligoplex; Cascara Sagrada Puler; Natulax Plus; Veracolate†; *Austral.*: Colax†; Colax; Peritone; *Austria*: Silberne†; *Belg.*: Vethoine; *Braz.*: Chofraninа†; Eparema; Solvobil; *Canad.*: Bicholate†; Bilonat; Cas-Mag; Control†; Depuratif des Trappistes; Doulax; Eliminex; Formula B-1†; Formula T5 Tea†; Hepaticol; Herba Tone†; Herbal Laxative plus Yogurt†; Herbal Laxative†; Herbal Tabs†; Herbanat†; Herbolax†; Laxanat; Melange de Plantes Formula LI Laxatif†; Metab Herbs No 1†; Stomach Ease; Traditional Herbal Laxative†; Traditional Laxative; Ultra-Lax†; *Chile*: Bulgarolax†; *Fr.*: Dragees Fuca; Dragees Vegetales Rex; Imegul†; Mucinum a l'Extrait de Cascara; Spevin†; *Hong Kong*: Mucinum†; *India*: Hepachol; Livotone; *Ital.*: Alosen†; Amaro Medicinale; Combilax; Confetti Lassativi CM; Dis-Cinil Complex; Draverex; Eparema-Levul; Eparema; Estilax; Eupatol; Fave di Fuca; Grani di Vals†; Hepatos B12; Hepatos; Solvobil†; *Neth.*: Temoe Lawak; *Norw.*: Cosylan; *Port.*: Doce Alivio; Mucinum; *S.Afr.*: Moultons Herbal Extract†; *Spain*: Crislaxo; Fave de Fuca; Favilax; Fucapan; Laxodiex; Lipograsil†; Nico Hepatocyn; Pildoras Zeninas; *Switz.*: Padma-Lax; Padmed Laxan; *Thai.*: Corisul; Flataco; Flatulence†; Hemolax†; Patarcolate; Patarsul; Veracolate†; *UK*: Cassilax; Dual-Lax Extra Strong; Dual-Lax Normal Strength; Jacksons Herbal Laxative; Laxative Tablets; Modern Herbals Laxative; Modern Herbals Pile; Napiers Oral Skin Soother Herbal Relief; Natural Herb Tablets; Out-of-Sorts; Pileabs; Piletabs; Rhuaka; Senokot Dual Relief; Skin Eruptions Mixture; *USA*: Concentrated Milk of Magnesia-Cascara†; Detox; *Venez.*: Gameral.

Homoeopathic Preparations. *Canad.*: Cynara Complex†.

Pharmacopoeial Preparations
BP 2014: Cascara Tablets;
USP 36: Aromatic Cascara Fluidextract; Cascara Sagrada Extract; Cascara Sagrada Fluidextract; Cascara Tablets.

Casopitant *(rINN)*

Capsipitant; Casopitantum; GW-679769; Казопитант.
(2*R*,4*S*)-4-(4-Acetylpiperazin-1-yl)-*N*-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl]-2-(4-fluoro-2-methylphenyl)-*N*-methylpiperidine-1-carboxamide.
$C_{30}H_{35}F_7N_4O_2$=616.6
CAS — 414910-27-3.
ATC — A04AD13.
ATC Vet — QA04AD13.
UNII — 3B03KPM27L.

Casopitant Mesilate *(rINNM)*

Casopitant, Mésilate de; Casopitant Mesylate (USAN); Casopitanti Mesilas; GW-679769B; Mesilato de casopitant; Казопитанта Мезилат.
(2*R*,4*S*)-4-(4-Acetylpiperazin-1-yl)-*N*-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl]-2-(4-fluoro-2-methylphenyl)-*N*-methylpiperidine-1-carboxamide methanesulfonate.
$C_{30}H_{35}F_7N_4O_2CH_3SO_3H$=712.7
CAS — 414910-30-8.
ATC — A04AD13.
ATC Vet — QA04AD13.
UNII — 7VSV9BL497.

Profile

Casopitant is a neurokinin-1 receptor antagonist like aprepitant (p. 1819.2) that has been investigated for the prevention of chemotherapy-induced nausea and vomiting.

References.
1. Ruhlmann C, Herrstedt J. Casopitant: a novel NK(1)-receptor antagonist in the prevention of chemotherapy-induced nausea and vomiting. *Ther Clin Risk Manag* 2009; 5: 375–84.
2. Grunberg SM, *et al.* Efficacy and safety of casopitant mesylate, a neurokinin 1 (NK1)-receptor antagonist, in prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based highly emetogenic chemotherapy: a randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; 10: 549–58.
3. Herrstedt J, *et al.* Phase III trial of casopitant, a novel neurokinin-1 receptor antagonist, for the prevention of nausea and vomiting in patients receiving moderately emetogenic chemotherapy. *J Clin Oncol* 2009; 27: 5363–9.

Cassia Pulp

Fístula, pulpa de caña; Мякоть Амалтас.
ATC Herb — HA06AX5001 (Cassia fistula: fruit).

Profile

Cassia pulp is the evaporated aqueous extract of crushed ripe cassia fruits (cassia pods), *Cassia fistula* (Leguminosae). It is a mild anthraquinone stimulant laxative with general properties similar to those of senna (p. 1885.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Fitolax†; Florlax; Fontolax; Laxtam; Naturetti; Tamaril; Tamarine; Tamarine; *Fr.*: Benetransit†; *Gr.*: Tamarine; *Ital.*: Tamarine; *Mex.*: MD Lax; Naturetti; *Rus.*: Pilex (Пайлекс); *Spain*: Pruina; *Ukr.*: Softovak (Софтовак).

Cerium Oxalate

Cerii Oxalas; Cerio, oxalato de; Ceriumoksalaatti; Ceriumoxalat; Церия Оксалат.
CAS — 139-42-4 (anhydrous cerous oxalate); 15053-73-3 (cerous oxalate decahydrate).
ATC — A04AD02.
ATC Vet — QA04AD02.
UNII — 96P72VE680 (cerium oxalate); 0UV74P3R0J (cerium oxalate nonahydrate).

NOTE. Cerium oxalate has been defined as consisting of abou 50% of cerous oxalate ($(C_2O_4)_3Ce_2.10H_2O$) with th oxalates of numerous other rare earths, especiall lanthanum, praseodymium, and neodymium. Oxalates o the form $(C_2O_4)_3Ce_2.xH_2O$ are also referred to as cerium o cerous oxalate.

Profile

Cerium oxalate has been used as an antiemetic.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Canad.*: Ubicoenzyme; *Fr.*: Aurun Complexe No 38†; Badiaga Complexe No 47.

Cetraxate Hydrochloride *(JAN, rINNM)*

Cétraxate, Chlorhydrate de; Cetraxati Hydrochloridum, Cetraxato, hidrocloruro de; DV-1006; Hidrocloruro de cetraxato; Цетраксата Гидрохлорид.
4-(2-Carboxyethyl)phenyl tranexamate hydrochloride; 4-(2-Carboxyethyl)phenyl *trans*-4-aminomethylcyclohexanecarboxylate hydrochloride.
$C_{17}H_{23}NO_4.HCl$=341.8
CAS — 34675-84-8 (cetraxate); 27724-96-5 (cetraxate hydrochloride).
UNII — 08IT6P8VHY.

NOTE. The names Eluglilu, Lacmarze, LK, and Reslart hav been used as trade marks for cetraxate hydrochloride.

Pharmacopoeias. In *Jpn*.

Profile

Cetraxate hydrochloride is stated to be a mucosal protectan with actions on gastric microcirculation as well a prostaglandin synthesis and kallikrein. It is used in th treatment of gastritis and peptic ulcer disease (p. 1813.2) i oral doses of 600 to 800 mg daily in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Neuer.

Chalk

Creta; Prepared Chalk; Men.
$CaCO_3$=100.1
CAS — 13397-25-6.

Pharmacopoeias. In *Br*.

BP 2014: (Chalk). A native form of calcium carbonate free from most of its impurities by elutriation and dried. I consists of the calcareous shells and detritus of variou foraminifera and contains not less than 97.0% and not mor than 100.5% of $CaCO_3$, calculated with reference to th dried substance.

White or greyish-white, odourless or almost odourless amorphous, earthy, small friable masses, usually conical i form, or in powder. Practically insoluble in water; slightl soluble in water containing carbon dioxide; it absorbs wate readily.

Profile

Chalk has been used as an adsorbent antidiarrhoeal Calcium carbonate (precipitated chalk) is used as an antacid calcium supplement, and phosphate binder, see p. 1824.3.

Calabash chalk, also known as Calabar stone, la craie o argile, nzu, mabele, ebumba, or ulo, is ingested by some pregnant women to alleviate morning sickness. It i traditionally used by Nigerian or West African women in th form of blocks, pellets, or powders. Calabash chalk eithe occurs naturally or is produced from clay and mud that may be mixed with other ingredients including sand, wood ash and sometimes, salt. However, it contains high levels o lead, as well as arsenic (see Contamination, below).

Contamination. Concern with regard to the safety of calabash chalk has arisen, particularly with regard to its lead and arsenic content.[1-4] Analysis of calabash chalk samples available in the UK found that the major component of calabash chalk was an aluminium silicate hydroxide from the kaolin clay group. Lead concentrations in the samples were found to be about 40 mg/kg, almost 40 times the EU recommended guidelines. Potentially toxic chromium con centrations (dependent on the oxidation state) were also found. Arsenic, cadmium, and mercury were not detect

able in any of the analysed samples. Persistent organic pollutants were also identified in one sample.[1] Calabash chalk is traditionally used by pregnant women, often those from Nigerian and West African communities, as a remedy for morning sickness. Health authorities in various countries have issued warnings, and advised people, especially pregnant and breast-feeding women, not to consume calabash chalk.[2-4]

1. Dean JR, *et al.* Characterisation and analysis of persistent organic pollutants and major, minor and trace elements in calabash chalk. *Chemosphere* 2004; 57: 21–5.
2. Health Canada. Calabash chalk may pose health risk for pregnant and breastfeeding women (issued 2nd October 2007). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2007/2007_136_e.html (accessed 03/10/07)
3. Food Standards Agency. Lead contamination of calabash chalk (issued 15th October 2002). Available at: http://www.food.gov.uk/enforcement/alerts/2002/oct/94151 (accessed 03/10/07)
4. FDA. Nzu, traditional remedy for morning sickness (issued 31st December 2009). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm196045.htm (accessed 01/03/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *S.Afr.*: Behoedmiddel vir Kinders; *Thal.*: Antidiarrhoeals for children.

Pharmacopoeial Preparations
BP 2014: Compound Magnesium Trisilicate Oral Powder.

Ciclonium Bromide *(rINN)*

Asta-3746; Bromuro de ciclonio; Ciclonii Bromidum; Cidonio, bromuro de; Ciclonium, Bromure de; Циклония бромид.
Diethylmethyl[2-[(α-methyl-α-5-norborneni-2-ylbenzyl)oxy]ethyl]ammonium bromide.
$C_{22}H_{34}BrNO$=408.4
CAS — 29546-59-6.
UNII — 72R7F44611.

NOTE. The name Cyclonium or Ciclonium Iodide has been used to describe an unrelated antispasmodic, Oxapium Iodide (p. 1874.3).

Profile

Ciclonium bromide is an antimuscarinic that has been used in the treatment of gastrointestinal and urinary-tract disorders associated with smooth muscle spasm.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Turk.*: Doladamon.

Cimetidine *(BAN, USAN, rINN)*

Cimetidin; Cimetidina; Cimetidinas; Cimétidine; Cimetidinum; Cymetydyna; Simetidiini; Simetidin; SKF-92334; Циметидин.
2-Cyano-1-methyl-3-[2-(5-methylimidazol-4-ylmethylthio)ethyl]guanidine.
$C_{10}H_{16}N_6S$=252.3
CAS — 51481-61-9.
ATC — A02BA01.
ATC Vet — QA02BA01.
UNII — 80061L1WGD.

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

Ph. Eur. 8: (Cimetidine). A white or almost white, polymorphic powder. Slightly soluble in water; soluble in alcohol; practically insoluble in dichloromethane. It dissolves in dilute mineral acids. Protect from light.

USP 36: (Cimetidine). A white to off-white crystalline powder, odourless or with a slight mercaptan odour. Slightly soluble in water and in chloroform; soluble in alcohol and in macrogol 400; practically insoluble in ether; sparingly soluble in isopropyl alcohol; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

Cimetidine Hydrochloride *(BANM, USAN, rINNM)*

Cimetidina, hidrocloruro de; Cimétidine, chlorhydrate de; Cimetidin-hidroklorid; Cimetidinhydroklorid; Cimetidin-hydrochlorid; Cimetidinhydroklorid; Cimetidini Hydrochloridum; Cimetidino hidrochloridas; Hidrocloruro de cimetidina; Simetidiinihydrokloridi; Циметидина Гидрохлорид.
$C_{10}H_{16}N_6S.HCl$=288.8
CAS — 70059-30-2.
ATC — A02BA01.
ATC Vet — QA02BA01.
UNII — WE10491673.

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

Ph. Eur. 8: (Cimetidine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; sparingly soluble in dehydrated alcohol. A 1% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 36: (Cimetidine Hydrochloride). Store in airtight containers. Protect from light.

Uses and Administration

Cimetidine is a histamine H_2-antagonist and inhibits actions of histamine mediated by H_2-receptors such as gastric acid secretion and pepsin output. It is used where inhibition of gastric acid secretion may be beneficial, as in peptic ulcer disease, including stress ulceration (p. 1813.2), gastro-oesophageal reflux disease (p. 1807.2), selected cases of persistent dyspepsia (p. 1806.3), scleroderma of the oesophagus, pathological hypersecretory states such as the Zollinger-Ellison syndrome (p. 1814.3), and in patients at risk of acid aspiration (p. 1804.2) during general anaesthesia or child birth. Cimetidine may also be used to reduce malabsorption and fluid loss in patients with the short bowel syndrome and to reduce the degradation of enzyme supplements given to patients with pancreatic insufficiency.

Cimetidine may be given orally or parenterally by the intravenous or intramuscular routes; the total daily dose by any route should not normally exceed 2.4 g. Although some formulations are prepared as the hydrochloride, strengths and doses are expressed in terms of the base. Cimetidine 100 mg is equivalent to about 114.5 mg of cimetidine hydrochloride. Doses should be reduced in renal impairment and may also need to be reduced in hepatic impairment (see below).

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

In the management of benign **gastric** and **duodenal ulceration** a single daily oral dose of 800 mg at bedtime or 400 mg twice daily is recommended, which should be given for at least 4 weeks for duodenal ulcers (6 weeks for gastric ulcers, 8 weeks for NSAID-associated ulcers); when necessary the dose may be increased to 400 mg four times daily. Where appropriate a maintenance dose of 400 mg may then be given once daily at bedtime, or twice daily in the morning and at bedtime. Other regimens have also been used for treatment and maintenance.

In **gastro-oesophageal reflux disease** the recommended oral dose is 400 mg four times daily (with meals and at bedtime), or 800 mg twice daily, for 4 to 12 weeks. In pathological hypersecretory conditions, such as the **Zollinger-Ellison syndrome**, an oral dose of 300 or 400 mg four times daily is normally used, although sometimes higher doses may be necessary.

Doses of 200 to 400 mg orally every 4 to 6 hours are recommended for prophylaxis of haemorrhage from **stress ulceration**. In patients at risk of developing the **acid aspiration syndrome**, an oral dose of 400 mg may be given 90 to 120 minutes before the induction of anaesthesia, or at the start of labour (in obstetric practice), and doses of up to 400 mg may be repeated at intervals of 4 hours if required.

Doses of up to 800 mg daily in divided doses have been taken for non-ulcer **dyspepsia**; 100 mg at night has been used in the prophylaxis of nocturnal heartburn.

For **scleroderma of the oesophagus**, the usual dose is 1.2 g orally in divided doses.

For **short bowel syndrome**, an initial oral dose of cimetidine 400 mg twice daily is adjusted according to response.

To reduce the degradation of pancreatic enzyme supplements, patients with **pancreatic insufficiency**, as in cystic fibrosis (p. 177.2), may be given oral cimetidine 800 mg to 1.6 g daily in 4 divided doses, 60 to 90 minutes before meals.

PARENTERAL ADMINISTRATION.

Cimetidine may be diluted before intravenous use; commonly used intravenous solutions such as sodium chloride 0.9%, glucose 5 or 10%, and lactated Ringer's solution are compatible. Parenteral dosage recommendations are 300 mg every 6 to 8 hours by intramuscular injection or by slow intravenous injection, diluted to 20 mL, over at least 5 minutes; the same dosage may be given by intermittent intravenous infusion, diluted to at least 50 mL, over 15 to 20 minutes. If higher doses are required, intravenous injections or infusions may be given more frequently up to the maximum total daily dose of 2.4 g. For continuous intravenous infusion (diluted in up to 1 litre) the recommended rate is 37.5 mg/hour, which may be preceded by 150 mg as an intravenous loading dose. Higher rates may be required in some patients; a rate of 50 mg/hour is recommended for prevention of stress ulceration.

Administration in children. Cimetidine is used in children in the management of conditions where gastric acid reduction is beneficial including benign duodenal and gastric ulceration, reflux oesophagitis, and Zollinger-Ellison syndrome. Experience in children is more limited than that in adults and regulatory authorities in some countries do not recommend its use unless the benefits of cimetidine outweigh its potential risks; an oral or intravenous dose of 20 to 40 mg/kg daily in divided doses has been suggested for children under 16 years of age. Licensed oral doses for children over 1 year of age range from 20 to 30 mg/kg daily in divided doses. An oral dose of 20 mg/kg daily in divided doses has been suggested for infants under 1 year. A lower dose of 10 to 15 mg/kg daily in 4 to 6 divided doses is recommended for neonates.

For differences in pharmacokinetics in children which may affect dosing, see p. 1831.2.

Administration in hepatic impairment. The bioavailability of cimetidine may be increased in patients with cirrhosis[1,2] and a dosage reduction of up to 40% has been suggested in patients with portal systemic encephalopathy.[3] However, UK and US licensed product information does not include recommendations for dosage adjustment in hepatic impairment.

1. Gugler R, *et al.* Altered disposition and availability of cimetidine in liver cirrhotic patients. *Br J Clin Pharmacol* 1982; 14: 421–30.
2. Cello JP, Øie S. Cimetidine disposition in patients with Laennec's cirrhosis during multiple dosing therapy. *Eur J Clin Pharmacol* 1983; 25: 223–9.
3. Ziemniak JA, *et al.* Hepatic encephalopathy and altered cimetidine kinetics. *Clin Pharmacol Ther* 1983; 34: 375–82.

Administration in renal impairment. The dosage of cimetidine should be reduced in patients with renal impairment. UK licensed product information suggests the following oral doses according to creatinine clearance (CC):

- CC over 50 mL/minute: normal dosage
- CC 30 to 50 mL/minute: 200 mg four times daily
- CC 15 to 30 mL/minute: 200 mg three times daily
- CC 0 to 15 mL/minute: 200 mg twice daily

US licensed product information suggests a dose of 300 mg every 12 hours orally or by intravenous injection in those with severe impairment, increasing the frequency with caution if required. Patients with a creatinine clearance of < 30 mL/minute who are being treated for prevention of stress ulceration should be given half the usual intravenous dose, see Uses and Administration, above.

Cimetidine is removed by haemodialysis, but not significantly removed by peritoneal dialysis.

Bladder disorders. Cimetidine effectively relieved symptoms in patients with painful bladder disease (encompassing conditions including cystitis, painful bladder syndrome, and urethral syndrome), especially suprapubic pain and nocturia, despite no apparent histological change in the bladder mucosa after treatment.[1]

1. Thilagarajah R, *et al.* Oral cimetidine gives effective symptom relief in painful bladder disease: a prospective, randomized, double-blind placebo-controlled trial. *BJU Int* 2001; 87: 207–12.

Dapsone toxicity. Cimetidine might reduce methaemoglobinaemia associated with dapsone. For references supporting this suggestion, see Effects on the Blood, under Dapsone, p. 282.2.

Diagnostic use. Cimetidine blocks renal tubular secretion of creatinine and has been used experimentally to improve the accuracy of estimations of glomerular filtration rate from creatinine clearance.[1] Although the optimal dose has not been established, in renal transplant recipients an oral dose of 1 g given in 4 divided doses seemed to provide a useful measure of glomerular filtration rate when the plasma creatinine concentration was below 2.5 mg/litre. At higher creatinine concentrations, a higher dose was required to block tubular excretion effectively.

1. Kabat-Koperska J, *et al.* Creatinine clearance after cimetidine administration— is it useful in the monitoring of the function of transplanted kidney? *Ren Fail* 2007; 29: 667–72.

Echinococcosis. Cimetidine has been given with albendazole to increase its effect (by inhibiting its metabolism) in the treatment of echinococcosis (p. 145.2).

Immunomodulation. Studies in *mice* and humans have shown that H_2-antagonists have an immunoregulatory effect.[1] T-lymphocyte suppressor cells have histamine H_2 receptors and cimetidine has been reported to reduce activity of these cells, thus enhancing immune response.[1,2] There is also some evidence that it enhances cellular immunity, notably natural killer cell activity.[3] This discovery has led to the investigation of cimetidine in disorders associated with alteration of the immune response including eosinophilic fasciitis, herpesvirus infections, mucocuta-

neous candidiasis,[4] hypogammaglobulinaemia,[5] and various malignancies.[1]

1. Kumar A. Cimetidine: an immunomodulator. *DICP Ann Pharmacother* 1990; 24: 289–95.
2. Snyman JR, *et al.* Cimetidine as modulator of the cell-mediated immune response in vivo using the tuberculin skin test as parameter. *Br J Clin Pharmacol* 1990; 29: 257–60.
3. Katoh J, *et al.* Cimetidine and immunoreactivity. *Lancet* 1996; 348: 404–5.
4. Polizzi B, *et al.* Successful treatment with cimetidine and zinc sulphate in chronic mucocutaneous candidiasis. *Am J Med Sci* 1996; 311: 189–90.
5. White WB, Ballow M. Modulation of suppressor-cell activity by cimetidine in patients with common variable hypogammaglobulinemia. *N Engl J Med* 1985; 312: 198–202.

EOSINOPHILIC FASCIITIS. Eosinophilic fasciitis is a scleroderma-like syndrome of inflammation of the muscle fascia and associated eosinophilia and hypergammaglobulinaemia. Although it responds well to corticosteroid therapy in most cases, cimetidine has also been tried. The effect of cimetidine on eosinophilic fasciitis is unpredictable with both remission[1-4] and lack of response[5,6] having been reported in a few patients. In one case series of 17 patients, 9 remitted with initial cimetidine treatment, while 5 showed a partial response.[7]

1. Solomon G, *et al.* Eosinophilic fasciitis responsive to cimetidine. *Ann Intern Med* 1982; 97: 547–9.
2. Laso FJ, *et al.* Cimetidine and eosinophilic fasciitis. *Ann Intern Med* 1983; 98: 1026.
3. Garcia-Morteo O, *et al.* Cimetidine and eosinophilic fasciitis. *Ann Intern Med* 1984; 100: 318–19.
4. Farrell AM, *et al.* Eosinophilic fasciitis associated with autoimmune thyroid disease and myelodysplasia treated with pulsed methylprednisolone and antihistamines. *Br J Dermatol* 1999; 140: 1185–7.
5. Loftin EB. Cimetidine and eosinophilic fasciitis. *Ann Intern Med* 1983; 98: 111–12.
6. Herson S, *et al.* Cimetidine in eosinophilic fasciitis. *Ann Intern Med* 1990; 113: 412–13.
7. Naschitz JE, *et al.* The fasciitis-panniculitis syndromes: clinical and pathologic features. *Medicine (Baltimore)* 1996; 75: 6–16.

HERPESVIRUS AND PAPILLOMAVIRUS INFECTIONS. Although there have been numerous isolated and anecdotal reports of a beneficial response to cimetidine in patients with infections due to various *herpesviruses* (p. 954.1), including genital herpes simplex,[1] infectious mononucleosis,[2,3] and herpes zoster[4-7] some of these reports have been criticised[8,9] mainly on the grounds that the majority of cases of herpes zoster will resolve within 2 to 3 weeks whether any treatment is given or not. Also, a double-blind placebo-controlled study involving 63 patients with herpes zoster[10] found no evidence that cimetidine relieved the pain or accelerated the rate of healing of lesions.

There are reports[11] of benefit from the use of cimetidine in patients with *viral warts* (p. 1689.3) and an 8-year retrospective analysis of 216 patients with plantar warts reported a success rate of about 80%, although warts recurred in 12 patients.[12] However, controlled studies have failed to show significant benefit,[13,14] and a review concluded that use of H_2-antagonists for warts could not be recommended based on the available evidence.[15]

1. Wakefield D. Cimetidine in recurrent genital herpes simplex infection. *Ann Intern Med* 1984; 101: 882.
2. Goldstein JA. Cimetidine and mononucleosis. *Ann Intern Med* 1983; 99: 410–11.
3. Goldstein JA. Cimetidine, ranitidine, and Epstein-Barr virus infection. *Ann Intern Med* 1986; 105: 139.
4. Hayne ST, Mercer JB. Herpes zoster: treatment with cimetidine. *Can Med Assoc J* 1983; 129: 1284–5.
5. Shandera R. Treatment of herpes zoster with cimetidine. *Can Med Assoc J* 1984; 131: 279.
6. Mavligit GM, Talpaz M. Cimetidine for herpes zoster. *N Engl J Med* 1984; 310: 318–19.
7. Arnot RS. Herpes zoster and cimetidine. *Med J Aust* 1984; 141: 903.
8. Tyrrell DL. Course of herpes zoster. *Can Med Assoc J* 1984; 130: 1109.
9. Giles KE. Herpes zoster and cimetidine. *Med J Aust* 1985; 142: 283.
10. Levy DW, *et al.* Cimetidine in the treatment of herpes zoster. *J R Coll Physicians Lond* 1985; 19: 96–8.
11. Glass AT, *et al.* Cimetidine therapy for recalcitrant warts in adults. *Arch Dermatol* 1996; 132: 680–2.
12. Mullen BR, *et al.* Cimetidine as a first-line therapy for pedal verruca: eight-year retrospective analysis. *J Am Podiatr Med Assoc* 2005; 95: 229–34.
13. Karabulut AA, *et al.* Is cimetidine effective for nongenital warts: a double-blind, placebo-controlled study. *Arch Dermatol* 1997; 133: 533–4.
14. Rogers CJ, *et al.* Cimetidine therapy for recalcitrant warts in adults: is it any better than placebo? *J Am Acad Dermatol* 1999; 41: 123–7.
15. Pit KE, Williams PC. Use of histamine$_2$-antagonists for the treatment of verruca vulgaris. *Ann Pharmacother* 2007; 41: 1222–6.

MALIGNANT NEOPLASMS. Because of its immunomodulatory effects cimetidine has been tried as an adjuvant in the management of a variety of malignant neoplasms such as those of the gastrointestinal tract (see p. 705.2). Cimetidine may also have inhibitory effects on tumour growth and inhibit cancer cell migration and adhesion to epithelial cells.[1] Positive effects on survival have been reported in some studies in gastrointestinal cancer,[2-4] although a large, randomised, placebo-controlled study with cimetidine,[5] and a similar study with ranitidine,[6] failed to show any benefit. A study in colorectal cancer found improved survival and a reduced frequency of metastasis with cimetidine in patients whose tumour cells expressed high levels of the sialyl Lewis-X and sialyl Lewis-A antigens. The presence of these antigens mediates the adhesion of cancer cells to endothelium and is considered to lead to metastasis.[7]

Famotidine has also been investigated as an adjunct in patients with malignant neoplasms, usually given with interleukin-2; some success has been reported in small numbers of patients.[8,9]

1. Lefranc F, *et al.* Cimetidine, an unexpected anti-tumor agent, and its potential for the treatment of glioblastoma (review). *Int J Oncol* 2006; 28: 1021–30.
2. Tennesen H, *et al.* Effect of cimetidine on survival after gastric cancer. *Lancet* 1988; ii: 990–2.
3. Adams WJ, Morris DL. Short-course cimetidine and survival with colorectal cancer. *Lancet* 1994; 344: 1768–9.
4. Matsumoto S. Cimetidine and survival with colorectal cancer. *Lancet* 1995; 346: 115.
5. Langman MJS, *et al.* Prospective, double-blind, placebo-controlled randomized trial of cimetidine in gastric cancer. *Br J Cancer* 1999; 81: 1356–62.
6. Primrose JN, *et al.* A prospective randomised controlled study of the use of ranitidine in patients with gastric cancer. *Gut* 1998; 42: 17–19.
7. Matsumoto S, *et al.* Cimetidine increases survival of colorectal cancer patients with high levels of sialyl Lewis-X and sialyl Lewis-A epitope expression on tumour cells. *Br J Cancer* 2002; 86: 161–7.
8. Parshad R, *et al.* Effect of preoperative short-course famotidine on TILs and survival in breast cancer. *Indian J Cancer* 2005; 42: 185–90.
9. Quan WD, Quan FM. Activity of continuous infusion + pulse interleukin-2 with famotidine in metastatic melanoma. *Cancer Biother Radiopharm* 2009; 24: 1–6.

Mastocytosis. Cimetidine, alone or with an antihistamine (histamine H_1-antagonist), has been reported to relieve gastrointestinal symptoms,[1,2] pruritus, and urticaria[3,4] in patients with mastocytosis (p. 1226.3).

1. Hirschowitz BI, Groarke JF. Effect of cimetidine on gastric hypersecretion and diarrhea in systemic mastocytosis. *Ann Intern Med* 1979; 90: 769–71.
2. Linde R, *et al.* Combination H1 and H2 receptor antagonist therapy in mastocytosis. *Ann Intern Med* 1980; 92: 716.
3. Simon RA. Treatment of systemic mastocytosis. *N Engl J Med* 1980; 302: 231.
4. Prieri M, *et al.* Comparison of the therapeutic efficacy of cromolyn sodium with that of combined chlorpheniramine and cimetidine in systemic mastocytosis: results of a double-blind clinical trial. *Am J Med* 1985; 78: 9–14.

Paracetamol toxicity. It has been suggested that cimetidine might be of use in the treatment of paracetamol poisoning (see p. 116.2) because of its inhibition of the cytochrome P450 system. However, there appears to be no strong evidence to support its use.[1,2]

1. Kaufenberg AJ, Shepherd MF. Role of cimetidine in the treatment of acetaminophen poisoning. *Am J Health-Syst Pharm* 1998; 55: 1516–19.
2. Brok J, *et al.* Interventions for paracetamol (acetaminophen) overdose. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 11/03/09).

Porphyria. There are reports[1-3] of patients with acute intermittent porphyria (p. 1556.1) showing clinical and biochemical improvement during treatment with cimetidine.

1. Baccino E, *et al.* Cimetidine in the treatment of acute intermittent porphyria. *JAMA* 1989; 262: 3000.
2. Horie Y, *et al.* Clinical usefulness of cimetidine treatment for acute relapse in intermittent porphyria. *Clin Chim Acta* 1995; 234: 171–5.
3. Cherem JH, *et al.* Cimetidine and acute intermittent porphyria. *Ann Intern Med* 2005; 143: 694–5.

Skin disorders. Cimetidine has been used alone[1-6] or with an antihistamine (H_1-antagonist)[5,8,9] in various skin disorders. H_2-antagonists such as cimetidine and ranitidine have produced improvement in certain types of *urticaria* (p. 1689.2), especially those associated with cold or angioedema. Although they may act by antagonism of H_2-receptors on cutaneous blood vessels, other mechanisms of action may be involved.[6] A pharmacokinetic interaction between cimetidine and hydroxyzine resulting in increased serum concentrations of hydroxyzine has been reported when such a combination was given, see p. 631.2. Routine use of H_2-antagonists in urticaria is controversial, but in practice they may be added to conventional treatment in resistant cases.[10-12] Little additional benefit has been found with combination therapy in dermographic urticaria.[13]

Patients with *pruritus* (p. 1687.3) of various causes may also respond to H_2-antagonists,[1,2,6,7,9] but studies in larger groups of patients have found no benefit.[3-5,14]

1. Easton P, Galbraith PR. Cimetidine treatment of pruritus in polycythemia vera. *N Engl J Med* 1978; 299: 1134.
2. Hess CE. Cimetidine for the treatment of pruritus. *N Engl J Med* 1979; 300: 370.
3. Harrison AR, *et al.* Pruritus, cimetidine and polycythemia. *N Engl J Med* 1979; 300: 433–4.
4. Scott GL, Horton RJ. Pruritus, cimetidine and polycythemia. *N Engl J Med* 1979; 300: 434. Correction. *ibid.*; 936.
5. Zappacosta AR, Hauss D. Cimetidine doesn't help pruritus of uremia. *N Engl J Med* 1979; 300: 1280.
6. Schapira DV, Bennett JM. Cimetidine for pruritus. *Lancet* 1979; i: 726–7.
7. Aynaud JP, *et al.* Cimetidine for pruritus in Hodgkin's disease. *BMJ* 1980; 280: 151–2.
8. Theoharides TC. Histamine$_2$ (H_2)-receptor antagonists in the treatment of urticaria. *Drugs* 1989; 37: 345–55.
9. Deutsch PH. Dermatographism treated with hydroxyzine and cimetidine and ranitidine. *Ann Intern Med* 1984; 101: 569.
10. Advenier C, Queille-Roussel C. Rational use of antihistamines in allergic dermatological conditions. *Drugs* 1989; 38: 634–44.
11. Ormerod AD. Urticaria: recognition, causes, and treatment. *Drugs* 1994; 48: 717–30.
12. Greaves MW. Chronic urticaria. *N Engl J Med* 1995; 332: 1767–72.
13. Sharpe GR, Shuster S. In dermographic urticaria H_2 receptor antagonists have a small but therapeutically irrelevant additional effect compared with H_1 antagonists alone. *Br J Dermatol* 1993; 129: 575–9.
14. Raisch DW, *et al.* Evaluation of a non-food and drug administration-approved use of cimetidine: treatment of pruritus resulting from epidural morphine analgesia. *DICP Ann Pharmacother* 1991; 25: 716–8.

Adverse Effects

Adverse reactions to cimetidine and other histamine H_2-antagonists are generally infrequent. The commonest adverse effects reported have been diarrhoea and other gastrointestinal disturbances, dizziness, tiredness, headache, and rashes. Myalgia and arthralgia can occur.

Altered liver function tests have occurred and there have been rare reports of hepatotoxicity. Reversible confusional states, especially in the elderly or in seriously ill patients such as those with renal failure, have occasionally occurred. Other adverse effects that have been reported rarely are hypersensitivity reactions and fever, reversible alopecia, blood disorders including agranulocytosis, leucopenia, and thrombocytopenia, acute pancreatitis, interstitial nephritis, hallucinations and depression, and cardiovascular disorders including bradycardia, tachycardia, and heart block. Rapid intravenous injection should be avoided as there have been rare associations with cardiac arrest and arrhythmias; transient hypotension has also been seen.

In patients such as the elderly, those with chronic lung disease, diabetes mellitus, or the immunocompromised, treatment with H_2-antagonists may be associated with an increased risk of developing community-acquired pneumonia.

Cimetidine has a weak anti-androgenic effect and gynaecomastia and impotence have also occasionally occurred in men; these are usually reversible.

Incidence of adverse effects. In a meta-analysis of 24 double-blind placebo-controlled studies,[1] the incidence of adverse effects with cimetidine was not significantly different from placebo. The most common adverse effects reported by patients taking cimetidine who were followed up for at least one year[2,3] were diarrhoea, headache, fatigue, skin rash or pruritus, and gynaecomastia. The incidence of adverse effects was dose-related and decreased with length of treatment.[3] No fatal adverse effect of cimetidine could be found in a mortality survey involving 9928 patients taking cimetidine and 9351 controls;[4] although the mortality rate was higher in the cimetidine patients, this was explained by the presence of underlying disease (known or unknown) before starting cimetidine treatment and the use of cimetidine to counter adverse gastric effects of other drugs. Follow-up of 9377 of these cimetidine-treated patients for a further 3 years[5] still revealed no fatal disorder attributable to cimetidine treatment and a steady fall in the excess death rate in cimetidine users was seen with increasing length of follow-up; by the fourth year there was little difference between the observed and expected death rate. Cimetidine still appeared to be safe after 10 years of follow-up.[6]

1. Richter JM, *et al.* Cimetidine and adverse reactions: a meta-analysis of randomized clinical trials of short-term therapy. *Am J Med* 1989; 87: 278–84.
2. Colin Jones DG, *et al.* Post-marketing surveillance of the safety of cimetidine: twelve-month morbidity report. *Q J Med* 1985; 54: 253–68.
3. Bardhan KD, *et al.* Safety of longterm cimetidine (CIM) treatment: the view from one centre. *Gut* 1990; 31: A599.
4. Colin-Jones DG, *et al.* Postmarketing surveillance of the safety of cimetidine: 12 month mortality report. *BMJ* 1983; 286: 1713–16.
5. Colin-Jones DG, *et al.* Postmarketing surveillance of the safety of cimetidine: mortality during second, third, and fourth years of follow up. *BMJ* 1985; 291: 1084–8.
6. Colin-Jones DG, *et al.* Postmarketing surveillance of the safety of cimetidine: 10 year mortality report. *Gut* 1992; 33: 1280–4.

Carcinogenicity. An association between H_2-antagonists and gastric cancer was proposed after individual case reports, the finding of tumours in long-term high-dose *animal* studies, and the possibility that nitrites and nitroso compounds may be produced, but seemed of little clinical relevance.[1,2] Although a small increase in the risk of gastric cancer has been reported with the use of H_2-antagonists,[3] the excess risk in patients taking cimetidine[4-7] or ranitidine[7] decreases with time and there is no evidence for any long-term persistence of the effect.[7] The increased risk may be explained by misdiagnosis and inappropriate cimetidine treatment of existing malignancy,[4-6] or by confounding by indication,[3] since the excessive gastric-acid production for which the drugs are given may itself be associated with an increased risk of gastric cancer. An apparently protective effect has been seen for H_2-antagonist use starting 10 or more years before diagnosis of gastric cancer.[7]

The observed excess risk for cancers of the respiratory system is probably related to smoking, since this is causally related to both peptic ulcer and lung cancer and the excess risk does not decline with time.[4-6]

The hormonal effects of cimetidine have also led to study into its association with cancers of the breast or prostate. In general, use of cimetidine or other H_2-antagonists has no

affected the risk of breast cancer,[8-10] although current use of ranitidine was associated with an increased risk for hormone receptor-positive ductal carcinoma in one study.[9] In prostate cancer, a large cohort study found an increased risk only in men who took cimetidine daily over 10 years compared with men who did not use H_2-antagonists.[11] Prostate cancer risk was not affected by less frequent cimetidine use or by any use of other H_2-antagonists. Another study[10] found a modest increase in the risk of prostate cancer only in men who had received more than 20 prescriptions for cimetidine, compared with patients who had taken other H_2-antagonists.

1. Penston J, Wormsley KG. H_2-receptor antagonists and gastric cancer. *Med Toxicol* 1986; 1: 163–8.
2. Møller H, *et al.* Use of cimetidine and other peptic ulcer drugs in Denmark 1977–1990 with analysis of the risk of gastric cancer among cimetidine users. *Gut* 1992; 33: 1166–9.
3. Tamim H, *et al.* Association between use of acid-suppressive drugs and risk of gastric cancer: a nested case-control study. *Drug Safety* 2008; 31: 675–84.
4. Colin-Jones DG, *et al.* Postmarketing surveillance of the safety of cimetidine: 12 month mortality report. *BMJ* 1983; 286: 1713–16.
5. Colin-Jones DG, *et al.* Postmarketing surveillance of the safety of cimetidine: mortality during second, third, and fourth years of follow up. *BMJ* 1985; 291: 1084–8.
6. Møller H, *et al.* Cancer occurrence in a cohort of patients treated with cimetidine. *Gut* 1989; 30: 1558–62.
7. La Vecchia C, *et al.* Histamine-2-receptor antagonists and gastric cancer risk. *Lancet* 1990; 336: 355–7.
8. Coogan PF, *et al.* Cimetidine and other histamine$_2$-receptor antagonist use in relation to risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2005; 14: 1012–15.
9. Mathes RW, *et al.* Relationship between histamine$_2$-receptor antagonist medications and risk of invasive breast cancer. *Cancer Epidemiol Biomarkers Prev* 2008; 17: 67–72.
10. Rossing MA, *et al.* Cimetidine use and risk of prostate and breast cancer. *Cancer Epidemiol Biomarkers Prev* 2000; 9: 319–23.
11. Velicer CM, *et al.* Cimetidine use and the risk for prostate cancer: results from the VITAL cohort study. *Ann Epidemiol* 2006; 16: 895–900.

Effects on the blood. A review[1] in 1988 noted that leucopenia, thrombocytopenia, and pancytopenia have all been reported with cimetidine and ranitidine, with neutropenia and agranulocytosis occurring most often. There were also isolated reports of haemolytic anaemia and leucocytosis associated with cimetidine therapy. The overall incidence of cimetidine-associated blood cytopenia was estimated as 2.3 per 100 000 treated patients; the incidence for ranitidine was less and although there were reports with famotidine the incidence had not been determined. A subsequent case-control study,[2] concluded that the risk of hospitalisation due to neutropenia in patients receiving a 6-week course of cimetidine was no more than 1 in 116 000, while agranulocytosis did not occur in more than 1 in 573 000 patients.

A review[3] of the safety profile of famotidine noted that as of May 1992 there had been 60 reports of serious blood dyscrasias in patients receiving famotidine, of which 22 were considered possibly related to drug therapy (6 cases of pancytopenia or bone marrow depression, 5 of thrombocytopenia, 4 of leucopenia, 3 of combined leucopenia and thrombocytopenia, and 3 of agranulocytosis).

1. Aymard J-P, *et al.* Haematological adverse effects of histamine H_2-receptor antagonists. *Med Toxicol* 1988; 3: 430–48.
2. Strom BL, *et al.* Is cimetidine associated with neutropenia? *Am J Med* 1995; 99: 282–90.
3. Howden CW, Tytgat GNJ. The tolerability and safety profile of famotidine. *Clin Ther* 1996; 18: 36–54.

Effects on bone. An observational study[1] of the role of histamine in bone turnover, found that bone mineral density (BMD) at the femoral neck was reduced in patients taking H_2-antagonists, especially when calcium or vitamin D intake was reduced. The authors concluded that although the risk estimates of the BMD changes did not seem to be large, the clinical sequelae were uncertain.

1. Kinjo M, *et al.* Antihistamine therapy and bone mineral density: analysis in a population-based US sample. *Am J Med* 2008; 121: 1085–91.

Effects on the cardiovascular system. Reports of cardiovascular effects associated with H_2-antagonists have mostly involved dysrhythmias;[1] bradycardia, AV block, sinus or cardiac arrest, atrial fibrillation, ventricular extrasystoles, tachycardia, and ventricular fibrillation have all been reported with cimetidine, the oldest H_2-antagonist. Similar adverse effects have been reported with ranitidine; with famotidine, QT prolongation has also been described.[2,3] Although cardiovascular adverse effects are considered infrequent, they have occurred after intravenous and oral dosage, as well as after single-dose or long-term treatment.[1]

Studies into the haemodynamic effects of H_2-antagonists have reported disparate results. Apparent differences in effect have been seen for different H_2-antagonists at equipotent doses.[1] Some studies in healthy subjects,[4-6] and critically ill[7,8] and other[9] patients being treated with H_2-antagonists found no adverse haemodynamic effects with cimetidine, famotidine, or ranitidine. However, other studies in healthy subjects have noted negative inotropic effects with both famotidine and nizatidine. Falls in heart rate and cardiac output with nizatidine were not reproduced after pre-treatment with ranitidine[10] or pirenzepine,[11] and falls in cardiac output and stroke volume with famotidine[12] were delayed by pre-treatment with ranitidine.[10] It has been suggested that there is a small proportion of patients more susceptible to the cardiovascular effects of H_2-antagonists.[5] Caution is recommended if H_2-antagonists are given intravenously to patients with cardiovascular disease (see Precautions, p. 1830.2).

See also under Overdosage, p. 1830.1.

1. Hinrichsen H, *et al.* Clinical aspects of cardiovascular effects of H_2-receptor antagonists. *J Clin Pharmacol* 1995; 35: 107–16.
2. Endo T, *et al.* Famotidine and acquired long QT syndrome. *Am J Med* 2000; 108: 438–9.
3. Lee KW, *et al.* Famotidine and long QT syndrome. *Am J Cardiol* 2004; 93: 1325–7.
4. Hilleman DE, *et al.* Impact of chronic oral H_2-antagonist therapy on left ventricular systolic function and exercise capacity. *J Clin Pharmacol* 1992; 32: 1033–7.
5. Hughes DG, *et al.* Cardiovascular effects of H_2-receptor antagonists. *J Clin Pharmacol* 1989; 29: 472–7.
6. Rocha GR, *et al.* Effects of cimetidine on chronotropic response to cardiopulmonary exercise testing. *Arq Bras Cardiol* 2006; 86: 206–10.
7. Vohra SB, *et al.* The haemodynamic effects of ranitidine injected centrally in optimally resuscitated patients. *Br J Hosp Med* 1989; 42: 149.
8. Helseiman DE, *et al.* Hemodynamic status during famotidine infusion. *DICP Ann Pharmacother* 1990; 24: 1163–5.
9. Jackson G, Upward JW. Cimetidine, ranitidine, and heart rate. *Lancet* 1982; 2: 265.
10. Mescheder A, *et al.* Changes in the effects of nizatidine and famotidine on cardiac performance after pretreatment with ranitidine. *Eur J Clin Pharmacol* 1993; 45: 151–6.
11. Hinrichsen H, *et al.* Dose-dependent heart rate reducing effect of nizatidine, a histamine H_2-receptor antagonist. *Br J Clin Pharmacol* 1993; 35: 461–6.
12. Hinrichsen H, *et al.* Hemodynamic effects of different H_2-receptor antagonists. *Clin Pharmacol Ther* 1990; 48: 302–8.

Effects on the endocrine system. Cimetidine has dose-related mild anti-androgenic properties and reduced sperm counts and raised serum-prolactin concentrations have been reported in men during cimetidine treatment[1] as have gynaecomastia, breast tenderness, and impotence.[2] Those symptoms resolved after withdrawal of cimetidine,[1,2] reduction of the dose,[2] or transfer to ranitidine.[2]

A study by the Boston Collaborative Drug Surveillance Program, using data from 81 535 men in the UK, found that cimetidine was associated with an incidence of 3.29 cases of gynaecomastia per 1000 person years, representing a relative risk 7.2 times greater than that of non-users.[3] The period at highest risk seemed to be between the seventh and twelfth month after starting treatment, and the occurrence was related to dose, with most of the risk associated with doses over 1 g daily. This large study found no significant risk of gynaecomastia with ranitidine or omeprazole.

Unlike cimetidine, famotidine, nizatidine, and ranitidine are considered to have little, if any, anti-androgenic effect. Studies in men taking ranitidine for the management of duodenal ulcer[4,5] reported no significant changes in the plasma concentrations of testosterone, luteinising hormone, follicle-stimulating hormone, or prolactin after up to 2 years of treatment; no significant changes in sperm concentration, motility, or morphology were noted.[4] However, there have been isolated reports of galactorrhoea with famotidine,[6] gynaecomastia with ranitidine,[7,8] hyperprolactinaemia with famotidine[6,9] and ranitidine,[8] and impotence with famotidine,[10] nizatidine,[10] and ranitidine.[8,10]

1. Wang C, *et al.* Effect of cimetidine on gonadal function in man. *Br J Clin Pharmacol* 1982; 13: 791–4.
2. Jensen RT, *et al.* Cimetidine-induced impotence and breast changes in patients with gastric hypersecretory states. *N Engl J Med* 1983; 308: 883–7.
3. García Rodríguez LA, Jick H. Risk of gynaecomastia associated with cimetidine, omeprazole, and other antiulcer drugs. *BMJ* 1994; 308: 503–6. Correction. *ibid.*: 819.
4. Wang C, *et al.* Ranitidine does not affect gonadal function in man. *Br J Clin Pharmacol* 1983; 16: 430–2.
5. Knigge U, *et al.* Plasma concentrations of pituitary and peripheral hormones during ranitidine treatment for two years in men with duodenal ulcer. *Eur J Clin Pharmacol* 1989; 37: 305–7.
6. Güven K, Kelestimur F. Hyperprolactinemia and galactorrhea with standard-dose famotidine therapy. *Ann Pharmacother* 1995; 29: 788.
7. Tosi S, Cagnoli M. Painful gynaecomastia with ranitidine. *Lancet* 1982; 2: 160.
8. Bera F, *et al.* Impuissance et gynécomastie secondaires à une hyperprolactinémie induite par la ranitidine. *Therapie* 1994; 49: 361–2.
9. Delpre G, *et al.* Hyperprolactinaemia during famotidine therapy. *Lancet* 1993; 342: 868.
10. Kassianos GC. Impotence and nizatidine. *Lancet* 1989; 1: 963.

Effects on the eyes. Ocular pain, blurred vision, and a rise in intra-ocular pressure occurred in a patient with chronic glaucoma during treatment with cimetidine; ocular symptoms associated with raised intra-ocular pressure subsequently developed during ranitidine treatment.[1] However, a study suggested that cimetidine had no effect on intra-ocular pressure.[2] A cohort study involving 140 128 patients receiving anti-ulcer therapy, 68 504 of whom received cimetidine, found no evidence that any of the drugs were associated with a major increased risk of vascular or inflammatory disorders of the eye.[3]

1. Dobrilla G, *et al.* Exacerbation of glaucoma associated with both cimetidine and ranitidine. *Lancet* 1982; 1: 1078.
2. Feldman F, Cohen MM. Intraocular pressure and H_2 receptor antagonists. *Lancet* 1982; 1: 1359.
3. García Rodríguez LA, *et al.* A cohort study of the ocular safety of anti-ulcer drugs. *Br J Clin Pharmacol* 1996; 42: 213–16.

Effects on the kidneys. A review[1] of the nephrotoxicity and hepatotoxicity of H_2-antagonists noted that mild elevation of serum-creatinine was relatively common after use of cimetidine but appeared to have no clinical significance. However, the authors found 25 published reports of acute interstitial nephritis associated with this class of drug (20 with cimetidine, 4 with ranitidine, and 1 with famotidine) and 16 cases reported to the Australian Drug Reaction Advisory Committee (ADRAC) between 1972 and 1999 (11 with cimetidine, 4 with ranitidine, and 1 with famotidine). Symptoms were mostly non-specific, and did not seem to be associated with the rash, arthralgia, and flank pain that may be seen in nephritis induced by other drugs. Nephritis was rare (an earlier analysis estimated an incidence of around 1 in 100 000 treated patients[2]) and invariably resolved when the drug was withdrawn. In 6 cases, rechallenge resulted in prompt return of clinical features, although there was some evidence that patients who developed nephrotoxicity with one H_2-antagonist might be able to tolerate substitution with another.

1. Fisher AA, Le Couteur DG. Nephrotoxicity and hepatotoxicity of histamine H_2 receptor antagonists. *Drug Safety* 2001; 24: 39–57.
2. Rowley-Jones D, Flind AC. Cimetidine-induced renal failure. *BMJ* 1982; 285: 1422–3.

Effects on the liver. Hepatotoxicity has been reported with cimetidine,[1,2] ranitidine,[3-5] and famotidine.[1,6] A cohort study[7] involving 108 891 patients given cimetidine, ranitidine, famotidine, or omeprazole between 1990 and 1993, found 33 cases meeting the authors' definition of clinically serious liver injury (cholestatic in 8 cases, hepatocellular in 15 and mixed in 10), most of whom presented with jaundice. Of these cases of liver injury, 12 were among current users of cimetidine, compared with 5 among users of ranitidine and 1 omeprazole user. It was estimated that the incidence of hepatotoxicity among patients using cimetidine was 2.3 cases per 10 000 users, and the adjusted relative risk was 5.5 times that of non-users. The relative risk for use of ranitidine or omeprazole was calculated at 1.7 and 2.1 respectively. The risk with cimetidine was greatest at high doses (800 mg daily or above) and at the beginning of therapy. A review concluded that although hepatotoxicity is very rare, it can occur with all H_2-antagonists and can include both hepatocellular and cholestatic features.[8]

1. Boyd PT, *et al.* Chronic active hepatitis associated with cimetidine. *BMJ* 1989; 298: 324–5.
2. Hashimoto F, *et al.* Hepatitis following treatments with famotidine and then cimetidine. *Ann Pharmacother* 1994; 28: 37–9.
3. Souza Lima MA. Ranitidine and hepatic injury. *Ann Intern Med* 1986; 105: 140.
4. Ramrakhiani S, *et al.* Possible cholestatic injury from ranitidine with a review of the literature. *Am J Gastroenterol* 1998; 93: 822–6.
5. Liberopoulos EN, *et al.* Possible ranitidine-induced cholestatic jaundice. *Ann Pharmacother* 2002; 36: 172.
6. Ament PW, *et al.* Famotidine-induced mixed hepatocellular jaundice. *Ann Pharmacother* 1994; 28: 40–2.
7. García Rodríguez LA, *et al.* The risk of acute liver injury associated with cimetidine and other acid-suppressing anti-ulcer drugs. *Br J Clin Pharmacol* 1997; 43: 183–8.
8. Fisher AA, Le Couteur DG. Nephrotoxicity and hepatotoxicity of histamine H_2-receptor antagonists. *Drug Safety* 2001; 24: 39–57.

Effects on the nervous system. CNS reactions have been reported with all H_2-antagonists.[1] These reactions occurred within 2 weeks of starting therapy in most cases, and resolved within 3 to 7 days of stopping treatment. After a reaction, it has been reported that most patients tolerate a different H_2-antagonist, but some will react to more than one. Confusion, disorientation, agitation, hostility, delirium, and hallucinations were most commonly described; obtundation, drowsiness, psychosis, and paranoia have also been reported. Proposed risk factors for CNS reactions associated with H_2-antagonist use include increasing age, critical illness, concomitant use of psychotropic medicines, pre-existing psychiatric disease, and liver or kidney disease. However, the evidence is sparse and the risk factors and the relative incidence of reactions with different H_2-antagonists remain to be established.

The effect of H_2-antagonists on cognitive function has also been studied. Despite early data suggesting their use was associated with a reduced risk of Alzheimer's disease, further analysis did not confirm the link.[2] Furthermore, a 5-year prospective study[3] suggested that continuous use of H_2-antagonists was associated with an increased risk of cognitive impairment in elderly African Americans.

1. Canrú TG, Korek JS. Central nervous system reactions to histamine-2 receptor blockers. *Ann Intern Med* 1991; 114: 1027–34.
2. Zandi PP, *et al.* Cache County Study Investigators. Reduced incidence of AD with NSAID but not H_2 receptor antagonists: the Cache County Study. *Neurology* 2002; 59: 880–6.
3. Boustani M, *et al.* The association between cognition and histamine-2 receptor antagonists in African Americans. *J Am Geriatr Soc* 2007; 55: 1248–53.

Effects on the skin. Widespread erythrosis-like lesions in a 36-year-old man were probably induced by cimetidine.[1]

There has been a report[2] of a skin eruption clinically consistent with erythema annulare centrifugum developing in a patient after 6 months of treatment with cimetidine; the eruption resolved after withdrawal of cimetidine and reappeared on rechallenge. The condition had not recurred during therapy with ranitidine. A mainly symmetrical, intertriginous pattern of erythema has also been reported with cimetidine use.[3] Erythema multiforme eruptions occurred after both cimetidine and famotidine in one patient.[4] There have been reports of the Stevens-Johnson syndrome during cimetidine treatment in patients with a history of hypersensitivity to penicillin[5] or sulfonamides,[6] and toxic epidermal necrolysis has been reported with cimetidine[7] and famotidine.[8] Vasculitic rashes have been reported with cimetidine,[9] nizatidine,[10] and ranitidine.[11] Alopecia[12] has been associated with cimetidine treatment.

1. Angelini G, *et al.* Cimetidine and erythrosis-like lesions. *BMJ* 1979; i: 1147–8.
2. Merrett AC, *et al.* Cimetidine-induced erythema annulare centrifugum: no cross-sensitivity with ranitidine. *BMJ* 1981; 283: 698.
3. Helmbold P, *et al.* Symmetric ptychotropic and nonpigmenting fixed drug eruption due to cimetidine (so-called baboon syndrome). *Dermatology* 1998; 197: 402–3.
4. Horiuchi Y, Ikezawa K. Famotidine-induced erythema multiforme: cross-sensitivity with cimetidine. *Ann Intern Med* 1999; 131: 795.
5. Ahmed AR, *et al.* Stevens-Johnsun syndrome during treatment with cimetidine. *Lancet* 1978; ii: 433.
6. Guan R, Yeo PPB. Stevens-Johnson syndrome: was it cimetidine? *Aust N Z J Med* 1983; 13: 182.
7. Tidwell BH, *et al.* Cimetidine-induced toxic epidermal necrolysis. *Am J Health-Syst Pharm* 1998; 55: 163–4.
8. Brunner M, *et al.* Toxic epidermal necrolysis (Lyell syndrome) following famotidine administration. *Br J Dermatol* 1995; 133: 814–15.
9. Mitchell GG, *et al.* Cimetidine-induced cutaneous vasculitis. *Am J Med* 1983; 75: 875–6.
10. Suh J-G, *et al.* Leukocytoclastic vasculitis associated with nizatidine therapy. *Am J Med* 1997; 102: 216–17.
11. Haboubi N, Asquith P. Rash mediated by immune complexes associated with ranitidine treatment. *BMJ* 1988; 296: 897.
12. Khalsa JH, *et al.* Cimetidine-associated alopecia. *Int J Dermatol* 1983; 22: 202–4.

Fever. There are reports of febrile reactions associated with cimetidine,[1-4] famotidine,[5] and ranitidine.[1,6]

1. Potter HP, *et al.* Fever after cimetidine and ranitidine. *J Clin Gastroenterol* 1986; 8: 275–6.
2. Parenti CM, Hoffman JE. Hyperpyrexia associated with intravenous cimetidine therapy: report of a case. *Arch Intern Med* 1986; 146: 1821–2.
3. Hiraide A, *et al.* IgE-mediated drug fever due to histamine H2-receptor blockers. *Drug Safety* 1990; 5: 455–7.
4. Chia JK, *et al.* Recurrent fever, leukocytosis, and abdominal pain due to treatment with cimetidine. *Clin Infect Dis* 1994; 18: 468–9.
5. Norwood J, *et al.* Famotidine and hyperpyrexia. *Ann Intern Med* 1990; 112: 632.
6. Kavanagh GM, *et al.* Ranitidine fever. *Lancet* 1993; 341: 1422.

Hypersensitivity. Facial oedema,[1] laryngospasm,[1] pruritus,[2,3] rash,[2,3] angioedema[3] and anaphylaxis[4] have been reported in patients receiving cimetidine orally or intravenously. Respiratory stridor and a diffuse urticarial rash occurred in a patient shortly after taking the first oral dose of ranitidine;[5] the symptoms responded to subcutaneous adrenaline. Anaphylaxis has also been reported after famotidine.[6] See also Effects on the Skin, p. 1829.3.

It has also been suggested that cimetidine might potentiate hypersensitivity reactions to other antigens through its actions on histamine and H_2-receptors.[7]

1. Delaunois L. Hypersensitivity to cimetidine. *N Engl J Med* 1979; 300: 1216.
2. Hadfield WA. Cimetidine and giant urticaria. *Ann Intern Med* 1979; 91: 128–9.
3. Sandhu BS, Requena R. Hypersensitivity to cimetidine. *Ann Intern Med* 1982; 97: 138.
4. Knapp AB, *et al.* Cimetidine-induced anaphylaxis. *Ann Intern Med* 1982; 97: 374–5.
5. Brayko CM. Ranitidine. *N Engl J Med* 1984; 310: 1601–2.
6. Kim YI, *et al.* A case of famotidine-induced anaphylaxis. *J Investig Allergol Clin Immunol* 2010; 20: 166–9.
7. Evans RDL, *et al.* Cimetidine and a delayed hypersensitivity reaction. *Clin Podiatr Med Surg* 2000; 17: 371–5.

Infection. For discussion of the possible increased risk of infections with acid suppressing drugs, see Omeprazole, p. 1870.1.

Malabsorption. A case-control study[1] in elderly patients found that chronic use (12 months or more) of acid-suppressive therapy, including H_2-antagonists, increased the risk of vitamin B_{12} deficiency. It has been suggested that deficiency might result from impaired release of vitamin B_{12} from food protein, which requires gastric acid and pepsin.[2]

1. Valuck RJ, Ruscin JM. A case-control study on adverse effects: H2 blocker or proton pump inhibitor use and risk of vitamin B_{12} deficiency in older adults. *J Clin Epidemiol* 2004; 57: 422–8.
2. Ruscin JM, *et al.* Vitamin B_{12} deficiency associated with histamine$_2$-receptor antagonists and a proton-pump inhibitor. *Ann Pharmacother* 2002; 36: 812–16.

Overdosage. No serious toxic effects were noted in reports[1-3] of overdosage in patients who took cimetidine 5.2 to 20 g (including one patient who took about 12 g daily for 5 days[1]). Resultant plasma concentrations had been up to 57 micrograms/mL compared with a usual peak plasma concentration of 1 microgram/mL after a 200-mg dose. However, an overdose of about 12 g produced high pulse rate, dilated pupils, speech disturbances, agitation and disorientation in one patient[4] and respiratory depression in another patient who had chronic schizophrenia and was also taking trifluoperazine and hydroxyzine.[5] Also, fatal bradycardia has been reported after overdosage with an unknown amount of cimetidine and diazepam.[6] In a review of 881 cases of cimetidine overdose, excluding cases where several drugs were taken, it was concluded that the toxicity of cimetidine after acute overdose was very low.[7] No symptoms were seen in 79% of cases, which included ingestions of up to 15 g of cimetidine, and only 3 patients had moderate clinical manifestations (dizziness and bradycardia; CNS depression; vomiting). No patients had major medical outcomes and there were no fatalities. Gastric emptying was performed in 34% of cases but supportive measures and symptomatic treatment alone may be adequate. Forced diuresis does not appear to enhance the excretion of cimetidine from the body, and is not recommended.[3]

1. Gill GV. Cimetidine overdose. *Lancet* 1978; i: 99.
2. Illingworth RN, Jarvie DR. Absence of toxicity in cimetidine overdosage. *BMJ* 1979; i: 453–4.
3. Meredith TJ, Volans GN. Management of cimetidine overdose. *Lancet* 1979; ii: 1367.
4. Nelson PG. Cimetidine and mental confusion. *Lancet* 1977; ii: 928.
5. Wilson JB. Cimetidine overdosage. *BMJ* 1979; i: 955.
6. Hiss J, *et al.* Fatal bradycardia after intentional overdose of cimetidine and diazepam. *Lancet* 1982; ii: 982.
7. Krenzelok EP, *et al.* Cimetidine toxicity: an assessment of 881 cases. *Ann Emerg Med* 1987; 1: 1217–21.

Precautions

Before giving cimetidine or other histamine H_2-antagonists to patients with gastric ulcers the possibility of malignancy should be considered since these drugs may mask symptoms and delay diagnosis. They should be given in reduced dosage to patients with renal impairment.

Intravenous injections of cimetidine should be given slowly and intravenous infusion is preferred, particularly for high doses and in patients with cardiovascular impairment.

Allergy testing. A small study in 21 patients found that ranitidine suppressed the cutaneous response to allergens in skin-prick tests.[1] The authors highlighted the importance of considering the possible influence of H_2-antagonists on allergy diagnosis and treatment.

1. Kupczyk M, *et al.* Ranitidine (150 mg daily) inhibits wheal, flare, and itching reactions in skin-prick tests. *Allergy Asthma Proc* 2007; 28: 711–15.

Breast feeding. In the UK, licensed product information advises that mothers receiving cimetidine avoid breast feeding. Cimetidine is reported to be actively transported into breast milk, resulting in a milk:serum ratio 5.5 times higher than that expected with passive diffusion.[1] In one case, where cimetidine was detected in the milk of a nursing mother in concentrations higher than in her plasma, it was calculated[2] that the maximum amount of cimetidine that an infant could ingest assuming an intake of about 1 litre of milk daily and fed at the time of peak concentrations would be about 6 mg. However, the Committee on Drugs of the American Academy of Pediatrics has pointed out that there was no evidence of signs or symptoms attributable to the drug in the infant in this case,[3] despite 6 months of breast feeding, and cimetidine has been classified by that body as usually compatible with breast feeding.[4]

1. Oo CY, *et al.* Active transport of cimetidine into human milk. *Clin Pharmacol Ther* 1995; 58: 548–55.
2. Somogyi A, Gugler R. Cimetidine excretion into breast milk. *Br J Clin Pharmacol* 1979; 7: 627–9.
3. Berlin CM. Cimetidine and breast-feeding. *Pediatrics* 1991; 88: 1294.
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 07/05/04)

Burns. The clearance of cimetidine has been reported to be increased in burn patients, with the increase correlating to the size of the burn.[1] Despite another study that reported a decreased renal clearance (but an increased non-renal clearance) early in the evolution of burn injury,[2] it has been recommended that the dosage of cimetidine be increased in patients with burns, depending on the extent of injury. A requirement for increased dosage has also been noted in paediatric burns patients.[3]

1. Martyn JAJ, *et al.* Increased cimetidine clearance in burn patients. *JAMA* 1985; 253: 1288–91.
2. Ziemniak JA, *et al.* Cimetidine kinetics during resuscitation from burn shock. *Clin Pharmacol Ther* 1984; 36: 228–33.
3. Martyn JAJ, *et al.* Alteration by burn injury of the pharmacokinetics and pharmacodynamics of cimetidine in children. *Eur J Clin Pharmacol* 1989; 36: 361–7.

Helicobacter pylori testing. A study in 118 patients with *Helicobacter pylori* infection showed that 14 days of treatment with ranitidine could produce false negative results with urea breath testing, regardless of the dose used.[1] All breath tests became positive within 14 days of stopping treatment. The manufacturers of the breath test recommend it should not be performed for at least 2 weeks after stopping antisecretory drug therapy.

1. Savarino V, *et al.* Negative effect of ranitidine on the results of urea breath test for the diagnosis of Helicobacter pylori. *Am J Gastroenterol* 2001; 96: 348–52.

Hepatic impairment. An increased resistance to H_2-receptor antagonists has been reported in patients with cirrhosis.[1] Plasma concentrations were higher in responders than nonresponders; however, the authors considered concentrations in both groups to be sufficient for an effect and could not account for the results.

For a suggestion that dosage reduction of cimetidine may be required in patients with portal systemic encephalopathy, see Administration in Hepatic Impairment, p. 1827.3

1. Walker S, *et al.* Frequent non-response to histamine H_2-receptor antagonists in cirrhotics. *Gut* 1989; 30: 1105–9.

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

For reference to clinical and biochemical improvement in porphyric patients receiving cimetidine, see p. 1828.2.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. Data from prospective[1,2] and retrospective[3] cohort studies in pregnant women who had taken H_2-antagonists mainly during the first trimester, have not indicated an increased risk of major malformations. H_2-antagonists were also not associated with perinatal mortality, low birth-weight, or low Apgar scores;[1-3] although one study noted a higher rate of preterm births in the group exposed to H_2-antagonists,[2] this was not supported by other studies.[1,3] Additionally, UK licensed product information states that ranitidine has been given to women in labour or undergoing caesarean section without any adverse effects on labour, delivery, or the child. However, product information for cimetidine and ranitidine advises they should be avoided during pregnancy unless essential, as both cross the placenta.

1. Ruigómez A, *et al.* Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. *Am J Epidemiol* 1999; 150: 476–81.
2. Garbis H, *et al.* Pregnancy outcome after exposure to ranitidine and other H2-blockers: a collaborative study of the European Network of Teratology Information Services. *Reprod Toxicol* 2005; 19: 453–8.
3. Matok I, *et al.* The safety of H_2-blockers use during pregnancy. *J Clin Pharmacol* 2010; 50: 81–7.

Interactions

Cimetidine and other H_2-antagonists can reduce the absorption of drugs such as dasatinib, ketoconazole, itraconazole, and possibly posaconazole, whose absorption is dependent on an acid gastric pH. For the effect of itraconazole on cimetidine see Antifungals, p. 1831.1.

Cimetidine may inhibit the hepatic metabolism of many drugs by binding to cytochrome P450 isoenzymes, including CYP1A2, CYP2C9, CYP2D6, CYP3A3, CYP3A4, and CYP2C18. Although many such interactions may occur, only a few are considered clinically significant, notably those with phenytoin, theophylline, lidocaine, and oral anticoagulants. Avoidance of the combination, or a reduction in the dosage of these drugs may be required.

Cimetidine can affect many drugs[1-4] but these interactions are of clinical significance for only a few, particularly those that have a narrow therapeutic index where the risk of toxicity may necessitate adjustment of dosage. The majority of interactions are due to binding of cimetidine to cytochrome P450 isoenzymes in the liver with subsequent inhibition of microsomal oxidative metabolism and increased bioavailability or plasma concentrations of drugs metabolised by these enzymes. A few interactions are due to competition for renal tubular secretion. Other mechanisms of interaction such as changes in hepatic blood flow play only a minor role.

Significant interactions have occurred with:

- antiarrhythmics such as dofetilide (p. 1367.2), lidocaine (p. 1991.2), and procainamide (p. 1477.2)
- antiepileptics such as phenytoin (p. 544.3) and carbamazepine (p. 517.3)
- biguanide antidiabetics (p. 469.1)
- moclobemide (p. 438.1)
- nifedipine (p. 1454.1)
- opioid analgesics (p. 111.3)
- nitrosoureas such as carmustine (p. 762.1)
- sildenafil (p. 2366.3)
- theophylline (p. 1236.1)
- tricyclic antidepressants such as amitriptyline (p. 407.1)
- warfarin and other oral anticoagulants (p. 1534.1)
- zalcitabine (p. 1023.3)
- zolmitriptan (p. 682.3)

Combinations of these drugs and cimetidine should be avoided or used with caution, with monitoring of effects or

plasma-drug concentrations and reductions in dosage as appropriate.

Famotidine, nizatidine, and ranitidine do not inhibit cytochrome P450, and the potential for drug interactions is therefore reduced.

1. Penston J, Wormsley KG. Adverse reactions and interactions with H_2-receptor antagonists. *Med Toxicol* 1986; **1**: 192–216.
2. Somogyi A, Muirhead M. Pharmacokinetic interactions of cimetidine 1987. *Clin Pharmacokinet* 1987; **12**: 321–66.
3. Smith SR, Kendall MJ. Ranitidine versus cimetidine: a comparison of their potential to cause clinically important drug interactions. *Clin Pharmacokinet* 1988; **15**: 44–56.
4. Shinn AP. Clinical relevance of cimetidine drug interactions. *Drug Safety* 1992; **7**: 245–67.

Alcohol. Any interaction between H_2-antagonists and alcohol is generally thought unlikely to be clinically significant (see p. 1735.2).

Antacids. Single-dose studies of the interaction between cimetidine famotidine, or ranitidine and antacids[1] have generally shown a reduced bioavailability of H_2-antagonist. The neutralising capacity of the antacid appears to be a factor in determining whether an interaction occurs and a dose with less than 50 mmol neutralising capacity will have little, if any, effect on H_2-antagonist absorption. Smaller doses of antacid taken separately from the H_2-antagonist should reduce the impact of this interaction, and there are some data to suggest that absorption is not as greatly affected with concomitant longer-term use.

1. Gugler R, Allgayer H. Effects of antacids on the clinical pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1990; **18**: 210–19.

Antifungals. *Itraconazole* increased the area under the concentration-time curve of cimetidine, and reduced the total plasma clearance and renal tubular secretory clearance of cimetidine in a pharmacokinetic study in 8 healthy subjects.[1] The authors proposed that this was due to inhibition of P-glycoprotein-mediated renal tubular secretion.

1. Karyekar CS, *et al.* Renal interaction between itraconazole and cimetidine. *J Clin Pharmacol* 2004; **44**: 919–27.

Antihistamines. Cimetidine may increase the serum concentration of hydroxyzine, see p. 631.2.

Antimuscarinics. The antimuscarinic *propantheline* delays gastric emptying and reduces intestinal motility and has been reported to reduce the bioavailability of cimetidine.[1]

1. Kanto J, *et al.* The effect of metoclopramide and propantheline on the gastrointestinal absorption of cimetidine. *Br J Clin Pharmacol* 1981; **11**: 629–31.

Histamine. For the effect of cimetidine on histamine given exogenously, see p. 2525.3.

Melatonin. For the effect of cimetidine on melatonin, see p. 2552.2.

Probenecid. Probenecid reduced the clearance of both cimetidine[1] and famotidine[2] in small studies in healthy subjects. It was suggested that probenecid inhibited renal tubular secretion, although it was felt that the interaction was unlikely to be clinically significant.[1]

1. Giscion LG, *et al.* The effect of probenecid on the renal elimination of cimetidine. *Clin Pharmacol Ther* 1989; **45**: 444–52.
2. Inotsume N, *et al.* The inhibitory effect of probenecid on renal excretion of famotidine in young, healthy volunteers. *J Clin Pharmacol* 1990; **30**: 50–6.

Prokinetic drugs. *Metoclopramide* may reduce the bioavailability of cimetidine possibly due to reduction of gastrointestinal transit time.[1-3] A similar interaction has been reported between the prokinetic drug *cisapride* and both cimetidine[4] and ranitidine.[5] The clinical significance of this interaction is questionable since such combinations may be clinically effective, although the use of cisapride is now restricted in many countries. For the effect of cimetidine on cisapride, see p. 1833.1.

1. Gugler R, *et al.* Impaired cimetidine absorption due to antacids and metoclopramide. *Eur J Clin Pharmacol* 1981; **20**: 225–8.
2. Kanto J, *et al.* The effect of metoclopramide and propantheline on the gastrointestinal absorption of cimetidine. *Br J Clin Pharmacol* 1981; **11**: 629–31.
3. Barzaghi N, *et al.* Effects on cimetidine bioavailability of metoclopramide and antacids given two hours apart. *Eur J Clin Pharmacol* 1989; **37**: 409–10.
4. Kirch W, *et al.* Cisapride-cimetidine interactions: enhanced cisapride bioavailability and accelerated cimetidine absorption. *Ther Drug Monit* 1989; **11**: 411–14.
5. Rowbotham DJ, *et al.* Effect of single doses of cisapride and ranitidine administered simultaneously on plasma concentrations of cisapride and ranitidine. *Br J Anaesth* 1991; **67**: 302–5.

Sucralfate. Licensed product information for the mucosal protectant sucralfate states that it has been shown to reduce the bioavailability of cimetidine and other H_2-antagonists, presumably due to binding in the gastrointestinal tract. The effect can be avoided by separating doses of the two drugs by 2 hours, but it is not clear whether the interaction has a clinical significance.

Pharmacokinetics

Cimetidine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur after about an hour when given on an empty stomach; a second peak may be seen after about 3 hours. Food delays the rate and may slightly decrease the extent of absorption, with the peak plasma concentration occurring after about 2 hours.

The bioavailability of cimetidine after oral doses is about 60 to 70%, due to hepatic first-pass metabolism. Cimetidine is widely distributed and has a volume of distribution of about 1 litre/kg and is weakly bound, about 20%, to plasma proteins. The elimination half-life from plasma is about 2 hours and is increased in renal and hepatic impairment. Cimetidine is partially metabolised in the liver to the sulfoxide and to hydroxymethylcimetidine. About 50% of an oral dose, and 75% of an intravenous dose, is excreted unchanged in the urine in 24 hours. After an oral or parenteral dose of 300 mg, blood concentrations remain above that required to provide 80% inhibition of basal gastric acid secretion for 4 to 5 hours. Cimetidine crosses the placental barrier and is distributed into breast milk.

Reviews.
1. Somogyi A, Gugler R. Clinical pharmacokinetics of cimetidine. *Clin Pharmacokinet* 1983; **8**: 463–95.
2. Lin JH. Pharmacokinetic and pharmacodynamic properties of histamine H_2-receptor antagonists: relationship between intrinsic potency and effective plasma concentrations. *Clin Pharmacokinet* 1991; **20**: 218–36.
3. Gladziwa U, Klotz U. Pharmacokinetics and pharmacodynamics of H_2-receptor antagonists in patients with renal insufficiency. *Clin Pharmacokinet* 1993; **24**: 319–32.

Children. Renal function is limited in the first few months of life and half-lives of 1.1 to 3.7 hours have been reported for cimetidine in neonates;[1-3] less frequent dosing may therefore be required for preterm neonates and those with renal impairment.[1]

In older infants and children maturation of renal function is complete and the clearance of cimetidine is increased compared with that in adults; younger children show higher clearance values than older children.[4]

For details of doses used in children, see Administration in Children, p. 1827.3.

1. Ziemniak JA, *et al.* The pharmacokinetics and metabolism of cimetidine in neonates. *Dev Pharmacol Ther* 1984; **7**: 30–8.
2. Lloyd CW, *et al.* The pharmacokinetics of cimetidine and metabolites in a neonate. *Drug Intell Clin Pharm* 1985; **19**: 203–5.
3. Stile IL, *et al.* Pharmacokinetic evaluation of cimetidine in newborn infants. *Clin Ther* 1985; **7**: 361–4.
4. Somogyi A, *et al.* Cimetidine pharmacokinetics and dosage requirements in children. *Eur J Pediatr* 1985; **144**: 72–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ulcerfen; ***Austral.***: Cimehexal†; Magicul; Tagamet; ***Austria***: Cimetag†; Neutromed; Neutronorm; Sodexx Cimetidinet; Ulcometin†; Ulcostad; ***Belg.***: Doccimeti†; Nuardin; ***Braz.***: Cigamete†; Cimedax; Cimetidan; Cimetilab; Cimetinax; Cimetival; Cintag; Cintidina; Etidine; Pristonal; Prometidine; Tagaliv; Tagamet; Ulcedine; Ulcenon; Ulceract†; Ulcimet; Ulcinax; Ulcitrat; ***Canad.***: Novo-Cimetine; Nu-Cimet; ***China***: A Li Wei (阿立维); Changfu YouShu (长富优舒); Hai Fu Xin (海扶鑫); Nuo Mei Shu (诺美舒); Tagamet (泰胃美); Tang Feng (唐丰); Xiweining (希卫宁); Ying Qu (英曲); You Ni Ding (尤尼丁); Cz.: Primamet†; ***Fr.***: Stomedine; Tagamet†; ***Ger.***: Cimebeta†; Cimehexal†; CimLich†; H 2 Blocker; ***Gr.***: Alkastom; Besidin; Campanex; Cimeton; Gastrolene; Grinolon; Haldin; Ipirovet; Medelan; Metracine; Oskoval; Pallosixanet; Piovalen; Sasapir; Tagamet; Tamper; Tanapas; Therapelcin; Tinder; Trisolvenol; Ulcogranil; ***Hong Kong***: Cementin; Cimedine†; Cimeta; Citidine; Gastab†; Gastidine†; Magicul†; Maritidine†; Simaglen; Syncomet†; Tagamet; Timet†; Ulcerin; Ulcomet; ***India***: Cimetin; Lock-2; ***Indon.***: Cimexol; Corsamet; Licomet; Nulcer; Sanmetidin; Tagamet†; Ulcedine†; Ulcumet; Ulcusan†; Ulsikur; Xepamet; ***Irl.***: Cedine†; Cimagen†; Cimeldine; Dyspamet†; Galenamet†; Geramet†; Pinamet†; Rimatidine†; Tagamet†; ***Israel***: Cemidin; Cimetag†; Tagamet†; ***Ital.***: Biomag; Brumetidina†; Etideme; Tagamet; Temic; Ulcedin; Ulis; ***Malaysia***: Cimulcer; Shintamet; Tagamet; ***Mex.***: Cimebec†; Cimedul; Cimeffer; Cimetase; Colimet†; Gastrodina; Procimet†; Sercim; Sinegastrin†; Tagamet; Ulmarin; Ulserral; ***Neth.***: Tagamet†; ***NZ***: Cytine; ***Philipp.***: Antag†; Ciclem; Cimecid†; Cimulcer†; Duogastril; Montidin†; Shintamet; Tagamet; Temaril; Ulcenon†; ***Pol.***: Altramet†; Cimegast†; ***Port.***: Cim; Tagamet; ***Rus.***: Histodil (Гистодил)†; ***S.Afr.***: Aci-Med†; Acidown; Cimlok; Cinadine†; Cymi†; Hexamet; Lenamet; Lesacid; Secadine; Tagamet; Ulcim†; ***Singapore***: Cementin; Cimulcer; Citidine; Erimetin; Himetin; Shintamet; Tagamet; Xepamet; ***Spain***: Ali Veg†; Premet†; Tagamet†; ***Thai.***: Alserine; Cencamat; Chintamet; Cidine; Cigamet; Cimag; Cimet-P; Cimet; Cimetint†; Cimetine†; Ciminpac; Citidine; Clinimet; Duotric; Gastasil; GI; Iwamet†; KB Cymedin; Lakamed; Manomet; Milamet; Peptica†; Peptidine; Pondarmet†; Promet†; Rinadine†; Sertidine; Setard†; Shintamet†; Siamidine; Simaglen†; Simex†; Sincimet; Startidine; Stomedine; Tacamac; Tagapro; Ulcacin; Ulcedine†; Ulcemet; Ulcimet; Ulcinet†; Ulsamet; Umamet†; ***UAE***: Cimetag; ***UK***: Dyspamet; Galenamet; Tagamet; Zita; ***USA***: Tagamet; ***Venez.***: Gadol.

Pharmacopoeial Preparations

BP 2014: Cimetidine Injection; Cimetidine Oral Solution; Cimetidine Oral Suspension; Cimetidine Tablets;

USP 36: Cimetidine in Sodium Chloride Injection; Cimetidine Injection; Cimetidine Tablets.

Cimetropium Bromide *(rINN)*

Bromuro de cimetropio; Cimetropii Bromidum; Cimetropio, Bromuro de; Cimetropium, Bromure de; DA-3177; Hyoscine-*N*-(cyclopropylmethyl) Bromide; Циметропия бромид.

8-(Cyclopropylmethyl)-6β,7β-epoxy-3α-hydroxy-1αH,5αH-tropanium bromide, (-)-(*S*)-tropate.

$C_{21}H_{28}BrNO_4$=438.4

CAS — 51598-60-8.

ATC — A03BB05.

ATC Vet — QA03BB05.

UNII — 0C7M5WE60Q.

Profile

Cimetropium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been used as an antispasmodic in the treatment of gastrointestinal disorders, in usual doses of 50 mg two or three times daily orally or by rectal suppository. It has also been given intramuscularly or intravenously in usual doses of 5 mg.

References.
1. Dobrilla G, *et al.* Longterm treatment of irritable bowel syndrome with cimetropium bromide: a double blind placebo controlled clinical trial. *Gut* 1990; **31**: 355–8.
2. Marzio L, *et al.* Effect of cimetropium bromide on esophageal motility and transit in patients affected by primary achalasia. *Dig Dis Sci* 1994; **39**: 1389–94.
3. Savino F, *et al.* Cimetropium bromide in the treatment of crisis in infantile colic. *J Pediatr Gastroenterol Nutr* 2002; **34**: 417–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Alginor.

Cinitapride *(rINN)*

Cinitaprida; Cinitapridum; Цинитаприд.

4-Amino-*N*-[1-(3-cyclohexen-1'-ylmethyl)-4-piperidyl]-2-ethoxy-5-nitrobenzamide.

$C_{21}H_{30}N_4O_4$=402.5

CAS — 66564-14-5.

UNII — R8I9712L24.

Profile

Cinitapride is a substituted benzamide used for its prokinetic properties. It is given as the acid tartrate in oral doses of 1 mg three times daily before meals in the management of gastroparesis and gastro-oesophageal reflux disease (p. 1807.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cinigest; Paxapride; Rogastril; ***Mex.***: Binitab; Pemix; ***Spain***: Blaston; Cidine.

Multi-ingredient Preparations. ***Mex.***: Pridamiral Pack.

Cisapride *(BAN, USAN, rINN)*

Cisaprid; Cisaprida; Cisapridas; Cisapride monohydraté; Cisapridum; Cisapridum monohydricum; Ciszapryd; Cyzapryd jednowodny; R-51619; Sisapridi; Цизаприд.

cis-4-Amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidyl]-2-methoxybenzamide monohydrate.

$C_{23}H_{29}ClFN_3O_4.H_2O$=484.0

CAS — 81098-60-4 (anhydrous cisapride).

ATC — A03FA02.

ATC Vet — QA03FA02.

UNII — UVL329170W (cisapride); VZV0A4I38W (cisapride monohydrate).

Pharmacopoeias. *US.*

USP 36: (Cisapride). A white or almost white powder. Practically insoluble in water; sparingly soluble in methyl alcohol; soluble in dichloromethane; freely soluble in dimethylformamide. Protect from light.

Cisapride Tartrate *(BANM, rINNM)*

Cisaprida, tartrato de; Cisapride, Tartrate de; Cisapridi Tartras; Cisaprido tartratas; Cisaprid-tartarát; Cisapridtartrat; Cisza-

prid-tartarát; Sisapriditartraatti; Tartrato de cisaprida; Цизаприда Тартрат.

$C_{27}H_{35}ClFN_3O_{10}$=616.0

Uses and Administration

Cisapride is a substituted benzamide used for its prokinetic properties. It stimulates gastrointestinal motility, probably by increasing the release of acetylcholine in the gut wall at the level of the myenteric plexus, increases the resting tone of the lower oesophageal sphincter, and increases the amplitude of lower oesophageal contractions. Gastric emptying is accelerated and the mouth-to-caecum transit time is reduced. Colonic peristalsis is also increased which decreases colonic transit time. Cisapride apparently lacks antidopaminergic effects (unlike metoclopramide, p. 1862.2, to which it is chemically related) or direct parasympathomimetic activity and it does not affect prolactin release or gastric secretion. It is reported to be an agonist at serotonin-4 (5-HT_4) receptors.

Cisapride has been used mainly in the treatment of gastro-oesophageal reflux disease (p. 1807.2), in disorders associated with decreased gastric motility (p. 1805.2), and in non-ulcer dyspepsia. However, as mentioned under Effects on the Heart, below, its use is severely restricted by its propensity to cause cardiac arrhythmias, and it has been withdrawn completely in many countries, including the UK.

Cisapride is given as the monohydrate, but doses are calculated in terms of the anhydrous substance. Cisapride monohydrate 10.39 mg is equivalent to about 10 mg of anhydrous cisapride. It is taken orally 15 to 30 minutes before a meal and at bedtime, if necessary. Where still licensed, a usual oral dose is 5 to 10 mg three to four times daily up to a maximum daily dose of 40 mg. For discussion of dosage and use in children, see below.

Doses of cisapride should be reduced in patients with hepatic or renal impairment (see below).

Administration in children. Where still licensed, neonates, infants, and children have been given cisapride 200 micrograms/kg orally three or four times daily up to a maximum daily dose of 800 micrograms/kg. However, there are particular safety concerns over the use of cisapride in children because of the risk of cardiac arrhythmias (see Effects on the Heart, below). Special care is needed in neonates and cisapride is contra-indicated in premature neonates for 3 months after birth due to the increased risk of QT interval prolongation in this patient group.

Its efficacy has also been questioned and a systematic review[1] of the use of cisapride in children found no clear evidence that cisapride had a statistically significant effect in reducing symptoms of gastro-oesophageal reflux disease compared with placebo.

1. MacLennan S, *et al.* Cisapride treatment for gastro-oesophageal reflux in children. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2010 (accessed 15/07/10).

Administration in hepatic or renal impairment. In patients with hepatic impairment the dose of cisapride should be half the usual dose, followed by adjustment depending on clinical response. In cases where renal impairment is not considered to contra-indicate the use of cisapride, a similar reduction in dose has been recommended.

Adverse Effects

The most commonly reported adverse effects with cisapride are gastrointestinal disturbances including abdominal cramps, borborygmi, and diarrhoea. Headache and lightheadedness may also occur. Hypersensitivity (including rash, pruritus, and bronchospasm), convulsions, extrapyramidal effects, and increased urinary frequency, have occasionally been reported. Cases of arrhythmia, including ventricular tachycardia, ventricular fibrillation, torsade de pointes, and QT interval prolongation have occurred rarely; fatalities have resulted, and have led to severe restrictions on its use (see Effects on the Heart, below). There have been a few cases of disturbances in liver function among patients receiving cisapride.

Incidence of adverse effects. A comparison of data from prescription-event monitoring in over 13 000 recipients of cisapride and from a further 9726 recipients involved in a controlled study showed that diarrhoea, in about 2 to 4% of patients, was the commonest adverse effect reported.[1] Other relatively common adverse effects were headache, abdominal pain, nausea and vomiting, and constipation, all in around 1 to 1.5% of patients. There were 46 reports in the prescription-event monitoring data of increased urinary frequency (plus a further 20 among the controlled study patients), and 5 reports of arrhythmias.

1. Wager E, *et al.* A comparison of two cohort studies evaluating the safety of cisapride: prescription-event monitoring and a large phase IV study. *Eur J Clin Pharmacol* 1997; 52: 87–94.

Effects on the heart. Seven reports[1] of cardiac effects associated with cisapride were submitted to the WHO Programme for International Drug Monitoring between 1989 and 1991. They included palpitations in 4, tachycardia and hypertension in 1, and extrasystole in 2. Subsequent reports implicated cisapride in the development of prolonged QT interval and torsade de pointes or ventricular fibrillation or both.[2,3] By December 1999 the FDA had received 341 reports of heart rhythm abnormalities associated with cisapride use, including 80 reports of deaths. Most patients were either receiving other drugs known to impair cisapride metabolism (see Interactions, below) or had other factors predisposing to arrhythmias. In the light of earlier reports of cardiac effects and of evidence for a direct effect of cisapride on the heart at therapeutic concentrations, in 1998 the UK CSM **contra-indicated**[2] the use of cisapride in patients receiving drugs that could inhibit cisapride metabolism or that prolong the QT interval, as well as in patients with a history of QT interval prolongation, ventricular arrhythmia, or torsade de pointes, or other risk factors for arrhythmia (see Precautions, below). Neonates[4] (especially of low gestational age[5]) are vulnerable to cisapride-induced QT interval prolongation, and the CSM also specifically contra-indicated use in premature neonates[2] and noted that there were insufficient data to support use in children up to the age of 12. Other studies have also noted a prolongation of QT interval in children.[6,7] However, some commentators have questioned the general contra-indication in prematurity,[8] and one retrospective analysis estimated the rate of serious adverse events such as arrhythmia in premature newborns to be less than 1 in 11 000, excluding those cases related to concurrent treatment with a contra-indicated drug or to overdose.[9] Conversely, others emphasise the lack of objective evidence of benefit for cisapride in most paediatric indications.[10] The European Society of Paediatric Gastroenterology, Hepatology and Nutrition has published recommendations on the use of cisapride in paediatric gastro-oesophageal reflux disease,[11] including that the total daily dose of cisapride should rarely exceed 800 micrograms/kg, and that ECG monitoring should be performed before and after 3 days of treatment in certain groups such as premature infants.

The use of cisapride has also been the subject of warnings and restrictions in other countries. In the USA, prescribing information was amended in January 2000 to recommend that all patients should receive an ECG before beginning cisapride therapy and extending the contra-indications to use; the drug was subsequently **withdrawn** from general supply, remaining available only in severely restricted cases. In July 2000 cisapride was also withdrawn completely from the UK market.[12] In Europe, the European Commission decided that cisapride-containing products could be maintained with restricted indications; all patients given cisapride should be enrolled in either a study or registry of clinical safety, or a study of clinical efficacy.[13] Despite a withdrawal of cisapride from general supply, a retrospective cohort study in South Korea found that it was still in use there up to 2 years later; in many instances cisapride had been given with contra-indicated drugs, which was associated with an increase in the risk of all-cause mortality.[14]

1. Olsson S, Edwards IR. Tachycardia during cisapride treatment. *BMJ* 1992; 305: 748–9.
2. CSM/MCA. Cisapride (Prepulsid): risk of arrhythmias. *Current Problems* 1998; 24: 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023231&RevisionSelectionMethod=LatestReleased (accessed 14/06/06)
3. Wysowski DK, Bacsanyi J. Cisapride and fatal arrhythmia. *N Engl J Med* 1996; 335: 290–1.
4. Bernardini S, *et al.* Effect of cisapride on QTc interval in neonates. *Arch Dis Child Fetal Neonatal Ed* 1997; 77: F241–3.
5. Dubin A, *et al.* Cisapride associated with QTc prolongation in very low birth weight preterm infants. *Pediatrics* 2001; 107: 1313–16.
6. Hill SL, *et al.* Proarrhythmia associated with cisapride in children. *Pediatrics* 1998; 101: 1053–6.
7. Khongphatthanayothin A, *et al.* Effects of cisapride on QT interval in children. *J Pediatr* 1998; 133: 51–6.
8. Lander A, Desai A. The risks and benefits of cisapride in premature neonates, infants, and children. *Arch Dis Child* 1998; 79: 469–71.
9. Ward RM, *et al.* Cisapride: a survey of the frequency of use and adverse events in premature newborns. *Pediatrics* 1999; 103: 469–72.
10. Cairns P. The risks and benefits of cisapride. *Arch Dis Child* 1999; 80: 493.
11. Vandenplas Y, *et al.* The role of cisapride in the treatment of pediatric gastroesophageal reflux: the European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 1999; 28: 518–28.
12. CSM/MCA. Cisapride (Prepulsid) withdrawn. *Current Problems* 2000; 26: 9–10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074606&RevisionSelectionMethod=LatestReleased (accessed 14/06/06)
13. CSM/MHRA. Cisapride: licences cancelled. *Current Problems* 2004; 30: 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074486&RevisionSelectionMethod=LatestReleased (accessed 14/06/06)
14. Chot N-K, *et al.* Increase in mortality rate following coprescription of cisapride and contraindicated drugs. *Ann Pharmacother* 2007; 41: 667–73.

Effects on the respiratory system. Chest tightness, wheezing, and a fall in peak flow rate occurred in a patient with severe brittle asthma after taking cisapride 10 mg.[1] Four other cases of bronchospasm associated with cisapride were discussed in a subsequent report;[2] in 2 of these cases symptoms resolved on withdrawal and recurred on rechallenge.

1. Nolan P, *et al.* Cisapride and brittle asthma. *Lancet* 1990; 336: 1443.
2. Pillans P. Bronchospasm associated with cisapride. *BMJ* 1995; 311: 14.

Effects on the urinary tract. There had been 12 cases of urinary disturbances associated with use of cisapride[1] reported to the Australian Adverse Drug Reactions Advisory Committee between March 1991 and July 1993. Five reports were of urinary incontinence, 8 involved frequency, and individual reports involved cystitis, hesitancy, and urinary retention. The majority of the cases involved women, and most patients were elderly.

1. Boyd IW, Rohan AP. Urinary disorders associated with cisapride. *Med J Aust* 1994; 160: 579–80.

Precautions

Cisapride should not be used when stimulation of muscular contractions might adversely affect gastrointestinal conditions as in gastrointestinal haemorrhage, obstruction, perforation, or immediately after surgery.

Cisapride is **contra-indicated** in the following patients:

- those receiving potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 such as macrolide antibacterials, azole antifungals, HIV-protease inhibitors, or nefazodone (see also Interactions, below)
- those taking other drugs that predispose to electrolyte disturbances or that prolong the QT interval
- those with a personal or family history of QT interval prolongation
- those with a history of ventricular arrhythmia or torsade de pointes

Furthermore, it should not be given to those with other risk factors for arrhythmia including:

- clinically significant heart disease
- uncorrected electrolyte disturbances (particularly hypokalaemia and hypomagnesaemia)
- renal failure
- respiratory failure

Use is also contra-indicated in premature infants for up to 3 months after birth.

Cisapride should be used with caution and in reduced doses in patients with hepatic or renal impairment. All patients should have their ECG, serum electrolytes, and renal function monitored before and during treatment.

Care should be taken not to exceed the recommended dose.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving cisapride, and the American Academy of Pediatrics considered[1] 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 07/05/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cisapride 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 06/10/11)

Interactions

Cisapride is metabolised by the cytochrome P450 isoenzyme CYP3A4. Use with drugs that significantly inhibit this enzyme is contra-indicated as it may result in increased plasma concentrations of cisapride and hence a greater risk of QT interval prolongation and ventricular arrhythmias. Examples of such drugs include the azole antifungals ketoconazole, fluconazole, itraconazole, and miconazole; the macrolide antibacterials troleandomycin, azithromycin, erythromycin, and clarithromycin; the NNRTIs delavirdine and efavirenz; and the HIV-protease inhibitors. Nefazodone may interact similarly.

Cisapride should not be used in patients receiving other medication known to prolong the QT interval, including quinine or halofantrine, terfenadine, astemizole, certain antiarrhythmics such as amiodarone or quinidine, some antidepressants such as amitriptyline, phenothiazine antipsychotics, and sertindole. Cimetidine may enhance cisapride bioavailability. Grapefruit juice also increases the bioavailability of cisapride and they should not be taken together. In addition, drugs such as potassium-sparing diuretics, or insulin in acute settings, can result in altered electrolyte balance, and use with cisapride may also increase the risk of arrhythmias.

Antimuscarinics and possibly opioid analgesics may antagonise the gastrointestinal effects of cisapride. Because

cisapride increases intestinal motility it may affect the absorption of other drugs, either diminishing absorption from the stomach or enhancing absorption from the small intestine. Prothrombin times may be increased in some patients receiving oral anticoagulants, and the effects of alcohol and some other CNS depressants may be enhanced.

Reviews.
1. Bedford TA, Rowbotham DJ. Cisapride: drug interactions of clinical significance. *Drug Safety* 1996; 15: 167–75.
2. Michalets EL, Williams CR. Drug interactions with cisapride: clinical implications. *Clin Pharmacokinet* 2000; 39: 49–75.

Cardiovascular drugs. Near syncope and a prolonged QT interval occurred in a patient taking cisapride and *diltiazem*.[1] Diltiazem may have inhibited the metabolism of cisapride. For mention of cisapride possibly reducing the absorption of *digoxin*, see p. 1357.3.

1. Thomas AR, *et al.* Prolongation of the QT interval related to cisapride-diltiazem interaction. *Pharmacotherapy* 1998; 18: 381–5.

H_2-antagonists. *Cimetidine*[1] but not *ranitidine*[2] has been reported to enhance the bioavailability of oral cisapride, possibly by inhibition of cisapride metabolism (cimetidine is an inhibitor of the cytochrome P450 isoenzyme CYP3A4). Cisapride conversely increases the rate of absorption and decreases the oral bioavailability of both cimetidine[1] and ranitidine (see Prokinetic Drugs, p. 1831.1).

1. Kirch W, *et al.* Cisapride-cimetidine interaction: enhanced cisapride bioavailability and accelerated cimetidine absorption. *Ther Drug Monit* 1989; 11: 411–14.
2. Rowbotham DJ, *et al.* Effect of single doses of cisapride and ranitidine administered simultaneously on plasma concentrations of cisapride and ranitidine. *Br J Anaesth* 1991; 67: 302–305.

Pharmacokinetics

Cisapride is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 2 hours after an oral dose. It undergoes extensive first-pass metabolism in the liver and gut wall, resulting in an absolute bioavailability of 35 to 40%. The main metabolic pathways are oxidative *N*-dealkylation by the cytochrome P450 isoenzyme CYP3A4, producing the major metabolite norcisapride, and aromatic hydroxylation. More than 90% of a dose is excreted as metabolites in the urine and faeces in about equal amounts. A small amount is distributed into breast milk. The elimination half-life is about 10 hours. Cisapride is about 98% bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cispride; Fabrapride†; Pulsar; *Belg.*: Prepulsid†; *Braz.*: Prepulsid; *Chile*: Gastromet; Ondax; *China*: Bi Na Wei (必纳维); Chang Wei Xi (畅维禧); Ge Rui Xi (格瑞西); Prepulsid (普瑞博思); Wei Pu Lai (维富莱); Yirui (怡瑞); *Fr.*: Prepulsid†; *Gr.*: Alimix; Bozaktral; Cefanyl; Cevilor; Circocric; Cisarid; Desonil; Dolyzinax; Elpegon; Epasan; Evifix; Gastridol; Kinussen; Lamafer; Lasapride; Lirebin; Lycalin; Minsk; Nastilox; Oferin; Ruvetine; Saprimix; Spabucol; Systilan; Zenopar; *India*: Alipride; Cenz; Cisalone; Cisanorm; Cisapid; Cisapro; Cisariv; Cisaten DT; Cisawal; Cispel; Ciszy; Ciza; Cizafast; Cizap; Esorid; Gastro; Gastron; Gastropen; Kemopride; Lakpride; *Indon.*: Acpulsif; Disflux; Ethiprid; Guarposid; Pridesia; Stimulit; *Israel*: Prepulsid†; *Mex.*: Aposada; Cepriser; Enteropride; Eriken; Expril†; Kinestase; Maprilex; Mavisid; Nodrix; Presistin; Prixin; Profercol; Sapriken; Unamol; *Neth.*: Prepulsid†; *Pol.*: Gasprid; Gastronax†; *Port.*: Prepulsid†; *S.Afr.*: Prepulsid†; *Singapore*: Prepulsid; *Thai.*: Cipasid; Cisapac; Cisapid; Cisaride; Palcid; Pri-De-Sid; *Venez.*: Cisamod.

Multi-ingredient Preparations. *India*: Alipride MPS; Cisacone; Cisapid-MPS; Ciza-MPS; Cizap-MPS; Esorid MPS; Eza MPS; Gastro MPS; Gastropen-MPS; Kemopride MPS; Manotac Plus; *Mex.*: Ergex.

Clebopride *(BAN, USAN, rINN)*

Cleboprida; Clébopride; Clebopridum; LAS-9273; Клебоприд.

4-Amino-*N*-(1-benzyl-4-piperidyl)-5-chloro-*o*-anisamide.

$C_{20}H_{24}ClN_3O_2$=373.9

CAS — 55905-53-8.

ATC — A03FA06.

ATC Vet — QA03FA06.

UNII — I0A84520Y9.

Clebopride Malate *(BANM, rINNM)*

Clebopride, malato de; Clébopride, Malate de; Clebopridi Malas; Clebopridmalat; Kleboprid malát; Klebopridimalaatti; Klebopridmalat; Klebopríd-malát; Kleboprido malatas; Malato de cleboprida; Клебоприда малат.

$C_{20}H_{24}ClN_3O_2.C_4H_6O_5$=508.0

CAS — 57645-91-7.

ATC — A03FA06.

ATC Vet — QA03FA06.

UNII — H9490V5216.

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

Ph. Eur. 8: (Clebopride Malate). A white or almost white, crystalline powder. Sparingly soluble in water and in methyl alcohol; slightly soluble in dehydrated alcohol; practically insoluble in dichloromethane. The pH of a 1% solution in water is 3.8 to 4.2. Protect from light.

Profile

Clebopride is a substituted benzamide similar to metoclopramide (p. 1862.2), that is used for its antiemetic and prokinetic actions in nausea and vomiting (p. 1811.3) and various other gastrointestinal disorders. It is given as the malate but doses are expressed in terms of the base. Clebopride malate 679 micrograms is equivalent to about 500 micrograms of clebopride.

Clebopride malate is given in a usual oral dose equivalent to clebopride 500 micrograms three times daily before meals or 0.5 to 1 mg by intramuscular or intravenous injection for acute symptoms. For dosage in children see below.

Administration in children. Adolescents aged 12 to 20 years may be given clebopride malate orally in a dose equivalent to clebopride 250 micrograms three times daily. An oral dose of 15 to 20 micrograms/kg daily in 3 divided doses may be used for children under 12; the following doses have been recommended:

- 1 to 4 years: 50 micrograms 3 times daily
- 4 to 8 years: 100 micrograms 3 times daily
- 8 to 10 years: 150 micrograms 3 times daily
- 10 to 12 years: 200 micrograms 3 times daily

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Gastridin; *China*: Si Wei Si (思清斯); Wei Heng (维恒); *Indon.*: Clast; *Ital.*: Cleboril; Motilex; *Mex.*: Eborix; *Port.*: Clebofex; Clebutec; *Spain*: Cleboril.

Multi-ingredient Preparations. *Arg.*: Eudon; Gastridin-E; Somasedan; *Spain*: Clanzoflat†; Flatoril.

Clidinium Bromide *(BAN, USAN, rINN)*

Bromuro de clidinio; Clidinii Bromidum; Clidinio, bromuro de; Clidinium, Bromure de; Klidiniumbromid; Klidiniumbromidi; Klidinyum Bromür; Ro-2-3773; Клидиния бромид.

3-Benziloyloxy-1-methylquinuclidinium bromide.

$C_{22}H_{26}BrNO_3$=432.4

CAS — 7020-55-5 (clidinium); 3485-62-9 (clidinium bromide).

UNII — 91ZQW5JF1Z.

Pharmacopoeias. In *US*.

USP 36: (Clidinium Bromide). A white or nearly white, practically odourless, crystalline powder. Soluble in water and in alcohol; slightly soluble in ether and in benzene. Store in airtight containers. Protect from light.

Profile

Clidinium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been used alone or more often with chlordiazepoxide in the symptomatic treatment of peptic ulcer disease and other gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Thai.*: Chlordibrax.

Multi-ingredient Preparations. *Arg.*: Libraxin; *Canad.*: Apo-Chlorax; Librax; Pro Chlorax†; *Chile*: Gastrolen; Lerogin; Libraxin; Tensoliv; *Fin.*: Librax; *Fr.*: Librax; *Gr.*: Distedon; Librax; *Hong Kong*: Librax; *India*: Acirex; Alspas Forte; Cebrex Forte; Cebrex; Cibis; Clidox; Colinorm; Cypa; Dorpep; Equirex; IBS; Librax; Librospas; Neurospas-CD; Normaxin-RT; Normaxin; Orlidox-D; Orlidox; Spasrax; *Indon.*: Braxidin; Cliad; Klidibrax; Librax; Melidox; Renagas; *Israel*: Nirvaxal†; *Ital.*: Librax; *Malaysia*: Liblan; *Port.*: Librax; *S.Afr.*: Librax†; *Singapore*: Apo-Chlorax; Chlobax; Librax†; Medocalum†; Syntabrax; *Switz.*: Librax; Librocol; *Thai.*: Cebarax†; Dirax; Kenspa; Librax; Licon; Modurax; Pobrax; Radibrax; Tumax; Utorax; *Turk.*: Klipaks; Librax; *USA*: Clindex; Librax; *Venez.*: Librax.

Pharmacopoeial Preparations

USP 36: Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules.

Colocynth

Bitter Apple; Bitter Cucumber; Colocinto; Colocynth Pulp; Colocynthis; Coloquinte; Coloquintidas; Koloquinthen; Колоцинт.

UNII — Z70W98921V (Citrullus colocynthis); 0E49E3V9U6 (Citrullus colocynthis fruit); 23H32AOH17 (Citrullus colocynthis fruit pulp).

NOTE. The synonym Bitter Apple has also been applied to the fruits of *Solanum incanum*.

Pharmacopoeias. *Br.* includes Citrullus Colocynthis Fruit for Homoeopathic Preparations.

BP 2014: (Citrullus Colocynthis Fruit for Homoeopathic Preparations). The dried, peeled fruits of *Citrullus colocynthis* with the seeds removed.

Profile

Colocynth is the dried pulp of the fruit of *Citrullus colocynthis* (Cucurbitaceae). It has a drastic purgative and irritant action and has been superseded by less toxic laxatives.

Homoeopathy

Colocynth has been used in homoeopathic medicines under the following names: Colocynthis; Coloc.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Neth.*: Diarrheel S.

Homoeopathic Preparations. *Austral.*: Colic Relief; IBS Eze; Teething Relief; *Austria*: Diluplex; *Canad.*: Berberis-Homaccord†; Carduus Plex†; Cocyntal; Col 138†; Colic Comp-Drops 8 Uri-Tract†; Diarrhea; Formula ES 211; Formula FV 213; Hylands Formula MC; Hylands Kinder-CL†; Hylands Menstrual Cramps†; Kid's Colic Spascupreel; *Chile*: Lumboplex; *Cz.*: Hepeel; *Fr.*: Aloe Compose; Berberis Complexe No 83; Formica Rufa Compose; Gelsemium Complexe No 70; L 107; Ranunculus Complexe No 79; *Ger.*: Araniforce arthro; Carminativum Hevert; Chole-cyl L Ho-Len-Complex; Colintest-Gastreu; Cranio-cyl Ho-Len-Complex; Diluplex; Dolo-Injektopas; Entero-Gastreu S R4; gastri-loges N; Gastriselect N; Gelsemium Comp; Gelsemium Comp; HanoHepan; Intercostal-Gastreu; Lithias-cyl L Ho-Len-Complex; Lowe-Komplex Nr 6; Magen-Darm-Entoxin N; Neuralgie-Gastreu R70; Neuri-cyl N Ho-Len-Complex; Nuxal H; Pancreas-Gastreu N; Pascofemin spasmo; Pascosabal; Spascupreel; Spasmo-Bomaleb†; Spasmoject F; *Hung.*: Hepeel; Spascupreel; *Neth.*: Apo-STOM; Colocynthis-Homaccord; Entero-Gastreu R4; Gastrifleur; Homeocare Digesto; Kind 0-3 Cinababy; Nux Vomica-Homaccord; Spascupreel H; Spiroflor; *Rus.*: Menalgin (Менальгин); *Switz.*: Diarrheel S; Gastronol; Hepeel; *Ukr.*: Enterocind (Энтероцинд).

Crofelemer *(USAN)*

SP-303.

CAS — 148465-45-6.

Profile

Crofelemer is a proanthocyanidin from the bark latex of the tree *Croton lechleri* that acts locally on the intestinal lumen to normalise flow of chloride ions and water into the gastrointestinal tract. It is used in the management of non-infectious diarrhoea in patients with HIV and AIDS on antiretroviral therapy (see HIV-associated Wasting, p. 959.1). A dose of 125 mg is given orally twice daily.

Crofelemer is also under investigation in the treatment of other forms of secretory diarrhoea and diarrhoea-predominant irritable bowel syndrome.

References.
1. Mangel AW, Chaturvedi P. Evaluation of crofelemer in the treatment of diarrhea-predominant irritable bowel syndrome patients. *Digestion* 2008; 78: 180–6.
2. Crutchley RD, *et al.* Crofelemer, a novel agent for treatment of secretory diarrhea. *Ann Pharmacother* 2010; 44: 878–84.
3. Cotreau J, *et al.* Crofelemer for the treatment of secretory diarrhea. *Expert Rev Gastroenterol Hepatol* 2012; 6: 17–23.
4. Frampton JE. Crofelemer: a review of its use in the management of non-infectious diarrhoea in adult patients with HIV/AIDS on antiretroviral therapy. *Drugs* 2013; 73: 1121–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Fulyzaq.

Dantron *(BAN, rINN)*

Antrapurol; Chrysazin; Danthron; Dantrón; Dantrone; Dantroni; Dantronum; Dianthon; Dioxyanthrachinonum; Дантрон.

1,8-Dihydroxyanthraquinone.

$C_{14}H_8O_4$=240.2

CAS — 117-10-2.

ATC — A06AB03.

ATC Vet — QA06AB03.
UNII — Z4XE6I8F3V.

NOTE. Compounded preparations of dantron may be represented by the following names:
- Co-danthramer *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of dantron and poloxamer respectively
- Co-danthrusate (*BAN*)—dantron 5 parts and docusate sodium 6 parts (w/w).

Pharmacopoeias. In *Br.*

BP 2014: (Dantron). An orange, odourless or almost odourless, crystalline powder. Practically insoluble in water; very slightly soluble in alcohol; soluble in chloroform; slightly soluble in ether; dissolves in solutions of alkali hydroxides.

Uses and Administration

Dantron is an anthraquinone stimulant laxative but, unlike senna (p. 1885.1), it is not a glycoside. It is given orally to treat constipation (p. 1804.3) and is effective within 6 to 12 hours. However, because of concern over *rodent* carcinogenicity it has been withdrawn in some countries, and its use restricted in others. In the UK, it may be used only in terminally ill patients.

Dantron is given in doses of 25 to 75 mg when given with poloxamer 188 (p. 2202.1) as co-danthramer, and in doses of 50 to 150 mg when given with docusate sodium (p. 1836.2) as co-danthrusate. Doses are usually given at bedtime. For doses in children, see below.

Administration in children. In the UK, the use of dantron is restricted to the treatment of constipation in terminally ill patients; children under 12 years have been given dantron 12.5 to 25 mg orally as co-danthramer or 50 mg as co-danthrusate. Doses are usually given at bedtime. Children aged 12 years and over may be treated with the adult dose (see Uses and Administration, above).

The *BNFC* recommends similar doses to these, but restricts the use of co-danthramer to children aged 2 years and over, and the use of co-danthrusate to those aged 6 years and over.

Dantron should not be used in infants wearing nappies (diapers) as it may cause discoloration and superficial sloughing of the skin.

Adverse Effects and Precautions

As for Senna, p. 1885.3. Dantron may colour the urine pink or red. Discoloration and superficial sloughing of perianal skin can occur after prolonged contact, therefore dantron should not be used in infants wearing nappies (diapers) and should be used with caution in incontinent patients. The mucosa of the large intestine may be discoloured with prolonged use or high dosage.

In *rodents*, dantron has been associated with the development of intestinal and liver tumours. Consequently, its use has been restricted, see Uses and Administration, above.

References to adverse effects occurring with dantron-containing laxatives include individual cases of leucopenia with liver damage,[1] greyish-blue skin discoloration,[2] and orange vaginal discharge.[3] There has also been a report of intestinal sarcoma in an 18-year-old girl with a history of prolonged use of a dantron-containing laxative.[4] In May 2000 the UK CSM restricted the use of dantron to terminally ill patients on the grounds that pre-clinical evidence had increased and dantron was now established as a potential human carcinogen.[5]

1. Tolman KG, *et al.* Possible hepatotoxicity of Doxidan. *Ann Intern Med* 1976; 84: 290–2.
2. Darke CS, Cooper RG. Unusual case of skin discoloration. *BMJ* 1978; 1: 1188–9.
3. Greer IA. Orange periods. *BMJ* 1984; 289: 323.
4. Patel PM, *et al.* Anthraquinone laxatives and human cancer: an association in one case. *Postgrad Med J* 1989; 65: 216–17.
5. CSM/MCA. Dantron restricted to constipation in the terminally ill. *Current Problems* 2000; 26: 4. Also available at: http://www.mhra.gov.uk/home/idcpig?idcService=GET_FILE&dDocName=CON0074626&RevisionSelectionMethod=LatestReleased (accessed 08/11/06)

Breast feeding. The American Academy of Pediatrics[1] state that, although usually compatible with breast feeding, use of dantron by breast-feeding mothers has been reported to cause increased bowel activity in the infant.

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 08/11/06)

Pharmacokinetics

Dantron is metabolised by bacteria in the colon. Dantron or its metabolites are absorbed from the gastrointestinal tract, as indicated by discoloration of urine in some patients. Dantron or its metabolites are excreted in the faeces and the urine, and also in other secretions including breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile:* Modane; *Irl.:* Ailax†; Codalax; Cotron; *Mex.:* Modaton; *NZ:* Pinorax; *UK:* Capsuvac; Codalax; Danlax; Normax.

Pharmacopoeial Preparations
BP 2014: Co-danthrusate Capsules.

Dexlansoprazole *(USAN, rINN)*

Dexlansoprazol; Dexlansoprazolum; *R*-lansoprazole; T-168390; TAK-390; Декспансопразол.
(+)-2-{(*R*)-[[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulfinyl}-1*H*-benzamidazole.
$C_{16}H_{14}F_3N_3O_2S$=369.4
CAS — 138530-94-6.
UNII — UYE4T5I70X (dexlansoprazole); HS2S9VK3NH (dexlansoprazole sesquihydrate).

Uses and Administration

Dexlansoprazole, the *R*-isomer of the proton pump inhibitor lansoprazole (p. 1851.3), is given for the management of severe or symptomatic gastro-oesophageal reflux disease.

An oral dose of dexlansoprazole 60 mg is given once daily for up to 8 weeks to heal erosive oesophagitis. Once erosions have healed, 30 mg once daily is given for maintenance. For symptomatic non-erosive gastro-oesophageal reflux disease, 30 mg is given once daily for 4 weeks.

For doses in hepatic impairment, see below.

References.
1. Fass R, *et al.* Clinical trial: the effects of the proton pump inhibitor dexlansoprazole MR on daytime and nighttime heartburn in patients with non-erosive reflux disease. *Aliment Pharmacol Ther* 2009; 29: 1261–72.
2. Metz DC, *et al.* Review article: dual delayed release formulation of dexlansoprazole MR, a novel approach to overcome the limitations of conventional single release proton pump inhibitor therapy. *Aliment Pharmacol Ther* 2009; 29: 928–37.
3. Anonymous. Dexlansoprazole (Kapidex) for GERD and erosive esophagitis. *Med Lett Drugs Ther* 2009; 51: 21–2.
4. Abel C, *et al.* Dexlansoprazole in the treatment of esophagitis and gastroesophageal reflux disease. *Ann Pharmacother* 2010; 44: 871–7.
5. Croxtall JD, Scott LJ. Dexlansoprazole modified release: in erosive oesophagitis and non-erosive reflux disease. *Drugs* 2010; 70: 1593–1601.

Administration. Dexlansoprazole is given orally as capsules containing enteric-coated granules, which should be swallowed whole. Alternatively, capsules can be opened and the granules sprinkled on apple sauce before swallowing without chewing.

Administration in hepatic impairment. No dosage adjustment of dexlansoprazole is considered necessary for patients with mild hepatic impairment (Child-Pugh class A). For patients with moderate hepatic impairment (Child-Pugh class B), a daily oral dose of 30 mg should not be exceeded. There are limited data on the use of dexlansoprazole in patients with severe hepatic impairment (Child-Pugh class C).

Adverse Effects and Precautions

As for Omeprazole, p. 1868.1.

Interactions

As for Omeprazole, p. 1870.3.

Pharmacokinetics

After an oral dose of a delayed-release formulation of dexlansoprazole, peak plasma concentrations occur 1 to 2 hours after dosing, followed by a second peak within 4 to 5 hours. Plasma protein binding varies from about 96 to 99%. Dexlansoprazole is extensively metabolised in the liver to inactive metabolites. Oxidative metabolites are formed by cytochrome P450 isoenzymes CYP2C19 and CYP3A4. Dexlansoprazole has a half-life of about 1 to 2 hours. Metabolites are excreted in the urine and faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.:* Dexilant; *Jpn:* Kapidex†; *USA:* Dexilant.

Dicycloverine Hydrochloride

(BANM, rINNM)

Cloridrato de Dicicloverina; Diciclovérine, hidrocloruro de; Dicikloverin-hidroklorid; Dicikloverino hidrochloridas; Dicyclomine Hydrochloride; Dicyclovérine; Chlorhydrate de Dicycloverinhydrochlorid; Dicycloverini Hydrochloridum; Dicykloverin-hydrochlorid; Dicykloverinhydroklorid; Disyklo-verïinihydrokloridi; Hidrocloruro de diciclóverina; Дицикловерина Гидрохлорид.
2-Diethylaminoethyl bicyclohexyl-1-carboxylate hydrochloride.
$C_{19}H_{35}NO_2$,HCl=346.0
CAS — 77-19-0 (dicycloverine); 67-92-5 (dicycloverine hydrochloride).
ATC — A03AA07.
ATC Vet — QA03AA07.
UNII — CQ903KQA31.

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

Ph. Eur. 8: (Dicycloverine Hydrochloride). A white or almost white, crystalline powder. It shows polymorphism. Soluble in water; freely soluble in alcohol and in dichloromethane. A 1% solution in water has a pH of 5.0 to 5.5.

USP 36: (Dicyclomine Hydrochloride). A fine white practically odourless, crystalline powder. Soluble 1 in 13 of water, 1 in 5 of alcohol, 1 in 2 of chloroform and of glacial acetic acid, and 1 in 770 of ether. pH of a 1% solution in water is between 5.0 and 5.5.

Uses and Administration

Dicycloverine hydrochloride is a tertiary amine antimuscarinic with effects similar to but weaker than those of atropine (p. 1312.1); it also has a direct antispasmodic action.

Dicycloverine is used in gastrointestinal spasm particularly that associated with irritable bowel syndrome. An oral dose of 10 to 20 mg of dicycloverine hydrochloride is given 3 times daily; in the USA, up to 40 mg four times daily may be given where adverse effects permit.

Dicycloverine hydrochloride may be given intramuscularly in doses of 10 to 20 mg 4 times daily to patients in whom oral therapy is temporarily impractical, but should not be used for longer than 1 to 2 days.

For doses in children, see below.

Administration in children. Dicycloverine hydrochloride is used in children for symptomatic relief of gastrointestinal smooth muscle spasm. The following oral doses are given according to age:
- 6 months to 2 years: 5 to 10 mg three or four times daily, 15 minutes before meals; maximum daily dose of 40 mg
- 2 to 12 years: 10 mg three times daily
- over 12 years: adult doses may be given, see above

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. Dicycloverine hydrochloride should not be given to infants younger than 6 months of age.

Dicycloverine has been reported to suppress lactation. Inadvertent intravenous administration has resulted in thrombosis, thrombophlebitis, and injection site reactions including pain, oedema, skin colour changes, and reflex sympathetic dystrophy syndrome.

Dicycloverine should be used with caution in patients with hepatic or renal impairment; licensed product information states that there is a lack of data in such patients.

Apnoea. Reports[1-3] of severe apnoea in infants aged 5 to 10 weeks associated with the use of dicycloverine.

1. Williams J, Watkin-Jones R. Dicyclomine: worrying symptoms associated with its use in some small babies. *BMJ* 1984; 288: 901.
2. Edwards PDL. Dicyclomine in babies. *BMJ* 1984; 288: 1230.
3. Spoudeas H, Shribman S. Dicyclomine in babies. *BMJ* 1984; 288: 1230.

Pregnancy. For a review of the risks to the fetus of antiemetic therapy during pregnancy, with particular reference to *Debendox* (*Bendectin*: dicycloverine with doxylamine and pyridoxine), see under Antihistamines on p. 614.2.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Pharmacokinetics

Dicycloverine is rapidly absorbed after oral dosing with peak plasma concentrations occurring within 1 to 1.5 hours. The bioavailability after intramuscular injection is greater than that after oral dosing. Dicycloverine is excreted mainly in the urine (nearly 80% of a dose), with a small amount in the faeces (about 8%). The mean elimination half-life for the first 9 hours after a single dose is about 1.8 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.:* Babypasmil; *Braz.:* Bentyl; *Canad.:* Bentylol; Formulex; Lomine†; Protylol; *Hong Kong:* Cyclomine†; Dicymine; Uni-Cycolact†; *India:* Centwin; Coligon;

Colinet; Coliza; Cyclominol†; Cyclopam; Decolic; Diospas; Dysmen; Lupispas; Meftal-Spas; NT-Spas; Spasmo-Proxyvon; Spasmonil; *Israel*: Notensyl; *Mex.*: Bentyl; Clominal; Dicigon; Diclomin†; Sedicion; *Philipp.*: Bentyl; Dilomin; Relestal; Spasdon; *Rus.*: Trigan (Тригал); *S.Afr.*: Merbentyl†; *Thal.*: Dicomin†; Dicymine; Spasminar; *UK*: Merbentyl†; *USA*: Antispas; Bentyl; Byclomine†; Dibent†; Or-Tyl†; *Venez.*: Mabex.

Multi-ingredient Preparations. *Arg.*: Colchimax; Dafne; *Canad.*: Diclophen†; *Chile*: Profisin; *Gr.*: Dispalgine; *Hong Kong*: Berber CO†; Colimix; Cycolsim†; Dicymine Co; Epilon; Uni-Cycolac-SM†; Veragel; *India*: Actispas Plus; Actispas-R; Aglopam; Amidine Plus; Arsulide-D; Asimol-DC; Avid Plus; Avispas; Betaspasm Porte; Bral; Cataspa; Cebrex Forte; Centwin; Centwin; Cibis; Cloact; Colicspam; Colicspam; Colidex; Coligon Plus; Coligon-O; Colimef; Colimex; Colimex; Colinorm; Colitid; Colispas-P; Colispas; Colispas; Colixin MPS; Combispas; Comspa; Cyclo-P; Cyclocos; Cyclomeff; Cyclopam Plus; Cyclopam; Cyclopam; Cyclosym; Cyclowin; Cyclowin; Cyclozed-N; Cyclozed; Cyclozobid; Cypa; Dam-Spas DPS P; Dam-Spas; Decolic-V; Decolic; Deepas; Depas; Diclogesic Spas; Diclonil Spas; Diclospa; Dicomin; Dicydome-P; Dolospan; Domspas; DP-Spas; Duospan; Dymef; Dynamet; Dysmen; Dysmeryl; Dyspas; Efespas; Eginor; Endospas; Fri-Spas; Frispas-P; Gastrogyl Plus; Gefspass; Griprid; Haspas; Hyvon-Spas; Jagril-Spas; Kolispas; Litspas; Lowdol; Mafia; Medilop; *Mefac Spas*; *Mefamic-D*; *Mefar-PD*; Mefatin-Spas; Mefcil Spas; Mefdic; Mefdol Spas; Meflaxin; Mefmin Spas; Mefnic Spas; Mefsaid; Mefsym-Plus; Mefsym-Spas; Meftagesic; Meftal-Spas; Meftal-Spas; Mefze Spas; Mespas; Neurospas-CD; Neurospas-MF; Neurospas; Neurospas; Nicispas; Nidic; Nimkul DCM; Nimspa; Nimspas; Nimuspas; Niza-Spas; Normaxin-RT; Normaxin; Normospas; NT-Spas; NTSpass; Orlidox-D; Pamol DCM; Paracio; Paraspas; Parvon Spas; Spasmo-Flexon; Spasmo-Proxyvon Forte; Spasmo-Proxyvon; Spasmodip Plus; Spasmonil Plus; Spasmonil; Spasmonil; Trigan-D; Ze-Spas; *Ital.*: Merankol Pastiglie; *Malaysia*: Colimix; *Mex.*: Alphalox-D; Exhidrol; Parcolan; *Port.*: Nausefe; *Rus.*: Trigan-D (Тригал-Д); *S.Afr.*: Acugel†; Adco-Medigel; Adco-Neutragel D; Alkalite D†; Alumag D; Alumite D†; Aluspastyl†; Asic Betaclomin; Co-Gel; Gelumen; Kolantyl†; Microgel†; Neuragel-D†; Propan Gel-S; Remotrox†; Spasmogel; *Singapore*: Acolic; Colimix; Meclosil; Veragel; *Spain*: Colchimax; Neocolan†; *Thai.*: Anpuzz; Berclomine; Biodan; Cymine; Difemic; Kremil-S; Mainnox; Simcomine; Spasticone†; Tocid; Veragel; *UK*: Kolanticon; *Ukr.*: Diaremix (Диаремикс); Movespasm (Мовеспазм); No-Spasma (Но-Спазма)†; *Venez.*: Dicigel.

Pharmacopoeial Preparations
BP 2014: Dicycloverine Oral Solution; Dicycloverine Tablets;
USP 36: Dicyclomine Hydrochloride Capsules; Dicyclomine Hydrochloride Injection; Dicyclomine Hydrochloride Syrup; Dicyclomine Hydrochloride Tablets.

Difemerine Hydrochloride *(rINNM)*

Difemerina, hidrocloruro de; Difémérine, Chlorhydrate de; Difemerini Hydrochloridum; Hidrocloruro de difemerina; UP-57; Дифемерина Гидрохлорид.
2-Dimethylamino-1,1-dimethylethyl benzilate hydrochloride.
$C_{20}H_{25}NO_3$,HCl=363.9
CAS — 80387-96-8 (difemerine); 70280-88-5 (difemerine hydrochloride).
ATC — A03AA09.
ATC Vet — QA03AA09.
UNII — 00JM91Q28F.

Profile

Difemerine hydrochloride is an antimuscarinic with effects similar to those of atropine (p. 1312.1) and was used in the symptomatic treatment of visceral spasms.

Difenidol Hydrochloride *(BANM, rINNM)*

Difénidol, Chlorhydrate de; Difenidol, hidrocloruro de; Difenidoli Hydrochloridum; Diphenidol Hydrochloride (USAN); Hidrocloruro de difenidol; SKF-478 (difenidol); SKF-478-A; SKF-478-J (difenidol embonate); Дифенидола Гидрохлорид.
1,1-Diphenyl-4-piperidinobutan-1-ol hydrochloride.
$C_{21}H_{27}NO$,HCl=345.9
CAS — 972-02-1 (difenidol); 3254-89-5 (difenidol hydrochloride); 26363-46-2 (difenidol embonate).
UNII — DG35SXWQ4T.

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Difenidol hydrochloride is an antiemetic that probably acts through the chemoreceptor trigger zone. It is claimed to control vertigo by means of a specific effect on the vestibular apparatus. Difenidol also has a weak peripheral antimuscarinic action.

It has been used in the treatment of some forms of nausea and vomiting (p. 1811.3) such as those associated with surgery, radiotherapy, and cancer chemotherapy. It has also been used for the symptomatic treatment of vertigo (p. 612.3), nausea and vomiting due to Ménière's disease (p. 611.2), and other labyrinthine disturbances.

It has been given in oral doses equivalent to 25 to 50 mg of difenidol every 4 hours as required. Difenidol hydrochloride has also been given parenterally.

Preparations

Proprietary Preparations *(details are given in Volume B)*

Single-ingredient Preparations. *Chile*: Vontrol; *Jpn*: Cephadol; *Malaysia*: Cephadol†; *Mex.*: Biomitin; Diphafen; Docita; Hemetiken; Lansenol; Nautrol; Normavom; Serratol; Sons; Vontrol; Voxamine; *Philipp.*: Cephadol†; *Singapore*: Cephadol; *Thai.*: Cephadol†.

Difenoxin *(BAN, USAN, rINN)*

Difenoxilic Acid; Difenoxina; Difénoxine; Difenoxinum; Diphenoxylic Acid; McN-JR-15403-11; Дифеноксин.
1-(3-Cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid.
$C_{28}H_{28}N_2O_2$=424.5
CAS — 28782-42-5.
ATC — A07DA04.
ATC Vet — QA07DA04.
UNII — 3ZZ5BJ9F2Q.

Difenoxin Hydrochloride *(BANM, rINNM)*

Difenoxina, hidrocloruro de; Difénoxine, Chlorhydrate de; Difenoxini Hydrochloridum; Difenoxylic Acid Hydrochloride; Diphenoxylic Acid Hydrochloride; Hidrocloruro de difenoxina; R-15403; Дифеноксина Гидрохлорид.
$C_{28}H_{28}N_2O_2$,HCl=461.0
CAS — 35607-36-4.
ATC — A07DA04.
ATC Vet — QA07DA04.
UNII — VQZ63K01IW.

Profile

Difenoxin is the principal active metabolite of diphenoxylate (below) and has similar actions and uses. It is given orally as the hydrochloride, but doses are in terms of the base; difenoxin hydrochloride 1.1 mg is equivalent to about 1 mg of difenoxin.

In the treatment of diarrhoea (p. 1805.2), the usual dose in adults is the equivalent of difenoxin 2 mg initially, followed by 1 mg after each loose stool or every 3 to 4 hours as required, up to a maximum of 8 mg daily.

Preparations of difenoxin usually contain subclinical amounts of atropine sulfate in an attempt to discourage abuse.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Motofen.

Dihexyverine Hydrochloride *(USAN, rINNM)*

Dihexiverina, hidrocloruro de; Dihexiverine Hydrochloride; Dihexyvérine, Chlorhydrate de; Dihexyverini Hydrochloridum; Hidrocloruro de dihexiverina; JL-1078; Дигексиверина Гидрохлорид.
2-Piperidinoethyl bicyclohexyl-1-carboxylate hydrochloride.
$C_{20}H_{35}NO_2$,HCl=358.0
CAS — 561-77-3 (dihexyverine); 5588-25-0 (dihexyverine hydrochloride).
ATC — A03AA08.
ATC Vet — QA03AA08.
UNII — 336704VYVB.

Profile

Dihexyverine hydrochloride is an antimuscarinic with effects similar to those of atropine (p. 1312.1). It has been given in the symptomatic treatment of gastrointestinal spasm.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Spasmodex.

Dihydroxyaluminum Sodium Carbonate

Aluminium Sodium Carbonate Hydroxide; Carbonato sódico de dihidroxialuminio; Dihidroksialüminyum Sodyum Karbonat; Dihydroksialuminiumnatriumkarbonaatti; Dihydroxialuminiinatrii Carbonas; Dihydroxialuminiumnatriumkarbonat; Dihydroxyaluminium Sodium Carbonate; Дигидрооксиалюминия Натрия Карбонат.
Sodium (carbonato)dihydroxyaluminate(1-).
CH_2AlNaO_5=144.0
CAS — 41342-54-5 (carbaldrate); 12011-77-7 (dihydroxyaluminium sodium carbonate); 16482-55-6 (dihydroxyaluminium sodium carbonate).
ATC — A02AB04.
ATC Vet — QA02AB04.
UNII — 84H8Z9550J.

NOTE. The name Carbaldrate (*rINN*) has been applied to (CH_2AlNaO_5,nH_2O), a form of sodium (carbonato)dihydroxyaluminate(1-) hydrate.

Pharmacopoeias. In *US.*

USP 36: (Dihydroxyaluminum Sodium Carbonate). A fine white odourless powder. It loses not more than 14.5% of its weight on drying. Practically insoluble in water and in organic solvents; soluble in dilute mineral acids with the evolution of carbon dioxide. A 4% suspension in water has a pH of 9.9 to 10.2. Store in airtight containers.

Profile

Dihydroxyaluminum sodium carbonate is an antacid with general properties similar to aluminium hydroxide (p. 1817.2) that is given in oral doses of about 300 to 600 mg.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Antacidum†; *Denm.*: Noacid; *Ger.*: Kompensan; *Pol.*: Alugastrin; Gastrinal†; *Port.*: Kompensan; *Switz.*: Kompensan†; *Turk.*: Dank; Kompensan; Seskasid.

Multi-ingredient Preparations. *Port.*: Kompensan-S.

Pharmacopoeial Preparations
USP 36: Dihydroxyaluminum Sodium Carbonate Tablets.

Diisopromine Hydrochloride *(rINNM)*

Diisopromina, hidrocloruro de; Diisopromine, Chlorhydrate de; Diisopromine Hydrochloride; Diisopromini Hydrochloridum; Hidrocloruro de diisopromina; Диизопромина Гидрохлорид.
NN-Di-isopropyl-3,3-diphenylpropylamine hydrochloride.
$C_{21}H_{29}N$,HCl=331.9
CAS — 5966-41-6 (diisopromine); 24358-65-4 (diisopromine hydrochloride).
ATC — A03AX02.
ATC Vet — QA03AX02.
UNII — 9E8EN393AL.

Profile

Diisopromine hydrochloride is an antispasmodic used with sorbitol in various gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *S.Afr.*: Agofell†.

Diphenoxylate Hydrochloride

(BANM, rINNM)

Difenoksilaattihydrokloridi; Difenoksilat Hidroklorür; Difenoksilato hidroclorídas; Difenoxilát-hidroklorid; Difenoxilathydroklorid; Difenoxilato, hidrocloruro de; Difenoxylát-hydrochlorid; Diphénoxylate, Chlorhydrate de; Diphenoxylathydrochlorid; Diphenoxylati Hydrochloridum; Hidrocloruro de difenoxilato; R-1132; Дифеноксилата Гидрохлорид.
Ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylate hydrochloride.
$C_{30}H_{32}N_2O_2$,HCl=489.1
CAS — 915-30-0 (diphenoxylate); 3810-80-8 (diphenoxylate hydrochloride).
ATC — A07DA01.
ATC Vet — QA07DA01.
UNII — W24OD7YW48.

NOTE. Compounded preparations of diphenoxylate hydrochloride may be represented by the following names:
- Co-phenotrope (*BAN*)—diphenoxylate hydrochloride 100 parts and atropine sulfate 1 part (w/w).

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

Ph. Eur. 8: (Diphenoxylate Hydrochloride). A white or almost white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 36: (Diphenoxylate Hydrochloride). A white odourless crystalline powder. Slightly soluble in water and in isopropyl alcohol; sparingly soluble in alcohol and in acetone; freely soluble in chloroform; practically insoluble in ether and in petroleum spirit; soluble in methyl alcohol. A saturated solution in water has a pH of about 3.3.

Uses and Administration

Diphenoxylate hydrochloride is a synthetic derivative of pethidine (p. 121.3) with little or no analgesic activity; it reduces intestinal motility and is used in the symptomatic treatment of acute and chronic diarrhoea (p. 1805.2). It may also be used to reduce the frequency and fluidity of the stools in patients with colostomies or ileostomies.

Preparations of diphenoxylate usually contain subclinical amounts of atropine sulfate in an attempt to discourage abuse; UK preparations are all in the form of co-phenotrope (see NOTE, p. 1835.3).

In **acute diarrhoea** the usual initial dose is 10 mg orally, followed by 5 mg every six hours, later reduced as the diarrhoea is controlled. For doses in children, see below.

Similar initial doses are used for **chronic diarrhoea**, and subsequently reduced as necessary. If clinical improvement is not seen after 10 days of treatment with the maximum daily dose of 20 mg (in adults) further use is unlikely to result in any benefit.

Administration in children. Diphenoxylate hydrochloride can be used in children as an adjunct in the symptomatic treatment of acute diarrhoea, and to reduce the frequency and fluidity of the stools in patients with colostomies or ileostomies. In the UK, it is licensed for children from 4 years of age; recommended oral doses of diphenoxylate hydrochloride (given as co-phenotrope) are:

- 4 to 9 years: 2.5 mg three times daily
- 9 to 12 years: 2.5 mg four times daily
- 12 to 16 years: 5 mg three times daily

While emphasising that antimotility drugs are not recommended for acute diarrhoea in children under 12 years of age, the *BNFC* allows for a dose of 1.25 mg three times daily for children aged 2 to 4 years.

In the USA, diphenoxylate is licensed for children from the age of 2 years and an initial dose of 300 to 400 micrograms/kg (up to an effective maximum of 10 mg) daily in 4 divided doses is suggested for children aged 2 to 12 years.

For the view that antidiarrhoeal drugs should not be used at all in children with acute diarrhoea, see p. 1805.2.

Diarrhoea. Co-phenotrope (see NOTE, p. 1835.3) may be considered as an alternative to loperamide in the management of faecal incontinence in adults, see Diarrhoea, under Loperamide, p. 1854.3.

Substance dependence. Diphenoxylate may be useful[1] in the symptomatic management of diarrhoea associated with opioid withdrawal syndromes (p. 109.2).

1. DOH. *Drug misuse and dependence: guidelines on clinical management.* London: HMSO, 1999. Also available at: http://www.dh.gov.uk/assetRoot/04/07/81/98/04078198.pdf (accessed 18/01/06)

Dependence and Withdrawal

Preparations of diphenoxylate usually contain subclinical amounts of atropine sulfate in an attempt to discourage abuse. Short-term use of diphenoxylate with atropine in the recommended dosage carries a negligible risk of dependence, although prolonged use or use of high doses may produce dependence of the opioid type (see p. 109.1).

Adverse Effects and Treatment

Diphenoxylate is related to the opioid analgesics and its adverse effects and their treatment are similar (p. 110.1), particularly in overdosage. Reported adverse effects include: gastrointestinal effects such as anorexia, nausea and vomiting, abdominal distension or discomfort, paralytic ileus, toxic megacolon, and pancreatitis; nervous system effects such as headache, drowsiness, dizziness, restlessness, euphoria, depression, numbness of the extremities; and hypersensitivity reactions including angioedema, urticaria, pruritus, and swelling of the gums. Signs of overdosage may be delayed and patients should be observed for at least 48 hours. Young children are particularly susceptible to the effects of overdosage.

The presence of subclinical doses of atropine sulfate in preparations containing diphenoxylate may give rise to the adverse effects of atropine in susceptible individuals or in overdosage—see Atropine Sulfate, p. 1312.1.

Precautions

Diphenoxylate hydrochloride should be avoided in patients with jaundice, intestinal obstruction, antibiotic-associated colitis, or diarrhoea associated with enterotoxin-producing bacteria, and should be used with caution in patients with hepatic impairment. It should also be used with caution in young children, in whom response is more variable, and is not generally recommended for use in infants. Patients with inflammatory bowel disease receiving diphenoxylate should be carefully observed for signs of toxic megacolon and diphenoxylate stopped promptly should abdominal distension occur.

Interactions

Because of the structural relationship of diphenoxylate to pethidine (p. 121.3) there is a theoretical risk of hypertensive crisis if diphenoxylate is used with MAOIs. Diphenoxylate may potentiate the effects of other CNS depressants such as alcohol, barbiturates, and some anxiolytics.

Pharmacokinetics

Diphenoxylate hydrochloride is well absorbed from the gastrointestinal tract. It is rapidly and extensively metabolised in the liver, mainly to diphenoxylic acid (difenoxin, p. 1835.2), which has antidiarrhoeal activity; other metabolites include hydroxydiphenoxylic acid. It is excreted mainly as metabolites and their conjugates in the faeces; lesser amounts are excreted in urine. It may be distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Lofenoxal; Lomotil; ***Braz.***: Lomotil; ***Canad.***: Lomotil; ***Cz.***: Reasec; ***Gr.***: Reasec; ***Hong Kong***: Dhamotil; Diamotil†; Diarest†; Diatrol†; Dimotil; Lomotil; Syncomil†; ***Hung.***: Reasec; ***India***: Lomotil; ***Irl.***: Lomotil; ***Malaysia***: Beamotil; Dhamotil; Diphenoxylate A; ***NZ***: Diastop; ***Pol.***: Reasec; ***S.Afr.***: Lomotil; ***Singapore***: Beamotil; Dhamotil; SP-Amox; ***Thai.***: Ditropine; Lomotil; Spasil; ***Turk.***: Lomotil; ***UAE***: Intard; ***UK***: Dymotil; Lomotil; ***USA***: Logen; Lomotil; Lonox.

Multi-ingredient Preparations. ***Braz.***: Colestase; ***India***: Lomofen; ***Singapore***: Sun-Dianox.

Pharmacopoeial Preparations

USP 36: Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution; Diphenoxylate Hydrochloride and Atropine Sulfate Tablets.

Docusates

Docusatos.

UNII — M7P27195AG.

Docusate Calcium *(USAN)*

Dioctyl Calcium Sulfosuccinate; Dioctyl Calcium Sulphosuccinate; Docusato cálcico; Докузат Кальция.

Calcium 1,4-bis(2-ethylhexyl) sulphosuccinate.

$C_{40}H_{74}CaO_{14}S_2$=883.2

CAS — 128-49-4.

UNII — 6K7YS503HC.

Pharmacopoeias. In *US*.

USP 36: (Docusate Calcium). A white amorphous solid with the characteristic odour of octil alcohol. Soluble 1 in 3300 of water; very soluble in alcohol, in macrogol 400, and in maize oil.

Docusate Potassium *(USAN)*

Dioctyl Potassium Sulfosuccinate; Dioctyl Potassium Sulphosuccinate; Docusato potásico; Докузат Калия.

Potassium 1,4-bis(2-ethylhexyl) sulphosuccinate.

$C_{20}H_{37}KO_7S$=460.7

CAS — 7491-09-0.

UNII — CIK9F54ZHR.

Pharmacopoeias. In *US*.

USP 36: (Docusate Potassium). A white amorphous solid with a characteristic odour suggestive of octil alcohol. Sparingly soluble in water; soluble in alcohol and in glycerol; very soluble in petroleum spirit.

Docusate Sodium *(BAN, USAN, rINN)*

Dioctyl Sodium Sulfosuccinate; Dioctyl Sodium Sulphosuccinate; Docusat-Natrium; Docusate Sodique; Docusato de sodio; Docusato sódico; Docusatum Natricum; Dokusaattinatrium; Dokusát sodná sůl; Dokusatnatrium; Dokuzát-nátrium; Dokuzato natrio druska; DSS; Natrii docusas; Sodium Dioctyl Sulphosuccinate; Sodu dokuzynian; Докузат Натрий.

Sodium 1,4-bis(2-ethylhexyl) sulphosuccinate.

$C_{20}H_{37}NaO_7S$=444.6

CAS — 577-11-7.

ATC — A06AA02.

ATC Vet — QA06AA02.

UNII — F05Q2T2JA0.

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

- Co-danthrusate (*BAN*)—docusate sodium 6 parts and dantron 5 parts.

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

Ph. Eur. 8: (Docusate Sodium). White or almost white, hygroscopic, waxy masses or flakes. Sparingly soluble in water; freely soluble in alcohol and in dichloromethane. Store in airtight containers.

USP 36: (Docusate Sodium). A white wax-like plastic solid with a characteristic odour suggestive of octil alcohol. Slowly soluble 1 in 70 of water; freely soluble in alcohol and in glycerol; very soluble in petroleum spirit.

Uses and Administration

Docusates are given as the calcium or sodium salt and are used as laxatives in the management of constipation (p. 1804.3) or to reduce straining in patients with haemorrhoids (p. 1808.1) or anal fissure. They are also used as adjuncts for bowel evacuation before abdominal radiological procedures. Docusate potassium has also been used.

Docusates are anionic surfactants which have been considered to act primarily by increasing the penetration of fluid into the faeces, but may also have other effects on intestinal fluid secretion, and probably act both as stimulants and as faecal softening agents.

The usual daily oral dose of docusate calcium is 240 mg. Docusate sodium is given in usual oral doses of 50 to 300 mg daily in divided doses, although doses of up to 500 mg daily may be used. (For doses in children, see below.) The effect is usually seen within 12 to 72 hours. When used as an adjunct to abdominal radiological procedures, an oral dose of 400 mg is given with the barium meal. It is also given rectally as an enema in doses of 120 mg; the effect is usually seen in 5 to 20 minutes. Docusate sodium is also used with anthraquinone stimulant laxatives such as casanthranol (p. 1826.1), dantron (p. 1833.3), and senna (p. 1885.1).

Docusate sodium is used for softening wax in the ear as ear drops containing 0.5 or 5%.

Docusate sodium and other docusate salts are widely used as anionic surfactants in pharmaceutical formulations.

Administration in children. Oral docusate sodium is licensed in the UK for the treatment of **chronic constipation** in children aged 6 months and over. More specific dose details are also provided in the *BNFC* as follows:

- 6 months to 2 years: 12.5 mg three times daily
- 2 to 12 years: 12.5 to 25 mg three times daily

Children aged 12 years and over may be given the adult doses for constipation, either orally or rectally (see Uses and Administration, above). Adult formulations are not licensed for use in children under 12 years.

In the USA, children aged 2 to 12 years may be given docusate sodium in doses of 50 to 150 mg daily, either as a single daily dose or in divided doses. Docusate *calcium* is generally only used in the USA for children aged 12 years and over.

Docusate sodium is also used as an **adjunct in abdominal radiological procedures.** UK licensed product information suggests that children may be given an oral dose of 75 mg (30 mL of docusate sodium paediatric solution 12.5 mg per 5 mL) with the barium meal. The *BNFC* recommends that those aged 12 years and over are given the usual adult dose (see above).

Ear wax removal. Cerumen or ear wax is a normal secretion of the ceruminous glands present in the lining of the external auditory canal. Excessive accumulation or impaction of ear wax may decrease hearing acuity, and may also produce dizziness, vertigo, reflex coughing, tinnitus, and otalgia.

Syringing of the external auditory canal with warm water may be used to remove wax from the ear. However, complications include pain, perforation of the ear drum, deafness, dizziness, vertigo, tinnitus, and infection.[1-6] Contra-indications to ear syringing include past perforation, ear infection, previous ear surgery; syringing may be difficult in children.[1,6]

A ceruminolytic agent may be given as ear drops to soften, loosen, or dissolve cerumen instead. They may also be used immediately before syringing, or for several days beforehand.[1-3,5,6] Traditionally, fixed oils such as arachis oil, olive oil, or almond oil have been used.[1] Some still advocate the use of olive oil to reduce the recurrence of impacted cerumen,[3] while others consider it to be ineffective.[5] Other ceruminolytics that have been reported as effective include docusates,[4,7,8] peroxides such as hydrogen peroxide or urea hydrogen peroxide,[4,9] and trolamine polypeptide oleate-condensate,[4,8] although some studies have found these to be

no more effective in removing wax than a saline control.[10,11] Other agents that have been used include acetic acid,[4] choline salicylate,[12] methyltrypsin solution,[5] and an oily solution of paradichlorobenzene and chlorobutanol.[4,12] Glycerol and sodium bicarbonate solution have also been used. However, a comparative study *in vitro* of the efficacy of various wax dispersing agents found the most effective to be water, which had originally been included as a control,[13] and a systematic review[14] concluded that saline or water ear drops seemed to be as good as proprietary agents for the removal of ear wax, although there was a lack of good quality studies on which to base recommendations.

Ear candling is a traditional folk remedy that has been used to remove cerumen, but studies indicate it is ineffective, and may deposit wax in the ear canal or cause burn injuries.[3,4]

1. Sharp JF, *et al.* Ear wax removal: a survey of current practice. *BMJ* 1990; 301: 1251–3.
2. Grossan M. Cerumen removal—current challenges. *Ear Nose Throat J* 1998; 77: 541–6, 548.
3. Grossan M. Safe, effective techniques for cerumen removal. *Geriatrics* 2000; 55: 80, 83–6.
4. Dimmitt P. Cerumen removal products. *J Pediatr Health Care* 2005; 19: 332–6.
5. Midani A, *et al.* Safety and efficacy of Sofenz ceruminolytic solution. *Ear Nose Throat J* 2006; 85: 87–8, 90–2.
6. Aung T, Mulley GP. Removal of ear wax. *BMJ* 2002; 325: 27.
7. Chen DA, Caparosa RJ. A nonprescription cerumenolytic. *Am J Otol* 1991; 12: 475–6.
8. Singer AJ, *et al.* Ceruminolytic effects of docusate sodium: a randomized, controlled trial. *Ann Emerg Med* 2000; 36: 228–32.
9. Fabmey S, Whitefield M. Multicentre clinical trial of Exterol as a cerumenolytic. *Br J Clin Pract* 1982; 36: 197–204.
10. Whatley VR, *et al.* Randomized clinical trial of docusate, triethanolamine polypeptide, and irrigation in cerumen removal in children. *Arch Pediatr Adolesc Med* 2003; 157: 1177–80.
11. Roland PS, *et al.* Randomized, placebo-controlled evaluation of Cerumenex and Murine earwax removal products. *Arch Otolaryngol Head Neck Surg* 2004; 130: 1175–7.
12. Dummer DS, *et al.* A single-blind, randomized study to compare the efficacy of two ear drop preparations ('Audax' and 'Cerumol') in the softening of ear wax. *Curr Med Res Opin* 1992; 13: 26–30.
13. Andaz C, Whittet HB. An in vitro study to determine efficacy of different wax-dispersing agents. *ORL J Otorhinolaryngol Relat Spec* 1993; 55: 97–9.
14. Burton MJ, Doree CJ. Ear drops for the removal of ear wax. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2009 (accessed 06/07/09).

Adverse Effects and Precautions

Adverse effects occur rarely with docusates; diarrhoea, nausea, abdominal cramps, and skin rash have been reported. Anorectal pain or bleeding have occasionally occurred after rectal doses.

Like all laxatives, docusates should not be used when intestinal obstruction or undiagnosed abdominal symptoms are present; prolonged use should be avoided. Docusate sodium should not be given rectally to patients with haemorrhoids or anal fissures.

Docusate sodium should not be used to soften ear wax when the ear is inflamed or the ear drum perforated.

Hypersensitivity. Docusate salts are widely used as anionic surfactants in pharmaceutical formulations. Allergic contact dermatitis has been reported from one such preparation; patch testing confirmed the reaction to docusate sodium.[1]

1. Lee A-Y, Lee K-H. Allergic contact dermatitis from dioctyl sodium sulfosuccinate in a topical corticosteroid. *Contact Dermatitis* 1998; 38: 355–6.

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

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. Hypomagnesaemia in a neonate, manifested by jitteriness, was considered to be secondary to maternal hypomagnesaemia caused by maternal use of docusate sodium during pregnancy.[1]

1. Schindler AM. Isolated neonatal hypomagnesaemia associated with maternal overuse of stool softener. *Lancet* 1984; ii: 822.

Interactions

Docusates may enhance the gastrointestinal uptake of other drugs, such as liquid paraffin (and the two should not be given together). Dosage of anthraquinone laxatives may need to be reduced if used with docusates. It has also been suggested that giving docusates with aspirin increases the incidence of adverse effects on the gastrointestinal mucosa.

Pharmacokinetics

Docusate salts are absorbed from the gastrointestinal tract and excreted in bile. Docusate sodium is also distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cerumex; Phillips; *Austral.*: Coloxyl; Rectalad†; Waxsol; *Belg.*: Norgalax; *Canad.*: Calax; Colace; Correctol Stool Softener; Selax; Silace; Soflax G; Soflax; Stool Softener; *China*: Yi Ke Long (依可隆); *Fr.*: Doculyse; Jamylene; Norgalax; *Ger.*: Otitex; Otowaxol†; *Hong Kong*: Pedia-Lax; Waxsol†; *India*: Cellubril; Doslax; Laxicon; Otosoft; *Indon.*: Forumen; Waxsol†; *Irl.*: Waxsol; *Malaysia*: Soluwax; *Neth.*: Norgalax; *NZ*: Coloxyl; Waxsol; *Philipp.*: Irwax; Otosol; Otowax; *Pol.*: Doculax; Laxol; Laxopol†; *Port.*: Norgalax; *S. Afr.*: Waxsol; *Singapore*: Solfen; Soluwax; Waxsol; *Switz.*: Norgalax; *Thai.*: Cusate; Dewax; Waxsol; *UK*: Clear Ear; Dioctyl; Docusol; DulcoEase; Molcer; Norgalax; Waxsol; *Ukr.*: Norgalax (Норгалакс); *USA*: Colace; D-S-S; DC Softgels; Dioctyn; DocQlace; Docusoft-S; Docusoft; Docusol; DOK; DOS Softgel; Dulcolax Stool Softener; Enemeez; Ex-Lax Stool Softener; Pedia-Lax; Silace; Sof-lax; Sulfolax; Surfak.

Multi-ingredient Preparations. *Arg.*: Candilax†; Nigalax; Nigalax; *Austral.*: Chemists Own Natural Laxative with Softener; Coloxyl with Senna; Coloxyl; Combilax†; Sennesoft; Soflax; *Austria*: Yal; *Belg.*: Laxavit; Softene; *Braz.*: Belpidex; *Canad.*: Gentlax S†; Senna-S; Senokot-S; *Cz.*: Yal; *Denm.*: Glyoktyl; Klyx; *Fin.*: Klyx; *Ger.*: Norgalax Miniklistier†; Norgalax Rektalgel; Yal; *Gr.*: Florisan; Heludril; *India*: Endos; Fejet-OD; *Israel*: Migraleve; *Ital.*: Macrolax; Sorbidlis; *Mex.*: Clyss-Go; *Neth.*: Klyx; *Norw.*: Klyx; *NZ*: Coloxyl with Senna; Coloxyl†; Laxsol; *Port.*: Clyss-Go; *Singapore*: Togilin; *Spain*: Docuxen†; Laxvital†; Migraleve; *Swed.*: Klyx; *Switz.*: Klyx Magnum†; Yal; *Thai.*: Bisolax; Chinta-lax; Hemorhin†; T Man Lax; *Turk.*: Yal; *UK*: Capsuvac; Normax; *USA*: Docusoft Plus; Dok Plus; Dulcolax Bowel Prep Kit; Enemeez Plus; Ex-Lax Gentle Strength†; Laxacin; Laxative & Stool Softener; Nu-Natal Advanced; Peri-Colace; PreNexa; Senna Plus; Senna-S; Senokot-S; Therevac Plus; Therevac SB; X-Prep Bowel Evacuant Kit-1†; *Venez.*: Senokot con Docusato.

Used as an adjunct in. *India*: Anofer; Blush; Hepasules†; Softer-on-Z; Softeron; *Indon.*: Fercee; Viliron; *Philipp.*: TriHEMIC; *USA*: Citracal Prenatal + DHA; Citracal Prenatal; CitraNatal Harmony; Embrex; Extra-Virt Plus DHA; FeRiva; Ferralet 90; Ferro-Dok; Hem Fe; Infanate Balance; Macnatal CN DHA; Natalvirt CA; Natalvirt DHA; Nephron FA; Nexa Plus; Nexa Select; Obstetrix; Optinate Omega-3; PNV OB+DHA; Prena-Care; Prenaissance DHA; Prenaissance Promise; Prenaissance; Prenatal; PreQue 10; TriHEMIC; Triveen-PRx RNF; Vinate GT; Virt-Select; VP-CH-PNV.

Pharmacopoeial Preparations

BP 2014: Co-danthrusate Capsules; Compound Docusate Enema; Docusate Capsules; Docusate Oral Solution; Paediatric Docusate Oral Solution;

USP 36: Docusate Calcium Capsules; Docusate Potassium Capsules; Docusate Sodium Capsules; Docusate Sodium Solution; Docusate Sodium Syrup; Docusate Sodium Tablets; Ferrous Fumarate and Docusate Sodium Extended-release Tablets.

Dolasetron Mesilate *(BANM, rINNM)*

Dolasétron, Mésilate de; Dolasetrón, mesilato de; Dolasetron Mesylate (USAN); Dolasetroni Mesilas; MDL-73147EF (dolasetron or dolasetron mesilate); Mesilato de dolasetrón; Доласетрона Мезилат.

(6*R*,8*r*,9a*S*)-3-Oxoperhydro-2*H*-2,6-methanoquinolizin-8-yl indole-3-carboxylate methanesulphonate.

$C_{19}H_{20}N_2O_3,CH_4O_3S$=420.5

CAS — 115956-12-2 (dolasetron); 115956-13-3 (dolasetron mesilate).

ATC — A04AA04.

ATC Vet — QA04AA04.

UNII — U3C8E5BWKR.

Pharmacopoeias. In *US.*

USP 36: (Dolasetron Mesylate). A white to off-white powder. Freely soluble in water and in propylene glycol; slightly soluble in alcohol and in sodium chloride 0.9%. Protect from light.

Stability. A study[1] of the stability of two extemporaneous oral suspensions of dolasetron mesilate 10 mg/mL prepared from commercially available tablets found them to be stable for at least 90 days when stored at 3 to 5 degrees and at 23 to 25 degrees.

1. Johnson CE, *et al.* Stability of dolasetron in two oral liquid vehicles. *Am J Health-Syst Pharm* 2003; 60: 2242–4.

Uses and Administration

Dolasetron is a 5-HT_3 antagonist with antiemetic actions similar to those of ondansetron (see p. 1872.2). It is used as the mesilate in the prevention of nausea and vomiting (p. 1811.3) associated with chemotherapy, and in the prevention and treatment of postoperative nausea and vomiting, although licensed indications and doses may vary from country to country. Dolasetron mesilate can be given orally or intravenously, either by bolus injection at a rate of up to 100 mg over 30 seconds or diluted to 50 mL with a suitable infusion solution such as sodium chloride 0.9% or glucose 5% and infused over up to 15 minutes.

For *prevention* of acute **nausea and vomiting** associated with **chemotherapy** dolasetron mesilate may be given orally in a dose of 100 mg or 200 mg within 1 hour before treatment. Alternatively, it may be given in an intravenous dose of 1.8 mg/kg, or 100 mg, about 30 minutes before chemotherapy. To protect against delayed emesis after the end of a chemotherapy cycle, some countries allow for further oral doses of 200 mg once daily. Dolasetron may be given for 4 to 7 consecutive days per chemotherapy cycle.

For the *prevention* of **postoperative** nausea and vomiting dolasetron mesilate may be given orally in a dose of 50 mg at the induction of anaesthesia, or 100 mg within 2 hours before surgery. Alternatively, a single intravenous dose of 12.5 mg may be given about 15 minutes before the end of anaesthesia, or at the end of anaesthesia. The same intravenous dose may be given for the *treatment* of postoperative nausea and vomiting.

For doses in children, see below.

Reviews.

1. Balfour JA, Goa KL. Dolasetron: a review of its pharmacology and therapeutic potential in the management of nausea and vomiting induced by chemotherapy, radiotherapy or surgery. *Drugs* 1997; 54: 273–98.
2. Anonymous. Dolasetron for prevention of nausea and vomiting due to cancer chemotherapy. *Med Lett Drug Ther* 1998; 40: 53–4.

Administration in children. The use of dolasetron mesilate in children is licensed in some countries, including the USA. However, others have not licensed such use and in Australia and Canada it is contra-indicated in children and adolescents under 18 years of age because they may be at increased risk of acute changes in the QT interval, and there have been reports of cardiac conduction disorders, cardiac arrest, and myocardial infarction in children treated with dolasetron.

In the USA, children from 2 years of age may be given dolasetron mesilate 1.8 mg/kg orally (within 1 hour before chemotherapy) up to a maximum dose of 100 mg, to prevent acute *chemotherapy-induced* nausea and vomiting. For prevention of *postoperative* nausea and vomiting, an oral dose of 1.2 mg/kg, up to a maximum of 100 mg, may be given within 2 hours before surgery; or an intravenous dose of 350 micrograms/kg, up to a maximum of 12.5 mg, may be given 15 minutes before the end of anaesthesia. The same intravenous dose may be given to treat established postoperative nausea and vomiting.

Pruritus. Dolasetron and other 5-HT_3 antagonists have been investigated for the management of pruritus (see under Ondansetron, p. 1873.1).

Adverse Effects and Precautions

As for Ondansetron, p. 1873.2. Diarrhoea, anorexia, and abdominal pain may also occur.

Various ECG changes have been noted with dolasetron. Dolasetron should be used with caution in patients who have, or may develop, prolongation of the QT interval or other alterations in cardiac conduction intervals, and in those with electrolyte imbalances. In some countries use is considered contra-indicated in children because they are thought to be at increased risk (see Administration in Children, above).

Other adverse effects include dyspepsia, flatulence, taste disturbances, fever, chills or shivering, sleep disorders, fatigue, and drowsiness. There have been rare reports of intestinal obstruction, pancreatitis, jaundice, seizures, bronchospasm, cardiac arrhythmias, and oedema. Local reactions may occur on intravenous use. No dosage reduction is considered necessary in renal or hepatic impairment, despite possible reductions in clearance.

Effects on the cardiovascular system. For a discussion of the effects of 5-HT_3 antagonists on the cardiovascular system, see under Ondansetron, p. 1873.3.

Phlebitis. Venous irritation has been reported after intravenous use of dolasetron; diluting subsequent doses with sodium chloride 0.9% and infusing it more slowly markedly reduced the frequency of phlebitis.[1]

1. Oshiro MM. Dolasetron-associated venous irritation. *Am J Health-Syst Pharm* 2000; 57: 1533–4.

Interactions

Plasma concentrations of hydrodolasetron, the active metabolite of dolasetron, are increased by cimetidine and atenolol and decreased by rifampicin. Dolasetron should be used with caution in patients taking drugs that prolong the QT interval, including those likely to cause electrolyte disturbances (see also p. 1874.2).

Pharmacokinetics

Dolasetron given orally or intravenously is rapidly converted to the active metabolite hydrodolasetron by carbonyl reductase, a ubiquitous enzyme. Peak plasma concentrations of hydrodolasetron occur 1 hour after oral, and 0.6 hours after intravenous, doses of dolasetron. The apparent oral bioavailability of dolasetron determined as hydrodolasetron is about 75%. It has a mean elimination half-life of about 7 to 8 hours.

Hydrodolasetron is partially metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP3A and about 50 to 60% is eliminated unchanged in the urine. Two thirds of a dose of dolasetron is recovered in the urine and one third in the faeces.

Clearance of hydrodolasetron is increased in children, but is not altered in the elderly. Clearance is reduced in severe hepatic impairment (Child-Pugh category B or C) and in severe renal impairment (creatinine clearance less than 10 mL/min) after oral use. After intravenous use, clearance is reduced in severe renal impairment but apparently unchanged in severe hepatic impairment.

References.
1. Lerman J, *et al.* Pharmacokinetics of the active metabolite (MDL 74,156) of dolasetron mesylate after oral or intravenous administration to anesthetized children. *Clin Pharmacol Ther* 1996; 60: 485–92.
2. Dempsey E, *et al.* Pharmacokinetics of single intravenous and oral doses of dolasetron mesylate in healthy elderly volunteers. *J Clin Pharmacol* 1996; 36: 903–10.
3. Stubbs K, *et al.* Pharmacokinetics of dolasetron after oral and intravenous administration of dolasetron mesylate in healthy volunteers and patients with hepatic dysfunction. *J Clin Pharmacol* 1997; 37: 926–36.
4. Dimmitt DC, *et al.* Pharmacokinetics of oral and intravenous dolasetron mesylate in patients with renal impairment. *J Clin Pharmacol* 1998; 38: 798–806.
5. Dimmitt DC, *et al.* Effect of infusion rate on the pharmacokinetics and tolerance of intravenous dolasetron mesylate. *Ann Pharmacother* 1998; 32: 39–44.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Anzemet; *Braz.*: Anzemet; *Canad.*: Anzemet; *China*: Li Bi Pu (立必复); *Fr.*: Anzemet†; *Ger.*: Anemet†; *Gr.*: Anzemet; *Ital.*: Anzemet; *Mex.*: Anzemet; *S.Afr.*: Zamanon; *Switz.*: Anzemet†; *UK*: Anzemet†; *USA*: Anzemet; *Venez.*: Anzemet.

Pharmacopoeial Preparations
USP 36: Dolasetron Mesylate Injection; Dolasetron Mesylate Oral Solution; Dolasetron Mesylate Oral Suspension; Dolasetron Mesylate Tablets.

Domperidone *(BAN, USAN, rINN)*

Domperidon; Domperidona; Domperidonas; Dompéridone; Domperidoni; Domperidonum; R-33812; Домперидон.

5-Chloro-1-[1-[3-(2-oxobenzimidazolin-1-yl)propyl]-4-piperidyl]benzimidazolin-2-one.

$C_{22}H_{24}ClN_5O_2$=425.9

CAS — 57808-66-9.

ATC — A03FA03.

ATC Vet — QA03FA03.

UNII — 5587267Z69.

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

Ph. Eur. 8: (Domperidone). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; soluble in dimethylformamide. Protect from light.

Domperidone Maleate *(BANM, rINNM)*

Domperidona, maleato de; Dompéridone, maléate de; Domperidoni maleas; Domperidonimaleaatti; Domperidonmaleat; Domperidon-maleát; Domperidon-maleinát; Domperidono maleatas; Maleato de domperidona; Домперидона Малеат.

$C_{22}H_{24}ClN_5O_2.C_4H_4O_4$=542.0

CAS — 99497-03-7.

ATC — A03FA03.

ATC Vet — QA03FA03.

UNII — 899U5WF46A.

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

Ph. Eur. 8: (Domperidone Maleate). A white or almost white powder; it exhibits polymorphism. Very slightly soluble in water and in alcohol; sparingly soluble in dimethylformamide; slightly soluble in methyl alcohol. Protect from light.

Uses and Administration

Domperidone is a dopamine antagonist with actions and uses similar to those of metoclopramide (p. 1862.2). It is used as an antiemetic for the short-term treatment of nausea and vomiting of various aetiologies (p. 1811.3). It is not considered suitable for chronic nausea and vomiting, nor for the routine prophylaxis of postoperative vomiting. Domperidone is also used for its prokinetic actions in dyspepsia (p. 1806.3) and has been tried in diabetic gastroparesis (see Diabetic Neuropathy, p. 465.2). It has been given with paracetamol in the symptomatic treatment of migraine (p. 670.3).

Domperidone is used as the maleate in tablet preparations and as the base in suppositories and the oral suspension; doses are expressed in terms of the base. Domperidone maleate 12.73 mg is equivalent to about 10 mg of domperidone. Domperidone has been given parenterally, but this route has been associated with severe adverse effects (see below).

For the treatment of **nausea and vomiting** and for the symptomatic management of non-ulcer **dyspepsia**, domperidone may be given in oral doses of 10 to 20 mg three or four times daily up to a maximum daily dose of 80 mg or it may be given rectally in a dose of 60 mg twice daily. The initial course of treatment is up to 4 weeks. For doses in children see below.

The hydrochloride salt and domperidone betadex (domperidone betacyclodextrin) have also been used.

Reviews.
1. Prakash A, Wagstaff AJ. Dompetidone: a review of its use in diabetic gastropathy. *Drugs* 1998; 56: 429–45.
2. Barone JA. Domperidone: a peripherally acting dopamine$_2$-receptor antagonist. *Ann Pharmacother* 1999; 33: 429–40.
3. Ahmad N, *et al.* Making a case for domperidone in the treatment of gastrointestinal motility disorders. *Curr Opin Pharmacol* 2006; 6: 571–6.
4. Reddymasu SC, *et al.* Domperidone: review of pharmacology and clinical applications in gastroenterology. *Am J Gastroenterol* 2007; 102: 2036–45.

Administration in children. Domperidone is used in children as an antiemetic for nausea and vomiting and as a motility stimulant for gastrointestinal stasis. For nausea and vomiting, UK licensed product information states that children may be given domperidone in oral doses equivalent to 250 to 500 micrograms/kg three or four times daily; a total daily dose of 2.4 mg/kg or 80 mg, whichever is less, should not be exceeded. Alternatively, children weighing more than 15 kg may be given a rectal dose of 30 mg twice daily. Children over 12 years and weighing 35 kg or more may be given adult doses either orally or rectally, see above.

Although unlicensed for gastrointestinal stasis in the UK, the *BNFC* suggests oral doses given before food, according to age:

- neonates: 100 to 300 micrograms/kg four to six times daily
- 1 month to 12 years: 200 to 400 micrograms/kg (to a maximum of 20 mg) three or four times daily
- 12 years and over: doses similar to those used in adults for nausea and vomiting may be given

Similar doses may be used in infants and young children with gastro-oesophageal reflux disease, but see below.

Gastro-oesophageal reflux disease. A systematic review of the use of domperidone in infants and young children with gastro-oesophageal reflux (GORD; p. 1807.2), which identified 4 randomised controlled studies of such use, considered that there was very little evidence of its efficacy in reducing symptoms.[1] Some suggest that it has been overused because of the lack of a suitable alternative after withdrawal of cisapride in many countries.[2] The *BNFC* reinforces the idea that evidence for the long-term efficacy of motility stimulants (including domperidone) in the management of GORD is unconvincing. If domperidone is to be used, the *BNFC* suggests doses similar to those used for gastrointestinal stasis in children, see above.

1. Pritchard DS, *et al.* Should domperidone be used for the treatment of gastro-oesophageal reflux in children? Systematic review of randomized controlled trials in children aged 1 month to 11 years old. *Br J Clin Pharmacol* 2005; 59: 725–9.
2. Vandenplas Y, *et al.* The diagnosis and management of gastro-oesophageal reflux in infants. *Early Hum Dev* 2005; 81: 1011–24.

Parkinsonism. Domperidone is used to control gastrointestinal effects of dopaminergic drugs given in the management of parkinsonism (p. 889.1). It may be of use in those patients who have peripheral effects with levodopa despite the use of peripheral dopa-decarboxylase inhibitors and for patients using dopamine agonists such as bromocriptine or apomorphine since peripheral dopa-decarboxylase inhibitors are ineffective for preventing the peripheral effects of these drugs. Although domperidone does not readily cross the blood-brain barrier there have been isolated reports of extrapyramidal effects associated with its use (see p. 1839.1). Consequently there has been concern over its potential to produce central effects and some consider that domperidone should only be used in patients with parkinsonism when safer antiemetic measures have failed.[1,2] However, this view has been contested both by the manufacturers and other authors.[3,4] In a subsequent review of the use of domperidone in Parkinson's disease it was considered[5] that domperidone might produce central blockade of the therapeutic effects of levodopa if given at a high oral dosage such as 120 mg daily for prolonged periods but also noted that such high doses were rarely required to control levodopa-induced vomiting.

Domperidone was found to significantly improve anorexia, nausea, vomiting, abdominal bloating, and regurgitation in patients taking levodopa.[6] Dysphagia and constipation were unaffected; these are thought to be more likely a reflection of the disease process. Doses ranged from 50 to 120 mg daily, with most patients responding to 80 mg daily. No central effects were noted.

1. Leeser J, Bateman DN. Domperidone. *BMJ* 1985; 290: 241.
2. Bateman DN. Domperidone. *BMJ* 1985; 290: 1079.
3. Lake-Bakaar G, Cameron HA. Domperidone. *BMJ* 1985; 290: 241–2.
4. Critchley P, *et al.* Domperidone. *BMJ* 1985; 290: 788.
5. Parkes JD. Domperidone and Parkinson's disease. *Clin Neuropharmacol* 1986; 9: 517–32.
6. Soykan I, *et al.* Effect of chronic oral domperidone therapy on gastrointestinal symptoms and gastric emptying in patients with Parkinson's disease. *Mov Disord* 1997; 12: 952–7.

Adverse Effects

Dry mouth occurs commonly with domperidone; other adverse effects occur more rarely. Plasma-prolactin concentrations may increase with use of domperidone, which may lead to galactorrhoea, gynaecomastia, or amenorrhoea. Breast pain and tenderness may also occur. Domperidone does not readily cross the blood-brain barrier and the incidence of central effects such as extrapyramidal reactions or drowsiness may be lower than with metoclopramide (p. 1863.2); however, there have been reports of dystonic reactions and convulsions.

Domperidone has been associated with QT prolongation, serious ventricular arrhythmias, and sudden cardiac death. Fatalities have restricted intravenous use.

Hypersensitivity reactions include anaphylaxis and angioedema. Skin reactions such as rash, pruritus, and urticaria have occurred. Diarrhoea and transient intestinal cramps can also occur. There have been reports of anxiety or nervousness, agitation, loss of libido, asthenia, and headache. Urinary retention, abnormal liver function tests, and oculogyric crisis have also been reported.

Effects on the cardiovascular system. Between 1985 and 2006 Health Canada received 9 reports of heart rate and rhythm disorders suspected of being associated with domperidone use.[1] An increased QT interval was described in 2 cases, torsade de pointes in 4 cases, and the remaining 3 cases described arrhythmia, atrial fibrillation, ventricular tachycardia, bradycardia, and palpitation. Causality was hard to establish as most cases were complex, with multiple medicines prescribed. Prolongation of the QT interval has been reported in an infant given *oral* domperidone, with normalisation after the drug was stopped.[2] A prolonged QT interval was also reported in a small study in neonates given oral domperidone for gastro-oesophageal reflux disease; no cardiac arrhythmias developed.[3] A serum potassium concentration at the upper limit of normal or a gestational age of 32 weeks or more were risk factors for QT prolongation.

Sudden death has occurred in cancer patients given domperidone *intravenously* in high doses.[4-6] Four cancer patients had cardiac arrest after high intravenous doses[7] and 2 of 4 similar patients had ventricular arrhythmias.[8] After such reports the injection has been withdrawn from general use in many countries, including the UK.

A case-control study to investigate the association between the use of domperidone and the occurrence of serious ventricular arrhythmias found that current use of domperidone in high doses (defined as more than 30 mg daily; route not specified) was associated with a substantially increased risk of sudden cardiac death; non-fatal ventricular arrhythmias could not be assessed due to the lack of confirmed cases.[9]

1. Health Canada. Domperidone: heart rate and rhythm disorders. *Can Adverse React News* 2007; 17: 2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n1-eng.pdf (accessed 12/06/09)
2. Rocha CMG, Barbosa MM. QT interval prolongation associated with the oral use of domperidone in an infant. *Pediatr Cardiol* 2005; 26: 720–3.
3. Djeddi D, *et al.* Effect of domperidone on QT interval in neonates. *J Pediatr* 2008; 153: 663–6.
4. Joss RA, *et al.* Sudden death in cancer patient on high-dose domperidone. *Lancet* 1982; i: 1019.
5. Giaconne G, *et al.* Two sudden deaths during prophylactic antiemetic treatment with high doses of domperidone and methylprednisolone. *Lancet* 1984; ii: 1336–7.
6. Weaving A, *et al.* Seizures after antiemetic treatment with high dose domperidone: report of four cases. *BMJ* 1984; 288: 1728.
7. Roussak JB, *et al.* Cardiac arrest after treatment with intravenous domperidone. *BMJ* 1984; 289: 1579.
8. Osborne RJ, *et al.* Cardiotoxicity of intravenous domperidone. *Lancet* 1985; ii: 385.
9. van Noord C, *et al.* Domperidone and ventricular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. *Drug Safety* 2010; 33: 1003–14.

Effects on the endocrine system. There have been reports of galactorrhoea with gynaecomastia[1] or mastalgia[2,3] generally associated with raised serum-prolactin concentra-

tions. Gynaecomastia without galactorrhoea has also been reported.[4]

1. Van der Steen M, *et al.* Gynaecomastia in a male infant given domperidone. *Lancet* 1982; ii: 884–5.
2. Cann PA, *et al.* Galactorrhoea as side effect of domperidone. *BMJ* 1983; 286: 1395–6.
3. Cann PA, *et al.* Oral domperidone: double blind comparison with placebo in irritable bowel syndrome. *Gut* 1983; 24: 1135–40.
4. Keating JP, Rees M. Gynaecomastia after long-term administration of domperidone. *Postgrad Med J* 1991; 67: 401–2.

Extrapyramidal effects. There are reports of extrapyramidal symptoms,[1,2] including acute dystonic reactions[3] and neuroleptic malignant syndrome[4] in individual patients given domperidone.

1. Sol P, *et al.* Extrapyramidal reactions due to domperidone. *Lancet* 1980; ii: 802.
2. Debontridder O. Extrapyramidal reactions due to domperidone. *Lancet* 1980; ii: 802. Correction. *ibid.*: 1259.
3. Casteels-Van Daele M, *et al.* Refusal of further cancer chemotherapy due to antiemetic drug. *Lancet* 1984; i: 57.
4. Spirt MJ, *et al.* Neuroleptic malignant syndrome induced by domperidone. *Dig Dis Sci* 1992; 37: 946–8.

Precautions

Domperidone is not recommended for chronic use or for the routine prophylaxis of postoperative nausea and vomiting. Domperidone should be used with great caution if given intravenously, because of the risk of arrhythmias, especially in patients predisposed to cardiac arrhythmias or hypokalaemia.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given domperidone, and the last available guidance from the American Academy of Pediatrics considered[1] domperidone to be usually compatible with breast feeding. However, the FDA in the USA has issued a warning against the use of domperidone to increase milk production because of the possibility of serious adverse effects.[2] Others have commented that these warnings were based on data from patients with malignant disease receiving high doses of intravenous domperidone, and that if the mother were taking smaller oral doses, the total amount of drug ingested by an infant would be extremely small. They recommend that low-dose domperidone should still be considered for lactating women with decreased milk supply who are unresponsive to non-pharmacological measures to enhance lactation. However, patients should be warned of the risk of arrhythmias at high doses, and women with known cardiac disease should not take domperidone.[3]

In a small controlled study to determine the effect of domperidone on the nutrient composition of breast milk, breast milk volume was increased with domperidone use, nutrient composition was not substantially altered, and no significant adverse effects were seen in mothers or infants.[4]

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 07/05/04)
2. FDA. FDA warns against women using unapproved drug, domperidone, to increase milk production (June 7, 2004). Available at: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm173886.htm (accessed 17/12/10)
3. da Silva OP, Knoppert DC. Domperidone for lactating women. *Can Med Assoc J* 2004; 171: 725–6.
4. Campbell-Yeo ML, *et al.* Effect of domperidone on the composition of preterm human breast milk. *Pediatrics* 2010; 125: e107–e114. Available at: http://pediatrics.aappublications.org/cgi/reprint/125/1/e107 (accessed 17/12/10)

Interactions

As with other dopamine antagonists (see Metoclopramide, p. 1864.3), there is a theoretical potential that domperidone may antagonise the hypoprolactinaemic effect of drugs such as bromocriptine. In addition, the prokinetic effects of domperidone may alter the absorption of some drugs. Opioid analgesics and antimuscarinics may antagonise the prokinetic effects of domperidone.

Domperidone is metabolised via the cytochrome P450 isoenzyme CYP3A4; use with ketoconazole has been reported to produce a threefold increase in plasma concentrations of domperidone, and an associated slight prolongation in QT interval. Similar increases in domperidone concentrations might theoretically be seen with other potent inhibitors of CYP3A4 such as erythromycin or ritonavir, and such combinations may be best avoided.

Pharmacokinetics

Although absorption is rapid, the systemic bioavailability of domperidone is only about 15% in fasting subjects given an oral dose; this is increased when domperidone is given after food. The low bioavailability is thought to be due to first-pass hepatic and intestinal metabolism. The bioavailability of rectal domperidone is similar to that after oral doses, although peak plasma concentrations are only about one-third that of an oral dose and occur after about an hour, compared with 30 minutes after an oral dose.

Domperidone is more than 90% bound to plasma proteins, and has a terminal elimination half-life of about 7.5 hours. It undergoes rapid and extensive hepatic metabolism. The main metabolic pathways are *N*-dealkylation by cytochrome P450 isoenzyme CYP3A4, and aromatic hydroxylation by CYP3A4, CYP1A2, and CYP2E1. About 30% of an oral dose is excreted in urine within 24 hours, almost entirely as metabolites; the remainder of a dose is excreted in faeces over several days, about 10% as unchanged drug. It does not readily cross the blood-brain barrier.

Small amounts of domperidone are distributed into breast milk; concentrations are 10 to 50% of those in maternal serum.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ecuamon; Euciton; Moperidona; Motilium; Peridon; ***Austral.***: Motilium; ***Austria***: Motilium; ***Belg.***: Docdomperi†; Domperitop; Motilium; Oroperidys; Zilium; ***Braz.***: Dompgran; Dompliv; Motilium; Peridal; Peridona; ***Chile***: Docivin; Domevol; Dompesin; Donegal; Dosin; Gasdol; Idon; Restol; Siligaz; ***China***: Bang Neng (邦能); Domperid (益动); Duo Pai Tong (多派通); Heng Bang (恒邦); Motilium (吗丁啉); You Ma Lin (优玛琳); Cz.: Motilium; Oroperidys; ***Denm.***: Motilium; ***Fr.***: Biperidys; Motilium; Oroperidys; Peridys; ***Ger.***: Domidon†; Motilium; ***Gr.***: Cilroton; Oroperidys; ***Hong Kong***: Apuldon; Costi; Dompeon†; Domper; Doridone; Floralin†; Motilium; Qualidom; Rabugen; Vicktilin†; Vicktilium†; ***Hung.***: Motilium; ***India***: Aglodom; Aldom; Aziorm; Casdom; Cosdome; Cudom; DMP; Dom-DT; Dom; Domacare; Domact; Dombus; Domcolic; Domday; Domden; Domdon; Domel-MT; Domerit; Domi; Domitil; Domkalr; Domlyx; Domne; Domped; Domperi; Domperistal; Domperon; Dompet; Dompon; Dompro; Domsi; Domsin; Domstal; Domtop; Doven; Emestal; Emidon; Emitin; Endopace; Gastractiv; Gastrium; Judom; Junidom; Motilium-M; Motinorm; Motiwin; Naushi; Nausidome; Nautigo†; Normetic; Otron-D; Ozo-D; Pantin-RD; Stopvom; Vomistop; ***Indon.***: Costil; DOM; Dombaz; Domedon; Domet†; Dometa; Dometic; Dominal; Galflux; Gerdilium; Monell; Motilium; Novotil; Regit; Tilidon; Vesperum; Vomecho; Vomerin; Vometa; Vomidone; Vomina; Vomistop; Vomitas; Vosedon; Yaridon; ***Irl.***: Domerid; Motilium; ***Israel***: Motilium; ***Ital.***: Alvavitaros; Cattalorex; Dalia; Diedafon; Digestivo Giuliani; Gastronorm†; Gerdi; Lauter; Motilium; Peridon; Permotil; Riges; Stalcare; ***Jpn***: Nauzelin; ***Malaysia***: Domper; Motidone; Motilium; Rabugen; ***Mex.***: Biolix; Emiken; Motidom; Motilium; Seronex; ***Neth.***: Actadomp; Motillum; ***NZ***: Motilium; ***Philipp.***: Andiogan; Domelong; Dompenyl; Domper; Domperone; Gasidone; Gastrodin; Gilax; Motilium; Pepridon; Perilax; Toridon; Vometa; ***Port.***: Cinet; Mogasinte†; Motilium; Nausidone; Oroperidys; Perinauz†; Remotil; ***Rus.***: Damelium (Дамелиум); Domet (Домет); Domstal (Домстал); Motilak (Мотилак); Motilium (Мотилиум); Motinorm (Мотинорм); Motonium (Мотониум); Passagix (Пассажикс); ***S.Afr.***: Motillum; Vomidon; ***Singapore***: Dompel; Domper; Doridone; Gastrium; Mirax; Motilium; Peptomet; ***Spain***: Motilium; ***Switz.***: Motilium; ***Thai.***: Auto; Avomit-M; Dany; Dolium; Domerdon; Domidone†; Domp-M; Domp; Domper-M; Domperdone; Donox†; Donum†; Doper†; Emex; Falium†; Meridone; Mirax; Mocydone; Modomed; Molax; Moticon; Motidom; Motilar; Motilin; Motilium; Movelium; Ninlium; Peridom-M; Pondperdone; Rabugen-M; Vesperidone; ***Turk.***: Motilium; Motis; ***UAE***: Mododom; ***UK***: Motilium; Vivadone; ***Ukr.***: Brullium (Брюллиум); Domidon (Домидон); Motilium (Мотилиум); Motorix (Моторикс); Peridonium (Перидониум)†; ***Venez.***: Agilam; Tilium; Tonum†.

Multi-ingredient Preparations. *Arg.*: Alplax Net; Ansielix Digest; Bigetric Bilagol Antigas; Dom Simecon; Dom-Polienzim; Euciton Complex; Euciton Reflux; Euciton Stress; Faradil Novo; Gastrosedol Plus; Megalex; Moperidona AF; Moperidona Enzimatica†; Praxis; Sidomal; Tensium Gastric; Tetralgin Novo; Vegestabil Digest; ***Belg.***: Touristil; ***Braz.***: Lansodom†; ***Chile***: Faronkal; ***India***: Abcid-D; Abcool-D; Abra-D; Acera; Achpilori-D; Aciban-DSR; Acidom; Acidopent-DSR; Acigone-D; Aciloc RD; Acio; Acistal-D; Acitec-D; Actidol-DP; Actiran-D; Adprazole-D; Adzole-DM; Affirab-D; Aldepraz-D; Alice-D; Alizole-DSR; Anatyl-D; Antuc DSR; Anzop-D; Apentral-D; Aptase-DSR HG; Aribzol-D; Aridom-C; Aripan-D; Arloc-D; Armcid D; Asalt-D; Asipan-D; Asirab-D; Atozol-D; Avizol-D; Avopan-D; Azinorm C; Azinorm O; Aztec-D; B-Joy Plus; Bemez-D; Biomac-D; Biopar; Bizo-D; Brazo-D; Brozol-D; Brozole-D; Bus-D; C-Praz-D; Canozol-D; Capcid-D; Capocid-DM; Casdom-P; Cazole-D; Cidrid; Cimdom; Cinact-D; Cinadil-D; Cingeron-D; Cinnasia-D; Cintac-D; Comvine; Concid-DM; Concid-DSR; Cool Zone D; Coszol-D; Coz-D; Cucid-DM; Cudom-P; Cupan-DSR; Curab-D; Cuzole-D; Cyclochek; Cypan-D; Cyra-D; D-Rabibit-D; Dazole-D; Decotram-PD; Deepen-D; Degurge-D; Demo D; Depam; Dexrobel-D; DGR-Plus; Didol-D; Digerab-D; Dilke; Diocid-D; Dirab-D; DMP Plus; Dols Plus; Dom-MPS; Dom-P; Domac; Domact-P; Domcet; Domci; Domden-P; Domepraz; Domeway; Domezol; Domizol-DS; Domkair-P; Domocid-PX; Domocid; Dompan; Dompar; Domped-OZ; Domperon Plus; Domperon-O; Dompon CZ; Dompon F; Dompon P; Dompra; Dompro-C; Domrab; Domsettler; Domsin-LA; Domsin-O; Domspas; Domstal MPS; Domstal-CZ; Domstal-O; Domstal-P; Domstal-RD; Domtac; Domtec-P; Domz; Domzole-R; Donriz; Dorafem; Dorcan-D; Doset Plus; Drag-D; Duogel; Dupent-D; Dyoflux; E-Pento-D; E-Zole-D; Egrin; Eldom-P; Elpra-D; Elrab-D; Emidon-OM; Emopaz-D; Eracid-D; Esofag-D; Esoga-RD; Esoz-D; Eupanta D; FB; Forzole-D; Fozole-D; FS-D; Fulpan-D; Furab-D; Gasorab-D; Gaspaz; Gastrazole-D; Genpen-D; Genrab-D; Gerdom; Gi-Fri; Glopan-D; GR8-OD; GR8; Gredol; Grenil; Happi-D; Helirab-D; Helkoss-D; Hurtiz-DSR; Hypa-D; Hyzole-DP; Icer-D; Ignis; Ingesic Forte; Inpan-D; Intapan-D; IPD; Izra-D; Jeprab-D; Jotac-D; Kandor CZ; Kapyl-D; Kenta-D; Kevtram-DP; Klenz-D; Konzol-D; Kurab-D; Kurepane-D; L-Dom; Lance-D; Lancidom; Lanip-D; Lans-DX; Lanspro-D; Lanzee-DM; Lapra-D; Lasole-D; Latop-D; Leedom; Leetop-D; Lesozap-D; Lexcid-DM; Litom-D; Liza-D; Locid-D; Lomecid-D; Lopra-D; Lupome-D; Mac-RD; Medipent-D; Meditin Plus; Mepraz-D; Meridol-D; Miliom-D; Minisec-AR; Mosic; Motinorm-P; Multipan-D; Mygran; Naprodom; Naxdom; Netom-D; Neutraflux; Neutral-O; Nexpro-RD; Nitpep-D; Nitzole-D; Nogacid D; Normocid; Nosirid-P; Novacid-D; Novagel-D; Novorab-D; Nucid-D; Nuloc-D; Nupan-D; Nura-D; Nutec MPS; O & D; O-Bit-DM; Ocid-D; Ocinil-D; Od; Odipan-D; Odipep; Odoman; Ogestrel-D; Okacid D; Okalan D; Olicap-D; Olla-D; Ombel-D; Ombest-D; Omcare-D; Omcure-D; Omdom; Omecer-D; Omecid-D; Omecid-RD; Omecip-D; Omecos-D; Omeezol-D; Omejel-DM; Omelax-D; Omen-D; Omentum-D; Omeraze-D; Omeris-D; Omesun-D; Omesym-D; Omevar-D; Omez-D; Omfact-D; Omibase-D; Omic-D; Omicas-D; Omicool-D; Omidec-ES; Omidec; Omidip; Omidom; Omiflux; Omig-DM; Omilee-D; Omitive-D; Omitop-DM; Omitop; Omizol-D; Omkair-D; Omlink-D; Omlo-D; Ommac Plus; Omore-D; Ompli-D; Ompraz-D; Omprest-D; Omracap-DM; Omriz-D; Omven-D; Omzee-D; Onazole-DP; Onazole-RD; Once-D; Oned; Onto-D; Op-Zole D; Opaz-DM; Opel-D; Opera-D; Opiate-PD; Orapan-D; Oraz-D; Oritop-D; Orole-D; Oshzol-D; Ospicid-D; Ossum-D; OTG-D; Otto-D; Oxokool Plus; Oxypan-D; Ozed-D; Ozodom; Ozol-D; Pacidom-C; Pacidom-O; Pacidom-P; Pacinac-NP; Palgic-D; Palin-D; Palio-D; Palzic-D; Pan-D; Pancas-D; Pandat-D; Pandiff; Pandom; Pandostal; Pandosun-D; Pandry D; Panfast-D; Pangy-DM; Pankai-D; Panlee-D; Panmint-D; Pano-D; Panopaz-D; Panor-D; Panpac-D; Panpari-D; Panpra-D; Panpro-D; Panrole-D; Pansa-D; Pansafe-D; Pansaul-D; Pansi-SD; Pansoft-D; Panstrike-D; Pantabit-D; Pantabol-D; Pantact-D; Pantadal-D; Pantadom; Pantagon-DM; Pantamep-D; Pantanib-D; Pantapil-D; Pantec-D; Pantest-D; Pantin-D; Pantium-D; Panto-D; Pantocar-D; Pantocid-D; Pantocos-D; Pantodac-D; Pantoday-D; Pantofer-D; Pantoflux; Pantol-D; Pantolex-D; Pantom-D; Pantomas-D; Pantomed-D; Pantomore-D; Pantonid-D; Pantop-D; Pantopik-D; Pantosec D; Pantosh D; Pantosig-D; Pantosym-D; Pantotive-D; Pantovar-D; Pantovom; Pantox-D; Pantoz-D; Pantozol-D; Pantra-D; Pantry-D; Pantz-D; Pantz-DM; Panum-D; Panz-D; Panz-SR; Panzac-D; Panzo-D; Praize-D; Vertigil; ***Philipp.***: Stugil; ***Rus.***: Domstal-O (Домстал-О); Omez D (Омез Д); ***Thai.***: Dominox; ***Ukr.***: Limzer (Лімзер); Omez-D (Омез-Д); Rabiril (Рабирил).

Pharmacopoeial Preparations
BP 2014: Domperidone Tablets.

Dosmalfate *(rINN)*

Dosmalfato; Dosmalfatum; F-3616; Дозмальфат.
[μ_7-[(Diosmin heptasulfato)(7-)]]tetracontahydroxytetradecaaluminium.
$C_{28}H_{60}Al_{14}O_{71}S_7$=2134.9
CAS — 122312-55-4.
UNII — P764IU074T.

Profile

Dosmalfate is a cytoprotective drug derived from diosmin (p. 2505.2), that has been used for the treatment of peptic ulcer disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain***: Diotul†.

Drofenine Hydrochloride *(pINNM)*

Drofenina, hidrocloruro de; Drofénine, Chlorhydrate de; Drofenini Hydrochloridum; Hexahydroadiphenine Hydrochloride; Hidrocloruro de drofenina; Дрофенина Гидрохлорид.
2-(Diethylamino)ethyl α-phenylcyclohexaneacetate hydrochloride.
$C_{20}H_{31}NO_2$,HCl=353.9
CAS — 1679-76-1 (drofenine); 548-66-3 (drofenine hydrochloride).
UNII — MVB31OPW0S.

Pharmacopoeias. In *Swiss*.

Profile

Drofenine hydrochloride is an antimuscarinic available in preparations for the treatment of visceral spasms.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Espasmo Cibalena; *Austria*: Spasmoplus; *Chile*: Espasmo Cibalgina Compuesta†; Espasmo Cibalgina; *Mex.*: Espasmo Cibalgina; *Switz.*: Lunadon†.

Dronabinol *(USAN, rINN)* ⊗

Dronabinolum; NSC-134454; Дронабинол.
(6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol.
$C_{21}H_{30}O_2$=314.5
CAS — 1972-08-3.
ATC — A04AD10 (dronabinol); N02BG10 (nabiximols).
ATC Vet — QA04AD10.
UNII — 7J8897W37S.

Pharmacopoeias. In *US*.

USP 36: (Dronabinol). Store at a temperature between 8 degrees and 15 degrees in airtight glass containers in an inert atmosphere. Protect from light.

Uses and Administration

Dronabinol, the major psychoactive constituent of cannabis (p. 2467.1), has antiemetic properties and is used for the control of **nausea and vomiting** associated with cancer chemotherapy (p. 1811.3) in patients who have failed to respond adequately to conventional antiemetics.

The usual initial oral dose of dronabinol is 5 mg/m² given 1 to 3 hours before the first dose of the antineoplastic drug with subsequent doses being given every 2 to 4 hours after chemotherapy to a maximum of 4 to 6 doses daily. If necessary, the dose may be increased by increments of 2.5 mg/m² to a maximum dose of 15 mg/m², if adverse effects permit.

Dronabinol also has appetite-stimulant effects and is used in the treatment of **anorexia** associated with weight loss in patients with AIDS. For this purpose 2.5 mg may be taken twice daily, before lunch and supper, reduced to a single 2.5-mg dose in the evening in patients who tolerate the drug poorly. If necessary, and if adverse effects permit, doses may also be increased up to 20 mg daily in divided doses.

A buccal spray preparation containing cannabis extracts, whose main active ingredients are dronabinol and cannabidiol, is used as adjunctive treatment for the symptomatic relief of **spasticity** and **neuropathic pain** in multiple sclerosis in adults; this combination is also used as adjunctive analgesic treatment in adult patients with advanced cancer (see Nabiximols, p. 2566.3) and is under investigation for several other conditions.

General references.

1. Voth EA, Schwartz RH. Medicinal applications of delta-9-tetrahydrocannabinol and marijuana. *Ann Intern Med* 1997; 126: 791–8.
2. Williamson EM, Evans FJ. Cannabinoids in clinical practice. *Drugs* 2000; 60: 1303–14.
3. Tramer MR, *et al.* Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ* 2001; 323: 16–21.
4. Berman JS, *et al.* Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain* 2004; 112: 299–306.
5. Costa B. On the pharmacological properties of Delta9-tetrahydrocannabinol (THC). *Chem Biodivers* 2007; 4: 1664–77.
6. Beaulieu P, Ware M. Reassessment of the role of cannabinoids in the management of pain. *Curr Opin Anaesthesiol* 2007; 20: 473–7.

Alzheimer's disease. There are limited data to suggest that dronabinol may decrease agitation in patients with Alzheimer's disease[1] or dementia.[2]

1. Volicer L, *et al.* Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 1997; 12: 913–19.
2. Walther S, *et al.* Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. *Psychopharmacology (Berl)* 2006; 185: 524–8.

Anorexia. Dronabinol is used for the management of anorexia in patients with HIV-associated wasting (p. 959.1). However, although dronabinol may stimulate appetite and prevent weight loss,[1] it does not appear to produce significant weight gain, and may produce less benefit than megestrol acetate.[2] Benefits were also less than those of megestrol in patients with anorexia associated with malignant disease.[3]

1. Beal JE, *et al.* Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage* 1995; 10: 89–97.
2. Timpone JG, *et al.* The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. *AIDS Res Hum Retroviruses* 1997; 13: 305–15.
3. Jatoi A, *et al.* Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol* 2002; 20: 567–73.

Multiple sclerosis. Anecdotal evidence has suggested that cannabinoids might improve symptoms in patients with multiple sclerosis (p. 996.3); a review[1] considered evidence of efficacy to be lacking. In a large placebo-controlled study, treatment with dronabinol or oral cannabis extract had no benefit on objective assessment of spasticity;[2] however, there were improvements in walking time, and subjective improvements in both spasticity and pain. A subsequent small controlled study found dronabinol to have a modest but clinically relevant effect on central neuropathic pain in patients with multiple sclerosis.[3]

A buccal spray preparation containing cannabis extracts, whose main active ingredients are dronabinol and cannabidiol, is used for the symptomatic relief of spasticity and neuropathic pain in multiple sclerosis in adults.

1. Killestein J, *et al.* Cannabinoids in multiple sclerosis: do they have a therapeutic role? *Drugs* 2004; 64: 1–11.
2. Zajicek J, *et al.* Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003; 362: 1517–26.
3. Svendsen KB, *et al.* Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ* 2004; 329: 253–7.

Tourette's syndrome. Preliminary studies[1,2] indicate that dronabinol may reduce tic severity in Tourette's syndrome (see Tics, p. 1030.1).

1. Müller-Vahl KR, *et al.* Treatment of Tourette's syndrome with Δ⁹-tetrahydrocannabinol (THC): a randomized crossover trial. *Pharmacopsychiatry* 2002; 35: 57–61.
2. Müller-Vahl KR, *et al.* Δ⁹-Tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. *J Clin Psychiatry* 2003; 64: 459–65.

Adverse Effects and Precautions

As for Nabilone, p. 1865.3. The most frequent adverse effects of dronabinol include abdominal pain, nausea and vomiting, dizziness, euphoria, paranoid reactions, and somnolence. Seizures and seizure-like activity have been reported; dronabinol should be used with caution in those with a history of seizure disorders, and therapy should be stopped if seizures occur.

Abuse. The abuse liability of dronabinol was rated as being substantially lower than that of cannabis.[1]

1. WHO. WHO expert committee on drug dependence: thirty-third report. *WHO Tech Rep Ser 915* 2003. Available at: http://libdoc.who.int/trs/WHO_TRS_915.pdf (accessed 03/07/08)

Breast feeding. US licensed product information states that dronabinol is concentrated in breast milk and recommends that it should not be used in breast-feeding mothers.

Pharmacokinetics

After oral doses dronabinol is slowly and erratically absorbed from the gastrointestinal tract; the bioavailability of an oral dose is about 10 to 20%, due to extensive first-pass metabolism. Peak plasma concentrations of dronabinol and its 11-hydroxy metabolite occur about 2 to 4 hours after an oral dose. It is widely distributed and is extensively protein bound, with a volume of distribution of about 10 litres/kg. Elimination is biphasic, with an initial half-life of about 4 hours, and a terminal half-life of about 25 to 36 hours.

Dronabinol is extensively metabolised, mainly in the liver by cytochrome P450 isoenzymes; the primary metabolite, 11-hydroxydronabinol is also active. The 11-hydroxy metabolite is converted to other, more polar and acidic compounds which are excreted in faeces via the bile, and in the urine. About 50% of an oral dose is recovered in faeces within 72 hours and 10 to 15% in urine. Many of the metabolites have relatively prolonged half-lives, and accumulation may occur with repeated dosage.

Dronabinol is distributed into breast milk and crosses the placenta.

References.

1. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 2003; 42: 327–60.
2. McGilveray IJ. Pharmacokinetics of cannabinoids. *Pain Res Manag* 2005; 10: 15A–22A.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: MarinoH; *USA*: Marinol.

Pharmacopoeial Preparations
USP 36: Dronabinol Capsules.

Ecabet Sodium *(rINN)*

Ecabet sódico; Écabet Sodique; Natrii Ecabetum; 12-Sulphodehydroabietic Acid, Monosodium Salt; TA-2711; Экабет Натрий.
13-Isopropyl-12-sulphopodocarpa-8,11,13-trien-15-oic acid pentahydrate, sodium salt.
$C_{20}H_{27}NaO_5S.5H_2O$=492.6
CAS — 33159-27-2 (ecabet); 86408-72-2 (ecabet sodium).
UNII — 51MO2B2O5B.

Profile

Ecabet sodium is a cytoprotective drug used in the treatment of peptic ulcer disease (p. 1813.2). The suggested oral dose is 1 g of ecabet sodium twice daily.

It is also under investigation as eye drops in the management of dry eye.

References.

1. Murata H, *et al.* Combination therapy of ecabet sodium and cimetidine compared with cimetidine alone for gastric ulcer: prospective randomized multicenter study. *J Gastroenterol Hepatol* 2003; 18: 1029–33.
2. Lee JH, *et al.* Efficacy and safety of ecabet sodium on functional dyspepsia: a prospective, double-blinded, randomized, multi-center controlled trial. *World J Gastroenterol* 2006; 12: 2756–61.

Administration. The use of ecabet sodium as a rectal enema has been investigated in patients with ulcerative colitis.[1,2]

1. Kono T, *et al.* Effect of ecabet sodium enema on mildly to moderately active ulcerative proctosigmoiditis: an open-label study. *Am J Gastroenterol* 2001; 96: 793–7.
2. Iizuka M, *et al.* Efficacy of ecabet sodium enema on steroid resistant or steroid dependent ulcerative colitis. *Gut* 2006; 55: 1523.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Gastrom (盖亥); *Jpn*: Gastrom.

Egualen Sodium *(rINN)*

Azuletil Sodium; Egualen Sodium Hydrate; Égualène Sodique; Egualeno sódico; KT-1-32; Natrii Egualenum Натрий Эгуален.
Sodium 3-ethyl-7-isopropyl-1-azulenesulfonate.
$C_{15}H_{17}O_3SNa$=300.3
CAS — 97683-31-3.

Profile

Egualen sodium is a mucosal protectant used with H_2 receptor antagonists for the treatment of gastric ulceration

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Azuloxa.

Enoxolone Aluminium *(BANM, rINNM)*

Aluminii Enoxolonum; Aluminium Glycyrrhetate; Aluminium Glycyrrhetinate; Enoxolona de aluminio; Enoxolone Aluminum; Énoxolone d'Aluminium; Алюминий Эноксолон.
3β-Hydroxy-11-oxo-olean-12-en-30-oic acid, aluminium salt.
$(C_{30}H_{46}O_4)_3Al$=1439.1
CAS — 4598-66-7.
ATC — D03AX10.
ATC Vet — QD03AX10.

Profile

Enoxolone aluminium is an analogue of carbenoxolone (p. 1825.3) that has been used in preparations for the treatment of peptic ulcer disease and other gastrointestinal disorders. It has also been used in preparations for skin disorders and mouth and throat disorders.

Pulmonary hypertension. *In-utero* exposure to enoxolone was implicated in a fatal case of neonatal pulmonary arterial hypertension; the mother had used a lotion for prurigo that contained enoxolone and the authors supposed it had contributed at least in part to the pulmonary hypertension.[1]

1. Navarre-Belhassen C, *et al.* An unexpected case of primary pulmonary hypertension of the neonate (PPHN): potential role of topical administration of enoxolone. *J Perinat Med* 2002; 30: 437–9.

Eseridine Salicylate *(rINNM)*

Eseridina, salicilato de; Éséridine, Salicylate d'; Eseridini Salicylas; Eserine Aminoxide Salicylate; Eserine Oxide Salicylate; Physostigmine Aminoxide Salicylate; Physostigmine *N*-Oxide Salicylate; Salicilato de eseridina; Эзеридина Салицилат.
(4a*S*,9a*S*)-2,3,4,4a,9,9a-Hexahydro-2,4a,9-trimethyl-1,2-oxazino[6,5-*b*]indol-6-ylmethylcarbamate salicylate.
$C_{15}H_{21}N_3O_3.C_7H_6O_3$=429.5
CAS — 25573-43-7 (eseridine); 5995-96-0 (eseridine salicylate).

Profile

Eseridine salicylate, a derivative of physostigmine (p. 2009.3), is an inhibitor of cholinesterase activity that has been given orally for dyspepsia in doses of up to 4.5 mg 3 times daily, taken 30 minutes before meals.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Pr.*: Geneserine.

Esomeprazole *(BAN, rINN)*

Esomepratsoli; Esomeprazol; Esoméprazole; Esomeprazolum; H-199/18; Perprazole; Эзомепразол.

5-Methoxy-2-{(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}benzimidazole.

$C_{17}H_{19}N_3O_3S$=345.4

CAS — 119141-88-7.

ATC — A02BC05.

ATC Vet — QA02BC05.

UNII — N3PA6559FT.

Esomeprazole Magnesium *(BANM, USAN, rINNM)*

Esomeprazol magnésico; Esoméprazole Magnesique; Esomeprazole magnésique; Esomeprazolum magnesicum; Magnesii Esomeprazolum; Магния Эзомепразол.

$C_{34}H_{36}MgN_6O_6S_2.3H_2O$=767.2

CAS — 217087-09-7.

ATC — A02BC05.

ATC Vet — QA02BC05.

UNII — R6DXU4WAY9.

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

Ph. Eur. 8: (Esomeprazole Magnesium Trihydrate). A white or slightly coloured, slightly hygroscopic powder. Slightly soluble in water; soluble in methyl alcohol; practically insoluble in heptane. Store in airtight containers. Protect from light.

USP 36: (Esomeprazole Magnesium). A white to slightly coloured powder. Slightly soluble in water; soluble in methyl alcohol; practically insoluble in heptane. Store in airtight containers. Protect from light.

Esomeprazole Potassium *(BANM, USAN, rINNM)*

Esomeprazol potásico; Esoméprazole Potassique; Kalii Esomeprazolum; Калия Эзомепразол.

$C_{17}H_{18}KN_3O_3S$=383.5

CAS — 161796-84-5.

ATC — A02BC05.

ATC Vet — QA02BC05.

UNII — F37S7G37O2.

Esomeprazole Sodium *(BANM, USAN, rINNM)*

Esomeprazol sódico; Esoméprazole Sodique; Natrii Esomeprazolum; Натрия Эзомепразол.

$C_{17}H_{18}N_3NaO_3S$=368.4

CAS — 161796-78-7.

ATC — A02BC05.

ATC Vet — QA02BC05.

UNII — L2C9GWQ43H.

Esomeprazole Strontium *(USAN, rINNM)*

Esomeprazol estroncio; Esoméprazole Strontium; FM-0F67; Эзомепразол Стронция.

$(C_{17}H_{18}N_3O_3S)_2Sr.4H_2O$=848.5

CAS — 934714-36-0.

UNII — C5N2SH3803.

Uses and Administration

Esomeprazole is the *S*-isomer of the proton pump inhibitor omeprazole (p. 1867.2) and is used similarly in the treatment of peptic ulcer disease and NSAID-associated ulceration (p. 1813.2), in gastro-oesophageal reflux disease (p. 1807.2), and the Zollinger-Ellison syndrome (p. 1814.3). It is given as the magnesium, sodium, or strontium salts but doses are calculated in terms of esomeprazole. Esomeprazole magnesium 22.2 mg, esomeprazole sodium 21.3 mg, and esomeprazole strontium 24.7 mg are each equivalent to about 20 mg of esomeprazole.

Usual oral doses in **peptic ulcer disease**, for *Helicobacter pylori* eradication as a component of a triple therapy regimen with amoxicillin and clarithromycin, are the equivalent of 20 mg esomeprazole twice daily for 7 days, or 40 mg once daily for 10 days.

Oral doses of 20 mg daily, for 4 to 8 weeks, are used in the treatment of **NSAID-associated ulceration**; a dose of 20 or 40 mg daily may also be used for prophylaxis in patients at risk of such lesions who require continued NSAID treatment.

In the UK, the dose for treatment of severe (erosive) **gastro-oesophageal reflux disease** is 40 mg once daily for 4 weeks, extended for a further 4 weeks if necessary; in the USA, where doses of 20 or 40 mg daily are permitted for initial treatment, a further 4 to 8 weeks of treatment may be considered for patients who do not heal after 4 to 8 weeks. For maintenance, or for symptomatic disease without erosive oesophagitis, doses equivalent to 20 mg of esomeprazole daily may be used in both countries.

For the treatment of **Zollinger-Ellison syndrome**, the recommended initial oral dose of esomeprazole is 40 mg twice daily, which is then adjusted as needed. The majority of patients can be controlled on doses between 80 and 160 mg daily, although daily doses of 240 mg have been given. Doses above 80 mg daily should be given in 2 divided doses. For doses in children, see below.

PARENTERAL DOSAGE.

Similar doses to the above may be given intravenously for gastro-oesophageal reflux disease and NSAID-associated ulceration. Esomeprazole is given as the sodium salt by slow intravenous injection over at least 3 minutes or by intravenous infusion over 10 to 30 minutes.

For the **prevention of rebleeding** of gastric and duodenal ulcers after therapeutic endoscopy, 80 mg esomeprazole can be given as an intravenous infusion over 30 minutes, followed by a continuous intravenous infusion of 8 mg/hour over 72 hours. This parenteral treatment period is then followed by oral therapy; 40 mg is given once daily for 4 weeks.

Doses of esomeprazole may need to be reduced in patients with hepatic impairment (see below).

References.

1. Maton PN, *et al.* Safety and efficacy of long term esomeprazole therapy in patients with healed erosive oesophagitis. *Drug Safety* 2001; 24: 625–35.
2. Keating GM, Figgitt DP. Intravenous esomeprazole. *Drugs* 2004; 64: 875–82.
3. Metz DC, *et al.* Comparison of the effects of intravenously and orally administered esomeprazole on acid output in patients with symptoms of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2005; 22: 813–21.
4. Edwards SJ, *et al.* Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis - a comparison of esomeprazole with other PPIs. *Aliment Pharmacol Ther* 2006; 24: 743–50.
5. Morgner A, *et al.* Esomeprazole: prevention and treatment of NSAID-induced symptoms and ulcers. *Expert Opin Pharmacother* 2007; 8: 975–88.
6. Blandizzi C, *et al.* Clinical efficacy of esomeprazole in the prevention and healing of gastrointestinal toxicity associated with NSAIDs in elderly patients. *Drugs Aging* 2008; 25: 197–208.
7. McKeage K, *et al.* Esomeprazole: a review of its use in the management of gastric acid-related diseases in adults. *Drugs* 2008; 68: 1571–1607.
8. Sung JJY, *et al.* Peptic Ulcer Bleed Study Group. Intravenous esomeprazole for prevention of recurrent peptic ulcer bleeding: a randomized trial. *Ann Intern Med* 2009; 150: 455–64.

Administration. *In-vitro* studies found that almost the entire contents of an esomeprazole capsule is deliverable through small calibre and standard sizes of nasogastric and gastrostomy tubes.[1,2]

1. White CM, *et al.* Delivery of esomeprazole magnesium enteric-coated pellets through small caliber and standard nasogastric tubes and gastrostomy tubes in vitro. *Am J Health-Syst Pharm* 2002; 59: 2085–8.
2. Shah SA, *et al.* Delivery of esomeprazole magnesium through nasogastric and gastrostomy tubes using an oral liquid vehicle as a suspending agent in vitro. *Am J Health-Syst Pharm* 2006; 63: 1882–7.

Administration in children. Esomeprazole is given orally to children for the treatment of gastro-oesophageal reflux disease and erosive oesophagitis,[1,2] and for duodenal ulcers caused by *Helicobacter pylori*.

For gastro-oesophageal reflux disease, children aged from 1 to 11 years and weighing 10 kg and over are given 10 mg once daily for up to 8 weeks.

In erosive oesophagitis, doses are based on body-weight and given once daily for 8 weeks:

- 10 kg up to 20 kg: 10 mg
- ⩾ 20 kg: 10 or 20 mg

For the eradication of *H. pylori* in duodenal ulceration in children over 4 years of age, oral esomeprazole is given with amoxicillin and clarithromycin for 1 week; doses are according to weight:

- < 30 kg: 10 mg twice daily
- ⩾ 30 kg: 20 mg twice daily

Regardless of indication, children from 12 years of age may be given adult doses, see above.

For doses in children with hepatic impairment, see below.

Esomeprazole is unlicensed in children under 1 year of age; however, a pharmacokinetic study in preterm and term neonates with gastro-oesophageal reflux disease found oral esomeprazole 500 micrograms/kg once daily for 7 days reduced oesophageal acid exposure and gastric acidity but had no effect on bolus reflex characteristics, findings that were consistent with those reported in adults. Systemic exposure to esomeprazole was proportionally higher in neonates compared with older infants.[3]

For findings from a review regarding the efficacy and safety of proton pump inhibitors in infants, children, and adolescents, see Administration in Children, under Omeprazole, p. 1867.3.

1. Croxtall JD, *et al.* Esomeprazole: in gastroesophageal reflux disease in children and adolescents. *Paediatr Drugs* 2008; 10: 199–205.
2. Guimarães EV, *et al.* Management of gastroesophageal reflux disease and erosive esophagitis in pediatric patients: focus on delayed-release esomeprazole. *Ther Clin Risk Manag* 2010; 6: 531–7.
3. Omari T, *et al.* Pharmacodynamics and systemic exposure of esomeprazole in preterm infants and term neonates with gastro-esophageal reflux disease. *J Pediatr* 2009; 155: 222–8.

Administration in hepatic impairment. No dosage adjustment of esomeprazole is considered necessary for patients with mild to moderate hepatic impairment (Child-Pugh Classes A and B, respectively). In severe hepatic impairment (Child-Pugh Class C), US licensed product information recommends that a daily dose of 20 mg, orally or intravenously, should not be exceeded. In the UK, licensed product information specifies a maximum daily intravenous dose of esomeprazole 20 mg in those aged 18 years and over, although when given for prevention of rebleeding of gastric and duodenal ulcers after endoscopy in those with severe hepatic impairment, an initial intravenous infusion of 80 mg over 30 minutes, may be followed by a continuous intravenous infusion of 4 mg/hour over about 72 hours. A maximum daily oral dose of esomeprazole 20 mg is recommended in patients from 12 years of age, and 10 mg in those aged 1 to 11 years.

Administration in renal impairment. Although no dosage adjustment is considered necessary in patients with renal impairment, UK licensed product information advises caution in those with severe renal impairment, as experience in these patients is limited.

Adverse Effects and Precautions

As for Omeprazole, p. 1868.1.

General references.

1. Davies M, *et al.* Safety profile of esomeprazole: results of a prescription-event monitoring study of 11 595 patients in England. *Drug Safety* 2008; 31: 313–23.

Effects on the cardiovascular system. For discussion of cardiac effects ostensibly seen with esomeprazole, see under Omeprazole, p. 1868.2.

Effects on the kidneys. For reports of interstitial nephritis associated with esomeprazole see p. 1869.1.

Effects on the skin. For mention of exacerbation of vitiligo with esomeprazole, see p. 1869.2.

Fever. For a report of hyperpyrexia associated with esomeprazole, see p. 1869.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies esomeprazole 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 03/10/11)

Interactions

As for Omeprazole, p. 1870.3.

References.

1. Andersson T, *et al.* Drug interaction studies with esomeprazole, the (S)-isomer of omeprazole. *Clin Pharmacokinet* 2001; 40: 523–37.

Pharmacokinetics

Esomeprazole is rapidly absorbed after oral doses and peak plasma levels occur after about 1 to 2 hours. It is acid labile and an enteric-coated formulation has been developed. Bioavailability of esomeprazole increases on repeated dosage to about 68 and 89% for doses of 20 and 40 mg respectively. Food delays and decreases the absorption of esomeprazole, but this does not significantly change its effect on intragastric acidity. Esomeprazole is about 97% bound to plasma proteins. It is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP2C19 to hydroxy and desmethyl metabolites, which have no effect on gastric acid secretion. The remainder is metabolised by the cytochrome *P450* isoenzyme CYP3A4 to esomeprazole sulfone. With repeated dosage, there is a decrease in first-pass metabolism and systemic clearance, probably caused by an inhibition of the CYP2C19 isoenzyme. However, there is no accumulation during once daily use. The plasma elimination half-life is about 1.3 hours. Almost 80% of an oral dose is eliminated as metabolites in the urine, the remainder in the faeces.

References.

1. Andersson T, *et al.* Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole. *Clin Pharmacokinet* 2001; 40: 411–26.

2. Sostek MB, *et al.* Effect of timing of dosing in relation to food intake on the pharmacokinetics of esomeprazole. *Br J Clin Pharmacol* 2007; 64: 386–90.

Metabolism. As for omeprazole (p. 1871.2), the cytochrome P450 isoenzyme CYP2C19 is involved in the metabolism of esomeprazole, and individuals who are deficient in this enzyme are poor metabolisers of esomeprazole. However, there is some suggestion that the metabolism of esomeprazole is less dependent on this genotype, as there may be a metabolic shift towards the CYP3A4-mediated pathway.[1]

1. Schwab M, *et al.* Esomeprazole-induced healing of gastroesophageal reflux disease is unrelated to the genotype of CYP2C19: evidence from clinical and pharmacokinetic data. *Clin Pharmacol Ther* 2005; 78: 627–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Esomax; Esoprazol; Nexium; Ultrex; *Austral.*: Nexium; *Austria*: Nexium; *Belg.*: Nexiam; *Braz.*: Nexium; *Canad.*: Nexium; *Chile*: Cor; Cronopep; Emezol; Exicross; Neoren; Nexium; Ulcratex; *China*: Nexium (耐信); *Cz.*: Emanera; Emozul; Esomylan; Helides; Moproc; Nexium†; Prazectol; *Denm.*: Emanera; Emprozal†; Eprasol†; Escadra; Esodec; Esomel; Esompro†; Esopral; Esotar; Essec†; Eudresc†; Ezoret; Hydresc†; Inexium; Nexium; Slodra†; *Fin.*: Nexium; *Fr.*: Inexium; *Ger.*: Nexium; *Gr.*: Nexium; *Hong Kong*: Nexium; *Hung.*: Emozul; Nexium; Raciper; *India*: Ceso; Cucid-ES; Es-Care; Es-OD; Esocool; Esofag; Esoflo; Esomac; Esorest; Esoriv; Esotrax; Esoz; Espra; Estab; Izra; Neksium; Nexpro; Nuloc; Omipure; Sompraz; *Indon.*: Nexium; *Irl.*: Emazole; Nepramel; Nexium; *Israel*: Nexium; *Ital.*: Axagon; Esopral; Espeyen; Ezoran; Lucen; Nexium; *Jpn*: Nexium; *Malaysia*: Nexium; *Mex.*: Nexium; *Neth.*: Esobax; Esopral; Nexium; Zolex; *Norw.*: Esopral; Inexium; Nexium; *Philipp.*: Esomep; Nexium; *Pol.*: Emanera; Nexium; *Port.*: Nexium; *Rus.*: Nexium (Нексиум); *S.Afr.*: Nexiam; *Singapore*: Nexium; *Spain*: Axiago; Nexium; *Swed.*: Nexium; *Switz.*: Esomep; Nexium; *Thai.*: Nexium; *Turk.*: Nexium; *UK*: Emozul; Nexium; *Ukr.*: Esonexa (Эзонекса); Esoxium (Эзоксиум); Ezolong (Езолонг); Nexium (Нексиум); *USA*: Nexium; *Venez.*: Esoz; Nexium.

Multi-ingredient Preparations. *Austral.*: Nexium Hp; *Canad.*: Nexium 1-2-3 A; *India*: Esofag-D; Esoz-D; Ignis; Izra-D; Neutraflux; Nexpro-RD; Omidec-ES; *Swed.*: Nexium Hp; *Ukr.*: Esoxium Combi (Эзоксиум Комби).

Used as an adjunct in: *Austral.*: Vimovo; *Belg.*: Aspaxa; Vimovo; *Canad.*: Vimovo; *Cz.*: Axanum; Vimovo; *Denm.*: Vimovo; *Fin.*: Vimovo; *Ger.*: Axanum; *Irl.*: Vimovo; *Israel*: Vimovo; *Ital.*: Vimovo; *Neth.*: Axanum; Vimovo; *Norw.*: Axanum; Vimovo; *NZ*: Vimovo; *Singapore*: Vimovo; *Spain*: Vimovo; *Swed.*: Vimovo; *Switz.*: Axanum; Vimovo; *UK*: Vimovo; *USA*: Vimovo.

Pharmacopoeial Preparations

USP 36: Esomeprazole Magnesium Delayed-Release Capsules.

Euonymus

Bonetero; Bonetillo; Evónimo; Fusain Noir Pourpré; Spindle Tree Bark; Wahoo Bark; Бересклетова Кора.

ATC Herb — HC01EB5015 (Euonymus atropurpureus: *bark*); *HA06AX5003* (Euonymus atropurpureus: *bark*); *HA05WA5008* (Euonymus atropurpureus: *bark*).

UNII — 1H5XDT80QO (euonymus); WJK59V19EW (Euonymus atropurpureus *bark*).

Profile

Euonymus is the dried root-bark of *Euonymus atropurpureus* (=*Evonymus atropurpurea*) (Celastraceae). It is reported to have laxative, choleretic, and diuretic activity.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Jecopeptol†; *UK*: Acidosis; GB Tablets; Indigestion Mixture.

Famotidine (BAN, USAN, rINN)

Famotidini; Famotidin; Famotidina; Famotidinas; Famotidinum; L-64334; MK-208; YM-11170; Фамотидин.

3-[2-(Diaminomethyleneamino)thiazol-4-ylmethylthio]-*N*-sulphamoylpropionamidine.

$C_8H_{15}N_7O_2S_3$=337.4.

CAS — 76824-35-6.

ATC — A02BA03.

ATC Vet — QA02BA03.

UNII — SQZO15J2ZB.

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

Ph. Eur. 8: (Famotidine). A white or yellowish-white, crystalline powder or crystals. It exhibits polymorphism. Very slightly soluble in water and in dehydrated alcohol; freely soluble in glacial acetic acid; practically insoluble in ethyl acetate. It dissolves in dilute mineral acids. Protect from light.

USP 36: (Famotidine). A white to pale yellowish-white crystalline powder. Very slightly soluble in water; practically insoluble in alcohol, in acetone, in chloroform, in ether, and in ethyl acetate; freely soluble in dimethylformamide and in glacial acetic acid; slightly soluble in methyl alcohol. Protect from light.

Stability. References.

1. Quercia RA, *et al.* Stability of famotidine in an extemporaneously prepared oral liquid. *Am J Hosp Pharm* 1993; 50: 691–3.
2. Dentinger PJ, *et al.* Stability of famotidine in an extemporaneously compounded oral liquid. *Am J Health-Syst Pharm* 2000; 1340–2.

Uses and Administration

Famotidine is a histamine H_2-antagonist with actions and uses similar to those of cimetidine (see p. 1827.2).

Famotidine may be given orally or intravenously.

In the management of benign **gastric** and **duodenal ulceration** (see Peptic Ulcer Disease, p. 1813.2) the dose is 40 mg daily orally at bedtime, for 4 to 8 weeks. A dose of 20 mg twice daily has also been given. A maintenance dose of 20 mg at bedtime may be given to prevent recurrence of duodenal ulceration. In **gastro-oesophageal reflux disease** (p. 1807.2) the recommended oral dose is 20 mg twice daily for 6 to 12 weeks, or up to 40 mg twice daily if there is oesophageal erosion or ulceration. A maintenance dose of 20 mg twice daily may be given to prevent recurrence. For the short-term symptomatic relief of heartburn or non-ulcer **dyspepsia** (p. 1806.3) a dose of 10 mg up to twice daily is suggested. In the **Zollinger-Ellison syndrome** (p. 1814.3) the initial oral dose is 20 mg every 6 hours, increased as necessary; doses up to 800 mg daily have been used.

The usual dose of famotidine by the intravenous route is 20 mg and may be given by injection over at least 2 minutes or as an infusion over 15 to 30 minutes; the dose may be repeated every 12 hours.

Doses of famotidine should be reduced in patients with renal impairment (see below). For doses in children, see below.

Administration. Although famotidine is usually given as a film-coated tablet, an alternative wafer formulation, designed to dissolve on the tongue without the need for water, has also been developed.[1]

Parenteral formulations of famotidine are also available in some countries. Licensed product information recommends intravenous injection over at least 2 minutes or intravenous infusion over 15 to 30 minutes; however, a study that compared rapid intravenous injection (over up to 1 minute) with slow intravenous infusion found rapid injection to be comparable with infusion in terms of safety.[2] Continuous infusion has however been reported by others[3] to be more effective in the prevention of stress ulceration than bolus injection.

1. Schwartz JI, *et al.* Novel oral medication delivery system for famotidine. *J Clin Pharmacol* 1995; 35: 362–7.
2. Fish DN. Safety and cost of rapid iv injection of famotidine in critically ill patients. *Am J Health-Syst Pharm* 1995; 52: 1889–94.
3. Baghaie AA, *et al.* Comparison of the effect of intermittent administration and continuous infusion of famotidine on gastric pH in critically ill patients: results of a prospective, randomized, crossover study. *Crit Care Med* 1995; 23: 687–91.

Administration in children. Famotidine is licensed for use in children in some countries, including the USA. It is used to inhibit gastric acid secretion and may be given orally or intravenously.

In the management of **gastro-oesophageal reflux disease**, the following initial oral doses of famotidine are suggested, according to age:

- under 3 months: 500 micrograms/kg once daily
- 3 months up to 1 year: 500 micrograms/kg twice daily
- 1 to 16 years: 500 micrograms/kg twice daily; up to 40 mg twice daily may be given

Famotidine may also be given intravenously to children from 1 to 16 years. An initial dose of 250 micrograms/kg is suggested for gastro-oesophageal reflux disease, given by injection over at least 2 minutes or as an infusion over 15 minutes, and repeated every 12 hours. Up to 40 mg daily may be given.

In the management of **peptic ulcers**, famotidine may be given to children from 1 to 16 years in an initial oral dose of 500 micrograms/kg daily, either in a single dose at night or in 2 divided doses; up to 40 mg daily may be given.

Administration in renal impairment. In patients with renal impairment, famotidine clearance is reduced and the elimination half-life increased, resulting in increased serum-drug concentrations. The half-life of famotidine in healthy subjects is about 3 hours, but in patients with a creatinine clearance (CC) less than 38 mL/min[1] or those with end-stage renal disease[2] it has been reported to be 19.3 hours and 27.2 hours, respectively. A reduced dose has therefore been recommended in patients with renal impairment, although it may not be sufficient to adjust the dose only on the basis of creatinine clearance since famotidine is partly eliminated by tubular secretion, which may also be diminished.[1] Licensed product information recommends reducing the dose by half or increasing the dosage interval to 36 to 48 hours for patients with moderate or severe renal impairment (CC less than 50 mL/min). A chart review[3] in patients with end-stage renal disease suggested that most patients would tolerate a dose of 20 mg daily, although a few might need further adjustment to prevent mental status changes.

Haemodialysis does not effectively remove famotidine from the systemic circulation. The proportion removed depends on the type of membrane used; with a high flux polysulfone membrane about 16% is reported to be removed, but only 6% with a cuprophan membrane.[2] Continuous ambulatory peritoneal dialysis removes about 5% of a dose.[2] Continuous haemofiltration may remove about 16% of a dose[2] and intermittent haemofiltration is reported to remove about 4%[4] or 8%.[2] Dosage supplements of famotidine are not required during or after dialysis or filtration procedures.

1. Inotsume N, *et al.* Pharmacokinetics of famotidine in elderly patients with and without renal insufficiency and in healthy young volunteers. *Eur J Clin Pharmacol* 1989; 36: 517–20.
2. Gladziwa U, *et al.* Pharmacokinetics and dynamics of famotidine in patients with renal failure. *Br J Clin Pharmacol* 1988; 26: 315–21.
3. Redmond AM, *et al.* Use of famotidine in adult patients with end-stage renal disease: assessment of dosing and mental status changes. *Am J Med Sci* 2005; 330: 8–10.
4. Salma S, *et al.* Hemofiltrability of H_2-receptor antagonist, famotidine, in renal failure patients. *J Clin Pharmacol* 1990; 30: 159–62.

Immunomodulation. For reference to the use of H_2-antagonists as immunomodulators, see Cimetidine p. 1827.3.

Schizophrenia. There are reports of improvement in schizophrenic symptoms (p. 1031.3) in patients given famotidine.[1-4]

1. Kaminsky R, *et al.* Effect of famotidine on deficit symptoms of schizophrenia. *Lancet* 1990; 335: 1351–2.
2. Rosse RB, *et al.* Famotidine adjunctive pharmacotherapy of schizophrenia: a case report. *Clin Neuropharmacol* 1995; 18: 369–74.
3. Rosse RB, *et al.* An open-label study of the therapeutic efficacy of high-dose famotidine adjuvant pharmacotherapy in schizophrenia: preliminary evidence for treatment efficacy. *Clin Neuropharmacol* 1996; 19: 341–8.
4. Martinez MC. Famotidine in the management of schizophrenia. *Ann Pharmacother* 1999; 33: 742–7.

Adverse Effects

As for Cimetidine, p. 1828.3. Unlike cimetidine, famotidine is reported to have little or no anti-androgenic effect, although there are isolated reports of gynaecomastia and impotence.

General references.

1. Howden CW, Tytgat GNJ. The tolerability and safety profile of famotidine. *Clin Ther* 1996; 18: 36–54.

Precautions

As for Cimetidine, p. 1830.2.

Hepatic impairment. For a report of increased resistance to H_2-antagonists in patients with liver cirrhosis, see Cimetidine, p. 1830.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies famotidine 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 07/10/11)

Pregnancy. For information on the use of H_2-antagonists during pregnancy, see Cimetidine, p. 1830.3.

Interactions

Unlike cimetidine (see p. 1830.3) famotidine does not inhibit cytochrome P450 isoenzymes, and therefore is considered to have little effect on drugs metabolised by this route. However, like other H_2-antagonists its effects on gastric pH may affect the absorption of drugs whose absorption is dependent on an acid gastric pH.

Antacids. For discussion of the effect of antacids on the bioavailability of H_2-antagonists including famotidine, see Cimetidine, p. 1831.1.

Probenecid. For mention of the reduced clearance of famotidine when given with probenecid, see Cimetidine, p. 1831.1.

Sucralfate. For information on the effect of sucralfate on the bioavailability of H_2-antagonists, see Cimetidine, p. 1831.1.

Theophylline. Although famotidine is considered not to interfere with the metabolism of other drugs there is a report of a clinically significant interaction with theophylline—see p. 1236.1.

Pharmacokinetics

Famotidine is readily but incompletely absorbed from the gastrointestinal tract with peak concentrations in plasma occurring 1 to 3 hours after oral doses. The bioavailability of oral famotidine is about 40 to 45% and is not significantly affected by the presence of food.

The elimination half-life from plasma is reported to be about 3 hours and is prolonged in renal impairment (see also Administration in Renal Impairment, p. 1842.2). Famotidine is weakly bound, about 15 to 20%, to plasma proteins. A small proportion of famotidine is metabolised in the liver to famotidine *S*-oxide. About 25 to 30% of an oral dose, and 65 to 70% of an intravenous dose, is excreted unchanged in the urine, primarily by active tubular secretion. Famotidine is also found in breast milk.

Reviews.

1. Echizen H, Ishizaki T. Clinical pharmacokinetics of famotidine. *Clin Pharmacokinet* 1991; 21: 178–94.

Children. Famotidine 300 micrograms/kg intravenously was given to 10 children aged 2 to 7 years, after cardiac surgery and before extubation, to prevent aspiration.[1] This dose (equivalent to about 20 mg in adults) induced a rise in the intragastric pH within 1 hour of being given and the pH remained above 3.5 for about 9 hours. The mean elimination half-life was 3.3 hours, similar to the value in healthy adults and it was considered that doses in children need therefore only be adjusted according to body-weight and renal function. This conclusion was supported by a review of 8 studies in children over 1 year of age.[2] Conversely, in infants aged 5 to 19 days, the mean elimination half-life was prolonged (10.5 hours) secondary to reduced renal clearance.[3] This was confirmed by another study,[4] which indicated that reduced clearance was found in infants under 3 months of age, but that pharmacokinetics in older infants were similar to those previously reported for children and adults.

1. Kraus G, *et al.* Famotidine: pharmacokinetic properties and suppression of acid secretion in paediatric patients following cardiac surgery. *Clin Pharmacokinet* 1990; 18: 77–81.
2. James LP, Kearns GL. Pharmacokinetics and pharmacodynamics of famotidine in paediatric patients. *Clin Pharmacokinet* 1996; 31: 103–10.
3. James LP, *et al.* Pharmacokinetics and pharmacodynamics of famotidine in infants. *J Clin Pharmacol* 1998; 38: 1089–95. Correction. *ibid.* 2000; 40: 1298.
4. Wenning LA, *et al.* Pharmacokinetics of famotidine in infants. *Clin Pharmacokinet* 2005; 44: 395–406.

Distribution into breast milk. The peak concentration of famotidine in breast milk, which occurred in 8 women 6 hours after a 40 mg oral dose, was similar to the peak plasma concentration, which occurred 2 hours after the dose.[1]

1. Courtney TP, *et al.* Excretion of famotidine in breast milk. *Br J Clin Pharmacol* 1988; 26: 639P.

Enterohepatic recirculation. Some individuals have a second peak in the plasma concentration of famotidine, which could be due to enterohepatic recirculation. However, a maximum of 0.43% of a dose of famotidine was excreted in the bile of 2 patients after single doses of 20 mg intravenously or 40 mg orally indicating that significant recirculation had not occurred.[1]

1. Klotz U, Walker S. Biliary excretion of H_2-receptor antagonists. *Eur J Clin Pharmacol* 1990; 39: 91–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ulcelac; *Austral.*: Arfam; Ausfam; Famohexal†; Pamacid; Pepcidine; Pepzan; *Austria*: Famohexal; *Famosin*; *Sodexx Famotidine*; Ulcusan; *Braz.*: Famoset; Famotid; Famox; *Canad.*: Acid Control; Maalox H_2 Acid Controller†; Pepcid; Peptic Guard; Ulcidine; *Chile*: Anulcer; Gastrium; *China*: An Wei Te (安威特); Bei Lan De (贝兰德); Bin Xin (滨欣); Bo La Kang Wei (博拉康唯); Ding Huan (丁缓); Duo An (道安); Duo Yi (朵颐); Gai Shi Te (盖世特); Gaster (高舒达); Jie Ke Da (捷可达); Kai Su Te (凯速特); Li Luo Lan (利洛兰); Lifuding (立复丁); Wei Tian (唯天); Wei Xin (维欣); Xinfading (信法丁); Cz.: Famosan; Quamatel; Ulfamid; *Fin.*: Pepcid; Pepcidin†; *Fr.*: Pepcidac; Pepdine†; *Ger.*: Fadul†; Famobeta; Famonerton†; Pepdul; *Gr.*: Ansilan; Banatin; Cepal; Citilat; Esseldon; Gasterogen; Imposergon; Mostrelan; *Panaiba*; Peptan; Rosagenus; Sedanium-R; Vexurat; *Hong Kong*: Aulzadin†; Ausfam; Beilande; Facidin†; Fadine†; Famine†; Famocid†; Famodine†; Famolta; Famonox†; Famopsin†; Famotab†; Famotin; Famox; Gastrodomina†; Interfam; LAfamo†; Marmodine†; Motidine; Pepcidine; Phyzidine; Quamatel†; Unicidine†; Vickmodine†; Vida Famodine†; *Hung.*: Motidin; Quamatel; *India*: Acilo; Acipep; Acredin; Autidine; Blocacid; Facid; Fadine; Faltidin; Famocid; Famodin; Famonext; Famonite; Famopril; Famotin; Famowal; Famtac; Famtin; Febcid; Femidin; Fontain; Fudone; Noctin; Ulcimax; *Indon.*: Antidine; Corocyd; Denufam; Faberdin†; Facid; Famocid; Fluktant†; Gasfamin; Gaster; Gestofam; Ifamul†; Interfam; Lexmodine; Nulcefam; Pompaton; Pratifar; Promocid; Purifam†; Regastin; Renapepsa; Tismafam; Ulcerid; Ulfam†; Ulmo; *Irl.*: Famulco†; Pepcid; *Israel*: Famo; Gastro; Rogasti; *Ital.*: Famodil; Gastridin; Motiax; *Jpn*: Gaster; *Malaysia*: Famodine; Famopsin; Pepcidine†; Pepzan; Ulceran; Voker; *Mex.*: Adiatin; Androtin†; Durater; Fabutin†; Famoxal; Ludex†; Pepcidine; Sertidine; Ultidin; *Neth.*: Pepcid†; Pepcidin†; *Norw.*: Pepcid; Pepcidin†; *NZ*: Famox; Pepzan; *Philipp.*: Acrilo; Pamorila; Famtine; H2 Bloc; Hista-Bloc; Modin; Motid; Pepcidine†; Peptodin; Ulcefam; *Pol.*: Famidyna; Famogast; Quamatel; Ulfamid; *Port.*: Fatidin†; Lasa; Pepcidina; *Rus.*: Famocid (Фамоцид)†; Famonit (Фамонит)†; Famosan (Фамосан); Gastrosidin (Гастросидин); Quamatel (Квамател); Ulceran (Ульцеран)†; Ulfamid (Ульфамид); *Singapore*: Famoc; Famodine; Famonit; Famopsin; Famotin; Famox†; Febcid; Motidine; Pepcidine; Pepzan; Sunpepcin; Ulceran; *Spain*: Confobos†; Cronol; Digervin†; Eviantrina†; Fagastril†; Famulcer†; Gastrodomina†; Ingastri†; Nost†; Nulcerin; Nulcex; Pepcid; Tairal†; Tamin†; Tipodex†; Ulcetrax; Vagostal†; *Swed.*: Pepcid; *Thai.*: Agufam†; Fad; Famoc†; Famocid; Famonox; Pamopac; Famopsin; Famosia; Famotab; Fasidine; Motidine†; Pepcidine†; Pepcine†; Pepdenal; Pepfamin; Peptoci; Pharmotidine; Ulceran; Ulfamet; Vesmotidine; *Turk.*: Duovel; Fagastril; Famec; Famo; Famodin; Famogast; Famoser; Famotep; Famotsan; Gasterol; Gastifam; Gastrofam; Gastrosidin; Neotab; Nevofam; Notidin; Pepdif; Seskatidin; Ulcusar; *UAE*: Famotec; *UK*: Pepcid†; Ultra Heartburn Relief; *Ukr.*: Famodinhexal (Фамодингексал)†; Quamatel (Квамател); *USA*: Pepcid; *Venez.*: Dinamot; Famogel; Famulcer; Isomina; Klinotal; Medalin; Neutracid; Ulcenol.

Multi-ingredient Preparations. *Arg.*: Actual; Lyncis; Megalex Antiacido; Mylanta Extra; *Canad.*: Pepcid Complete; *China*: Jin Nuo (津诺); Shi Wei (仕卫); Wei Nuo Ping (唯诺平); WeiPing (谓屏); *Fin.*: Pepcid Duo; *Fr.*: Pepcidduo; *Ger.*: Pepcidual†; *India*: Diclosef; Dipal-F; Dompon F; Mefatin-Spas; Neutracaine; *Indon.*: Antasida Plus Famotidine; Magard FA; Neosanmag; Polysilane Max; Promag Double Action; *Irl.*: Pepcidtwo; *Ital.*: Pepciddual; *Mex.*: Facidex Total; Gex; *Norw.*: Pepciduo; *Spain*: Pepdual†; *Swed.*: Pepcid Duo; *UK*: Pepcidtwo; *Ukr.*: Gastromax (Гастромакс); *USA*: Dual Action Complete; Pepcid Complete; Tums Dual Action.

Used as an adjunct in: *USA*: Duexis.

Pharmacopoeial Preparations

BP 2014: Famotidine Tablets;
USP 36: Famotidine for Oral Suspension; Famotidine Injection; Famotidine Tablets.

Fig

Carica; Ficus; Higo; Инжир; Фикус.
ATC Herb — HA06AX5004 (Ficus carica: fruit).
UNII — TGD87RII2U.

Pharmacopoeias. In *Br.* and *Swiss.*

BP 2014: (Fig). The sun-dried succulent fruit of *Ficus carica* containing not less than 60.0% of water-soluble extractive. Store in a dry place.

Profile

Fig is a mild laxative and demulcent usually used with other laxatives.

Effects on the skin. Skin reactions and photodermatitis have followed application of home-made decoctions of fig leaves to the skin.[1,2]

1. Ozdamar E, *et al.* An unusual cause of burn injury: fig leaf decoction used as a remedy for a dermatitis of unknown etiology. *J Burn Care Rehabil* 2003; 24: 229–33.
2. Bassioukas K, *et al.* Erythrodermic phytophotodermatitis after application of aqueous fig-leaf extract as an artificial suntan promoter and sunbathing. *Contact Dermatitis* 2004; 51: 94–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Carilax; Frugelletten; Neda Fruchtewurfel; *Fr.*: Preservation; Resource Prunogil†; *Ger.*: florabio Manna-Feigen†; *Switz.*: Agarol Soft†; Dragees aux figues avec du sene; Fruttasan†; Pursana; Valverde Constipation dragees; Valverde Constipation sirop; *UK*: Califig; Califig.

Homoeopathic Preparations. *Fr.*: Poconeol no 79.

Fosaprepitant *(BAN, rINN)*

Fosaprépitant; Fosaprepitantum; Фозапрепитант.
(3-[((2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy)-3-(4-fluorophenyl)morpholin-4-yl)methyl]-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]phosphonic acid.
$C_{23}H_{22}F_7N_4O_6P$=614.4
CAS — 172673-20-0.
UNII — 6L8OF9XRDC.

Fosaprepitant Meglumine *(rINNM)*

Fosaprepitant Dimeglumide (BANM); Fosaprepitant Dimeglumine; Fosaprepitant meglumina; Fosaprépitant Méglumine; Meglumini Fosaprepitantum; MK-0517; Меглумина Фозапрепитант.
1-Deoxy-1-(methylamino)-D-glucitol (3-[((2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy)-3-(4-fluorophenyl)-4-morpholinyl)methyl]-2,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl] phosphonate.
$C_{23}H_{22}F_7N_4O_6P$, $2C_7H_{17}NO_5$=1004.8
CAS — 265121-04-8.
UNII — D35FM8T64X.

Stability. US licensed product information states that, once reconstituted and diluted as directed in sodium chloride 0.9%, a solution of fosaprepitant meglumine is stable for 24 hours at room temperature (at or below 25 degrees).

Uses and Administration

Fosaprepitant is a prodrug of the antiemetic aprepitant (p. 1819.2), which is a neurokinin-1 receptor antagonist. Fosaprepitant meglumine is used for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic or moderately emetogenic cancer chemotherapy. Doses are expressed in terms of the base; 188 mg of fosaprepitant meglumine is equivalent to about 115 mg of fosaprepitant. It is given intravenously 30 minutes before the start of chemotherapy, with a corticosteroid such as oral dexamethasone and a 5-HT_3 antagonist:

- *either* as a single intravenous dose equivalent to fosaprepitant 150 mg infused over 20 to 30 minutes on day 1 of the chemotherapy regimen
- *or* as an intravenous dose equivalent to fosaprepitant 115 mg infused over 15 minutes on day 1, followed by an oral dose of aprepitant 80 mg on days 2 and 3

The reconstituted dose of fosaprepitant is diluted in sodium chloride 0.9% to a final concentration of 1 mg/mL.

References.

1. Navari RM. Fosaprepitant (MK-0517): a neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting. *Expert Opin Invest Drugs* 2007; 16: 1977–85.
2. Van Belle SJP, Cocquyt V. Fosaprepitant dimeglumine (MK-0517 or L-785,298), an intravenous neurokinin-1 antagonist for the prevention of chemotherapy induced nausea and vomiting. *Expert Opin Pharmacother* 2008; 9: 3261–70.

Adverse Effects and Precautions

As for Aprepitant, p. 1819.3.

Interactions

As for Aprepitant, p. 1820.1.

Pharmacokinetics

Fosaprepitant is rapidly converted to aprepitant; for the pharmacokinetics of aprepitant, see p. 1820.1.

Bioavailability. A pharmacokinetic study found fosaprepitant 115 mg by intravenous infusion to be bioequivalent to an oral dose of aprepitant 125 mg, suggesting that these doses could be used interchangeably (see Uses and Administration, above).[1]

1. Lasseter KC, *et al.* Tolerability of fosaprepitant and bioequivalency to aprepitant in healthy subjects. *J Clin Pharmacol* 2007; 47: 834–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Emend; *Austria*: Ivemend; *Canad.*: Emend; *Cz.*: Ivemend; *Denm.*: Ivemend†; *Fr.*: Ivemend†; *Ger.*: Ivemend; *Gr.*: Ivemend; *Irl.*: Ivemend; *Israel*: Emend; *Jpn*: Proemend; *Neth.*: Ivemend; *Norw.*: Ivemend; *NZ*: Emend; *Pol.*: Ivemend; *Port.*: Ivemend; *Singapore*: Emend; *Spain*: Ivemend; *Swed.*: Ivemend; *Switz.*: Ivemend; *UK*: Ivemend; *USA*: Emend.

Frangula Bark

Alder Buckthorn Bark; Amieiro Negro; Bourdaine; Faulbaumrinde; Frángula, corteza de; Frangulabark; Frangulae cortex; Kora kruszyny; Krušinová kůra; Kutyabengekéreg; Paatsamankuori; Rhamni Frangulae Cortex; Šaltekšnių žievė; Kopa Крушины.
CAS — 8057-57-6 (frangula extract).
ATC Herb — HA06AB5013 (Rhamnus frangula: *bark*).
UNII — S2D77IH61R.

NOTE. The name Buckthorn Bark has also been used; distinguish Frangula Bark from Buckthorn (p. 1824.2) and from Sea Buckthorn (p. 2611.3).

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

Ph. Eur. 8: (Frangula Bark). The dried, whole or fragmented bark of the stems and branches of *Rhamnus frangula* (=*Frangula alnus*). It contains not less than 7.0% of glucofrangulins, expressed as glucofrangulin A ($C_{27}H_{30}O_{14}$=578.5) and calculated with reference to the dried drug. Protect from light.

Profile

Frangula bark is an anthraquinone stimulant laxative with actions and uses similar to those of senna (p. 1885.1).

Homoeopathy

Frangula bark has been used in homoeopathic medicines under the following names: Frangula; Rhamnus frangula; Rhamnus frang; Rham. fr.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Pol.*: Altra; Figura 2; Normolax; *Switz.*: Arkocaps Bourdaine; Elixir frangulae compositum.

Multi-ingredient Preparations. *Arg.*: Gastricur; *Austral.*: Normacol Plus; *Austria*: Artin†; Laxalpin†; Mag Kottas Krauterexpress Abfuhrtee; Planta Lax; *Canad.*: Bilonat; Formula T5 Tea†; Herbal Laxative†; Kalenite†; Laxatil; Laxolax; Linoforce; *Cz.*: Cholagol; Reduktan; The Salvat; *Denm.*: Ferroplex-frangula; *Fr.*: Boldoflorine; Boribel Tisane No 13†; Dragees Fuca; Dragees Vegetales Rex; Tonilax; Yerbalaxa; *Gr.*: Normacol Plus; *Hong Kong*: Hepatofalk†; Normacol Plus†; *Hung.*: Cholagol; *India*: Kanormal†; *Irl.*: Normacol Plus; *Israel*: Rekiv†; *Ital.*: Alosen†; Draverex; Estilax; Fave di Fuca; Ginolax; Lactolas; *Neth.*: Roteroblong Maagtabletten; *NZ*: Granocol†; Normacol Plus; *Pol.*: Alax; Cholavisol; Cholesol; Gastro†; Laxantol†; Normosan†; Rhelax; Senalax K; Tabletki Przeciw Niestrawnosci; Tabulettae Laxantes; *Port.*: Normacol Plus; *Rus.*: Vicair (Викаир); *S.Afr.*: Normacol Plus; *Singapore*: Normacol Plus; *Spain*: Fave de Fuca; Favilax; Fucapan; Laxodiex; LinoMed; *Switz.*: Colosan plus; Lapidar 10; Linoforce; LinoMed; Padma-Lax; Padmed Laxan; Phyto-Laxia†; *UK*: Herbulax; Linoforce; Lustys Herbalene; Natravene; Normacol Plus; *Ukr.*: Vicair (Викаир); Vicalin (Викалин).

Homoeopathic Preparations. *Canad.*: Homeo-Form S†; Vegetal Tonic; Weight Control; *Fr.*: Digeoslor; Tonique Vegetal.

Pharmacopoeial Preparations

Ph. Eur.: Frangula Bark Dry Extract, Standardised.

Gefarnate *(BAN, rINN)*

DA-688; DE-099; Gefarnate; Gefarnato; Gefarnatum; Geranyl Farnesylacetate; Гефарнат.

A mixture of stereoisomers of 3,7-dimethylocta-2,6-dienyl 5,9,13-trimethyltetradeca-4,8,12-trienoate.

$C_{27}H_{44}O_2$=400.6

CAS — 51-77-4.

ATC — A02BX07.

ATC Vet — QA02BX07.

UNII — 11SE2Y6ULA.

Profile

Gefarnate is a cytoprotective that has been used in the treatment of peptic ulcer disease and gastritis. An ophthalmic preparation is under investigation for the treatment of corneal and conjunctival epithelial disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Wycakon-G (慕加强-G); *Jpn*: Gefanil.

Ginger

Gengibre; Gingembre; Gyömbér gyökértörzs; Imbieru šakniastiebiai; Ingefära; Ingwer; Ingwerwurzelstock; Inkivääri; Jengibre; Zázvorový oddenek; Zingib.; Zingiber; Zingiberis rhizoma; Имбирь.

ATC Herb — HM01AW5029 (Zingiber officinale: rhizome); HC01EB5024 (Zingiber officinale: rhizome); HA04WX5004 (Zingiber officinale: rhizome); HA03AW5067 (Zingiber officinale: rhizome); HA09WX5003 (Zingiber officinale: rhizome).

UNII — C5529G5JPQ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*. *US* also includes the powdered form.

Ph. Eur. 8: (Ginger). The dried, whole or cut rhizome of *Zingiber officinale*, with the cork removed, either completely or from the wide flat surfaces only. Whole or cut, it contains not less than 1.5% of essential oil, calculated with reference to the anhydrous drug. It has a characteristic aromatic odour. Protect from light.

The BP 2014 states that ginger may be known in commerce as unbleached ginger.

USP 36: (Ginger). The scraped, partially scraped, or unscraped rhizome of *Zingiber officinale* (Zingiberaceae), known in commerce as unbleached ginger. It contains not less than 4.5% of alcohol-soluble extractive and not less than 10% of water-soluble extractive. Store at 8 degrees to 15 degrees. Protect from light and moisture.

Profile

Ginger has carminative properties. It is used as a flavouring agent and has been tried for the prophylaxis of motion sickness and nausea and vomiting in pregnancy, although it does not seem to be effective for postoperative nausea and vomiting (p. 1811.3).

Ginger oil is used in aromatherapy.

Homoeopathy

Ginger has been used in homoeopathic medicines under the following names: Zingiber; Zingiber officinale; Zing.

General reviews.

1. Afzal M, *et al.* Ginger: an ethnomedical, chemical and pharmacological review. *Drug Metabol Drug Interact* 2001; 18: 159–90.
2. Chrubasik S, *et al.* Zingiberis rhizoma: a comprehensive review on the ginger effect and efficacy profiles. *Phytomedicine* 2005; 12: 684–701.
3. Shukla Y, Singh M. Cancer preventive properties of ginger: a brief review. *Food Chem Toxicol* 2007; 45: 683–90.
4. Ali BH, *et al.* Some phytochemical, pharmacological and toxicological properties of ginger (Zingiber officinale Roscoe): a review of recent research. *Food Chem Toxicol* 2008; 46: 409–20.
5. Nicoll R, Henein MY. Ginger (Zingiber officinale Roscoe): a hot remedy for cardiovascular disease? *Int J Cardiol* 2009; 131: 408–9.

Nausea and vomiting. Ginger has been widely used as an antiemetic, although good evidence of efficacy has sometimes been rather scanty.

Systematic reviews and meta-analyses.

1. Ernst E, Pittler MH. Efficacy of ginger for nausea and vomiting: a systematic review of randomized clinical trials. *Br J Anaesth* 2000; 84: 367–71.
2. Betz O, *et al.* Ist Ingwer ein klinisch relevantes Antiemetikum? Eine systematische übersicht randomisierter kontrollierter Studien. *Forsch Komplementarmed Klass Naturheilkd* 2005; 12: 14–23.
3. Chaiyakunapruk N, *et al.* The efficacy of ginger for the prevention of postoperative nausea and vomiting: a meta-analysis. *Am J Obstet Gynecol* 2006; 194: 95–9.

Osteoarthritis. A report that included information from 3 randomised studies found oral ginger to have moderately beneficial effects in reducing pain and disability in osteoarthritis patients.[1]

1. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/Files/Complementary%20and%20alternative%20medicines_110120101543331.pdf (accessed 15/06/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: EziTravel†; Travacalm Natural; *Austria*: Zintona; *Canad.*: Gravol Natural Source; *Ger.*: Zintona; *Ital.*: Novomit; *Pol.*: Zingibir; *Rus.*: Avioplant (Авиоплант); *UK*: Puncto Digest; Puncto Travel; Tradimed; Travel Sickness; Zinaxin; *Ukr.*: Avioplant (Авиоплант)†.

Multi-ingredient Preparations. *Austral.*: AB Carsa Giox; AB Oriostin; Airborne Immunity; Arthro-Eze; Asa Right Powder†; Bioflex†; Boswellia Complex; Boswellia Compound; Broncafect; Cal Alkyline†; Cramplex; Curcuminoid; DiaCo; Digest Aid; DiGest; Digestive Aid; Dyzco†; Extrallfe Arthri-Care†; Fe-Max; Feminine Herbal Complex; Ginger-Vite Forte†; Mindac Morning Sickness Formula; Natal Plus; Peritone; PM Meno-Care; Psylli-Mucil Plus†; ResCo; Vegie Digestaid; *Austria*: Klosterfrau Melissengeist; Mariazeller; Pervivo; *Braz.*: Broncol†; *Canad.*: Laxolax Phyto†; *Cz.*: Klosterfrau Melisana; *Fr.*: Aromadigest†; Aromavital†; Cuivramine; Doluperine; Evacrine; Fibromyalgine; Phytemag; Trikatu; *Ger.*: Gallexier; Gastrysat†; Klosterfrau Melissengeist; *Hong Kong*: Magesto; *Hung.*: Antifront; Antifront; Bittner; Herbadict; Klosterfrau Melisana; Munipyrin; Travelon; *India*: Abana; Aglotus; Aptizooom; Arthopack; Artrex; Carmicide; Cephagraine; Cephagraine; EC-Morning; Evepearl-PMS; Happy'tizer†; Nicy Days; Papytazyme; Tummy Ease†; *Indon.*: Afomix; Avogin; Pectum; Pregnasea; Prenatal EM; Vitamam 1; Vomil; *Irl.*: Seven Seas Active Sport†; *Israel*: Emetics; *Ital.*: Donalg; Lik-Gel†; Lozione Same Urto; No Gas Enzimi; Pik Gel; *Jpn*: Bofutsushosan; Boiogito; Bukuryoin; Bukuryoingohangekobokuto; Chikujountanto; Chotosan; Daibofuto; Daikenchuto; Daisaikoto; Eppikajutsuto; Goshakusan; Goshuyuto; Hainosankyuto; Hangebyakujutsutemmato; Hangekobokuto; Hangeshashinto; Heiisan; Hochuekkito; Ireito; Jinsoin; Jumihaidokuto; Kakkonto; Kakkontokasenkyushin'i; Kamikihito; Kamishoyosan; Keishikajutsubuto; Keishikaryukotsuboreito; Keishikashakuyakudaioto; Keishikashakuyakuto; Keishininjinto; Keishito; Kihito; Kososan; Nichinto; Nijutsuto; Ninjinto; Ogikenchuto; Orento; Rikkunshito; Ryokankyomishingeninto; Ryokyojutsukanto; Saibokuto; Saikanto; Saikokaryukotsuboreito; Saikokeishikankyoto; Saikokeishito; Saireito; Seihaito; Shakanzoto; Shikunshito; Shimbuto; Shohangekabukuryoto; Shokenchuto; Shomakakkonto; Shosaikoto; Shosaikotokakikyosekko; Shoseiryuto; Sokeikakketsuto; Tokikenchuto; Tokishigyakukagoshuyushokyoto; Tokito; Unkeito; *Malaysia*: Strepsils Cough Lozenge†; Strepsils Cough Syrup†; *Philipp.*: Bo-D-Fense†; Ruflex; *Pol.*: Melisana Klosterfrau; Per vivo; *Rus.*: Dipana (Дипана); Doktor Mom (Доктор Мом); Doktor Mom Herbal Cough Lozenges (Доктор Мом Растительные Пастилки От Кашля); Maraslavin (Мараславин); Original Grosse Bittner Balsam (Оригинальный Большой Бальзам Биттнера) Sodecor (Содекор); Suprima-Broncho (Суприма-бронхо); Travisil (Трависил); Zinaxin (Зинаксин); *S.Afr.*: Helmontskruie† Lewensessens; Wonderkroonessens; *Singapore*: Artrex; Ruflex Strepsils Cough Lozenge (with natural herbs); Strepsils Cough Syrup†; *Switz.*: Padma-Lax; Padmed Laxan; Tisane pour les problemes de prostate; Wala Elixir amer; *Thai.*: Carminative Patar; Carminative Sahakarn; Caryopin; Corisul; Flataco; Flatulence†; Magesto; Mesto-Of; Mist Carminative; Patarsul; Zinaxin Plus†; *UK*: Arheumacare; Digestive; HRI Golden Seal Digestive Indian Brandee; Indigestion Relief; Jointace; Neo Baby Gripe Mixture; Neo Gripe Mixture; Wind & Dyspepsia Relief; Zinopin; *Ukr.*: Antifront (Антифронт); Antifront (Антифронт); Apitol (АПИТОЛ); Bon-Apetit (Бон-Аппетит); Bronchomed (Бронхомед); Bronchomed (Бронхомед); Doctor Cough (Доктор Кашель); Doktor Mom (Доктор Мом сироп); Doktor Mom Herbal Cough Lozenges (Доктор Мом Растительные Пастилки От Кашля); Ektis (Эктис); Lipomin (Липомин); Liponorm (Липонорм); Maraslavin (Мараславин); Memory Booster (Мемори Бустер); Osteoartisi Active (Остеоартизи Актив); Osteoartisi Active Plus (Остеоартизи Актив Плюс); Travisil (Трависил); Trypsidan (Трипсидан)†; Vitrum Beauty Elite (Витрум Бьюти Элит); Zinaxin (Зинаксин); *USA*: B-Nexa; Prenate AM with Quatrefolic; VP-GGR-B6; *Venez.*: Ervossil; Jengimiel Sabila; Jengimiel; Jengimiel.

Pharmacopoeial Preparations

BP 2014: Aromatic Cardamom Tincture; Strong Ginger Tincture; Weak Ginger Tincture;

USP 36: Ginger Capsules; Ginger Tincture.

Granisetron Hydrochloride

(BANM, USAN, rINNM)

BRL-43694A; Granisétron, chlorhydrate de; Granisetrón, hidrocloruro de; Granisetron-hydrochlorid; Granisetronhydrochlorid; Granisetronhydroklorid; Granisetroni Hydrochloridum; Granisetronihydrokloridi; Granisetrono hidrochloridas; Hidrocloruro de granisetrón; Гранисетрона Гидрохлорид.

1-Methyl-*N*-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1*H*-indazole-3-carboxamide hydrochloride.

$C_{18}H_{24}N_4O$, HCl=348.9

CAS — 109889-09-0 (granisetron); 107007-99-8 (granisetron hydrochloride).

ATC — A04AA02.

ATC Vet — QA04AA02.

UNII — 318F6L70J8.

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

Ph. Eur. 8: (Granisetron Hydrochloride). A white or almost white powder. Freely soluble in water; sparingly soluble in dichloromethane; slightly soluble in methyl alcohol. A 1% solution in water has a pH of 4.0 to 6.5.

USP 36: (Granisetron Hydrochloride). A white or almost white powder. Freely soluble in water; slightly soluble in methyl alcohol; sparingly soluble in dichloromethane. A 1% solution in water has a pH of 4.0 to 6.5. Protect from light.

Uses and Administration

Granisetron is a 5-HT_3 antagonist with an antiemetic action similar to that of ondansetron (p. 1872.2). It is used in the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy and for the prevention and treatment of postoperative nausea and vomiting (p. 1811.3). Granisetron is given as the hydrochloride, but doses are expressed in terms of the base. Granisetron hydrochloride 1.1 mg is equivalent to about 1 mg of granisetron base. The efficacy of granisetron may be enhanced by the use of corticosteroids such as dexamethasone or methylprednisolone.

For acute **nausea and vomiting** associated with **chemotherapy** granisetron is used in *prevention* and *treatment* in similar doses.

In the UK, a dose equivalent to 1 or 3 mg of granisetron as a 1 mg/mL solution is given intravenously within 30 minutes before the start of chemotherapy, either diluted in 20 to 50 mL of a suitable infusion solution and given over 5 minutes, or added to 4 times its own volume of infusion solution and given as a bolus over at least 30 seconds. Any further doses should be given at least 10 minutes apart. The recommended oral dose is 1 to 2 mg within one hour before therapy begins, then 2 mg daily as a single dose or in 2 divided doses for up to 1 week after chemotherapy. The total maximum dose by any route in 24 hours is granisetron 9 mg.

In the USA, lower intravenous doses of the equivalent of granisetron 10 micrograms/kg are recommended, beginning within 30 minutes before chemotherapy. Oral doses are similar to those described for the UK above: a single dose of

2 mg may be given up to 1 hour before chemotherapy, or, alternatively, 1 mg can be taken up to 1 hour before chemotherapy with another dose of 1 mg 12 hours later. Granisetron is given only on the days that chemotherapy is administered.

Granisetron can also be delivered transdermally to prevent nausea and vomiting caused by moderately or highly emetogenic chemotherapy. One patch supplying 3.1 mg granisetron per 24 hours is applied to the upper arm 24 to 48 hours before chemotherapy and removed at least 24 hours after chemotherapy ends. The patch can be worn for up to 7 days.

For the *prevention* of nausea and vomiting associated with **radiotherapy** the recommended oral dosage is 2 mg daily taken within 1 hour of irradiation. The drug is also given intravenously for the *treatment and prevention* of nausea and vomiting associated with radiotherapy, in the same doses as those recommended above for emetogenic chemotherapy in the UK.

For doses in children, see below.

For the *prevention* of **postoperative** nausea and vomiting 1 mg is diluted to 5 mL and given before the induction of anaesthesia by slow intravenous injection. For *treatment*, the same dose may be repeated up to a maximum of 3 mg in 24 hours.

Intranasal formulations of granisetron are under investigation.

References.

1. Adams VR, Valley AW. Granisetron: the second serotonin-receptor antagonist. *Ann Pharmacother* 1995; 29: 1240–51. Correction. *ibid.* 1996; 30: 1043.
2. Blower PR. Granisetron: relating pharmacology to clinical efficacy. *Support Care Cancer* 2003; 11: 93–100.
3. Minami M. Granisetron: is there a dose-response effect on nausea and vomiting? *Cancer Chemother Pharmacol* 2003; 52: 89–98.
4. Prentice HG. Granisetron in the control of nausea and vomiting associated with bone marrow transplantation: a review of its efficacy and tolerability. *Support Care Cancer* 2003; 11: 501–8.
5. Corman SL, *et al.* Low-dose granisetron for postoperative nausea and vomiting prophylaxis. *Ann Pharmacother* 2004; 38: 710–13.
6. Goldsmith B. First choice for radiation-induced nausea and vomiting—the efficacy and safety of granisetron. *Acta Oncol* 2004; 43 (suppl 15): 19–22.
7. Aapro M. Granisetron: an update on its clinical use in the management of nausea and vomiting. *Oncologist* 2004; 9: 673–86.
8. Duggan ST, Curran MP. Transdermal granisetron. *Drugs* 2009; 69: 2597–2605.

Administration in children. In the UK and USA, granisetron hydrochloride is licensed for use in children from 2 years of age for the management of acute nausea and vomiting associated with chemotherapy. Similar doses are used for both prevention and treatment.

- An intravenous infusion equivalent to granisetron 10 to 40 micrograms/kg, up to a maximum of 3 mg is given before the start of chemotherapy; doses should be diluted in 10 to 30 mL of infusion fluid, and given over 5 minutes. One additional dose may be given within 24 hours, but at least 10 minutes after the original infusion.
- The *BNFC* suggests that granisetron can also be given to children aged from 1 month; doses are as for those used in older children.

Oral granisetron may be given to children from 12 years of age; the adult dose can be used, see p. 1844.3.

Although not licensed in the UK, the *BNFC* recommends that similar intravenous doses to those given above can be used for both the treatment and prevention of radiotherapy-induced nausea and vomiting in children from 1 month and over.

Pain. For reference to the use of granisetron in various painful syndromes see under Uses and Administration of Ondansetron, p. 1873.1

Adverse Effects and Precautions

As for Ondansetron, p. 1873.2, although no dosage reduction is considered necessary in renal or hepatic impairment.

Carcinogenicity. The manufacturer (*Roche*) has reported an increased incidence of hepatic neoplasms in *rodents* given very high doses of granisetron for prolonged periods, but the clinical relevance of these results is unknown. Although mutagenicity and genotoxicity have not been seen in some tests, others have reported an increased incidence of polyploidy or unscheduled DNA synthesis in exposed cells.

Effects on the cardiovascular system. For a discussion of the effects of 5-HT_3 antagonists on the cardiovascular system, see under Ondansetron, p. 1873.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies granisetron 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 07/10/11)

Interactions

The metabolism of granisetron is induced by phenobarbital.

Pharmacokinetics

Granisetron is rapidly absorbed after oral doses and peak plasma concentrations occur after about 2 hours. Oral bioavailability is about 60% as a result of first-pass hepatic metabolism. Granisetron has a large volume of distribution of around 3 litres/kg; plasma protein binding is about 65%. The pharmacokinetics exhibit considerable interindividual variation, and the elimination half-life after an intravenous dose is reported to be around 4 to 5 hours in healthy subjects but about 9 to 12 hours in cancer patients. It is metabolised in the liver, primarily by *N*-demethylation, with less than 20% of a dose recovered unchanged in urine, the remainder being excreted in faeces and urine as metabolites. Granisetron clearance is not affected by renal impairment, but is lower in the elderly and in patients with hepatic impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aludal; Granitron; *Austral.*: Kytril; *Austria*: Granitron; Kytril; *Belg.*: Kytril; *Braz.*: Kidazom; Kytril; *Canad.*: Kytril; *Chile*: Kytril; *China*: An Si Ping (安斯平); Ba Tai (巴泰); Bai Hong (百宏); BiLi (比立); Da Fen Ke Quan (达芬可泉); Da Sheng Xin Er (大生欣尔); Ge Nai Ya (格奈雅); Ge Ou Shu (格欧舒); Ge Rui Tong (格瑞同); Gudi (古迪); Jie Dan (洁丹); Jun Kai (君凯); KangXin (康欣); Ke Rui Qi (珂瑞琦); Kytril (凯特瑞); Lai Qi (莱琪); Lei Sai Long (雷赛隆); Ling Ding (凌顶); Mei Pu Qiong (美芙琼); Ou Ke Ning (欧可宁); Ou Pu Ding (欧普定); Ou Zhi Ning (欧智宁); Pa Rui Da (帕瑞达); Qi Ke Ou (奇克欧); Qiong Sha Ao (琼沙奥); Run Dan (润丹); Sheng Jin Nuo (盛金诺); Shu Er Zhi (舒尔止); Si Nuo Kang Xin (斯诺康欣); Sulingqiong (苏今琼); Tu Ting (图婷); Wei Kun (唯坤); Xin Ge (新革); Yi Ge (伊格); YiXin (怡新); Zuo Tan (佐坦); Zuxin (枢星); Cz.: Emegar; Granegis; Grateva; Kytril; *Denm.*: Kytril†; *Fin.*: Kytril; *Fr.*: Kytril; *Ger.*: Axigran; Kevatril; Ribosetron; *Gr.*: Dialgyl; Granitron; Granitryl; Kytril; Toribix; *Hong Kong*: Kytril; *Hung.*: Granegis; Granigen; Kytril; *India*: Cadigran; Emegran; Grandem; Granicip; Graniforce; Graniset; Granisol; Granitero; Nisley; *Indon.*: Granon; Kytril; *Irl.*: Kytril; *Israel*: Kytril; Setron; *Ital.*: Kytril; *Jpn*: Kytril; *Malaysia*: Kytril; *Mex.*: Kogra; Kytril; Vogracen; *Neth.*: Kytril; *NZ*: Kytril†; *Philipp.*: Kytril; Sancuso; *Port.*: Kytril; *Rus.*: Kytril (Китрил); Notirol (Нотирол); *S.Afr.*: Granicip; Granitril; Kytril; *Singapore*: Kytril; *Spain*: Kytril; *Swed.*: Kytril; *Switz.*: Kytril; *Thai.*: Kytril; *Turk.*: Emetril; Granexa; Kytril; Neoset; Setron; Sinarex; *UK*: Kytril; Sancuso; *Ukr.*: Granitron (Гранитрон); Vomitran (Вомитран); *USA*: Granisol; Kytril†; Sancuso; *Venez.*: Granicip; Kytril; Rubrum.

Pharmacopoeial Preparations

USP 36: Granisetron Hydrochloride Injection; Granisetron Hydrochloride Oral Suspension; Granisetron Hydrochloride Tablets.

Hydrotalcite *(BAN, rINN)*

Hidrotalcita; Hidrotalsit; Hydrotalcit; Hydrotalcitum; Hydrotalsiitti; Гидротальцит.

Aluminium magnesium carbonate hydroxide hydrate.

$Mg_6Al_2(OH)_{16}CO_3.4H_2O$=604.0

CAS — 12304-65-3.

ATC — A02AD04.

ATC Vet — QA02AD04.

UNII — 17432CG1KU.

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

- *Co-simalcite x/y (BAN)*—where *x* and *y* are the strengths in milligrams of simeticone and hydrotalcite respectively.

Pharmacopoeias. In *Br.*

BP 2014: (Hydrotalcite). A hydrated form of an aluminium magnesium basic carbonate corresponding to the formula $Al_2Mg_6(OH)_{16}CO_3.4H_2O$. It contains not less than 15.3% and not more than 18.7% of Al_2O_3 and not less than 36.0% and not more than 44.0% of MgO. The ratio of Al_2O_3 to MgO is not less than 0.40 and not more than 0.45. A white or almost white, free-flowing, granular powder. Practically insoluble in water; it dissolves in dilute mineral acids with slight effervescence. A 4% suspension in water has a pH of 8.0 to 10.0.

Profile

Hydrotalcite is an antacid (see p. 1803.1) that is given in oral doses of up to about 1 g.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Talcid; Talidat; *China*: An Da (安达); Hai Di Te (海地特); Tai Er Sai Ke (泰尔赛克); Talcid (达喜); Wei Di Mei (威地美); Wei Tai (唯泰); *Cz.*: Rutacid; Talcid; Talidat; *Fr.*: Rennieliquo; *Ger.*: Ancid†; Megalac; Talcid; Talidat; *Gr.*: Talcid; *Hung.*: Talcid; Tisacid; *Malaysia*: Swecon; *Mex.*: Talcid; *Neth.*: Ultacit; *Philipp.*: Gaspen; *Pol.*: Malgacid; Rutacid†; Talcid; Ulcetal; *Port.*: Talcid†; *Rus.*: Rutacid (Рутацид); Talcid (Тальцид); Tisacid (Тисацид); *S.Afr.*: Altacite†; *Spain*: Talcid†; *Switz.*: Rennie Gel; *Turk.*: Hidrasit; Medalcite; Talcid.

Multi-ingredient Preparations. *Indon.*: Promag; *Jpn*: Cabe 2 New; Eki Cabe S; Eki Cabe U; *Philipp.*: Simeco; *Rus.*: Gastal (Гастал); *UK*: Altacite Plus.

Pharmacopoeial Preparations

BP 2014: Hydrotalcite Tablets.

Hyoscine *(BAN)*

Escopolamina; Hioscina; Hioscyna; Hyoscin; Hyoscinum; Hyoskiini; Scopolamin; Scopolamine; Scopolaminum; Skopolamiini; Skopolamin; Skopolamina; Tropato de epoxitropina; Гиосцин.

(-)-(1*S*,3*s*,5*R*,6*R*,7*S*,8*s*)-6,7-Epoxy-3-[(*S*)-tropoyloxy] tropane.

$C_{17}H_{21}NO_4$=303.4

CAS — 51-34-3.

ATC — A04AD01; N05CM05; S01FA02.

ATC Vet — QA04AD01; QN05CM05; QS01FA02.

UNII — DL48G20X8X.

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

Burundanga.

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

Ph. Eur. 8: (Hyoscine). A white or almost white, crystalline powder or colourless crystals. M.p. 66 degrees to 70 degrees. Soluble in water; freely soluble in alcohol.

Hyoscine Butylbromide *(BANM)*

Butilbromuro de hioscina; Butylscopolamine Bromide; Butylscopolaminii Bromidum; Butylscopolaminiumbromid; *N*-Butylscopolammonium Bromide; Butylscopolamonii Bromidum; Butylskopolaminium-bromid; Escopolamina, butilbromuro de; Hioscino butilbromidas; Hioszcin-butilbromid; Hyosin Bütilbromür; Hyoscinbutylbromid; Hyoscine-*N*-butyl Bromide; Hyoscini Butylbromidum; Hyoskiinibutyylibromidi; Scopolamine *N*-Butyl Bromide; Scopolamine Butylbromide; Scopolamine, butylbromure de; Scopolamini Butylbromidum; Scopolomini Butylbromidum; Skopolamino butilbromidas; Szkopolamin-butilbromid; Гиосцина бутилбромид.

(-)-(1*S*,3*s*,5*R*,6*R*,7*S*,8*r*)-6,7-Epoxy-8-butyl-3-[(*S*)-tropoyloxy]tropanium bromide.

$C_{21}H_{30}BrNO_4$=440.4

CAS — 149-64-4.

ATC — A03BB01.

ATC Vet — QA03BB01.

UNII — 0GH9JX37C8.

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

Ph. Eur. 8: (Hyoscine Butylbromide). A white or almost white, crystalline powder. Freely soluble in water and in dichloromethane; sparingly soluble in dehydrated alcohol. A 5% solution in water has a pH of 5.5 to 6.5.

Hyoscine Hydrobromide *(BANM)*

Bromhidrato de Escopolamina; Escopolamina, hidrobromuro de; Hidrobromuro de hioscina; Hioscino hidrobromidas; Hioscyny bromowodorek; Hioszcin-hidrobromid; Hyosin Hidrobromür; Hyoscinhydrobromid; Hyoscini Hydrobromidum; Hyoskiinihydrobromidi; Ioscina Bromidrato; Scopolamine Bromhydrate; Scopolamine, bromhydrate de; Scopolamine Hydrobromide; Scopolaminhydrobromid; Scopolamini Hydrobromidum; Scopolamini Hydrobromidum Trihydricum; Skopolaminihydrobromidi; Skopolamin-bromid trihydrát; Skopolaminhydrobromid; Skopolamino hidrobromidas; Szkopolamin-butilbromid; Гиосцина гидробромид.

(-)-(1*S*,3*s*,5*R*,6*R*,7*S*)-6,7-Epoxytropan-3-yl (*S*)-tropate hydrobromide trihydrate.

$C_{17}H_{21}NO_4HBr.3H_2O$=438.3

CAS — 114-49-8 (anhydrous hyoscine hydrobromide); 6533-68-2 (hyoscine hydrobromide trihydrate).

ATC — A04AD01; N05CM05; S01FA02.

ATC Vet — QA04AD01; QN05CM05; QS01FA02.

UNII — 451IF8OGX8.

NOTE. HYO is a code approved by the BP 2014 for use on single unit doses of eye drops containing hyoscine hydrobromide where the individual container may be too small to bear all the appropriate labelling information.

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

Ph. Eur. 8: (Hyoscine Hydrobromide). A white or almost white, efflorescent, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol. A 5% solution in water has a pH of 4.0 to 5.5. Store in well-filled airtight containers of small capacity. Protect from light.

USP 36: (Scopolamine Hydrobromide). Colourless or white crystals, or white granular powder. Is odourless and slightly efflorescent in dry air. Soluble 1 in 1.5 of water and 1 in 20 of alcohol; slightly soluble in chloroform; insoluble in ether. pH of a 5% solution in water is between 4.0 and 5.5. Store in airtight containers. Protect from light.

Hyoscine Methobromide (BAN)

Epoxymethamine Bromide; Escopolamina, metilbromuro de; Hyoscine Methylbromide; Methscopolamine Bromide; Metilbromuro de hioscina; Metobromuro de escopolamina; Metobromuro de hioscina; Scopolamine Methobromide; Scopolamine Methylbromide; Гиосцина Метобромид.

(-)-(1*S*,3*s*,5*R*,6*R*,7*S*)-6,7-Epoxy-8-methyl-3-[(*S*)-tropoyloxy]tropanium bromide.

$C_{18}H_{24}BrNO_4$=398.3

CAS — 155-41-9.

ATC — A03BB03; S01FA03.

ATC Vet — QA03BB03; QS01FA03.

UNII — RTN51LK7WL.

Pharmacopoeias. In *US*.

USP 36: (Methscopolamine Bromide). Store in airtight containers. Protect from light.

Hyoscine Methonitrate (BANM)

Escopolamina, metilnitrato de; Hyoscine Methylnitrate; Methscopolamine Nitrate; Methylhyoscini Nitras; Methylscopolamine Nitrate; Methylscopolamini Nitras; Metilnitrato de hioscina; Metonitrato de escopolamina; Metonitrato de hioscina; Metylskopolaminnitrat; Metyylliskopolamiininitraatti; Scopolamine Methonitrate; Scopolamine Methylnitrate; Гиосцина Метонитрат.

(-)-(1*S*,3*s*,5*R*,6*R*,7*S*)-6,7-Epoxy-8-methyl-3-[(*S*)-tropoyloxy]tropanium nitrate.

$C_{18}H_{24}N_2O_7$=380.4

CAS — 6106-46-3.

ATC — A03BB03; S01FA03.

ATC Vet — QA03BB03; QS01FA03.

UNII — K0813KQM3V.

Uses and Administration

Hyoscine is a tertiary amine antimuscarinic with central and peripheral actions (see Action of Antimuscarinics, p. 1310.3). It is a more powerful suppressant of salivation than atropine, and usually slows rather than increases heart rate, especially in low doses. Its central action differs from that of atropine in that it depresses the cerebral cortex and produces drowsiness and amnesia. Hyoscine hydrobromide is also a tertiary amine, whereas hyoscine butylbromide, hyoscine methobromide, and hyoscine methonitrate are quaternary ammonium derivatives.

Hyoscine and hyoscine hydrobromide are used in the management of motion sickness and other forms of nausea and vomiting (below); hyoscine hydrobromide is also given as a premedicant in anaesthesia (below), and to produce mydriasis and cycloplegia (below). Hyoscine butylbromide and other quaternary ammonium derivatives are used in conditions associated with visceral spasms. Hyoscine methobromide has also been employed as an adjunct in the treatment of peptic ulcer disease (below).

Other hyoscine salts or derivatives that have been used include hyoscine borate, hyoscine hydrochloride, and hyoscine oxide hydrobromide.

Anaesthesia. The role of antimuscarinics, including hyoscine, in anaesthesia is discussed under Atropine on p. 1311.1. For the use of hyoscine in the prevention of postoperative nausea and vomiting, see below.

For premedication hyoscine hydrobromide is injected subcutaneously or intramuscularly in doses of 200 to 600 micrograms, usually with papaveretum about half to one hour before induction of general anaesthesia. In the UK, a dose of 15 micrograms/kg is licensed in children (the *BNFC* suggests that this dose is appropriate from 1 to 12 years of age; older children may be given the adult dose). If necessary for acute use, the same doses may be given by intravenous injection.

Anoxic seizures. For mention of the use of transdermal hyoscine as an alternative to atropine in the management of reflex anoxic seizures in children, see p. 1311.3.

Biliary and renal colic. Hyoscine has been used as an adjunct to opioid analgesics for symptomatic relief of biliary or renal colic (see p. 6.3) although the evidence for such use is weak. Hyoscine butylbromide 20 mg is given by intramuscular or slow intravenous injection; this may be repeated after 30 minutes if necessary to a maximum daily dose of 100 mg. See also Palliative Care, below.

References.

1. Holdgate A, Oh CM. Is there a role for antimuscarinics in renal colic? A randomized controlled trial. *J Urol (Baltimore)* 2005; 174: 572–5.

Cardiac disorders. Although hyoscine is not one of the conventional therapies for heart failure (p. 1262.3) or myocardial infarction (p. 1257.1), low-dose transdermal hyoscine can increase cardiac vagal activity and thereby reduce the autonomic imbalance seen in patients with these conditions.[1-3] Improved exercise tolerance has been reported after 1 week of treatment with transdermal hyoscine in a small open study in 14 patients with mild to moderate heart failure.[4]

1. Casadei B, *et al.* Low doses of scopolamine increase cardiac vagal tone in the acute phase of myocardial infarction. *Circulation* 1993; 88: 353–7.
2. La Rovere MT, *et al.* Scopolamine improves autonomic balance in advanced congestive heart failure. *Circulation* 1994; 90: 838–43.
3. Venkatesh G, *et al.* Double blind placebo controlled trial of short term transdermal scopolamine on heart rate variability in patients with chronic heart failure. *Heart* 1996; 76: 137–43.
4. De Vecchis R, *et al.* Different impact of carvedilol and transdermal scopolamine on cardiovascular performance of mild-moderate chronic heart failure patients: evidence of useful effects of scopolamine on tolerance to work load. *Minerva Cardioangiol* 2000; 48: 393–401.

Depression. Rapid reductions in severity of depression were seen after intravenous hyoscine hydrobromide 4 micrograms/kg was given to patients with major depressive disorders or bipolar disorders (see Depression, p. 398.1). Repeat doses showed more benefit than single doses. Clinical effects persisted beyond the treatment period, which led the authors to conclude the effects were not due to anticholinergic euphoria. While noting that the optimal schedule and potential long-term use of hyoscine as an antidepressant needed further study, they also concluded that hyoscine could be a relatively safe and well-tolerated intervention for achieving a rapid initial antidepressant response.[1]

1. Furey ML, Drevets WC. Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. *Arch Gen Psychiatry* 2006; 63: 1121–9.

Dysmenorrhoea. Hyoscine as the butylbromide or hydrobromide has been used for its antispasmodic action in the treatment of dysmenorrhoea. (p. 8.2), but the *BNF* considers that antispasmodics do not generally provide significant relief.

Eye disorders. Hyoscine hydrobromide is used in the eye for its mydriatic and cycloplegic actions (p. 2000.2) usually in a concentration of 0.25%. It has a faster onset and shorter duration of action than atropine although the effects may still persist for up to 3 to 7 days. It may be useful for patients who are hypersensitive to atropine.

Hyperhidrosis. Adverse effects of antimuscarinics given orally generally preclude their use by this route for the management of hyperhidrosis (p. 1685.1), but some, such as hyoscine, have been applied topically as alternatives to aluminium salts. Hyoscine hydrobromide applied as a 3% cream was successful in reducing gustatory sweating, consisting of flushing and sweating over the right mandible during eating, in a patient who had previously undergone surgical excision of the right submandibular salivary gland.[1] The use of transdermal or injectable hyoscine was reported[2] to be effective for the control of opioid-associated sweating in 2 patients receiving palliative care (see also below for other uses of hyoscine in palliative care).

1. Bailey BMW, Pearce DE. Gustatory sweating following submandibular salivary gland removal. *Br Dent J* 1985; 158: 17–18.
2. Mercadante S. Hyoscine in opioid-induced sweating. *J Pain Symptom Manage* 1998; 15: 214–15.

Nausea and vomiting. Hyoscine is effective in the prevention of **motion sickness** and is one of the principal drugs used. It may be given orally for short-term protection or by transdermal patch for a prolonged duration of action.

In the UK, a dose of hyoscine hydrobromide is taken 20 to 30 minutes before a journey, followed by the same dose every 6 hours if required up to a maximum of 3 doses in 24 hours. The usual dose in adults is 300 micrograms. Children aged 4 to 10 years may be given 75 to 150 micrograms and those over 10 years, 150 to 300 micrograms. Children aged 3 to 4 years may be given 75 micrograms, repeated once if necessary to a maximum total dose of 150 micrograms in 24 hours. Hyoscine is also given via a transdermal patch which is placed behind the ear and supplies 1 mg over 3 days. The patch is licensed in the UK for adults and children aged 10 years and over and should be applied 5 to 6 hours before travelling or on the preceding evening and removed at the end of the journey.

An intranasal formulation of hyoscine hydrobromide has been investigated for the treatment and prevention of motion sickness.

Transdermal hyoscine has been used in adults and children for the prevention of **postoperative nausea and vomiting.**

Hyoscine hydrobromide has also been given by intravenous, subcutaneous, or intramuscular injection for its antiemetic effect in doses ranging from 200 micrograms to 1 mg in adults.

The other drugs used in the management of motion sickness and postoperative nausea and vomiting are discussed on p. 1811.3.

References.

1. Kranke P, *et al.* The efficacy and safety of transdermal scopolamine for the prevention of postoperative nausea and vomiting: a quantitative systematic review. *Anesth Analg* 2002; 95: 133–43.
2. Nachum Z, *et al.* Transdermal scopolamine for prevention of motion sickness: clinical pharmacokinetics and therapeutic applications. *Clin Pharmacokinet* 2006; 45: 543–66.
3. Spinks AB, *et al.* Scopolamine (hyoscine) for preventing and treating motion sickness. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 03/04/08).

Palliative care. The *BNF* includes doses for hyoscine in palliative care. *Hyoscine hydrobromide* is used in palliative care for the treatment of bowel colic and to reduce excessive respiratory secretions, although care should be taken to avoid the discomfort of a dry mouth. The following parenteral doses have been suggested for adults:

- 400 micrograms by subcutaneous injection, usually given every 4 hours when required, although hourly use is sometimes necessary

or

- 1.2 to 2 mg by continuous subcutaneous infusion over 24 hours

To reduce excessive respiratory secretions in children, the *BNFC* suggests parenteral doses of:

- 10 micrograms/kg (maximum 600 micrograms) by subcutaneous or intravenous injection every 4 to 8 hours

or

- 40 to 60 micrograms/kg by continuous subcutaneous or intravenous infusion over 24 hours

Oral and sublingual doses have also been suggested for children, according to age:

- 2 to 12 years: 10 micrograms/kg (maximum 300 micrograms) four times daily
- 12 to 18 years: 300 micrograms four times daily

Alternatively, hyoscine hydrobromide may be given as a transdermal patch in the following doses:

- 1 month to 3 years: 250 micrograms (quarter of a patch) every 72 hours
- 3 to 10 years: 500 micrograms (half a patch) every 72 hours
- 10 to 18 years: 1 mg (one patch) every 72 hours

Hyoscine has also been used transdermally in adults for reducing respiratory secretions; one regimen uses 2 to 4 mg (two to four patches) every 72 hours with additional parenteral doses of glycopyrronium bromide (see p. 2520.1).[1]

Hyoscine butylbromide is also used in palliative care; the *BNF* suggests the following doses for adults:

- bowel colic: 60 to 300 mg by continuous subcutaneous infusion over 24 hours
- excessive respiratory secretions: 20 to 120 mg by continuous subcutaneous infusion over 24 hours

or

- bowel colic and excessive respiratory secretions: 20 mg by subcutaneous injection, usually given every 4 hours when required, although hourly use is sometimes necessary

The use of hyoscine in palliative care has been reviewed.[2,3] Hyoscine hydrobromide may be more effective than glycopyrronium bromide in drying secretions, and has a rapid onset of action, but it can produce both sedation and agitation;[4] there is no clear evidence favouring one antimuscarinic over another.[4,5]

1. Klintzel PE, *et al.* Anticholinergic medications for managing noisy respirations in adult hospice patients. *Am J Health-Syst Pharm* 2009; 66: 458–64.
2. Muir JC, von Gunten CF. Antisecretory agents in gastrointestinal obstruction. *Clin Geriatr Med* 2000; 16: 327–34.
3. Spiller JA, Fallon M. The use of Scopoderm in palliative care. *Hosp Med* 2000; 61: 782–4.
4. Bennett M, *et al.* Association for Palliative Medicine. Using anti-muscarinic drugs in the management of death rattle: evidence-based guidelines for palliative care. *Palliat Med* 2002; 16: 369–74.
5. Wee B, Hillier R. Interventions for noisy breathing in patients near to death. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 04/06/09).

Smooth muscle spasm. Hyoscine has been used as an antispasmodic (p. 1803.3) to relieve the pain of smooth muscle spasm associated with the gastrointestinal tract and genito-urinary tract. In adults, *hyoscine butylbromide* 20 mg

may be given orally four times daily; children aged 6 to 12 years may be given 10 mg three times daily. It is also used in adults with irritable bowel syndrome (p. 1810.3); the recommended oral starting dose is 10 mg three times daily which may be increased to 20 mg four times daily, if necessary. Hyoscine butylbromide may also be given by intramuscular or slow intravenous injection for acute spasm and as an antispasmodic in diagnostic procedures. Adults may be given a dose of 20 mg, repeated after 30 minutes if necessary, up to a maximum of 100 mg daily. Although hyoscine butylbromide injection is unlicensed in the UK for use in children, the *BNFC* suggests the following doses repeated after 30 minutes if necessary (but more frequently in endoscopy):

- 2 to 6 years: 5 mg (maximum 15 mg daily)
- 6 to 12 years: 5 to 10 mg (maximum 30 mg daily)
- 12 to 18 years: 20 mg (maximum 80 mg daily)

As an adjunct in the treatment of peptic ulcer disease; *hyoscine methobromide* has been licensed in the USA in a dose of 2.5 mg half an hour before meals and 2.5 to 5 mg at bedtime.

References.

1. Tytgat GN. Hyoscine butylbromide: a review of its use in the treatment of abdominal cramping and pain. *Drugs* 2007; 67: 1343–57.

Urinary incontinence. Antimuscarinics have been used in the management of urge incontinence (p. 2349.2) but the incidence of adverse effects can be high. Results of a small study[1] suggested that transdermal hyoscine might be of benefit in females with detrusor instability.

1. Muskat Y, *et al.* The use of scopolamine in the treatment of detrusor instability. *J Urol (Baltimore)* 1996; 156: 1989–90.

Vertigo. Hyoscine has a long history of use in the management of vertigo, although other drugs are now preferred (p. 612.3).

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. In contrast to atropine, hyoscine produces central depression at therapeutic doses and symptoms include drowsiness and fatigue. Toxic doses of hyoscine produce stimulation of the CNS in a similar manner to atropine. However, hyoscine does not stimulate the medullary centres and therefore does not produce the increases in respiration rate or blood pressure seen with atropine. Hyoscine may produce CNS stimulation rather than depression at therapeutic doses if used in the presence of pain without opioid analgesics; symptoms include excitement, restlessness, hallucinations, or delirium.

Patients who experience drowsiness should not drive or operate machinery. Caution has been advised in elderly patients and in patients with impaired liver, or kidney function, as adverse CNS effects have been stated to be more likely in these patients. There have been rare reports of an increase in frequency of seizures in epileptic patients.

The quaternary derivatives, such as the butylbromide, methobromide, or methonitrate, do not readily cross the blood-brain barrier, so central effects are rare.

Abuse. Hyoscine has been used by criminals to incapacitate and produce anterograde amnesia in their victims in crimes such as drug-facilitated rape ('date rape'), robbery, and kidnapping. In some countries in South America there has been a particular problem with the use of powders or extracts of plants containing hyoscine for such crimes. A powder, known locally as burundanga, prepared from the borrachero or borracchio tree (also referred to as cacao sabanero) has been blown into the victim's face or given in drinks, chocolate, or chewing gum.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of hyoscine by breast-feeding mothers, and that therefore it may be considered 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 19/01/06)

Effects on body temperature. Central anticholinergic syndrome was thought to be responsible for hyperthermia and consequent multi-organ failure in an adolescent with cerebral palsy who was receiving symptomatic treatment with transdermal hyoscine.[1] Although the condition was rare in children it should be considered in those being given antimuscarinics if fever developed, particularly in the absence of sweating.

1. Frampton A, Spinks J. Hyperthermia associated with central anticholinergic syndrome caused by a transdermal hyoscine patch in a child with cerebral palsy. *Emerg Med J* 2005; 22: 678–9.

Effects on the eyes. *ANISOCORIA.* Although bilateral mydriasis has occurred with the use of transdermal hyoscine, development of a unilateral fixed dilated pupil (anisocoria) may be due to contamination of a finger with hyoscine in handling the device, and then rubbing the eye.[1-6] Similarly, anisocoria has been attributed[7] to ocular contamination after handling broken hyoscine methobromide tablets.

1. Chiaramonte JS. Cycloplegia from transdermal scopolamine. *N Engl J Med* 1982; 306: 174.
2. Lepore FE. More on cycloplegia from transdermal scopolamine. *N Engl J Med* 1982; 307: 824.
3. McCrary JA, Webb NR. Anisocoria from scopolamine patches. *JAMA* 1982; 248: 353–4.
4. Bienia RA, *et al.* Scopolamine skin-disks and anisocoria. *Ann Intern Med* 1983; 99: 572–3.
5. Riddick FA, Jordan JD. Cruise ship anisocoria. *Ann Intern Med* 1992; 117: 95.
6. Lin Y-C. Anisocoria from transdermal scopolamine. *Paediatr Anaesth* 2001; 11: 626–7.
7. Nussdorf JD, Berman EL. Anisocoria associated with the medical treatment of irritable bowel syndrome. *J Neuroophthalmol* 2000; 20: 100–101.

GLAUCOMA. A few cases of angle-closure glaucoma, both unilateral[1] and bilateral,[2] have been associated with transdermal hyoscine devices.

1. Hamill MB, *et al.* Transdermal scopolamine delivery system (TRANSDERM-V) and acute angle-closure glaucoma. *Ann Ophthalmol* 1983; 15: 1011–12.
2. Praunfelder FT. Transdermal scopolamine precipitating narrow-angle glaucoma. *N Engl J Med* 1982; 307: 1079.

STRABISMUS. Strabismus developed in a 4-year-old boy during treatment with transdermal hyoscine patches for drooling.[1] The strabismus resolved shortly after stopping hyoscine.

1. Good WV, Crain LS. Esotropia in a child treated with a scopolamine patch for drooling. *Pediatrics* 1996; 97: 126–7.

Effects on mental function. There have been reports of psychotic reactions associated with the transdermal use of hyoscine.[1-6] Psychotic reactions have also occurred after instillation of hyoscine eye drops.[7]

1. Osterholm RK, Camoriano JK. Transdermal scopolamine psychosis. *JAMA* 1982; 247: 3081.
2. Rodysill KJ, Warren JB. Transdermal scopolamine and toxic psychosis. *Ann Intern Med* 1983; 98: 561.
3. MacEwan GW, *et al.* Psychosis due to transdermally administered scopolamine. *Can Med Assoc J* 1985; 133: 431–2.
4. Ziskind AA. Transdermal scopolamine-induced psychosis. *Postgrad Med* 1988; 84: 73–6.
5. Rubner O, *et al.* Ungewöhnlicher Fall einer Psychose infolge einer Langzeiteinwirkung mit einem Skopolaminmembranpflaster: Paranoid-halluzinatorische und delirante Symptomatik. *Nervenarzt* 1997; 68: 77–9.
6. Minagar A, *et al.* Transderm-induced psychosis in Parkinson's disease. *Neurology* 1999; 53: 433–4.
7. Barker DB, Solomon DA. The potential for mental status changes associated with systemic absorption of anticholinergic ophthalmic medications: concerns for the elderly. *DICP Ann Pharmacother* 1990; 24: 847–50.

Effects on the oesophagus. A patient developed pain on swallowing after 4 days of treatment with hyoscine. Endoscopy showed oesophageal ulceration, which healed completely after 8 weeks of esomeprazole treatment.[1]

1. Philcox S, Keegan A. A case of hyoscine-related oesophagitis. *Med J Aust* 2007; 186: 650–1.

Effects on the skin. Contact dermatitis occurred in 16 men being treated for seasickness with transdermal hyoscine for 6 weeks to 15 months.[1]

1. Gordon CR, *et al.* Allergic contact dermatitis caused by transdermal hyoscine. *BMJ* 1989; 298: 1220–1.

Migraine. A small case-control study[1] suggested that hyoscine could trigger or exacerbate migraine in patients with a history of the condition.

1. Ikeda K, *et al.* Scopolamine-induced migraine like headache. *Intern Med* 2009; 48: 681–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hyoscine butylbromide 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 07/10/11)

Pregnancy. A report[1] of hyoscine toxicity in a neonate born to a mother who had received a total of 1.8 mg of hyoscine in divided doses with pethidine and levorphanol before delivery. The neonate was lethargic, barrel chested, and had a heart rate of 200 beats/minute. Symptoms subsided when physostigmine 100 micrograms was given intramuscularly.

1. Evens RP, Leopold JC. Scopolamine toxicity in a newborn. *Pediatrics* 1980; 66: 329–30.

Withdrawal. A withdrawal syndrome of dizziness and nausea[1,2] can occur in patients who have used transdermal hyoscine patches for several days; hypersalivation and diarrhoea has also been described.[3] In reported cases, transdermal hyoscine had been used continuously for 7 or 10 days to prevent motion sickness. Symptoms usually begin 2 or 3 days after the last patch has been removed, and may last for a few days.

1. Meyboom RHB. More on Transderm Scop patches. *N Engl J Med* 1984; 311: 1377.
2. Saxena K, Saxena S. Scopolamine withdrawal syndrome. *Postgrad Med* 1990; 87: 63–6.
3. Feder RE. Transdermal scopolamine withdrawal syndrome. *Clin Neuropharmacol* 1999; 22: 120.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

The sedative effect of hyoscine may be enhanced by alcohol or other CNS depressants.

Pharmacokinetics

Hyoscine is readily absorbed from the gastrointestinal tract after oral doses of the hydrobromide. It is almost entirely metabolised, probably in the liver; only a small proportion of an oral dose is excreted unchanged in the urine. It crosses the blood-brain barrier and has been stated to cross the placenta. Hyoscine is also well absorbed after application to the skin.

The quaternary derivatives, such as the butylbromide or methobromide, are poorly absorbed from the gastrointestinal tract and do not readily pass the blood-brain barrier.

References.

1. Ebert U, *et al.* Pharmacokinetics and pharmacodynamics of scopolamine after subcutaneous administration. *J Clin Pharmacol* 1998; 38: 720–6.
2. Nachum Z, *et al.* Scopolamine bioavailability in combined oral and transdermal delivery. *J Pharmacol Exp Ther* 2001; 296: 121–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Buscapina; Cifespasmo; Colobolina; Excelentia Antiespasmodico; Luar-G; Pasmodina; Rupe-N; ***Austral.***: Buscopan; Kwells; Setacol; Stomex; Travacalm HO; ***Austria***: Buscapina; Buscopan; ***Belg.***: Buscopan; ***Braz.***: Belscopan; Buscopan; Hiospan; Uni Hioscin; ***Canad.***: Buscopan; Transderm-V; ***Chile***: Buscapina; ***China***: Buscopan; Gan Mei Duo Lan (甘美多兰); Kimite (可敌特); Cz.: Buscopan; ***Denm.***: Buscopan; Scopoderm; ***Fin.***: Buscopan; Scopoderm; ***Fr.***: Scoburen; Scopoderm TTS; ***Ger.***: Boro-Scopol; BS Carino; BS-ratiopharm; Buscopan; Scopoderm TTS†; Spasman scop†; ***Gr.***: Avotrin; Buscopan; Naftex; Scopoderm TTS; ***Hong Kong***: Ariel; BF-Horloten†; Buscopan; Busopin; Colospan†; Copan†; Dhacopan; Holomine†; Hyomide; Hysopan†; Spasmoliv†; Vidaspan†; ***Hung.***: Buscopan; ***India***: Belloid; Buscopan; Hyospan; Hyospas; Hyoswift; ***Indon.***: Buscopan; Dormi; Gitas; Hyscopan; Scobutrin; Scopamin; Scopma; Spashi; Spasmolit; Stomica; ***Irl.***: Buscopan; Kwells; ***Ital.***: Addofix; Buscopan; Transcop; ***Jpn***: Buscopan; ***Malaysia***: Buscopan; Buston; Copan; Dhacopan; Encodex; Pucon; Hyomide; Spasmoliv†; Vacopan; ***Mex.***: Alpin; Biomesina; Bipasmin; Brolamina†; Buscapina; Busina†; Busprina-S; Butiral; Cryopina; Espacil; Espafarm; Excosine-S; Grafin; Hiosultrina; Lemophar; Selpiran-S; Serralpina; ***Neth.***: Buscopan; Scopoderm TTS; ***Norw.***: Buscopan; Scopoderm; ***NZ***: Buscopan; Gastro-Soothe; Scopoderm TTS; ***Philipp.***: Amucin; Ascopen; Buscin; Buscomed; Buscopan; Busopin; Buston; Pucon; Gascopan; Gastride; Losil; Rotomide; Scolmin; Spasmosan; Xspas; ***Pol.***: Buscolysin; Buscopan; Scopolan; ***Port.***: Buscopan; ***Rus.***: Buscopan (Бускопан); ***S.Afr.***: Buscopan; Hyospasmol; Scopaject; Scopex; ***Singapore***: Buscopalamin; Buscopan; Colospan; Copan; Cospan; Dhacopan; Dividol; Pucon; Hyomide; Hyosun; Scopoderm TTS; SP-Anspaz; Spasmoliv; Vacopan; ***Spain***: Buscapina; ***Swed.***: Buscopan; Scopoderm; ***Switz.***: Buscopan; ***Thai.***: Amcopan; Antispa Plus; Antispa; Bacotan; Buscono; Buscopan; Butyl; Cencopan; Eralgavvv†; Pucon†; Higan†; Hy-Spa; Hybutyl; Hyosman; Hyosmed; Hyospan; Hyostan; Hyozin; Kanin; Myspa; Scopas; Spaloxt; Spascopan; Spasgone-H; Spasmo; U-Oscine; Uospan; Uricine†; Vacopan; Vescopolamine; ***Turk.***: Buscopan; Butopan; Molit; Spazmol; Spazmotek; ***UAE***: Scopinal; ***UK***: Buscopan; Joy-Rides; Kwells; Scopoderm TTS; ***Ukr.***: Spasmobru (Спазмобрю); ***USA***: Pamine; Scopace†; Transderm Scop; ***Venez.***: Buscapina; Hiocin.

Multi-ingredient Preparations. ***Arg.***: 6-Copin†; 6-Copin; Buscapina Compositum N; Buscapina Compositum; Buscapina Fem; Cifespasmo Compuesto; Colobolina D; Espasmo Biotenk; Espasmol; Feminity; Gastrolina Compuesta; Hioscina Compuesta; Ibu-Buscapina; Ibuxim Fem; Labsyna Fem; Lisalgil Compuesto; Luar-G Compositum; Novopasmil Compuesto; Pasmodina Compuesta; Rupe-N Compuesto; Tafirol Mujer; ***Austral.***: Donnagel; Donnalix; Donnatab; Travacalm; ***Austria***: Buscopan Compositum; ***Belg.***: Buscopan Compositum; ***Braz.***: Algexin; Atroveran Plus; Belspan; Binospan; Buscoduo; Buscopan Composto; Buscopan Plus; Buscoveran Composto; Butilamin†; Disbuspan†; Dorspan Composto; Espasmodid Composto; Hioariston; Hiospan Composto; Kindpasm†; Neocopan; Tropinal; Veratropan Composto†; ***Chile***: Algion†; Buscapina Compositum; Crotalgina; Dolcopin; Novalona; ***Ger.***: Buscopan Plus; ***Gr.***: Buscopan Plus; Colik; Spasmo-Apotel; ***Hong Kong***: Epilon; Unigan; Virulex Forte; ***Indon.***: Aludonna; Aludonna; Buscopan Plus; Dormi Comp; Gitas Plus; Procolic; Scopamin Plus; Scopma Plus; Spashi Plus; Spaslic; Spasmacine; Untheco†; ***Irl.***: Peminax; ***Ital.***: Buscopan Compositum; Spasmeridan†; ***Mex.***: Algosfar; Anadil; Benfol†; Biomesina Compuesta; Bipasmin Compuesto; Buscapina Compositum N; Buscapina Composi-

tum; Buscapina Fem; Busconet; Busepan; Busprina; Colepren; Doltrix; Donodol Compuesto; Escapin-N; Espacil Compuesto; Espasmogress; Hiosultrina-F; Infafren Compuesto†; Mebuxina; Neo-Pasmonal; Pasmodil†; Pirobutil; Precicol; Prestodol Compuesto; Retodol Compositum; Selpiran Compuesto; Selpiran; Serralpina Compuesta; Viladol Plus; Viladol-Met†; *Philipp.*: Buscopan Plus; Unigan; *Pol.*: Scopolan Compositum; Vegantalgin H; *Port.*: Buscopan Compositum N; *S.Afr.*: Buscopan Compositum; Donnatal†; Millerspas†; Respinol Compound†; Scopex Co; *Spain*: Buscapina Compositum; Midriatico†; Oragalin Espasmolitico; Psico Biocan†; *Swed.*: Spasmofen; *Thai.*: Amcopan Plus; Buscopan Plus†; Hyosman Plus; Pacopan; Spascopan-510; Spasgone; Unigan; *Turk.*: Buscopan Compositum†; Buscopan Plus; Molit Plus; Skopolin†; Spazmol Plus; Spazmotek Plus; Tanko-Buskas†; Tranko-Buskas; *UK*: Feminax; *USA*: AeroHist Plus; AeroKid; AH-chew; Alkabel; AllePak; AlleRx DF; AlleRx†; Antispasmodic Elixir; Bellahist-D; Bellatal; Chlor-Mes D†; Chlor-Mes; CPM PSE MSC; CPM/PE/MSC; DA Chewable; DA II; Dallergy PE†; Dehistine; Dexphen M; Donnatal; DriHist; DryMax; Dura-Vent/DA; Durahist D†; Durahist†; Ex-Histine; Extendryl DM; Extendryl PEM; Extendryl; Histatab D; Histor-D Timecelles; Hyosophen; Murocoll-2†; Nacon; NoHist Plus; Omnihist LA; Pamine FQ Kit; Pannaz; PB-Hyos; PCM; PE-CPM-MSN; PE-HCL-CPM-MSN; Prehist D; PSE MSC; Quadrapax; Ralix; Redur-PCM†; RelCof CPM; RelCof DN PE; RelCof DN PSE; RelCof PSE; Ryneze; Se-Donna PB HYOS; Servira; Stahist; Susano; SymPak II; SymPak PDX; SymPak†; *Venez.*: Brugesina; Buscapina Compositum; Buscapina Plus; Butilamina Compuesta; Vuscobras.

Used as an adjunct in:. *Singapore*: SP-Arnox.

Pharmacopoeial Preparations

BP 2014: Hyoscine Butylbromide Injection; Hyoscine Butylbromide Tablets; Hyoscine Eye Drops; Hyoscine Injection; Hyoscine Tablets;

USP 36: Methscopolamine Bromide Tablets; Scopolamine Hydrobromide Injection; Scopolamine Hydrobromide Ophthalmic Ointment; Scopolamine Hydrobromide Ophthalmic Solution; Scopolamine Hydrobromide Tablets.

Hyoscyamine *(BAN)*

Hiosciamina; Hyoscyamin; (-)-Hyoscyamine; *l*-Hyoscyamine; Hyoscyaminum; Hyoskyamiini; Гиосциамин.

(-)-(1*R*,3*r*,5*S*)-Tropan-3-yl (*S*)-tropate.

$C_{17}H_{23}NO_3$=289.4

CAS — 101-31-5.

ATC — A03BA03.

ATC Vet — QA03BA03.

UNII — PX44XO846X.

Description. Hyoscyamine is an alkaloid obtained from various solanaceous plants. It is the laevo-isomer of atropine into which it can be converted by heating or by the action of alkali.

Pharmacopoeias. In *US.*

USP 36: (Hyoscyamine). A white crystalline powder. M.p. 106 degrees to 109 degrees. Slightly soluble in water and in benzene; freely soluble in alcohol, in chloroform, and in dilute acids; sparingly soluble in ether. Its solutions are alkaline to litmus. Store in airtight containers. Protect from light.

Hyoscyamine Hydrobromide *(BANM)*

Bromidrato de Hiosciamina; Hiosciamina, hidrobromuro de; Hyoscyamine Bromhydrate; Гиосциамина Гидробромид.

$C_{17}H_{23}NO_3$,HBr=370.3

CAS — 306-03-6.

ATC — A03BA03.

ATC Vet — QA03BA03.

UNII — JWT5OP9S79.

Pharmacopoeias. In *US.*

USP 36: (Hyoscyamine Hydrobromide). White, odourless crystals or crystalline powder. M.p. not less than 149 degrees. Freely soluble in water; soluble 1 in 2.5 of alcohol, 1 in 1.7 of chloroform, and 1 in 2300 of ether. pH of a 5% solution in water is about 5.4. Store in airtight containers. Protect from light.

Hyoscyamine Sulfate *(BANM)*

Hiosciamina, sulfato de; Hiosciamino sulfatas; Hioscyjaminy siarczan; Hioszciamin-szulfát; Hyoscyamin sulfát dihydrát; Hyoscyamine, sulfate d'; Hyoscyamine Sulphate; Hyoscyamini sulfas; Hyoscyamini Sulfas Dihydricus; Hyoscyaminsulfat; Hyoscyaminum Sulfuricum; Hyoskyamiinisulfaatti; Iosciamina Solfato; Гиосциамина Сульфат.

$(C_{17}H_{23}NO_3)_2,H_2SO_4,2H_2O$=712.9

CAS — 620-61-1 (anhydrous hyoscyamine sulfate); 6835-16-1 (hyoscyamine sulfate dihydrate).

ATC — A03BA03.

ATC Vet — QA03BA03.

UNII — F2R8V82B84.

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

Ph. Eur. 8: (Hyoscyamine Sulfate). A white or almost white, crystalline powder or colourless needles. Very soluble in water; sparingly soluble or soluble in alcohol. A 2% solution in water has a pH of 4.5 to 6.2. Store in airtight containers. Protect from light.

USP 36: (Hyoscyamine Sulfate). A white or almost white, crystalline powder or colourless needles. It is deliquescent and affected by light. Soluble 1 in 0.5 of water and 1 in 5 of alcohol; practically insoluble in ether. pH of a 1% solution in water is about 5.3.

Uses and Administration

Hyoscyamine is a tertiary amine antimuscarinic with the actions of atropine (which is racemic hyoscyamine, see p. 1312.1); hyoscyamine, the laevo-isomer, has about twice the potency of atropine since the dextro-isomer has only very weak antimuscarinic activity. Hyoscyamine is used mainly in the relief of conditions associated with visceral spasm. It has also been given for rhinitis and was formerly used in the treatment of parkinsonism.

Hyoscyamine is given in usual oral doses of 150 to 300 micrograms up to four times daily, but it is more usually employed as the sulfate; the hydrobromide is also used. Suggested doses of hyoscyamine sulfate are 125 to 250 micrograms orally or sublingually every four hours as needed, up to a maximum of 1.5 mg in 24 hours. Modified-release oral preparations of hyoscyamine sulfate are available in some countries; dosage is specific to a particular formulation. Hyoscyamine sulfate has also been given by injection.

Homoeopathy

Hyoscyamine hydrobromide has been used in homoeopathic medicines under the following names: Hyoscyaminum hydrobromatum.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Egazil; *Hong Kong*: Levsin; *Norw.*: Egazil; *Swed.*: Egazil; *USA*: Anaspaz†; Cystospaz†; Donnamar; ED-SPAZ; Gastrosed; HyoMax; IB-Stat†; Levbid; Levsin; Levsinex†; Mar-Spas; Neosol†; NuLev; Oscimin; Symax.

Multi-ingredient Preparations. *Austral.*: Donnagel; Donnalix; Donnatab; *Braz.*: Neogrein; Ormigrein; Tropinal; *Indon.*: Aludonna; Feminax†; *S.Afr.*: Donnatal†; Millerspas†; *USA*: Alkabel; Antispasmodic Elixir; Atrosept; Bellacane; Bellahist-D; Bellatal; Darpaz†; Digex NF; Digext†; Donnatal; Hyophen; Hyosophen; MHP-A; MSP-Blu; PB-Hyos; PhenazoForte Plus; Phenazopyridine Plus; Phosphasal; Prosed/DS; Pyrelle HB†; Pyridium Plus; Quadrapax; Se-Donna PB HYOS; Servira; Stahist; Susano; Trellium Plus†; UAA; Urelief Plus; Urelle; Uretron; Urimar-T; Urimax; Uriseptic; Uritact; Uro Blue; Urogesic Blue; Uryl; Ustell; Uticap; Utira; Utrona-C.

Pharmacopoeial Preparations

USP 36: Hyoscyamine Sulfate Elixir; Hyoscyamine Sulfate Injection; Hyoscyamine Sulfate Oral Solution; Hyoscyamine Sulfate Tablets; Hyoscyamine Tablets.

Ilaprazole *(rINN)*

Gilaprazole; Ilaprazol; Ilaprazolum; IY-81149; Илапразол.

2-[(*RS*)-[(4-Methoxy-3-methylpyridin-2-yl)methyl]sulfinyl]-5-(1*H*-pyrrol-1-yl)-1*H*-benzimidazole.

$C_{19}H_{18}N_4O_2S$=366.4

CAS — 172152-36-2.

UNII — 776Q6XX45J.

Profile

Ilaprazole is a proton pump inhibitor that is under investigation for the treatment of peptic ulcer disease and gastro-oesophageal reflux disease.

References.

1. Li Y, *et al.* Pharmacokinetics of the new proton pump inhibitor ilaprazole in Chinese healthy subjects in relation to CYP3A5 and CYP2C19 genotypes. *Clin Chim Acta* 2008; 391: 60–7.
2. Ho KY, *et al.* Randomized, parallel, double-blind comparison of the ulcer-healing effects of ilaprazole and omeprazole in the treatment of gastric and duodenal ulcers. *J Gastroenterol* 2009; 44: 697–707.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Yi Li An (意丽安).

Indisetron Hydrochloride *(rINNM)*

Hidrocloruro de indisetrón; Indisétron, Chlorhydrate d'; Indisetron Dihydrochloride; Indisetroni Hydrochloridum; N-3389; Индисетрона Гидрохлорид.

N-(3,9-Dimethyl-*endo*-3,9-diazabicyclo[3.3.1]non-7-yl)-1*H*-indazole-3-carboxamide dihydrochloride.

$C_{17}H_{23}N_5O$,2HCl=386.3

CAS — 141549-75-9 (indisetron); 160472-97-9 (indisetron dihydrochloride).

UNII — NBN3HB12DW.

Profile

Indisetron is a 5-HT_3-receptor antagonist with general properties similar to those of ondansetron (p. 1872.1); it is also stated to be an antagonist at 5-HT_4 receptors. Indisetron hydrochloride is used as an antiemetic in the management of nausea and vomiting associated with chemotherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Sinseron.

Irsogladine Maleate *(rINNM)*

Irsogladina, maleato de; Irsogladine, Maléate d'; Irsogladini Maleas; Maleato de irsogladina; MN-1695; Ирсогладина Малеат.

2,4-Diamino-6-(2,5-dichlorophenyl)-*S*-triazine maleate.

$C_9H_7Cl_2N_5.C_4H_4O_4$=372.2

CAS — 57381-26-7 (irsogladine); 84504-69-8 (irsogladine maleate).

Profile

Irsogladine maleate is a cytoprotective drug that is used in the treatment of peptic ulcer disease (p. 1813.2) in a usual oral dose of 4 mg daily. It has also been investigated for mucositis and mouth ulceration.

References.

1. Hiroishi H, *et al.* Clinical trial: irsogladine maleate, a mucosal protective drug, accelerates gastric ulcer healing after treatment for eradication of *Helicobacter pylori* infection—the results of a multicentre, double-blind, randomized clinical trial (IMPACT study). *Aliment Pharmacol Ther* 2010; 31: 824–33.

Mucositis. Oral irsogladine maleate 2 mg twice daily has been reported[1] to reduce the incidence of aphthous stomatitis in a small study in patients being treated with methotrexate for rheumatoid arthritis.

1. Yoshida T, Hirakata M. Therapeutic benefits of irsogladine maleate on aphthous stomatitis induced by methotrexate in rheumatoid arthritis. *J Rheumatol* 2003; 30: 2082–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Gaslon N (盖世龙); Hengzhi (恒至); Ke Ma Nuo (科玛诺); Yi Ge Ding (一格定); *Jpn*: Gaslon N.

Isopropamide Iodide *(BAN, rINN)*

Ioduro de isopropamida; Isopropamida, ioduro de; Isopropamide, Iodure d'; Isopropamidi Iodidum; Изопропамида Йодид.

(3-Carbamoyl-3,3-diphenylpropyl)di-isopropylmethylammonium iodide.

$C_{23}H_{33}IN_2O$=480.4

CAS — 7492-32-2 (isopropamide); 71-81-8 (isopropamide iodide).

ATC — A03AB09.

ATC Vet — QA03AB09.

UNII — E0KNA372SZ.

Pharmacopoeias. In *US.*

USP 36: (Isopropamide Iodide). A white to pale yellow crystalline powder. Soluble 1 in 50 of water, 1 in 10 of alcohol, and 1 in 5 of chloroform; very slightly soluble in ether and in benzene. Protect from light.

Profile

Isopropamide iodide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been used as an adjunct in the treatment of peptic ulcer disease, in the relief of gastrointestinal and

urinary-tract disorders associated with smooth muscle spasm, in rhinitis, and for the relief of symptoms of colds.

Isopropamide bromide has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Raspon.

Multi-ingredient Preparations. *India*: Gastabid; *Ital.*: Influmed C; Influmed; Raffreddoremed; Valtrax; *Mex.*: Stelabid.

Pharmacopoeial Preparations
USP 36: Isopropamide Iodide Tablets.

Ispaghula

Egyiptomi útifűmag (ispaghula seed); Egyiptomi útifűmaghéj (ispaghula husk); Ispaghul; graine d' (ispaghula seed); Ispaghul (graine d'), tégument de la (ispaghula husk); Ispagula; Ispagula Kabuğu; Ispagulafrö (ispaghula seed); Ispagulafröskal (ispaghula husk); Ispagulansiemen (ispaghula seed); Ispagulansiemenkuori (ispaghula husk); Kepek; Kiaušininių gysločių sėklų luobelės (ispaghula husk); Kiaušininių gysločių sėklos (ispaghula seed); Łupina nasienna babki jajowatej (ispaghula husk); Nasienie babki jajowatej (ispaghula seed); Osemení jitrocele vejčitého (ispaghula husk); Plantaginis ovatae semen (ispaghula seed); Plantaginis ovatae seminis tegumentum (ispaghula husk); Psilio; Semeno jitrocele vejčitého (ispaghula seed); Zaragatona; Шелуха Исфарулы (ispaghula husk).

ATC Herb — HA06AC5010 (Plantago ovata: *seed husk*).

UNII — UD50RBY30F (Plantago ovata *seed*); *0SHC53407G* (*psyllium husk*); *NU5XN4136K* (Plantago ovata *seed coat*).

Pharmacopoeias. Monographs for the husk and seed are included in *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Ispaghula Husk; Plantaginis Ovatae Seminis Tegumentum). The episperm and collapsed adjacent layers removed from the seeds of *Plantago ovata* (*P. ispaghula*). The powdered drug loses not more than 12.0% of its weight on drying. Protect from light.

Ph. Eur. 8: (Ispaghula Seed; Plantaginis Ovatae Semen). The dried ripe seeds of *Plantago ovata* (*P. ispaghula*). The powdered drug loses not more than 10.0% of its weight on drying. Protect from light.

USP 36: (Psyllium Husk). The cleaned, dried seed coat (epidermis), in whole or in powdered form, separated by winnowing and threshing from the seeds of *Plantago ovata* (known in commerce as Blond Psyllium, Indian Psyllium, or Ispaghula), or from *Plantago arenaria* (*Plantago psyllium*), known in commerce as Spanish or French Psyllium.

USP 36: (Plantago Seed). The cleaned, dried, ripe seed of *Plantago ovata*, or of *Plantago psyllium*, or of *Plantago indica* (*P. arenaria*).

Psyllium Hemicellulose *(USAN)*

CAS — 9034-32-6.
UNII — Y2HNG56689.

Pharmacopoeias. In *US*.

USP 36: (Psyllium Hemicellulose). The alkali soluble fraction of the husk from *Plantago ovata* consisting of highly substituted arabinoxylan polysaccharides. These polysaccharides are linear chains of xylose units to which are attached single units of arabinose and additional xylose. Rhamnose, galactose, glucose, and rhamnosyluronic acid residues are also present as minor constituents. It contains not less than 75.0% of dietary soluble fibre, calculated on the dried basis. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Psyllium Seed

Blešníkové semeno; Bolhafúmag; Flea Seed; Flohsamen; Loppfrö; Nasienie plesznika; Psilio, semilla de; Psyllii semen; Psyllium, graine de; Psylliumínsiemen; Smiltyninių gysločių sėklos.

ATC — A06AC01.

ATC Vet — QA06AC01.

ATC Herb — HA06AC5008 (Plantago afra: *seed*); *HA07BW5004* (Plantago ovata: *seed*); *HA06AC5009* (Plantago ovata: *seed*); *HA07BW5003* (Plantago afra: *seed*).

UNII — 9C60Y73166.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *US* under the title of Plantago Seed.

Ph. Eur. 8: (Psyllium Seed). The ripe, whole, dry seeds of *Plantago afra* (*P. psyllium*) or *Plantago indica* (*P. arenaria*). It loses not more than 14.0% of its weight on drying. Protect from light and moisture.

USP 36: (Plantago Seed). The cleaned, dried, ripe seed of *Plantago ovata*, or of *Plantago psyllium*, or of *Plantago indica* (*P. arenaria*) (see also Ispaghula, above).

Uses and Administration

Ispaghula seed, ispaghula husk, and psyllium seed are bulk laxatives (p. 1804.1). They absorb water in the gastrointestinal tract to form a mucilaginous mass which increases the volume of faeces and hence promotes peristalsis. They are used in the treatment of constipation (p. 1804.3), especially in diverticular disease (p. 1806.2) and irritable bowel syndrome (p. 1810.3), and when excessive straining at stool must be avoided, for example after anorectal surgery or in the management of haemorrhoids. The ability to absorb water and increase faecal mass means that they may also be used in the management of diarrhoea (p. 1805.2) and for adjusting faecal consistency in patients with colostomies.

The usual oral dose is about 3.5 g one to three times daily, although higher doses have been given. It should be taken immediately after mixing in at least 150 mL water or fruit juice. The full effect may not be achieved for up to 3 days. For doses in children, see below.

Ispaghula is also given for mild to moderate hypercholesterolaemia as an adjunct to a lipid-lowering diet. The recommended dose is about 7.5 to 10 g daily.

Administration in children. Ispaghula husk can be given orally to treat constipation in children; doses vary slightly according to the preparation used. A typical preparation (*Fybogel; Reckitt Benckiser, UK*), which contains ispaghula husk 1.75 g per level 5-mL spoonful, recommends children aged 12 years and under be given ½ to 1 level 5-mL spoonful dissolved in water twice daily. The *BNFC* recommends the same dose, but restricts the use of ispaghula husk to children aged 6 years and over. Children aged 12 years and over are usually given adult doses, see above.

Hyperlipidaemias. Preparations of ispaghula have been reported[1-4] to lower serum-cholesterol concentrations in patients with mild to moderate hypercholesterolaemia. They have also been given with reduced doses of a bile-acid binding resin in the treatment of hyperlipidaemia,[5] which is reported to be effective and better tolerated than full doses of the resin alone. Similarly, psyllium supplementation with 10 mg of simvastatin was found to be as effective in lowering cholesterol as 20 mg of simvastatin alone.[6] However, ispaghula or psyllium should be regarded as adjuncts to dietary modification rather than substitutes for it. For a discussion of the hyperlipidaemias and their management, see p. 1248.1.

1. Anderson JW, *et al.* Cholesterol-lowering effect of psyllium hydrophilic mucilloid for hypercholesterolemic men. *Arch Intern Med* 1988; 148: 292–6.
2. Bell LP, *et al.* Cholesterol-lowering effects of psyllium hydrophilic mucilloid: adjunct therapy to a prudent diet for patients with mild to moderate hypercholesterolemia. *JAMA* 1989; 261: 3419–23.
3. Anderson JW, *et al.* Cholesterol-lowering effects of psyllium intake adjunctive to diet therapy in men and women with hypercholesterolemia: meta-analysis of 8 controlled trials. *Am J Clin Nutr* 2000; 71: 472–9.
4. Anderson JW, *et al.* Long-term cholesterol-lowering effects of psyllium as an adjunct to diet therapy in the treatment of hypercholesterolemia. *Am J Clin Nutr* 2000; 71: 1433–8.
5. Spence JD, *et al.* Combination therapy with colestipol and psyllium mucilloid in patients with hyperlipidemia. *Ann Intern Med* 1995; 123: 493–9.
6. Moreyra AE, *et al.* Effect of combining psyllium fiber with simvastatin in lowering cholesterol. *Arch Intern Med* 2005; 165: 1161–6.

Adverse Effects and Precautions

Large quantities of ispaghula and other bulk laxatives may temporarily increase flatulence and abdominal distension; hypersensitivity reactions have been reported. There is a risk of intestinal or oesophageal obstruction and faecal impaction, especially if such compounds are taken with insufficient fluid. Therefore, they should always be taken with at least 150 mL of water or other liquid. Ispaghula and bulk laxatives should not be taken immediately before going to bed because reduced gastric motility may impair intestinal passage and cause obstruction. They should be avoided by patients who have difficulty swallowing.

Bulk laxatives should not be given to patients with pre-existing faecal impaction, intestinal obstruction, or colonic atony.

Hypersensitivity. Hypersensitivity reactions associated with the ingestion or inhalation of ispaghula or psyllium have been reported.[1-9] Symptoms have included rash, rhinitis, urticaria, bronchospasm, and anaphylactic shock; in one case, anaphylaxis was fatal.[9] In most patients, sensitisation was thought to have occurred during occupational exposure.

1. Busse WW, Schoenwetter WF. Asthma from psyllium in laxative manufacture. *Ann Intern Med* 1975; 83: 361–2.
2. Gross R. Acute bronchospasm associated with inhalation of psyllium hydrophilic mucilloid. *JAMA* 1979; 241: 1573–4.
3. Suhonen R, *et al.* Anaphylactic shock due to ingestion of psyllium laxative. *Allergy* 1983; 38: 363–5.
4. Zaloga GP, *et al.* Anaphylaxis following psyllium ingestion. *J Allergy Clin Immunol* 1984; 74: 79–80.
5. Kaplan MJ. Anaphylactic reaction to "Heartwise". *N Engl J Med* 1990; 323: 1072–3.
6. Lantner RR, *et al.* Anaphylaxis following ingestion of a psyllium-containing cereal. *JAMA* 1990; 264: 2534–6.
7. Freeman GL. Psyllium hypersensitivity. *Ann Allergy* 1994; 73: 490–2.
8. Vaswani SK, *et al.* Psyllium laxative-induced anaphylaxis, asthma, and rhinitis. *Allergy* 1996; 51: 266–8.
9. Khalili B, *et al.* Psyllium-associated anaphylaxis and death: a case report and review of the literature. *Ann Allergy Asthma Immunol* 2003; 91: 579–84.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ispaghula 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 10/10/11)

Interactions

Ispaghula and other bulk-forming laxatives may delay or reduce the gastrointestinal absorption of other drugs such as cardiac glycosides, coumarin derivatives, lithium, or vitamins (such as vitamin B_{12}) and minerals (such as calcium, iron, or zinc). Intervals of 30 minutes to 1 hour are recommended between ispaghula and other drugs or food, although some recommend as much as 3 hours between bulk-forming laxatives and other drugs. The dose of insulin may need to be reduced in diabetic patients taking ispaghula.

Lithium. For reference to ispaghula possibly reducing the absorption of lithium, see Gastrointestinal Drugs, p. 432.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Agiofibras; CTabs-Correctol; Fibras Ewe; Konsyl; Lostamucil; Metamucil; Motional; Mucofalk†; Plantaben; Salutaris; *Austral.*: Agiofibe; Ford Fibre†; Pybogel; Metamucil; *Austria*: Agiocur; Plantaben; *Belg.*: Colofiber; Spagulax M; Spagulax; *Braz.*: Agiofibra; Fibracare†; Metamucil; Plantaben; *Canad.*: Easy Lax†; Fiber 5; Laxucil†; Metamucil; Mucillium; Musilax; Naturfibr†; Novo-Mucilax†; Super CC†; *Chile*: Euromucil; Fibrasol; Plantaben; *China*: Konsyl (悟司尔); *Denm.*: Vi-Siblin; *Fin.*: Agiocur; Laxamucil; Vi-Siblin; *Fr.*: Mucivital; Phytofibre†; Spagulax Mucilage; Spagulax; Transilane; *Ger.*: Agiocur; Flosine; Kneipp Cholesterin Control†; Metamucil; Mucofalk; Pascomucil; *Hong Kong*: Agiocur; Fibermate†; Metamucil; Mucofalk; Naturlax; Plantaben; Transilane†; *Hung.*: Colon Cleanse; Husk; Mucofalk; Nature Care; *India*: Cremadiet; Eva-Q; Fibradiet; Fibril; Pybogel; Husky; Igol; Inulax; Isbis; Isogel; Itworks; Laxataur; Naturolax; *Indon.*: Mucofalk†; Mulax; *Irl.*: Fybogel; Regulan; *Israel*: Agiocur; Kalsiv; Konsyl; Sivay Psyllium; *Ital.*: Agiofibre; Fibrolax; Plantalax; Planten; Psyllogel; *Malaysia*: Fybogel; Mucofalk†; *Mex.*: Agiofibra; Fibromucil; Finalax; Fybogel†; Hormolax†; Metamucil; Mucilag†; Mugasin; Naxar-P; Novagon; Plantaben; *Mon.*: Psylia; *Neth.*: Metamucil; Regucol†; Volcolon; *Norw.*: Lunelax; Vi-Siblin; *NZ*: Isogel†; Metamucil; Mucilax; *Philipp.*: Fibermate; Mucofalk; *Pol.*: Mucofalk; *Port.*: Agiocur; Agiofibra; Laxat†; Mucofalk; Pepsa-lax; Prontolax; Vetilax†; *Rus.*: Fiberlax (Файберлекс); Mucofalk (Мукофальк); Naturolax (Натуролакс); *S.Afr.*: Agiobulk; Fybogel; Ispagel; *Singapore*: Fybogel; Mucilin; Mucofalk†; *Spain*: Biolid; Cenat; Filaxan; Laxabene; Metamucil; Plantaben; Plantasor; Plantax; *Swed.*: Lunelax; Vi-Siblin; *Switz.*: Agiolax mite; Laxiplant Soft; Metamucil; Mucilar; *Thai.*: Agiocur; Detolax; Fybogel; Igol; Metamucil; Mucilin; Plantaben; *Turk.*: Otaci Musillium†; *UK*: Fibrelief†; Pybogel; Isogel; Ispagel; Regulan; *Ukr.*: Defenorm (Дефенорм); Mucofalk Orange (Мукофальк Апельсин); Transilan (Трансилан); *USA*: Fiber Therapy Original Texture; Fiberall; Geri-Mucil; Hydrocil Instant; Konsyl-D; Konsyl; Metamucil; Perdiem Fiber; Reguloid; Serutan; Syllact; *Venez.*: Agiofibe; Siliumbran.

Multi-ingredient Preparations. *Arg.*: Adelgazar; Agiolax; Gelax; Isalax Fibras; Medilaxan; Mermelax; Rapilax Fibras; *Austral.*: Agiolax; Colon Care; Detox Program; Nucolox†; Psylli-Mucil Plus†; *Austria*: Agiolax; *Belg.*: Agiolax; Spagulax K†; Spagulax Sorbitol†; *Braz.*: Agiolax; Parapsyl; *Canad.*: Fiber Plus; Floradix Kindervital†; Intestinal Bulking Agent II†; Laxolax; Metamucil plus Calcium; Special Formula Bulking Agent†; *Chile*: Bilaxil; *China*: Agiolax (艾者思); *Cz.*: Agiolax†; *Fin.*: Agiolax; *Fr.*: Agiolax; Imegul†; Parapsyllium; Spagulax au Citrate de Potassium†; Spagulax au Sorbitol†; *Ger.*: Agiolax; *Gr.*: Agiolax; *Hong Kong*: Agiolax; Lepicol; *Hung.*: Agiolax; Lipolest; Super Colon Cleanse; *India*: Bolax; Chitosyl; Consticare; Fibropil; Lactifiber; Laxive; Morease-L; *Irl.*: Agiolax; Fybogel Mebeverine; *Israel*: Agiolax; Biolax Protect; Biolax†; *Ital.*: Agiolax; Agioslim; Duofibra; Duolaxan; Fibranorm; Fibrolax Complex; Ginolax; Promolax; Psyllogel Fermenti; *Jpn*: Ryutanshakanto; Seishinrenshiin; *Malaysia*: Agiolax; *Mex.*: Agiolax; Psilumax†; *Neth.*: Agiolax; *Norw.*: Agiolax†; *Pol.*: Agiolax; Laxamix†; Otrebuski†; *Port.*: Agiolax; *S.Afr.*: Agiolax; *Spain*: Agiolax; *Swed.*: Agiolax†; *Switz.*: Agiolax; Mucilar Avena; *Thai.*: Agiolax; *Turk.*: Otaci Diyet Life Psyllium Plus†; *UK*: Cleansing Herbs; Fibre Dophilus; Fibre Plus; Fybogel Mebeverine; Lion Cleansing Herbs;

The symbol † denotes a preparation no longer actively marketed

Manevac *Ukr.*: Softovak (Софтовак); *USA*: Perdiem†; Senna Prompt; *Venez.*: Agiolax; Avensyl; Fiberfull.

Pharmacopoeial Preparations
BP 2014: Ispaghula Husk Effervescent Granules; Ispaghula Husk Granules; Ispaghula Husk Oral Powder;
USP 36: Psyllium Hydrophilic Mucilloid for Oral Suspension.

Itopride Hydrochloride *(rINNM)*

HC-803; Hidrocloruro de itoprida; HSR-803; Itoprida, hidrocloruro de; Itopride, Chlorhydrate d'; Itopridi Hydrochloridum; Итоприда Гидрохлорид.
N-[*p*-[2-(Dimethylamino)ethoxy]benzyl]veratramide hydrochloride.
$C_{20}H_{26}N_2O_4,HCl$=394.9
CAS — 122898-67-3 (itopride).
UNII — 2H9NV66W0I.

Profile

Itopride hydrochloride is a substituted benzamide with general properties similar to those of metoclopramide (p. 1862.2) that has been used for its prokinetic and antiemetic actions in oral doses of 50 mg three times daily before meals.

References.

1. Holtmann G, *et al.* A placebo-controlled trial of itopride in functional dyspepsia. *N Engl J Med* 2006; 354: 832–40.
2. Talley NJ, *et al.* Itopride in functional dyspepsia: results of two phase III multicentre, randomised, double-blind, placebo-controlled trials. *Gut* 2008; 57: 740–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ao Wei Xian (奥为仙); Bi Jia Si (比佳斯); Dai Lin (代林); Elthon (为力苏); Kai Ting (凯亭); Ruifulin (瑞复琳); WeiTai (威太); Yi Tian (伊天); *Cz.*: Ganaton; *India*: Ampty; Ganaton; Gepride; Gi-Tune; Itcan; Itokine; Itonorm; Itoprid; Itotor-OD; Itoz; Motiza; *Jpn*: Ganaton; *Malaysia*: Ganaton; *Philipp.*: Ganaton; *Rus.*: Ganaton (Ганатон); *Thai.*: Ganaton; *Ukr.*: Itomed (Итомед).

Multi-ingredient Preparations. *Cz.*: Kinito; *India*: Bizo-IT; Cool Rab-It; Ganaton Total; Gi-Tune MPS; Itorab; Itorbe; Mac-IT; Motiza-MPS; Nura-IT; Pantocid-IT.

Jalap

Jalap Root; Jalap Tuber; Jalapa; Jalapenwurzel; Vera Cruz Jalap; Ятана.
ATC Herb — HA06AB5009 (Ipomoea purga: tuber); HA06AB5008 (Ipomoea purga: resin).
UNII — 4UDO46YBK2.

Jalap Resin

Jalapa, resina de; Jalapenharz.
CAS — 9000-35-5.
UNII — E1C012DG4R.

Profile

Jalap is the dried tubercles of *Ipomoea purga* (=*Exogonium purga*) (Convolvulaceae). Jalap resin is a mixture of glycosidal resins obtained by extraction of jalap with alcohol and it has a drastic purgative and irritant action. It has been superseded by less toxic laxatives.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Herbal Laxative†; *S.Afr.*: SB 3 Triple Action Pills†.

Homoeopathic Preparations. *Fr.*: Dolisedal†; Noctium; *Switz.*: Sleepium.

Kaolin

Bolus Alba; Caolin; E559; Kaolini; Kaolinas; Kaolinum; Weisser Ton; Каолин.
CAS — 1332-58-7.
ATC — A07BC02.
ATC Vet — QA07BC02.
UNII — 24H4NWX5CO.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.* Some pharmacopoeias do not differentiate between the heavy and light varieties.

Ph. Eur. 8: (Kaolin, Heavy). A purified, natural, hydrated aluminium silicate of variable composition. It is a fine, white or greyish-white, unctuous powder. Practically insoluble in water and in organic solvents.

BP 2014: (Light Kaolin). A native hydrated aluminium silicate, freed from most of its impurities by elutriation, and dried. It contains a suitable dispersing agent. It is a light, white, odourless or almost odourless, unctuous powder free from gritty particles. Practically insoluble in water and in mineral acids.

The BP 2014 directs that when Kaolin or Light Kaolin is prescribed or demanded, Light Kaolin shall be dispensed or supplied, unless it is ascertained that Light Kaolin (Natural) is required.

BP 2014: (Light Kaolin (Natural)). It is Light Kaolin which does not contain a dispersing agent. It is a light, white, odourless or almost odourless, unctuous powder free from gritty particles. Practically insoluble in water and in mineral acids.

The BP 2014 directs that when Kaolin or Light Kaolin is prescribed or demanded, Light Kaolin shall be dispensed or supplied, unless it is ascertained that Light Kaolin (Natural) is required.

USP 36: (Kaolin). A native hydrated aluminium silicate, powdered and freed from gritty particles by elutriation. It is a soft, white or yellowish-white powder or lumps with an earthy or clay-like taste and when moistened with water assumes a darker colour and develops a marked clay-like odour. Insoluble in water, in cold dilute acids, and in solutions of alkali hydroxides.

Profile

Light kaolin and light kaolin (natural) are adsorbent antidiarrhoeal agents that have been used as adjuncts to rehydration therapy in the management of diarrhoea (p. 1805.2). Up to about 24 g daily may be taken orally in divided doses. Kaolin is often combined with other antidiarrhoeals, especially pectin.

Kaolin can form insoluble complexes with some drugs in the gastrointestinal tract and reduce their absorption; oral doses should not be taken at the same time.

Externally, light kaolin is used as a dusting powder. Kaolin is liable to be heavily contaminated with bacteria, and when used in dusting powders, it should be sterilised.

Heavy kaolin is used in the preparation of kaolin poultice, which is applied topically with the intention of reducing inflammation and alleviating pain (see Rubefacients and Topical Analgesia, p. 6.3).

Light kaolin is also used as a food additive.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Elusanes Calmodiger†; *UK*: Childrens Diarrhoea Mixture; Entrocalm.

Multi-ingredient Preparations. *Arg.*: Anusol-A; Argeal; Cleanance; Opocarbon; *Austral.*: Diarcalm†; Donnagel; *Belg.*: Alopate; Neutroses; Restofit; *Braz.*: Gastrobene; Kaomagma; *Chile*: Argeal; Furazolidona; Normaderm Concentrado Activo; *Fr.*: Argeal; Gastropax; Kaobrol; Kaologeais†; Kaomuth; Karayal; Keracnyl; Neutroses; Supro; *Gr.*: Enteromyk; Fissan-Pate; Kaopectate; Polypictine; *Hong Kong*: Diapectin†; Kaopectin; Pectolin†; Uni-Kaotin; *Hung.*: Bolus Adstringens; Bolus Laxans; Pasta Cool; *Indon.*: Diaend; Envios; Kaopectate†; Neo Diaform; Neo Kaocitin; Neo Kaolana; Neo Kaominal; Opidiar; *Israel*: Kaopectin; Zincod; *Ital.*: Katoxyn; Keromicil; Neutrose S Pellegrino; Streptomagma; *Mex.*: Ameban; Caopectar†; Colfur†; Colistin Magma†; Coralzul; Depofin; Dia-Par Compuesto; Dibapec Compuesto†; Estibal; Exofur; Facetin-D; Farpectol; Furoxona CP; Isocar; K-Omistron; Kaomycin†; Kaopectate†; Kapecfuran; Kediar; Lactopectin†; Neokap; Neoxil; Nineka; Olam†; Optazol; Quimefuran; Suyodil; Treda; Yodozona; *S.Afr.*: Adco-Biskapect†; Betapect; Bipectinol†; Bolus Eucalypti Comp†; Chloropect; Collodene†; Enterolyte; Gastropect; Kaostatex; Pectin-K†; Pectrolyte; SB Diarrhoea Mixture†; *Singapore*: Axcel Kaopec; Beakopectin; Bio-Taches Masque†; Diapectin; Kaomix; Pectolin; *Switz.*: Cicafissan; Creme vulneraire; Neo-Decongestine; Neutroses; Padma-Lax; Padmed Laxan; Phlogantin†; *Thai.*: Alkamine†; Alumag; Alupep; Cenopect†; Coccila; Coccila; Conmag; Diaropect; Difuran; Diocin; Disento PF; Disento; Droximag-P; Puramed; Furasian; Furopectal; Furopectin; Kaolin Mixture w/ Pectin; Kaolin Mixture; Kaopectal; Kaptate; Patarlin; Profura; Siemag; Suratin; *UAE*: Kaptin; *UK*: Collis Browne's; De Witt's Antacid; Junior Kao-C; KLN; Moorland; Opazimes; *USA*: K-C; Kao-Paverin; Kao-Spen; Kaodene Non-Narcotic; Mexsana; *Venez.*: Argeal; Klincosal; Niosilin.

Homoeopathic Preparations. *Ger.*: Phonix Silybum spag; Phonix Solidago spag; Phonix Thuja-Lachesis spag; Phonix Urtica-Arsenicum spag; *Neth.*: Phonix Hydrargyrum; *UK*: Bolus Eucalypti Comp.

Pharmacopoeial Preparations
BP 2014: Kaolin and Morphine Mixture; Kaolin Mixture; Kaolin Poultice.

Lactitol *(BAN, rINN)*

E966; β-Galactosido-sorbitol; Lactit; Lactitolum; Lactobiosit; Lactositol; Laktitol; Laktitoli; Laktitolis; Лактитол.
4-*O*-(β-D-Galactopyranosyl)-D-glucitol.
$C_{12}H_{24}O_{11}$=344.3
CAS — 585-86-4.
ATC — A06AD12.
ATC Vet — QA06AD12.
UNII — L2B0WJF7ZY (lactitol); UH2K6W1Y64 (lactitol monohydrate).

Pharmacopoeias. In *USNF*. *Eur.* (see p. vii) includes the monohydrate.

Ph. Eur. 8: (Lactitol Monohydrate). A white or almost white crystalline powder. Very soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane.

USNF 31: (Lactitol). It may be the anhydrous form, the monohydrate, or the dihydrate. White or light brown odourless, crystals. It has a mild, sweet taste, and no aftertaste.

Profile

Lactitol is a disaccharide analogue of lactulose (below) and has similar actions and uses.

Lactitol monohydrate is used as an oral powder or solution in the management of hepatic encephalopathy (p. 1808.2) and in constipation (p. 1804.3). Lactitol monohydrate 1.05 g is equivalent to about 1 g of anhydrous lactitol.

In the treatment of **hepatic encephalopathy**, lactitol monohydrate is given in usual oral doses of 500 to 700 mg/kg daily in 3 divided doses at meal times. The dose is subsequently adjusted to produce 2 soft stools daily.

In the treatment of **constipation**, lactitol monohydrate is given in an initial dose of 20 g daily as a single dose with the morning or evening meal, subsequently adjusted to produce one stool daily. A dose of 10 g daily may be sufficient for many patients.

Doses should be mixed with food or liquid, and 1 to 2 glasses of liquid should be drunk with the meal.

Lactitol is a permitted sweetener in foods.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lactitol 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 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Importal; *Belg.*: Importal; Normolaxil†; Portolac†; *Braz.*: Sigmalac; *China*: Kang Xin (康欣); *Fin.*: Importal Ex-Lax†; Lalax†; *Fr.*: Importal; *Ger.*: Importal†; *Gr.*: Importal; *India*: Encelax; Eva-Q; Lactihep; *Israel*: Novolax; *Ital.*: Portolac; *Jpn*: Portolac; *Neth.*: Importal; *NZ*: Importal; *Port.*: Importal; *Rus.*: Exportale (Экспортал); *Spain*: Emportal; Oponaf; *Swed.*: Importal; *Switz.*: Importal; *Thai.*: Importal†; *Turk.*: Importal.

Multi-ingredient Preparations. *India*: Lactifiber; *Ital.*: Levoplus.

Lactulose *(BAN, USAN, rINN)*

Lactulosa; Lactulosum; Laktuliozė; Laktuloosi; Laktulos; Laktulosa; Laktuloz; Laktulóz; Лактулоза.
4-*O*-β-D-Galactopyranosyl-D-fructose.
$C_{12}H_{22}O_{11}$=342.3
CAS — 4618-18-2.
ATC — A06AD11.
ATC Vet — QA06AD11.
UNII — 9U7D5QHSAE.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. *Chin.* only contains specifications for a solution. *US* only contains specifications for a solution and a concentrated liquid.

Ph. Eur. 8: (Lactulose). A white or almost white, crystalline powder. Freely soluble in water; sparingly soluble in methyl alcohol; practically insoluble in toluene.

Ph. Eur. 8: (Lactulose, Liquid; Lactulose Solution BP 2014). An aqueous solution of lactulose. It contains not less than 62.0% w/v of lactulose; it may contain other sugars including lactose, epilactose, galactose, tagatose, and fructose. It may contain a suitable antimicrobial preservative. It is a clear, colourless or pale brownish-yellow, viscous liquid. Miscible with water. It may be a supersaturated solution or may contain crystals that disappear on heating. A 10.0% solution in water has a pH of 3.0 to 7.0.

USP 36: (Lactulose Concentrate). A colourless to amber syrupy liquid that may exhibit some precipitation and

darkening on standing. Miscible with water. Store in airtight containers preferably at a temperature between 2 degrees and 30 degrees.

Uses and Administration

Lactulose is a synthetic disaccharide osmotic laxative (p. 1804.1) used in the treatment of constipation (p. 1804.3) and in hepatic encephalopathy (p. 1808.2). Lactulose is broken down by colonic bacteria mainly into lactic acid. This exerts a local osmotic effect in the colon resulting in increased faecal bulk and stimulation of peristalsis. It may take up to 48 hours before an effect is obtained. When larger doses are given for hepatic encephalopathy the pH in the colon is reduced significantly and the absorption of ammonium ions and other toxic nitrogenous compounds is decreased, leading to a fall in blood-ammonia concentration and an improvement in mental function.

Lactulose is usually given orally as a solution containing about 3.35 g of lactulose per 5 mL, with other sugars such as galactose and lactose; an oral powder formulation is also available in some countries. In the treatment of **constipation**, the usual initial dose is 10 to 20 g (15 to 30 mL) given daily in a single dose or in 2 divided doses; doses up to 45 mL daily of the solution (or up to 40 g of the reconstituted oral powder formulation) have been given. The dose is gradually adjusted according to the patient's needs. For doses in children, see below.

In **hepatic encephalopathy**, an oral dose of 60 to 100 g (90 to 150 mL) is given daily in 3 divided doses. The dose is subsequently adjusted to produce 2 or 3 soft stools each day. Lactulose solution 200 g (300 mL) mixed with 700 mL of water or sodium chloride 0.9% has been used as a retention enema; the enema is retained for 30 to 60 minutes, repeated every 4 to 6 hours until the patient is able to take oral medication.

References.
1. Clausen MR, Mortensen PB. Lactulose, disaccharides and colonic flora: clinical consequences. *Drugs* 1997; 53: 930–42.
2. Schumann C. Medical, nutritional and technological properties of lactulose: an update. *Eur J Nutr* 2002; 41 (suppl): I17–I25.

Administration in children. In the UK, children may be given the following oral doses of lactulose 3.35 g per 5 mL solution for constipation; doses may be adjusted according to response:

- 1 month to 1 year: 2.5 mL twice daily
- 1 to 5 years: 5 mL twice daily
- 5 to 10 years: 10 mL twice daily
- 10 to 18 years: 15 mL twice daily

Diagnosis and testing. *THE SUGAR ABSORPTION TEST.* In healthy individuals lactulose is largely unabsorbed from the gastrointestinal tract, but in, for example, coeliac disease there is increased permeability to disaccharides such as lactulose and a paradoxical decrease in the absorption of monosaccharides. This led to the development of the differential sugar absorption test in which 2 sugars are given simultaneously by mouth and the urinary recovery of each is determined; mannitol is commonly used as the monosaccharide component and lactulose as the disaccharide. Alternatives include mannitol plus cellobiose and rhamnose plus lactulose. This absorption test is useful in the investigation of intestinal disease.[1]

The lack of a standardised test solution has hampered comparison of test results. Although hyperosmolar solutions are better at determining intestinal damage,[2] some have preferred to use low osmolar solutions because of the risk of inducing osmotic diarrhoea, especially in children.

A study found the sugar absorption test to be strongly predictive of an organic cause of chronic diarrhoea; it may be useful in improving the selection of patients who need further evaluation.[3]

THE LACTULOSE BREATH TEST (hydrogen breath test). Lactulose is converted by bacteria in the large bowel to short chain fatty acids with the production of small quantities of hydrogen gas. The hydrogen is rapidly absorbed and is exhaled in the breath and measurement of its production is used to measure orocaecal transit time and carbohydrate malabsorption. However, even small doses of lactulose shortens transit time, which may limit the value of this test.[4]

The test is also diagnostic for bacterial overgrowth in the small intestine, which is increased in irritable bowel syndrome. Although hydrogen is produced in most subjects, methane is also produced in up to 50% of healthy subjects, and data suggest there may be clinical implications to different gas profiles. A study found that the presence of methane was associated with constipation, and with constipation-predominant irritable bowel syndrome. Methane production was infrequent in diarrhoea-predominant irritable bowel syndrome and virtually absent in inflammatory bowel disease. Diarrhoea and inflammatory bowel disease were associated with hydrogen production. Whether the type of bacterial flora causally determines symptoms is as yet unknown.[5] The diagnostic value of the test in irritable bowel syndrome has, however, been questioned.[6]

1. Ull JJ, *et al.* Clinical implications of the sugar absorption test: intestinal permeability test to assess mucosal barrier function. *Scand J Gastroenterol* 1997; 223 (suppl): 70–8.
2. Ull JJ, *et al.* Sensitivity of a hyperosmolar or "low" -osmolar test solution for sugar absorption in recognizing small intestinal mucosal damage in coeliac disease. *Dig Liver Dis* 2000; 32: 195–200.
3. Di Leo V, *et al.* Lactulose/mannitol test has high efficacy for excluding organic causes of chronic diarrhea. *Am J Gastroenterol* 2003; 98: 2245–52.
4. Miller MA, *et al.* Comparison of scintigraphy and lactulose breath hydrogen test for assessment of orocecal transit: lactulose accelerates small bowel transit. *Dig Dis Sci* 1997; 42: 10–18.
5. Pimentel M, *et al.* Methane production during lactulose breath test is associated with gastrointestinal disease presentation. *Dig Dis Sci* 2003; 48: 86–92.
6. Bratten JR, *et al.* Lactulose breath testing does not discriminate patients with irritable bowel syndrome from healthy controls. *Am J Gastroenterol* 2008; 103: 958–63.

Adverse Effects

Lactulose may cause abdominal discomfort associated with flatulence or cramps. Nausea and vomiting have occasionally been reported after high doses. Some consider the taste to be unpleasant; this can be minimised by dilution in water, fruit juice, or milk, or by mixing the dose with food. Prolonged use or excessive dosage may result in diarrhoea with excessive loss of water and electrolytes, particularly potassium. Hypernatraemia has been reported.

Lactic acidosis. Severe lactic acidosis developed in a patient with adynamic ileus who was being given lactulose for hepatic encephalopathy.[1]

1. Mann NS, *et al.* Lactulose and severe lactic acidosis. *Ann Intern Med* 1985; 103: 637.

Precautions

Lactulose should not be given to patients with galactosaemia or intestinal obstruction. It should not be used in patients on a low galactose diet and care should be taken in patients with lactose intolerance or in diabetic patients because of the presence of some free galactose and lactose.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lactulose 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 07/10/11)

Pharmacokinetics

Taken orally, lactulose passes essentially unchanged into the large intestine where it is metabolised by saccharolytic bacteria with the formation of simple organic acids, mainly lactic acid and small amounts of acetic and formic acids. The small amount of absorbed lactulose is subsequently excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Genocolan; Lactulon; Lafelax; Medixin; Tenualax; *Austral.*: Actilax; Duphalac; Genlac†; Lac-Dol; Lactocur; *Austria*: Bifteral†; Duphalac; Laevolac; *Belg.*: Bifiteral; Duphalac; *Braz.*: Colonac; Duphalac; Farlac; Lactuliv; Lactulona; Normolax; Pentalac; *Canad.*: Euro-Lac; Gen-Lac†; *Chile*: Axant; Dicelax; Dismam; Duphalac; *China*: Danilax (丹尼莱克); Duphalac (杜密克); Laevolac (拉韦); Lidong (利动); *Cz.*: Duphalac; Lactecon†; Lactorin; *Denm.*: Favolax†; Medilax; *Fin.*: Duphalac; Lactecon†; Laxorin; Levolac; *Fr.*: Duphalac; Laxaron; *Ger.*: Bifinorma†; Bifiteral; Eugalac†; Lactuflor; LactuGel; Lactulade; Lactuverlan†; Tulotract†; *Gr.*: Duphalac; Neosoldan; Purgolac; Purselect; *Hong Kong*: Danilax; Dhactulose; Duphalac; Laevolac; Martulose†; *Hung.*: Duphalac; Laevolac; *India*: Bowelac; Bowlease; Canphalac-Sol; Daffolac; Duphalac; Evacuate; Evict; Eziluk; Fresky; Gush; Lace; Laclouse; Lacrest; Lactucos; Lactulax; Lactulin; Lactusan; Laxan; Laxatin; Laxicare Soft; Laxil; Laxitose; Laxobus; Laxolin; Laxose; Livintact-EV; Livoluk; Looz; Loozit; Loozylax; MTLac; Normalac; Nostipan; Novalak; *Indon.*: Constipen; Dulcolactol; Duphalac; Lacons; Lactulax; Lantulos; Laxadilac†; Opilax; Pralax; Solac; *Irl.*: Duphalac; Gerelax†; Lactugal†; Laevolac; Laxose; *Israel*: Avilac; Gerelax; Laevolac; Normase; *Ital.*: Dia-Colon; Duphalac; Epalat EPS†; Epalfen; Laevolac; Lattulac; Normase; Osmolac; Verelait; *Jpn*: Monilac; *Malaysia*: Dhactulose; Duphalac; Lactul; *Mex.*: Duphalac; Lactulax; Quimtulac; Regulact; *Neth.*: Duphalac; Epalfen†; Kruidvat Laxeerdrank; Laevolac; Laxeerdrank; Laxeersiroop; Legendal; *Norw.*: Duphalac; Levolac; *NZ*: Duphalac; Laevolac†; *Philipp.*: Duphalac; Lactul; Lilac; Rilax; *Pol.*: Duphalac; Lactulol; Normalac; Normase†; *Port.*: Colsanac; Duphalac; Laevolac; Obstipar†; *Rus.*: Duphalac (Дюфалак); Gudlac (Гудлак); Livoluk-PB (Ливолюк-ПБ); Normase (Нормазе); Portalac (Порталак); Romfalak (Ромфалак); *S.Afr.*: Aculax; Adco-Liquilax; Duphalac; Lacson; Laxette; *Singapore*: Dhactulose; Duphalac; Lactus; *Spain*: Belmalax†; Duphalac; *Swed.*: Duphalac; Laktipex; *Switz.*: Duphalac; Gatinar; Legendal; Rudolac; *Thai.*: Duphalac; Hepalac; Laevolac; Losalac; Safex; *Turk.*: Duphalac; Lactulac; Laevolac; Laktol†; Osmolak; *UAE*: Soflax; *UK*: Duphalac; Lactugal; Lemlax; Regulose; *Ukr.*: Bioflorax (Биофлоракс)†; Duphalac (Дуфалак); Lactuvit (Лактувит); Laxarin (Лаксарин); Medulac (Медулак); Normase (Нормазе); Normolact (Нормолакт); *USA*: Cephulac; Chronulac†; Constilac†; Constulose; Duphalac†; Enulose; Generlac; Kristalose; *Venez.*: Lactulona; Moderan.

Multi-ingredient Preparations. *Arg.*: Bifidosa; *Belg.*: Transitol; *Fr.*: Melaxose; Transulose; *Ger.*: Eugalan Topfer†; *India*: Osmowin; *Indon.*: Laktoblon; *Ital.*: Combilax; Lactolas; Lactomannan; Levoplus; Naturalass; Phurilac; Transitol; Transulose; *Mex.*: Transilax; *Neth.*: Transulose; *Port.*: Melaxose; *Rus.*: Lactofiltrum (Лактофильтрум); *Ukr.*: Lactofiltrum-ECO (Лактофильтрум-Эко); Transuloza (Трансулоза).

Pharmacopoeial Preparations
BP 2014: Lactulose Oral Powder;
Ph. Eur.: Liquid Lactulose;
USP 36: Lactulose Solution.

Lafutidine *(rINN)*

FRG-8813; Lafutidina; Lafutidinum; Лафутидин.
(±)-2-(Furfurylsulfinyl)-*N*-[(*Z*)-4-[[4-(piperidinomethyl)-2-pyridyl]oxy]-2-butenyl]acetamide.
$C_{22}H_{29}N_3O_4S$=431.6
CAS — 118288-08-7.
ATC — A02BA08.
ATC Vet — QA02BA08.
UNII — 495407ADLC.

Profile

Lafutidine, like cimetidine (p. 1827.1), is a histamine H_2-antagonist. It is used in the management of peptic ulcer disease and gastritis. Lafutidine is given orally; a usual dose for peptic ulcers is 10 mg twice daily, and for gastritis, 10 mg daily in the evening. Care is required in patients with renal or hepatic impairment.

References.
1. Uesugi T, *et al.* The efficacy of lafutidine in improving preoperative gastric fluid property: a comparison with ranitidine and rabeprazole. *Anesth Analg* 2002; 95: 144–7.
2. Mikawa K, *et al.* Lafutidine vs cimetidine to decrease gastric fluid acidity and volume in children. *Can J Anaesth* 2003; 50: 425–6.
3. Inamori M, *et al.* Early effects of lafutidine or rabeprazole on intragastric acidity: which drug is more suitable for on-demand use? *J Gastroenterol* 2005; 40: 453–8.
4. Higuchi K, *et al.* Lafutidine can improve the quality of gastric ulcer healing in humans: a randomized, controlled, multicenter trial. *Inflammopharmacology* 2006; 14: 226–30.
5. Yamagishi H, *et al.* Stronger inhibition of gastric acid secretion by lafutidine, a novel H(2) receptor antagonist, than by the proton pump inhibitor lansoprazole. *World J Gastroenterol* 2008; 14: 2406–10.
6. Kim N, *et al.* Lafutidine versus lansoprazole in combination with clarithromycin and amoxicillin for one versus two weeks for Helicobacter pylori eradication in Korea. *Helicobacter* 2008; 13: 542–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: He Ke Di Si (赫克迪思); Lemeiting (乐美汀); Ning Wei Shu (宁维舒); Nuo Fei (诺非); Shun Ru (顺儒); Weisida (卫斯大); *Jpn*: Protecadin; Stogar†.

Lansoprazole *(BAN, USAN, rINN)*

A-65006; AG-1749; CG-4801; Lansopratsoli; Lansoprazol; Lansoprazolum; Лансопразол.
2-{[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl}sulphinylbenzimidazole.
$C_{16}H_{14}F_3N_3O_2S$=369.4
CAS — 103577-45-3.
ATC — A02BC03.
ATC Vet — QA02BC03.
UNII — 0K5C5T2QPG.

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

Ph. Eur. 8: (Lansoprazole). A white or brownish powder. Practically insoluble in water; soluble in anhydrous alcohol; very slightly soluble in acetonitrile. It exhibits polymorphism. Store in airtight containers. Protect from light.

USP 36: (Lansoprazole). A white to brownish-white powder. Practically insoluble in water; freely soluble in dimethylformamide. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Uses and Administration

Lansoprazole is a proton pump inhibitor with actions and uses similar to those of omeprazole (p. 1867.2). It is used in the treatment of peptic ulcer disease and in other conditions where inhibition of gastric acid secretion may be beneficial.

Lansoprazole is given orally as capsules, dispersible tablets, or suspension containing enteric-coated granules. Once daily regimens are taken before food in the morning. Lansoprazole has also been given intravenously.

For the relief of acid-related **dyspepsia** (p. 1806.3) intermittent courses of lansoprazole may be given in oral doses of 15 or 30 mg once daily, for 2 to 4 weeks.

In the treatment of **gastro-oesophageal reflux disease** (p. 1807.2) the usual oral dose is 15 to 30 mg once daily for 4 to 8 weeks; thereafter maintenance therapy can be continued with 15 or 30 mg once daily according to response.

Lansoprazole is given orally for the treatment of **peptic ulcer disease** (p. 1813.2); in the UK usual doses are 30 mg once daily. Treatment is continued for 2 to 4 weeks for duodenal and 4 to 8 weeks for gastric ulcer. In the USA, a dose of 15 mg daily for 4 weeks is recommended for duodenal ulcer, and 30 mg once daily is given for up to 8 weeks for gastric ulceration. When appropriate, 15 mg daily may be used as maintenance therapy for the prevention of relapse of duodenal ulcer. Lansoprazole may be combined with antibacterials in 7- to 14-day **triple therapy** regimens for the eradication of *Helicobacter pylori*. Effective regimens include lansoprazole 30 mg twice daily combined with clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily, or combined with clarithromycin 250 mg twice daily and metronidazole 400 mg twice daily; lansoprazole with amoxicillin and metronidazole has also been used. **Dual therapy** with lansoprazole 30 mg three times daily and amoxicillin for 14 days is also used, but may be less effective. In patients with **NSAID-associated ulceration** a dose of 30 mg daily for 4 to 8 weeks is recommended; 15 to 30 mg daily may be used as prophylaxis for patients who require continued NSAID treatment.

In the treatment of pathological hypersecretory states such as the **Zollinger-Ellison syndrome** (p. 1814.3) the initial oral dose is 60 mg once daily, adjusted as required. Doses of up to 90 mg twice daily have been used. Daily doses greater than 120 mg should be given in divided doses.

For doses in children and in hepatic impairment, see below.

General references. For general reviews of proton pump inhibitors, see Omeprazole, p. 1867.3.

1. Langtry HD, Wilde MI. Lansoprazole: an update of its pharmacological properties and clinical efficacy in the management of acid-related disorders. *Drugs* 1997; 54: 473–500.
2. Matheson AJ, Jarvis B. Lansoprazole: an update of its place in the management of acid-related disorders. *Drugs* 2001; 61: 1801–33.
3. Preston JW, *et al.* Lansoprazole for maintenance of remission of erosive oesophagitis. *Drugs* 2002; 62: 1173–84.
4. Dando TM, Plosker GL. Intravenous lansoprazole: in erosive oesophagitis. *Drugs* 2004; 64: 2085–9.
5. Croom KF, Scott LJ. Lansoprazole: in the treatment of gastro-oesophageal reflux disease in children and adolescents. *Drugs* 2005; 65: 2129–35.

Administration. Lansoprazole *capsules* should be swallowed whole and not crushed or chewed. Lansoprazole *dispersible tablets* should be placed on the tongue and allowed to disintegrate and the resultant granules swallowed; alternatively, the tablets may be swallowed whole with a glass of water. The tablets should not be crushed or chewed. The tablets may also be dispersed in a small amount of water and given via an oral syringe, or via a nasogastric tube. Lansoprazole *granules for oral suspension* should be reconstituted in a little water and swallowed immediately. Where the suspension formulation is not available, the contents of the capsules (enteric-coated granules) can be sprinkled on a small amount of soft food (such as yogurt or apple sauce) or mixed with a little fruit juice and swallowed. For dosage via a nasogastric tube, the contents of a capsule may be mixed with 40 mL of apple juice; additional apple juice may be used to flush the tube.

Administration in children. In the USA, children may be given lansoprazole for the short-term treatment of erosive oesophagitis and symptomatic gastro-oesophageal reflux disease. In children aged 1 to 11 years, the following oral doses may be given once daily for up to 12 weeks, according to body-weight:

- 30 kg or less: 15 mg
- over 30 kg: 30 mg

Doses of up to 30 mg twice daily have been used in children who remain symptomatic after 2 or more weeks of treatment.

In children aged from 12 to 17 years, oral lansoprazole 30 mg once daily for up to 8 weeks may be given for erosive oesophagitis, and 15 mg once daily for up to 8 weeks may be given for symptomatic non-erosive gastro-oesophageal reflux disease.

Although not licensed for children in the UK, the *BNFC* recommends lansoprazole in the treatment of gastro-oesophageal reflux disease, acid-related dyspepsia, duodenal and benign gastric ulcer including those complicating NSAID therapy, and fat malabsorption despite pancreatic enzyme replacement therapy in cystic fibrosis; comparable oral doses may be given once daily in the morning:

- up to 30 kg: 0.5 to 1 mg/kg (maximum 15 mg)
- over 30 kg: 15 to 30 mg

Studies of oral lansoprazole in infants with gastro-oesophageal reflux disease have produced conflicting results. Lansoprazole reduced symptoms in one study compared with treatment with a hydrolysed formula feed,[1] whereas another study found lansoprazole to be no more effective than placebo; a higher incidence of adverse effects was also reported with lansoprazole therapy.[2] For findings from a review (including these references) regarding the efficacy and safety of proton pump inhibitors in infants, children, and adolescents, see Administration in Children, under Omeprazole, p. 1867.3.

1. Khoshoo V, Dhume P. Clinical response to 2 dosing regimens of lansoprazole in infants with gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 2008; 46: 352–4.
2. Orenstein SR, *et al.* Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. *J Pediatr* 2009; 154: 514–20.

Administration in hepatic impairment. Exposure to lansoprazole is increased in patients with hepatic impairment. UK licensed product information suggests that patients with moderate to severe liver disease should be kept under supervision, and the oral daily dose reduced by 50%.

Adverse Effects and Precautions

As for Omeprazole, p. 1868.1.

Reviews.

1. Preston JW, *et al.* Safety profile of lansoprazole: the US clinical trial experience. *Drug Safety* 1999; 20: 195–205.
2. Claessens AA, *et al.* Safety review in 10,008 users of lansoprazole in daily practice. *Pharmacoepidemiol Drug Safety* 2000; 9: 383–91.

Effects on the blood. For a report of thrombocytopenia with lansoprazole, see under Omeprazole, p. 1868.2.

Effects on electrolytes. For mention of a fall in electrolytes during treatment with proton pump inhibitors including lansoprazole, see Omeprazole, p. 1868.3.

Effects on the endocrine system. For cases of gynaecomastia associated with lansoprazole, see p. 1868.3.

Effects on the gastrointestinal tract. Glossitis (associated in some cases with black tongue or stomatitis) has been reported in a few patients taking lansoprazole as part of a triple therapy regimen for *Helicobacter pylori* elimination in peptic ulcer disease.[1] Discoloured tongue has been reported in a patient taking lansoprazole alone.[2]

An increase in gastritis occurred in patients infected with *Helicobacter pylori* when given long-term lansoprazole therapy.[3] For further discussion of the link between *H. pylori*, gastritis, and proton pump inhibitor use, see Gastrointestinal Tumours, p. 1869.3.

For a suggestion that the incidence of diarrhoea may be greater with lansoprazole than omeprazole see Incidence of Adverse Effects, p. 1868.2. Cases of microscopic colitis have been reported with use of lansoprazole.[4] UK licensed product information states that stopping therapy should be considered in the case of severe and/or persistent diarrhoea.

1. Greco S, *et al.* Glossitis, stomatitis, and black tongue with lansoprazole plus clarithromycin and other antibiotics. *Ann Pharmacother* 1997; 31: 1548.
2. Scully C. Discoloured tongue: a new cause? *Br J Dermatol* 2001; 144: 1293–4.
3. Berstad AE, *et al.* Helicobacter pylori gastritis and epithelial cell proliferation in patients with reflux oesophagitis after treatment with lansoprazole. *Gut* 1997; 41: 740–7.
4. Hilmer SN, *et al.* Microscopic colitis associated with exposure to lansoprazole. *Med J Aust* 2006; 184: 185–6.

Effects on the musculoskeletal system. For reference to a case of eosinophilia and myalgia related to lansoprazole therapy, see p. 1869.1.

Effects on the skin. For mention of skin reactions to lansoprazole, see p. 1869.2.

Hypersensitivity. For a suggestion that lansoprazole may be tolerated in patients sensitive to omeprazole and pantoprazole see p. 1870.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lansoprazole 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 03/10/11)

Interactions

As for Omeprazole, p. 1870.3. Antacids and sucralfate may reduce the bioavailability of lansoprazole, and should not be taken within 1 hour of a dose of lansoprazole.

For reference to a lack of effect of lansoprazole on diazepam, see Gastrointestinal Drugs, p. 1069.3, and for a clinically insignificant effect on theophylline clearance, see p. 1236.1. For reference to glossitis occurring when lansoprazole was used with some antibacterials, see Effects on the Gastrointestinal Tract, above.

Pharmacokinetics

Lansoprazole is rapidly absorbed after oral doses and peak plasma concentrations occur after about 1.5 to 2 hours. Bioavailability is reported to be 80% or more even with the first dose, although the drug must be given in an enteric-coated form since lansoprazole is unstable at acid pH. Food slows the absorption of lansoprazole and reduces the bioavailability by about 50%. Lansoprazole is about 97% bound to plasma protein. It is extensively metabolised in the liver, primarily by cytochrome P450 isoenzyme CYP2C19 to form 5-hydroxyl-lansoprazole and by CYP3A4 to form lansoprazole sulfone. Metabolites are excreted mainly in faeces via the bile; only about 15 to 30% of a dose is excreted in urine. The plasma elimination half-life is around 1 to 2 hours but the duration of action is much longer. Clearance is decreased in elderly patients, and in hepatic impairment.

References.

1. Hussein Z, *et al.* Age-related differences in the pharmacokinetics and pharmacodynamics of lansoprazole. *Br J Clin Pharmacol* 1993; 36: 391–8.
2. Flouvat B, *et al.* Single and multiple dose pharmacokinetics of lansoprazole in elderly subjects. *Br J Clin Pharmacol* 1993; 36: 467–9.
3. Delhotal-Landes B, *et al.* Pharmacokinetics of lansoprazole in patients with renal or liver disease of varying severity. *Eur J Clin Pharmacol* 1993; 45: 367–71.
4. Delhotal Landes B, *et al.* Clinical pharmacokinetics of lansoprazole. *Clin Pharmacokinet* 1995; 28: 458–70.
5. Karol MD, *et al.* Lansoprazole pharmacokinetics in subjects with various degrees of kidney function. *Clin Pharmacol Ther* 1997; 61: 450–8.
6. Tran A, *et al.* Pharmacokinetic-pharmacodynamic study of oral lansoprazole in children. *Clin Pharmacol Ther* 2002; 71: 359–67.
7. Zhang W, *et al.* Age-dependent pharmacokinetics of lansoprazole in neonates and infants. *Paediatr Drugs* 2008; 10: 265–74.

Metabolism. As for omeprazole (p. 1871.2), the cytochrome P450 isoenzyme CYP2C19 (*S*-mephenytoin hydroxylase) is involved in the hydroxylation of lansoprazole, and individuals who are deficient in this enzyme are poor metabolisers of lansoprazole.[1,2] There is some suggestion that the effect of this genetic polymorphism on lansoprazole may be less than the effect on omeprazole.[3]

1. Pearce RE, *et al.* Identification of the human P450 enzymes involved in lansoprazole metabolism. *J Pharmacol Exp Ther* 1996; 277: 805–16.
2. Sohn DR, *et al.* Metabolic disposition of lansoprazole in relation to the S-mephenytoin 4'-hydroxylation phenotype status. *Clin Pharmacol Ther* 1997; 61: 574–82.
3. Kim K-A, *et al.* Enantioselective disposition of lansoprazole in extensive and poor metabolizers of CYP2C19. *Clin Pharmacol Ther* 2002; 72: 90–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lanzoacid; Lanzopral; Mesactol; ***Austral.***: Lanzopran; Zopral; Zoton; ***Austria***: Agopton; Lansobene; Lansohexal; ***Belg.***: Dakar; ***Braz.***: Alkazol†; Lanogastro; Lanz; Lanzol; Lanzopept; Lanzopran; Lispelin; Neozol; Ogastro; Prazol; Ulcestop; ***Canad.***: Prevacid; ***Chile***: Fudermex; Gastride; Langastrol; Lanzopral; Unimet; Unival; ***China***: Lan Xi Duo (兰悉多); Prevacid (普托平); Richwe (拉索脫); Takepron (达克普隆); Cz.: Lansoprol; Lansoram; Lanzul; ***Fin.***: Gasterix; Lanrec; Lantil; Lanvone; Zolt; ***Fr.***: Lanzor; Ogast; Ogastoro; ***Ger.***: Agopton; Lanso Tad†; Lanso-Q†; Lansogamma†; Lanzor†; ***Gr.***: Apradil; Elcodil; Lancirol; Lanso; Lanzol; Laprazol; Prevacid; Zoletad; ***Hong Kong***: Emlansa; Lanzol; Lasoprol; Takepron; ***Hung.***: Emillan; Landia; Lansacid; Lansogen; Lansone; Lansoptol; Levant†; Protonexa; Refluxon; ***India***: Aclanz; Arlan; Bal-Lanz; Cap Loc; Chexid; Culans; Juniorlanzol; L-30; Lampo; Lan; Lance; Lancer; Lanchek; Landbay; Lancid; Lancus; Lands; Lanip; Lanogard; Lanoz; Lanpro; Lans-OD; Lansec; Lanset; Lanso; Lansofast; Lansol; Lansomac; Lansoriv; Lansoz; Lanspep; Lanspro; Lanzap; Lanzee; Lanzip; Lanzo; Lanzol; Lanzopen; Lasole; Laz; Lepez; Levant; Lezo; Liza; Locid; LP; Lupizole; Okalan; Olez; ***Indon.***: Betalans; Caprazol; Compraz; Digest; Erphalanz; Gastrolan; Inhipraz; Lagas; Lancid; Lanpracid; Lapraz; Laproton; Lasgan; Laz; Lazol; Lexid; Loprezol; Nufaprazol; Prazotec; Prolanz†; Prosogan; Protica; Pysolan; Solans; Sopralan; Ulceran; ***Irl.***: ByLans; Lanziop†; Lanzol; Razolager; Zomel; Zoton; Zotrole; ***Israel***: Lanso; Lanton; Zoton; ***Ital.***: Ermes; Prilans; Krovaneg; Lansox; Levogenix; Limpidex; Lomevel; Peptirex; Pergastid; Zoton; ***Jpn***: Prevacid†; Takepron; ***Malaysia***: Gastrovex; Julphasole; Lanpro; Lans-OD; Lanso; Levant; Prevacid; ***Mex.***: Amdory; Arulart†; Bonzol; Gavonad; Ilsatec; Imidex; Keval†; Lafin; Lanodizol; Mavilan; Mediprim; Ogastro; Olan; Palatrin; Pranix; Safemar; Serax; Uldapril; Ulpax; ***Neth.***: Lanzatol; Prezal; ***Norw.***: Lanzo; ***NZ***: Lanzol; Solox; ***Philipp.***: Lansodin; Lanspro; Lanzep; Lanzobex†; Lanzole; Prevacid; Propilan; Pylison; Pysolan; Taquidine; ***Pol.***: Lanbax; LansoLek†; Lantrea; Lanzogen; Lanzostad; Lanzul; Rapilazole; Renazol; Zalanzo; ***Port.***: Alexin; Alprotec; Belmural; Dispepd; Doxatec; Gastrex; Gastrlbien; Gastrolanzo†; Gastroliber; Hepizol†; Lansox; Lanzogastro; Lapol; Ogasto; Pampe; Ulcertec; ***Rus.***: Acrilans (Акрилянс)†; Epicur (Эпикур); Helicol (Геликол); Lancid (Ланцид); Lansofed (Лансофед); Lansoptol (Лансоптол); Lanzabel (Ланзабел); Lanzap (Ланзап); Loenzar (Лоензар); ***S.Afr.***: Adco-Roznal; Gastrid; Lancap; Lansoloc; Lanzor; ***Singapore***: Lasoprol; Prevacid; ***Spain***: Bamalite†; Estomil; Eudiges†; Lanzol; Monolitum; Opiren; Pasgram†; Pro Ulco; Protoner; ***Swed.***: Lanzo; Nixacid; ***Switz.***: Agopton; Lansoprax;

Thai.: Prevacid; *Turk.*: Aprazol; Degastrol; Helicol; Lansazol; Lansoprol; Lansor; Lanzedin; Lukazrol; Ogastro; Opagis; Progis; Vogast; Zoprol; *UAE*: Lanfast; *UK*: Zoton; *Ukr.*: Lancerol (Ланцерол); Lansoprol (Лансопрол); Lanzap (Лянзап); *USA*: Prevacid; *Venez.*: Biolanz; Gastrazol; Lansovax; Lanzol; Lanzopral; Ogastro.

Multi-ingredient Preparations. *Braz.*: H Bacter; Helicopac; Helik-lar; Lansodom†; Lansoprid†; Pylorikit; Pyloripac Retrat; Pylori-pac; Pyloriset; Pyloritrat; *Canad.*: Hp-Pac; *Chile*: Lanzopral Heli-Pack; Pylopac; *Fin.*: Helipak A; Helipak K; Helipak T; *India*: Domsin-LA; Heligo; L-Dom; Lance-D; Landdom; Lanip-D; Lans-DX; Lansi Kit; Lanspro-D; Lanzee-DM; Lapra-D; Lasole-D; Leedom; Lesozap-D; Liza-D; Locid-D; LTC-Kit; Okalan D; Pylo-kit; *Mex.*: Pylopac; *Turk.*: Helipak; Trio; *USA*: Prevpac.

Used as an adjunct in:. *Turk.*: Napro-Pac; *USA*: Prevacid Napra-PAC†.

Pharmacopoeial Preparations
BP 2014: Gastro-resistant Lansoprazole Capsules; Gastro-resistant Lansoprazole Tablets;
USP 36: Lansoprazole Delayed-Release Capsules.

Lidamidine Hydrochloride *(USAN, rINNM)*

Hidrocloruro de lidamidina; Lidamidina, hidrocloruro de; Lidamidine, Chlorhydrate de; Lidamidini Hydrochloridum; WHR-1142A; Лидамидина Гидрохлорид.

N-(2,6-Dimethylphenyl)-*N'*-[imino(methylamino)methyl]urea hydrochloride.

$C_{11}H_{16}N_4O.HCl$=256.7.

CAS — 66871-56-5 (lidamidine); 65009-35-0 (lidamidine hydrochloride).

UNII — 3Q1Q4QJV3V.

Profile

Lidamidine is an alpha$_2$-adrenergic receptor stimulant used as the hydrochloride for the management of diarrhoea and other gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mex.*: Supra.

Linaclotide *(USAN, rINN)*

Linaclotida; Linaclotidum; Линакльотид.

[9-L-Tyrosine]heat-stable enterotoxin (Escherichia coli)-(6-19)-peptide.

$C_{59}H_{79}N_{15}O_{21}S_6$=1526.7.

CAS — 851199-59-2.

ATC — A06AX04.

ATC Vet — QA06AX04.

UNII — N0TXR0XR5X.

Linaclotide Acetate *(USAN, rINNM)*

Acetato de linaclotida; Linaclotide, Acétate de; Linaclotidi Acetas; MD-1100; MM-416775; Линакльотида Ацетат.

$C_{59}H_{79}N_{15}O_{21}S_6C_2H_4O_2$=1586.8.

CAS — 851199-60-5.

ATC — A06AX04.

ATC Vet — QA06AX04.

UNII — NSF067KU1M.

Uses and Administration

Linaclotide is a 14-amino acid synthetic peptide structurally related to the endogenous guanylin peptide family. Both linaclotide and its active metabolite bind as agonists to the guanylate cyclase-C receptor on the luminal surface of the intestinal epithelium. It is used in the treatment of constipation-predominant irritable bowel syndrome (p. 1810.3) and chronic idiopathic constipation (p. 1804.3). Oral doses are taken on an empty stomach, at least 30 minutes before the first meal of the day.

For constipation-predominant irritable bowel syndrome linaclotide 290 micrograms is taken orally once daily. If there is no improvement in symptoms after 4 weeks, continued treatment should be reconsidered.

For chronic idiopathic constipation linaclotide 145 micrograms is taken orally once daily.

References.
1. Wensel TM, Luthin DR. Linaclotide: a novel approach to the treatment of irritable bowel syndrome. *Ann Pharmacother* 2011; **45**: 1535–43.
2. Lembo AJ, *et al.* Two randomized trials of linaclotide for chronic constipation. *N Engl J Med* 2011; **365**: 527–36.
3. Rao S, *et al.* A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am J Gastroenterol* 2012; **107**: 1714–24.
4. Chey WD, *et al.* Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol* 2012; **107**: 1702–12.
5. Lee N, Wald A. Linaclotide: evidence for its potential use in irritable bowel syndrome and chronic constipation. *Core Evid* 2012; **7**: 39–47.

Adverse Effects and Precautions

The most commonly reported adverse effect of linaclotide is diarrhoea, and treatment may need to be withheld for severe diarrhoea or prolonged episodes lasting longer than 1 week. Other gastrointestinal effects include abdominal pain or distention, flatulence, vomiting, and dyspepsia. Headache, fatigue, viral gastroenteritis, upper respiratory-tract infections, and sinusitis have also been reported.

Linaclotide is not recommended for children or adolescents as it has not been studied in this population. Guanylate cyclase-C receptors are known to be over-expressed in infancy and children younger than 2 years may be particularly sensitive to linaclotide effects. Linaclotide is also not recommended in those with inflammatory bowel disease due to a lack of data. It should not be used in patients with known or suspected gastrointestinal obstruction.

Pharmacokinetics

Linaclotide has low bioavailability after oral dosing and is virtually undetectable in the plasma. It is broken down within the gastrointestinal tract by proteolysis to its main des-tyrosine active metabolite MM-419447, and then further degraded or reduced to smaller peptides and amino acids. About 4% of a dose is excreted in the faeces as the active metabolite.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Neth.*: Constella; *UK*: Constella; *USA*: Linzess.

Liquorice

Alcaçuz; Édesgyökér; Gancao; Glycyrrhiza; Korzeń lukrecji; Lakritsijuuri; Lakritsrot; Lékořicový kořen; Licorice; Liquiritiae Radix; Liquorice Root; Orozuz; Raiz de Regaliz; Raíz de regaliz; Regaliz; Réglisse, racine de; Saldymedžių šaknys; Süssholzwurzel; Лакрица.

ATC Herb — HR05WA5014 (Glycyrrhiza glabra: root); HA02WA5001 (Glycyrrhiza glabra: root).

UNII — 61ZBX54883 (liquorice); 2788Z9758H (Glycyrrhiza glabra root).

Description. The dried rhizome and roots of *Glycyrrhiza glabra* var. *typica* are known in commerce as Spanish Liquorice, those of *G. glabra* var. *glandulifera* as Russian Liquorice, and those of *G. glabra* var. β-*violacea* as Persian Liquorice.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*. *Eur.* (see p. vii) also includes Liquorice Dry Extract for Flavouring Purposes. *US* also includes Powdered Licorice and Powdered Licorice Extract. *Br.* also includes Liquorice Root for use in Traditional Chinese Medicine and Processed Liquorice Root for use in Traditional Chinese Medicine.

Ph. Eur. 8: (Liquorice Root; Liquorice BP 2014). The dried unpeeled or peeled, whole or cut root and stolons of *Glycyrrhiza glabra* and/or *G. inflata* and/or *G. uralensis*. It contains not less than 4% of 18β-glycyrrhizic acid. Protect from light.

USP 36: (Licorice). The roots, rhizomes, and stolons of *Glycyrrhiza glabra* or *G. uralensis*. It contains not less than 2.5% of glycyrrhizic acid, calculated on the dried basis. Store in a cool, dry place.

BP 2014: (Liquorice Root for use in TCM). It is the dried unpeeled root and rhizome of *Glycyrrhiza uralensis*, *G. inflata*, or *G. glabra*, or a mixture of these. For use in traditional Chinese medicines. It contains not less than 2.0% of glycyrrhizic acid calculated with reference to the dried material. Protect from moisture.

BP 2014: (Processed Liquorice Root for use in TCM). Liquorice Root for use in TCM which has been cleaned, softened, sliced transversely or longitudinally to form uniform pieces, and dried. It contains not less than 2.0% of glycyrrhizic acid calculated with reference to the dried material. Protect from moisture.

Uses and Administration

Liquorice is used as a flavouring and sweetening agent. It has demulcent and expectorant properties and has been used in cough preparations. It has ulcer-healing properties that may result from stimulation of mucus synthesis. It contains constituents that produce mineralocorticoid effects (see below). Liquorice may also possess some antispasmodic and laxative properties.

Deglycyrrhizinised liquorice has a reduced mineralocorticoid activity and has been used, usually with antacids, for the treatment of peptic ulcer disease (p. 1813.2).

Reviews.
1. Fiore C, *et al.* A history of the therapeutic use of liquorice in Europe. *J Ethnopharmacol* 2005; **99**: 317–24.

Adverse Effects and Precautions

Liquorice has mineralocorticoid-like actions manifesting as sodium and water retention and hypokalaemia (see below).

Deglycyrrhizinised liquorice is not usually associated with such adverse effects.

Mineralocorticoid effects. Mineralocorticoid effects have been reported after excessive or prolonged ingestion of liquorice. The liquorice may be ingested in confectionery (including liquorice-flavoured chewing gum), tea, soft drinks, herbal medicines, cough mixtures, or by chewing tobacco. The enzyme 11-β-hydroxysteroid dehydrogenase (cortisol oxidase) converts cortisol to cortisone, preventing cortisol gaining access to non-specific mineralocorticoid receptors. This enzyme is inhibited by glycyrrhetinic acid (produced by the hydrolysis of glycyrrhizic acid, a natural constituent of liquorice), resulting in increased concentrations of cortisol in the body, enhancing its physiological effects.[1-3]

Clinical manifestations include consequences of sodium retention such as hypertension,[4-10] and hypokalaemia, which can result in neuromuscular disturbances ranging from muscle weakness,[11] myoclonus,[12] and myopathy[10] to paralysis[13-15] and rhabdomyolysis.[15-18] Arrhythmias[16,19] and fatal cardiac arrest[20] have also been reported.

Increased amounts of cortisol in vascular smooth muscle may cause vasoconstriction. Vasospasm of vessels supplying the optic nerve may have caused transient visual disturbances reported after liquorice ingestion.[2] Liquorice has also been reported to cause symptoms including recurrent thunderclap headaches with intermittent loss of vision, severe transient hypertension, and seizures; reversible angiographic abnormalities and bilateral lobar haemorrhages suggested reversible cerebral vasoconstriction, whereas brain oedema was consistent with posterior reversible encephalopathy.[21]

Other reported effects of liquorice include growth retardation in a boy with Addison's disease;[22] liquorice was thought to have potentiated the effect of hydrocortisone.

Endocrine effects of liquorice have been reviewed.[23] Conflicting effects on testosterone and prolactin have been reported. Components of liquorice root (which has been tried for menopausal symptoms) have both oestrogenic and anti-oestrogenic activity, and it has reportedly caused gynaecomastia.

Individuals vary markedly in their susceptibility to liquorice-induced adverse effects.[1] Those consuming 400 mg glycyrrhetinic acid daily generally have adverse effects, but a regular daily intake of no more than 100 mg of glycyrrhetinic acid (about 50 g of liquorice sweets) has produced adverse effects in some who appear more sensitive to its effects. Some consider a daily intake of 10 mg glycyrrhetinic acid to be a safe daily dose for adults; the amount of salt consumed needs to be considered as even a low dose of liquorice may induce sodium overload in those consuming high amounts of sodium chloride.[3]

1. Walker BR, Edwards CR. Licorice-induced hypertension and syndromes of apparent mineralocorticoid excess. *Endocrinol Metab Clin North Am* 1994; **23**: 359–77.
2. Dobbins KRB, Saul RF. Transient visual loss after licorice ingestion. *J Neuroophthalmol* 2000; **20**: 38–41.
3. Frey FJ, Ferrari P. Pastis and hypertension—what is the molecular basis? *Nephrol Dial Transplant* 2000; **15**: 1512–14.
4. van Uum SH. Liquorice and hypertension. *Neth J Med* 2005; **63**: 119–20.
5. Dellow EL, *et al.* Pontefract cakes can be bad for you: refractory hypertension and liquorice excess. *Nephrol Dial Transplant* 1999; **14**: 218–20.
6. Woywodt A, *et al.* Turkish pepper (extra hot). *Postgrad Med J* 2000; **76**: 426–8.
7. Janse A, *et al.* The old lady who liked liquorice: hypertension due to chronic intoxication in a memory-impaired patient. *Neth J Med* 2005; **63**: 149–50.
8. Russo S, *et al.* Low doses of liquorice can induce hypertension encephalopathy. *Am J Nephrol* 2000; **20**: 145–8.
9. Hall RC, Clemett RS. Central retinal vein occlusion associated with liquorice ingestion. *Clin Experiment Ophthalmol* 2004; **32**: 341.
10. Hussain RM. The sweet cake that reaches parts other cakes can't! *Postgrad Med J* 2003; **79**: 115–16.
11. Yoshida S, Takayama Y. Licorice-induced hypokalemia as a treatable cause of dropped head syndrome. *Clin Neurol Neurosurg* 2003; **105**: 286–7.
12. Ishiguchi T, *et al.* Myoclonus and metabolic alkalosis from licorice in antacid. *Intern Med* 2004; **43**: 59–62.
13. Elinav E, Chajek-Shaul T. Licorice consumption causing severe hypokalemic paralysis. *Mayo Clin Proc* 2003; **78**: 767–8.
14. Lin S-H, *et al.* An unusual cause of hypokalemic paralysis: chronic licorice ingestion. *Am J Med Sci* 2003; **325**: 153–6.
15. van den Bosch AE, *et al.* Severe hypokalaemic paralysis and rhabdomyolysis due to ingestion of liquorice. *Neth J Med* 2005; **63**: 146–8.
16. Bauchart J-J, *et al.* Alcohol-free pastis and hypokalaemia. *Lancet* 1995; **346**: 1701.
17. Firenzuoli F, Gori L. Rabdomiolisi da liquirizia. *Recenti Prog Med* 2002; **93**: 482–3.

18. Lapi F, *et al.* Myopathies associated with red yeast rice and liquorice: spontaneous reports from the Italian Surveillance System of Natural Health Products. *Br J Clin Pharmacol* 2008; 66: 572–4.
19. Eriksson JW, *et al.* Life-threatening ventricular tachycardia due to liquorice-induced hypokalaemia. *J Intern Med* 1999; 245: 307–10.
20. Haberer JP, *et al.* Severe hypokalaemia secondary to overindulgence in alcohol-free "pastis". *Lancet* 1984; i: 575–6.
21. Chatterjee N, *et al.* Licorice-associated reversible cerebral vasoconstriction with PRES. *Neurology* 2010; 75: 1939–41.
22. Doecker BM, Andler W. Liquorice, growth retardation and Addison's disease. *Horm Res* 1999; 52: 253–5.
23. Armanini D, *et al.* History of the endocrine effects of licorice. *Exp Clin Endocrinol Diabetes* 2002; 110: 257–61.

Pregnancy. Studies in Finnish women indicated that heavy consumption of liquorice (equivalent to ≥ 500 mg/week of glycyrrhizic acid) during pregnancy was associated with an increased risk of preterm delivery.[1,2] Consumption of large amounts of liquorice was a social habit noted to occur in some northern European countries.

1. Strandberg TE, *et al.* Birth outcome in relation to licorice consumption during pregnancy. *Am J Epidemiol* 2001; 153: 1085–8.
2. Strandberg TE, *et al.* Preterm birth and licorice consumption during pregnancy. *Am J Epidemiol* 2002; 156: 803–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Alcalergin†; *China*: Toynox (泰诺); *Denm.*: Futura Hostlet; *Fr.*: Depiderm; Trio D; *India*: Anaproct; Bacup; Liv-Shreyas; Ned; Neo.

Multi-ingredient Preparations. *Arg.*: Drenocol; No-Tos Adultos; No-Tos Adultos; No-Tos Infantil; No-Tos Infantil; Noacid Diatest†; Urinefrol; *Austral.*: Adrenal Complex; Asa Tones†; Betaine Digestive Aid; Broncafect; Colon Care; Detox Program; DiaCo; Fe-Max; Feminine Herbal Complex; HiPep; HRF; Neo-Cleanse; Nyal Cough, Cold & Flu Day + Night; Nyal Night-Time Cough; Olf†; ResCo; Senega and Ammonia; Withania Complex; *Austria*: Heumann's Bronchialtee; Iberogast; Laxalpin†; Midro Tee; Neoplex; Pervivo; Sigman-Haustropfen; *Braz.*: Camomilina C; Fontolax; Laxtam; Naturetti; Tamaril; Tamarine; *Canad.*: Floradix Kindervital†; Formula T13 Tea†; Herbal Laxative plus Yogurt†; Herbal Laxative†; Herbolax†; Laxanat; Magen- und Darmtee N†; Melange de Plantes Formula L1 Laxatif†; Milk Thistle Extract Formula; Phytoestrin; Stomach Ease; Traditional Herbal Laxative†; Ultra-Lax†; *Chile*: Eucerin; Instalax; Naturlax†; NeoStrata; Pectokast; Pectoral Pasteur; *China*: Gan Han (甘含); Wei Tai Kang (谓泰康); *Cz.*: Biotussil; Cajova Smes pri Nachlazeni; Detska Cajova Smes; Detsky Caj s Hermankem; Diabetan; Iberogast; Projimava; Pruduskova; Pulmoran; Reduktan; Species Pectorales Planta; Tormentan; Zaludecni Cajova Smes; *Fr.*: Calmiflorine†; Mediflor Contre la Constipation Passagere No 7; Mediflor Hepatique No 5; Peptyl; Topialyse Sensitive; *Ger.*: Broncholitan; Gastritol; Heumann Bronchialtee Solubifix T; Heumann Magentee Solu-Vetan; Iberogast; Liquirit; Rabro N; Renob Blasen- und Nierentee†; *Hong Kong*: Brown Mixture†; Mist Expect Stim†; Phytoestrin†; *Hung.*: Antifront; Antifront; Bittner; Iberogast; Lactonic; Majvedo es Detoxikalo; Munipyrin; Tamarinlax; *India*: Abana; Almacarb; Alsarex; Alupectin DGL; Ampucare; Arowash†; Attentio; Britesite; Cephagraine; Cofeze; Dermec; Diabecon; Diakof; Diovol Forte DGL; Disocain; Disogel; Extrammune; FN-T-Tus†; Geriforte; Geriforte; Haleezy; Herbolax; Kofarest-H; Koflet; Lactacrat; Lactare; Lactare; Lactonic; Livosil-H; Manoll; Memtone; Menosan; Mentofer; Mustong; Neo-Cordial; Nilitan; Ojus; Oxitard; Paedritone; *Indon.*: Bio-Curliv; Bionam; Curliv Plus; Curliv Plus; Curliv; Enkasari; Fortusin; Ika Sariawan; Kafsir; OBH; OBHdryl; Pectum; Proliva; Transpulmin; *Israel*: Lido Tea†; Midro-Tea; *Ital.*: Allerlux; Cadifen; Cadimint; Dicalmir; Flodolor; Influ-Zinc Gola; Midro; Proctopure; Sciroppo Berta; Tamarine; Tussol; *Jpn*: Anchusan; Bakumondoto; Bofutsushosan; Boiogito; Byakkokaninjinto; Chikujountanto; Choijokito; Chotosan; Colgen Maoto; Daibofuto; Daiokanzoto; Eppikajutsuto; Gokoto; Gorinsan; Goshakusan; Hainosankyuto; Hangeshashinto; Heilsan; Hochuekkito; Ireito; Jidabokuippo; Jiinkokato; Jiinshihoto; Jinsoin; Jizusoippo; Jumihaidokuto; Junchoto; Juzentaihoto; Kakkonto; Kakkontokasenkyushin'i; Kambakutaisoto; Kamikihito; Kamishoyosan; Keigairengyoto; Keihito; Keishikajutsubuto; Keishikaryukotsuboreito; Keishikashakuyakudaioto; Keishikashakuyakuto; Keishininjinto; Keishito; Kihito; Kikyoto; Kososan; Kyukikyogaito; Makyokansekito; Makyoyokukanto; Maoto; Nichinto; Nijutsuto; Ninjin'yoeito; Ninjinto; Nyoshinsan; Ogikenchuto; Orento; Otsujito; Rikkosan; Rikkunshito; Ryokankyomishingeninto; Ryokeijutsukanto; Ryokyojutsukanto; Ryutanshakanto; Saibokuto; Saikanto; Saikokeishikankyoto; Saikokeishito; Saikoseikanto; Saireito; Sansoninto; Seihaito; Seijobofuto; Seishinrenshiin; Seishoekkito; Senkyuchachosan; Shakanzoto; Shakuyakukanzoto; Shigyakusan; Shikunshito; Shimpito; Shofusan; Shokenchuto; Shomakakkonto; Shosaikoto; Shosaikotokakikyosekko; Shoseiryuto; Sokeikakketsuto; Tokakujokito; Tokiinshi; Tokikenchuto; Tokishigyakukagoshuyushokyoto; Tokito; Tsudosan; Unkeito; Yokuininto; Yokukansan; Yokukansankachimpihange; *Malaysia*: Elgucare; Rumalaya; Strepsils Cough Lozenge†; Strepsils Cough Syrup†; Taisho Kampo; *Mex.*: MD Lax; Naturetti; *Mon.*: Blackoids du Docteur Meur; *Neth.*: Iberogast; Verzachtende Hoestsiroop met tijm; *Norw.*: Bronchosan†; Solvipect comp; Solvipect; *NZ*: Bonningtons Irish Moss; *Philipp.*: Boie Carminative (Carminasen); BSI Medicated Spray; Hemofer; *Pol.*: Alax; ApiHelix†; Gastrot†; Hedelicum; Herbogastrin; Iberogast; Padma 28; Pastylki Wykrztusne; Pectobonisol; Pervivo; PiniHelix; Reumpapai; Tussipect; *Rus.*: Amtersol (Амтерсол); Bonjigar (Бонджигар); Codelac (Коделак); Codelac Phyto (Коделак Фито); Diureticae Species No2 (Мочегонный Сбор 2); Doktor Mom (Доктор Мом); Doktor Mom Herbal Cough Lozenges (Доктор Мом Растительные Пастилки От Кашля); Elecasol (Элекасол); Evalar (Эвалар); Insti (Инсти); Kliophyt (Клиофит); Linkus (Линкас); Linkus Lor (Линкас Лор); Mixture Conta Tussis for Adults (Микстура От Кашля Для Взрослых); Mixture Conta Tussis for Children (Микстура От Кашля Для Детей); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Pectorales Elixir (Грудной Эликсир); Pectorales Species No 2 (Грудной Сбор 2); Pectorales Species No 3 (Грудной Сбор 3); Pectorales Species No 4 (Грудной Сбор 4); Phytogastrol (Фитогастрол); Proctophytol (Проктофитол); Prostanorm (Простанорм); Relcer (Рельцер); Sedativae Species No 2 (Седативный Сбор 2); Sodecor (Содекор); Suprima-Broncho (Суприма-бронхо); Travisil (Трависил); *S.Afr.*: Borsdruppels; Chamberlains Cough Remedy Regular†; Puma Cough Balsam†; *Singapore*: Clarico†; Disco; Imunomet; New Tonin Troche; Phytoestrin†; Pico's Cough; Robi's Cough; Septilin; Septilin; Strepsils Cough Lozenge (with natural herbs); Strepsils Cough Syrup†; Vi-Ron; Vyling Gastric; *Spain*: Iberogast; Pastillas Pectorales Kely†; *Swed.*: Iberogast; *Switz.*: Arteria-vita; Bronchosan; DAM Antacidum†; DemoPectol; DemoTussil; Iberogast; Impuls pastilles pour les bronches; Kernosan 24; Kernosan 26; Kernosan Eau Dentifrice†; Kernosan Elixir; Lapidar 10; Liberol Sirop contre la toux†; Makaphyt Gouttes antitussives†; Makaphyt Sirop†; Padma 28; Pastilles bronchiques S; Pastilles pectorales du Dr. Welti; Rotpunkt Apotheke pastilles pour les bronches avec codeine; Sirop pectoral contre la toux S; Strath Gouttes pour l'estomac; Tisane laxative; Tisane pectorale et antitussive; Tisane pectorale pour les enfants; *Thai.*: Brown Mixture; Caryopin; Iyara Ma-Weang; Meloids; Mist Tussis; Mixture Tussis; Ulgastrin; Venium; *Turk.*: Piyraleks; Sena-Oil; *UK*: Allens Pine & Honey; Asthma & Catarrh Relief; Bronchoforce Chesty Cough Ivy Complex; Chesty Cough Relief; Covonia Herbal Mucus Cough Syrup; Covonia Mentholated; Honey & Molasses; Jamaican Sarsaparilla; Lightning Cough Remedy; Nigroids; Padma 28; Padma Circosan; Potters Sugar Free Cough Pastilles; Red Sage Catarrh Remedy; Revitonil; Tickly Cough & Sore Throat Relief; Vegetable Cough Remover; Vocalzone; *Ukr.*: Antifront (Антифронт); Antifront (Антифронт); Bon-Apetit (Бон-Аппетит); Bonjigar (Бонджигар); Bronchomed (Бронхомед); Doctor Cough (Доктор Кашель); Doktor Mom (Доктор Мом сироп); Doktor Mom Herbal Cough Lozenges (Доктор Мом Растительные Пастилки От Кашля); Elecasol (Элкасол); Florised (Флорисед); Gastritol (Гастритол); Gynopower (Гинопауэр); Iberogast (Иберогаст); Insti (Инсти); Kofanol (Кофанол)†; Linkus (Линкас); Relcer (Рельцер)†; Septilin (Септилин); Softovak (Софтовак); Travisil (Трависил); Vitokan (Витокан); *USA*: Detox; Mucotrol.

Homoeopathic Preparations. *Austria*: Astomera.

Pharmacopoeial Preparations
Ph. Eur.: Liquorice Ethanolic Liquid Extract, Standardised;
USP 36: Licorice Fluidextract.

Loperamide Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de loperamida; Loperamid Hidroklorür; Loperamid hydrochlorid; Loperamida, hidrocloruro de; Lopéramide, chlorhydrate de; Loperamid-hidroklorid; Loperamidhydrochlorid; Loperamidhydroklorid; Loperamidi Hydrochloridum; Loperamidihydroklóridi; Loperamido hidrochloridas; R-18553; Лоперамида Гидрохлорид.

4-(4-*p*-Chlorophenyl-4-hydroxypiperidino)-*NN*-dimethyl-2,2-diphenylbutyramide hydrochloride.

$C_{29}H_{33}ClN_2O_2,HCl$=513.5

CAS — 53179-11-6 (loperamide); 34552-83-5 (loperamide hydrochloride).

ATC — A07DA03.

ATC Vet — QA07DA03.

UNII — 77T135393C.

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

Ph. Eur. 8: (Loperamide Hydrochloride). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water; freely soluble in alcohol and in methyl alcohol. Protect from light.

USP 36: (Loperamide Hydrochloride). A white to slightly yellow powder. Slightly soluble in water and in dilute acids; freely soluble in chloroform and in methyl alcohol; very slightly soluble in isopropyl alcohol.

Loperamide Oxide *(BAN, rINN)*

Loperamid oxid; Loperamida, óxido de; Lopéramide Oxyde; Lopéramide, oxyde de; Loperamidi Oxidum; Loperamidioksidi; Loperamido oksidas; Loperamidoxid; Loperamidum Oxidum; Óxido de loperamida; R-58425; Лоперамида Оксид.

$C_{29}H_{33}ClN_2O_3$=493.0

CAS — 106900-12-3.

ATC — A07DA05.

ATC Vet — QA07DA05.

UNII — H3VOT77DE1.

Pharmacopoeias. *Eur.* (see p. vii) includes the monohydrate.

Ph. Eur. 8: (Loperamide Oxide Monohydrate; Loperamidi Oxidum Monohydricum). A white or almost white, slightly hygroscopic, powder. Practically insoluble in water; freely soluble in alcohol and in dichloromethane. Store in airtight containers. Protect from light.

Uses and Administration

Loperamide is a synthetic derivative of pethidine that inhibits gut motility and may also reduce gastrointestinal secretions. It is given orally as an antidiarrhoeal drug as an adjunct in the management of acute and chronic diarrhoeas and may also be used in the management of colostomies or ileostomies to reduce the volume of discharge.

In **acute diarrhoea** the usual initial dose is loperamide hydrochloride 4 mg followed by 2 mg after each loose stool to a maximum of 16 mg daily; the usual daily dose is 6 to 8 mg.

In **chronic diarrhoea** the usual initial dose is 4 to 8 mg daily in divided doses subsequently adjusted as necessary; doses of 16 mg daily should not be exceeded. If no improvement has been seen after treatment with 16 mg daily for at least 10 days, further use is unlikely to be of benefit.

For doses in children, see below

Loperamide is also given as the prodrug, **loperamide oxide**, which is converted to loperamide in the gastrointestinal tract. It has been given for acute diarrhoea in doses of 2 to 4 mg initially followed by 1 mg after each loose stool, to a maximum of 8 mg daily.

Administration in children. Loperamide can be used in children as an adjunct in the symptomatic treatment of acute and chronic diarrhoeas, and in the management of colostomies or ileostomies to reduce the volume of discharge.

In **acute diarrhoea** dose regimens vary according to country. In the UK, it is licensed for children from 4 years of age; recommended oral doses of loperamide hydrochloride are:

- 4 to 8 years: 1 mg three or four times daily for up to 3 days
- over 8 years: 2 mg four times daily for up to 5 days

The *BNFC* suggests using adult doses (see above) in children from 12 years of age.

In the USA, loperamide is licensed for children from 2 years of age. The recommended initial oral dose for children aged 2 to 5 years is 1 mg three times daily.

For restrictions on the use of loperamide in children and the view that antidiarrhoeal drugs should not be used at all in children with acute diarrhoea, see Diarrhoea, below.

Although not licensed for use in children for **chronic diarrhoea**, in the UK the *BNFC* allows for the following oral doses:

- 1 month to 1 year: 100 to 200 micrograms/kg twice daily, given 30 minutes before feeds; up to a maximum of 2 mg/kg daily in divided doses may be required
- 1 to 12 years: 100 to 200 micrograms/kg (maximum dose 2 mg) three to four times daily; up to 1.25 mg/kg daily in divided doses may be required, to a maximum of 16 mg daily
- 12 to 18 years: adult doses can be given

Diarrhoea. The mainstay of treatment for acute diarrhoea (p. 1805.2) is rehydration therapy. Antidiarrhoeals may have a role for symptomatic relief in adults with acute diarrhoea, and loperamide is often chosen in such circumstances,[1] but WHO does not recommend the use of *any* antidiarrhoeal drug in children with diarrhoea. Similarly, in the UK the *BNFC* states that antimotility drugs are not recommended for acute diarrhoea in children under 12 years of age. There have been problems regarding the use of antidiarrhoeals such as loperamide in young children in developing countries. Manufacturers have considered that a lower age limit is acceptable in those countries than is recommended in the UK or USA; even that lower limit is not always observed in practice and there have been reports of serious toxicity in very young children.[3] In response to such reports the manufacturers withdrew concentrated drops of loperamide worldwide and the syrup from countries where the WHO had a programme for control of diarrhoeal diseases,[3] but tablets and capsules remain available. In some countries the use of antidiarrhoeals is now restricted by law.

In the UK, NICE states that loperamide is the antidiarrhoeal of first choice in adults with faecal incontinence;[4] it can be used long-term in doses from 500 micrograms to 16 mg daily as needed. Loperamide should be started at a very low dose which can be increased as needed, and then adjusted in response to stool consistency. It should not be given to those with hard or

infrequent stools, those with acute diarrhoea of unknown cause, or with acute ulcerative colitis. Patients who are unable to tolerate loperamide may be offered codeine phosphate (p. 40.2) or co-phenotrope (see Diphenoxylate Hydrochloride, p. 1835.3).

For mention of the use of loperamide in the management of diarrhoea caused by chemotherapy, see p. 731.3.

1. Wingate D, *et al.* Guidelines for adults on self-medication for the treatment of acute diarrhoea. *Aliment Pharmacol Ther* 2001; 15: 773–82.
2. Bhutta TI, Tahir KI. Loperamide poisoning in children. *Lancet* 1990; 335: 363.
3. Gussin RZ. Withdrawal of loperamide drops. *Lancet* 1990; 335: 1603–4.
4. NICE. Faecal incontinence: the management of faecal incontinence in adults (issued June 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/CG49NICEGuidance.pdf (accessed 31/03/08)

PRODRUG THERAPY. References to the use of *loperamide oxide* in diarrhoea.

1. Van Den Eynden B, *et al.* New approaches to the treatment of patients with acute, nonspecific diarrhea: a comparison of the effects of loperamide and loperamide oxide. *Curr Ther Res* 1995; 56: 1132–41.
2. Hughes IW, *et al.* First-line treatment in acute non-dysenteric diarrhoea: clinical comparison of loperamide oxide, loperamide and placebo. *Br J Clin Pract* 1995; 49: 181–5.
3. van Outryve M, Toussaint J. Loperamide oxide for the treatment of chronic diarrhoea in Crohn's disease. *J Int Med Res* 1995; 23: 335–41.
4. Sun WM, *et al.* Effects of loperamide oxide on gastrointestinal transit time and anorectal function in patients with chronic diarrhoea and faecal incontinence. *Scand J Gastroenterol* 1997; 32: 34–8.

Adverse Effects and Treatment

Abdominal pain or bloating, nausea, constipation, dry mouth, dizziness, fatigue, and hypersensitivity reactions including skin rashes have been reported. Loperamide has been associated with paralytic ileus, particularly in infants and young children, and deaths have been reported. Depression of the CNS, to which children or those with hepatic impairment may be more sensitive, may be seen in overdosage; constipation and urinary retention also occur. Naloxone hydrochloride (see p. 1563.3) has been recommended for treatment of severe overdosage.

Toxicity. Toxic megacolon has been reported[1,2] after use of loperamide. Severe effects reported in young children have included loss of consciousness[3,4] and delirium.[5] Several cases of paralytic ileus have also occurred in children,[6,7] some of which were fatal.[6]

1. Brown JW. Toxic megacolon associated with loperamide therapy. *JAMA* 1979; 241: 501–2.
2. Walley T, Milson D. Loperamide related toxic megacolon in Clostridium difficile colitis. *Postgrad Med J* 1990; 66: 582.
3. Minton NA, Smith PGD. Loperamide toxicity in a child after a single dose. *BMJ* 1987; 294: 1383.
4. Chanzy S, *et al.* Perte de connaissance chez une jeune enfant secondaire à la prise de lopéramide. *Arch Pediatr* 2004; 11: 826–7.
5. Schwartz RH, Rodriguez WJ. Toxic delirium possibly caused by loperamide. *J Pediatr* 1991; 118: 656–7.
6. Bhutta TI, Tahir KI. Loperamide poisoning in children. *Lancet* 1990; 335: 363.
7. Dudink J, *et al.* Ileus na gebruik van loperamide bij een kind met acute diarree. *Ned Tijdschr Geneeskd* 2003; 147: 670–2.

Precautions

Loperamide should not be used when inhibition of peristalsis is to be avoided, in particular where ileus or constipation occur, and should be avoided in patients with abdominal distension, acute inflammatory bowel disease, or antibiotic-associated colitis. Loperamide should not be used alone in patients with dysentery.

Loperamide should be used with caution in patients with hepatic impairment because of its considerable first-pass metabolism in the liver. It should also be used with caution in young children because of a greater variability of response in this age group; it is not recommended for use in infants (but see Administration in Children, p. 1854.3).

Breast feeding. Loperamide is distributed into breast milk in small amounts.[1] The American Academy of Pediatrics[2] states that there have been no reports of any clinical effect on the infant associated with the use of loperamide by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding.

1. Nikodem VC, Hofmeyr GJ. Secretion of the antidiarrhoeal agent loperamide oxide in breast milk. *Eur J Clin Pharmacol* 1992; 42: 695–6.
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 18/01/06)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies loperamide 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 06/10/11)

Pregnancy. A study[1] in 105 women who had used loperamide during pregnancy (89 in the first trimester) found no increase in major congenital defects compared with controls. However, another study[2] of loperamide use in early pregnancy in 638 women reported an increased risk of congenital malformations; the adjusted odds ratio was 1.41 (with a 95% confidence interval of 1.03-1.93) based on 43 affected children. The authors warned that the results could have arisen by chance and further studies were needed to verify the effect.

1. Einarson A, *et al.* Prospective, controlled, multicentre study of loperamide in pregnancy. *Can J Gastroenterol* 2000; 14: 185–7.
2. Källén B, *et al.* Maternal use of loperamide in early pregnancy and delivery outcome. *Acta Paediatr* 2008; 97: 541–5.

Interactions

Loperamide may increase the gastrointestinal absorption of desmopressin (p. 2357.1).

Antifungals. A pharmacokinetic study in 12 healthy subjects found that *itraconazole* significantly increased peak plasma concentrations and area under the concentration-time curve of loperamide, and also prolonged the half-life of loperamide. Itraconazole also inhibited metabolism of loperamide to *N*-desmethylloperamide, suggesting that metabolism of loperamide in humans concurs with *in-vitro* data (see Metabolism, below). Use of itraconazole with gemfibrozil (see Cardiovascular Drugs, below) synergistically increased exposure to loperamide.[1]

1. Niemi M, *et al.* Itraconazole, gemfibrozil and their combination markedly raise the plasma concentrations of loperamide. *Eur J Clin Pharmacol* 2006; 62: 463–72.

Antivirals. In a single-dose study,[1] oral *ritonavir* significantly increased the bioavailability of loperamide, possibly through inhibition of the cytochrome P450 isoenzyme CYP3A4, and not necessarily as originally supposed through P-glycoprotein inhibition. No serious adverse effects occurred. Licensed information for one UK preparation of loperamide (*Imodium; Janssen-Cilag, UK*) states that the clinical relevance of the pharmacokinetic interaction with P-glycoprotein inhibitors such as ritonavir is unknown.

For the effect of loperamide on *saquinavir*, and the corresponding effect of the antiviral on loperamide concentrations, see Gastrointestinal Drugs, under Interactions of Indinavir, p. 988.1.

1. Tayrouz Y, *et al.* Ritonavir increases loperamide plasma concentrations without evidence for P-glycoprotein involvement. *Clin Pharmacol Ther* 2001; 70: 405–14.

Cardiovascular drugs. A pharmacokinetic study in 12 healthy subjects found that *gemfibrozil* significantly increased peak plasma concentrations and area under the concentration-time curve of loperamide, and also prolonged the half-life of loperamide. Gemfibrozil also inhibited metabolism of loperamide to *N*-desmethylloperamide, suggesting that metabolism of loperamide in humans concurs with *in-vitro* data (see Metabolism, below). Use of gemfibrozil with itraconazole (see Antifungals, above) synergistically increased exposure to loperamide.[1]

1. Niemi M, *et al.* Itraconazole, gemfibrozil and their combination markedly raise the plasma concentrations of loperamide. *Eur J Clin Pharmacol* 2006; 62: 463–72.

Co-trimoxazole. Use with co-trimoxazole increases the bioavailability of loperamide,[1] apparently by inhibiting its first-pass metabolism.

1. Kamali F, Huang ML. Increased systemic availability of loperamide after oral administration of loperamide and loperamide oxide with cotrimoxazole. *Br J Clin Pharmacol* 1996; 41: 125–8.

Quinidine. A small study[1] found that giving quinidine with loperamide caused respiratory depression in 8 healthy subjects; when given with placebo, loperamide produced no respiratory depression. The authors supposed that inhibition of P-glycoprotein by quinidine had increased entry of loperamide into the CNS.

1. Sadeque AJM, *et al.* Increased drug delivery to the brain by P-glycoprotein inhibition. *Clin Pharmacol Ther* 2000; 68: 231–7.

Pharmacokinetics

About 40% of a dose of loperamide is reported to be absorbed from the gastrointestinal tract to undergo first-pass metabolism in the liver and excretion in the faeces via the bile as inactive conjugate; there is slight urinary excretion. Little intact drug reaches the systemic circulation. The elimination half-life is reported to be about 10 hours.

Metabolism. Loperamide is metabolised to desmethylloperamide through *N*-demethylation. An *in-vitro* study established that this occurs mainly via cytochrome P450 isoenzymes CYP2C8 and CYP3A4; CYP2B6 and CYP2D6 also play a role. Loperamide is also a substrate of P-glycoprotein.[1]

1. Kim K-A, *et al.* Identification of cytochrome P450 isoforms involved in the metabolism of loperamide in human liver microsomes. *Eur J Clin Pharmacol* 2004; 60: 575–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Colifilm; Contem; Custey; Dotalsec; Elcoman; Excelentia Antidiarreico; Ionet; Lansek A; Lefa Enteril L; Minicam; Nodiar; Normasec; Plexol; Florinoc; Regulane; Suprasec; Viltar; *Austral.*: Chemists Own Diarrhoea Relief; Diareze; Gastro-Stop; Harmonise; Imodium; Lopedium; *Austria*: Enterobene; Imodium; Normakut; *Belg.*: Imodium; Transityl; *Braz.*: Diafuran; Diasec; Imosec; Loperin; Magnostase; *Canad.*: Diarr-Eze; Diarrhea Relief; Imodium; Loperacap; *Chile*: Capent; Coliper; Lopediar†; Salvacoll; *China*: Pu Xie Ding (腹泻啶); Imodium (易蒙停); Luobaomai (罗宝迈); Ya Bang (雅邦); *Cz.*: Dissenten†; Imodium; Loperon; *Denm.*: Imodium; Imolope; Propiden; *Fin.*: Imocur; Imodium Pro†; Imodium; Lopacut; Lopex; *Fr.*: Altocel; Arestal; Diaretyl; Diastrolib; Dyspagon; Ercestop; Imodium; Imodiumcaps; Imodiumlingual; Indiaral; Peracel; *Ger.*: Imodium; Lop-Dia†; Lopedium†; Loperhoe; *Gr.*: Imodium; Neo-Enteroseptol; Neo-Septol; *Hong Kong*: Diacure†; Diatabs Reformulated; Imodium; Imodonl; Lopa; Loper; Loperamil; Loperax; Loperium†; Lopil†; Mar-Loper†; NT-Diorea†; Reximide†; Synodium†; Uni-Motil†; Vidaperamide†; *Hung.*: Enterobene; Imodium; Lopedium; *India*: Andial; Diarlop Plus; Diarlop; Eldoper; Imodium; Lofact; Lomin; Lopamide; Loperam; Loperiv; Lopona; Roko; *Indon.*: Alphamid†; Amerol; Antidia†; Colidium; Diadium; Diasec; Diaston; Imodan; Imodium; Imomed†; Imoret†; Imosa; Inamid; Lexadium; Licodium; Lodia; Loremid; Motilex; Normotil; Normudal; Opox; Oramide†; Primodium; Renamid; Rhomuz; Xepare; Zeroform; *Irl.*: Arret; Diareze†; Diarrest RF†; Imodium; *Israel*: Imodium; Loperid; Lopi-Care; Loprex; Rekamide; Shilshul X; Stopit; *Ital.*: Diarstene; Diarstop; Diarzero; Dissenten; Imodium; Lopemid; *Malaysia*: Beamodium; Imodium; Loperax†; Loperium; Lopermide; Loramide; Reximide; Vaconil; *Mex.*: Acanol; Acqta; Apo-Pera; Biolid; Cryoperacid; Deroser; Diaperol; Exclefin; Hurplex; Imodium; Lomidal; Lomotil; Lop; Nodiamex; Permidal; Pramidal; Rediarin; Top-Dal; Valfam; *Neth.*: Arestal; Diacure; Diarem†; Diarreeremmer; Imodium; Kruidvat Diarreeremmer; Trekpleister Diarreeremmer; *Norw.*: Imodium; *NZ*: Diamide; Dicap†; Imodium; Nodia; *Philipp.*: Bryper; Diamide; Diaperyl; Diastop; Diatabs (Reformulated); Gastromed; Imodium; LBX; Lomotil; Lormide; Permid†; Tymedon; *Pol.*: Imodium; Laremid; Stoperan; *Port.*: Dyspagon†; Fulcalrex†; Pulcralex†; Imodium; Lopitum; Loprex†; Loride; *Rus.*: Diara (Диара); Imodium (Имодиум); Lopedium (Лопедиум); Superilop (Суперилоп); *S.Afr.*: Betaperamide; Gastron; Imodium; Lenide-T†; Lopedium; Loperastat; Norimode; Prodium; *Singapore*: Colodium; Diatrol; Eldoper; Imodium; Loperamil; Loperax; Lopermide; Loramide; Lorpa; Reximide; SP-Emoloc; Vacontil; *Spain*: Diarfin; Elissan; Fortasec; Imodium; Loperan; Loperkey; Protector†; Salvacolina; Taguinol†; *Swed.*: Dimor; Imodium; Lopacut; Primodium; Travellof†; *Switz.*: Binaldan; Imodium; Lopimed; Lopisol; *Thai.*: Diara; Diarent; Diarine; Diarodil; Dicotil; Entermid; Imodium; Imonox; Impelium; KB Peramide; Leon; Lomide; Lomy; Lopela; Lopercin; Loperdium; Loperiat†; Lopermide†; Lopil; Mantil; Miderlar; Operium; Patardium; Perasian; Ropa; Ropermide; SBOB; Setonox; Tedium; *Turk.*: Diadef; Lopermid; *UK*: Arret; Boots Diarrhoea Relief; Diah-Limit; Diaquitte; Diareze; Diocalm Ultra; Diocaps; Entrocalm; Imodium; Norimode; Normaloe; *Ukr.*: Imodium (Имодиум); Lopedium (Лопедиум); Stoperan (Стоперан); *USA*: Imodium; K-Pek II; Kao-Paverin; Neo-Diaral; Pepto Diarrhea Control; *Venez.*: Glucitol; Imodium; Loperam.

Multi-ingredient Preparations. *Arg.*: Neo Kef; Neomas L; Regulane AF; *Austral.*: Imodium Advanced; *Austria*: Imodium Plus; *Belg.*: Imodium Duo; *Canad.*: Imodium Advanced; *Cz.*: Imodium Duo Action; Imodium Plus; *Denm.*: Imodium Plus; *Fin.*: Imodium Plus; *Fr.*: Imodiumduo; *Ger.*: Imodium akut N duo; Imodium complex†; Imodium Plus†; *Gr.*: Imodium Plus; *Hong Kong*: Imodium Plus; *India*: Dylock-LB; Eldoper Plus; Medilop; *Irl.*: Imodium Plus; *Israel*: Imodium Plus; *Mex.*: Imodium Plus; *Neth.*: Imodium Combi†; Imodium Duo; *Norw.*: Imodium Comp; *NZ*: Imodium Advanced; *Pol.*: Imodium Plus; *Port.*: Imodium Plus; *Rus.*: Imodium Plus (Имодиум Плюс); *S. Afr.*: Imodium Plus; *Spain*: Imodium Duo; *Swed.*: Imodium Plus; *Switz.*: Imodium Duo; *Thai.*: Imodium Plus†; *UK*: Imodium Plus; *Ukr.*: Diaremix (Диаремикс); *USA*: Imodium Advanced; Imodium Multi-Symptom Relief.

Pharmacopoeial Preparations

BP 2014: Loperamide Capsules;
USP 36: Loperamide Hydrochloride Capsules; Loperamide Hydrochloride Oral Solution; Loperamide Hydrochloride Tablets.

Loxiglumide *(rINN)*

CR-1505; CR-2017 (dexloxiglumide); Loxiglumida; Loxiglumidum; Локсиглумид.

(±)-4-(3,4-Dichlorobenzamido)-*N*-(3-methoxypropyl)-*N*-pentylglutaramic acid.

$C_{21}H_{30}Cl_2N_2O_5$=461.4

CAS — 107097-80-3 (loxiglumide); 119817-90-2 (dexloxiglumide).

UNII — 77MPX3N42I.

Profile

Loxiglumide is a specific cholecystokinin antagonist related to proglumide (see p. 1880.1), and has been investigated in

biliary and gastrointestinal dyskinesias, constipation and irritable bowel syndrome, and pancreatitis.

The *R*-isomer of loxiglumide, dexloxiglumide is also under investigation for constipation-predominant irritable bowel syndrome.

References.

1. Shiratori K, *et al.* Clinical evaluation of oral administration of a cholecystokinin-A receptor antagonist (loxiglumide) to patients with acute, painful attacks of chronic pancreatitis: a multicenter dose-response study in Japan. *Pancreas* 2002; 25: e1–e5.
2. Cremonini F, *et al.* Effect of CCK-1 antagonist, dexloxiglumide, in female patients with irritable bowel syndrome: a pharmacodynamic and pharmacogenomic study. *Am J Gastroenterol* 2005; 100: 652–63.
3. Persiani S, *et al.* Pharmacokinetic profile of dexloxiglumide. *Clin Pharmacokinet* 2006; 45: 1177–88.

Lubiprostone *(USAN, rINN)*

Lubiprostona; Lubiprostonum; RU-0211; SPI-0211; Лубипростон.

(-)-7-[(2*R*,4a*R*,5*R*,7a*R*)-2-(1,1-Difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[*b*]pyran-5-yl]heptanoic acid.

$C_{20}H_{32}F_2O_5$=390.5

CAS — 136790-76-6; 333963-40-9.

ATC — A06AX03.

ATC Vet — QA06AX03.

UNII — 7662KG2R6K.

Uses and Administration

Lubiprostone is a chloride-channel activator that acts locally in the gut to increase intestinal fluid secretion, which increases motility. It is used in the treatment of chronic idiopathic constipation (p. 1804.3) in a dose of 24 micrograms twice daily, taken orally with food. It is also used in women for the treatment of constipation-predominant irritable bowel syndrome (p. 1810.3) in a dose of 8 micrograms twice daily, taken orally with food.

References.

1. McKeage K, *et al.* Lubiprostone. *Drugs* 2006; 66: 873–9.
2. Anonymous. Lubiprostone (Amitiza) for chronic constipation. *Med Lett Drugs Ther* 2006; 48: 47–8.
3. Ambizas EM, Ginzburg R. Lubiprostone: a chloride channel activator for treatment of chronic constipation. *Ann Pharmacother* 2007; 41: 957–64.
4. Ginzburg R, Ambizas EM. Clinical pharmacology of lubiprostone, a chloride channel activator in defecation disorders. *Expert Opin Drug Metab Toxicol* 2008; 4: 1091–7.
5. Lacy BE, Chey WD. Lubiprostone: chronic constipation and irritable bowel syndrome with constipation. *Expert Opin Pharmacother* 2009; 10: 143–52.
6. Carter NJ, Scott LJ. Lubiprostone: in constipation-predominant irritable bowel syndrome. *Drugs* 2009; 69: 1229–37.
7. Barish CF, *et al.* Efficacy and safety of lubiprostone in patients with chronic constipation. *Dig Dis Sci* 2010; 55: 1090–7.
8. O'Brien CE, *et al.* Use of the chloride channel activator lubiprostone for constipation in adults with cystic fibrosis: a case series. *Ann Pharmacother* 2010; 44: 577–81.

Adverse Effects and Precautions

The most common adverse effect of lubiprostone is nausea, which is dose-dependent and may be severe in some patients. Symptoms can be reduced by taking lubiprostone with food. Diarrhoea also occurs commonly, and other gastrointestinal effects include abdominal distension and pain, flatulence, and vomiting. Other reported adverse effects include headache, dizziness, fatigue, dyspnoea, chest discomfort, and peripheral oedema. Intestinal functional disorder, constipation, cough, dysgeusia, eructation, decreased appetite, gastro-oesophageal reflux disease, gastritis, increased weight, and rectal haemorrhage have been reported rarely, as have muscle cramps, joint swelling, myalgia, fibromyalgia, hyperhidrosis, pain (including pharyngolaryngeal pain), anxiety, influenza, syncope, tremor, dry mouth, increased liver enzyme values, erythema, palpitations, urinary-tract infection, and depression.

Lubiprostone is contra-indicated in patients with a history of mechanical gastrointestinal obstruction.

Pharmacokinetics

A negligible amount of lubiprostone is absorbed after an oral dose. It is rapidly and extensively metabolised by carbonyl reductase, probably in the stomach and jejunum.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Amitiza; *Switz.*: Amitiza; *UK*: Amitiza; *USA*: Amitiza.

Magaldrate *(BAN, USAN, rINN)*

Aluminum Magnesium Hydroxide Sulfate; AY-5710; Hidroxidosulfato de aluminio y magnesio hidratado; Magaldraatti; Magaldrat; Magáldrát; Magaldratas; Magaldrato; Magaldratum; Маралдрат.

$Al_5Mg_{10}(OH)_{31}(SO_4)_2.xH_2O$=1097.3 (anhydrous)

CAS — 74978-16-8.

ATC — A02AD02.

ATC Vet — QA02AD02.

UNII — 0MFM55849I (anhydrous magaldrate); 6V88E24N5T (magaldrate hydrate).

NOTE. Magaldrate was formerly described as Aluminium Magnesium Hydroxide ($AlMg_2(OH)_7$ monohydrate, *CAS—1317-26-6*).

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

Ph. Eur. 8: (Magaldrate). A combination of aluminium and magnesium hydroxides (see p. 1817.2 and p. 1857.2 respectively) and sulfates. It contains the equivalent of 90 to 105% of $Al_5Mg_{10}(OH)_{31}(SO_4)_2$, calculated with reference to the dried substance. It contains a variable amount of water. A white or almost white crystalline powder. Practically insoluble in water and in alcohol; soluble in dilute mineral acids. It loses between 10 and 20% of its weight on drying at 200 degrees for 4 hours.

USP 36: (Magaldrate). A combination of aluminium and magnesium hydroxides and sulfates. It contains the equivalent of 90 to 105% of $Al_5Mg_{10}(OH)_{31}(SO_4)_2$, calculated on the dried basis. A white odourless crystalline powder. Insoluble in water and in alcohol; soluble in dilute solutions of mineral acids. It loses between 10 and 20% of its weight on drying at 200 degrees for 4 hours.

Profile

Magaldrate is an antacid (see p. 1803.1) that is given in oral doses of up to about 2 g.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Minicidez; Riopan; *Austria*: Riopan; *Belg.*: Gastricalm; Riopan; *Braz.*: Riopan; *Fr.*: Riopan; *Ger.*: Bisco-Magaldrat†; Gastripan†; Glysan; Magastron†; Marax; Riopan; *Gr.*: Atractylon; Felfar; Riopan; *Indon.*: Gestabil Forte; Gestabil; *Ital.*: Gadral; Magaltop; Magralibi; Riopan; *Pol.*: Malugastrin†; *Port.*: Riopan; *Rus.*: Magalphil (Магальфил); *S. Afr.*: Riopone†; *Spain*: Bemolan; Gastromol†; *Magion*: Minoton; *Switz.*: Riopan; *Ukr.*: Almagel T (Алмагель Т); Riopan (Рюпан); *USA*: Iosopan†; Riopan†; *Venez.*: Cremag.

Multi-ingredient Preparations. *Arg.*: Aci-Tip; *Austral.*: Mylanta Heartburn Relief; *Braz.*: Riopan Plus; *Chile*: Antiax; *India*: Acigone-D; Acihit; Acixx; Afocid; Afra-Z; Alcaine; Almag; Amalset; Anatyl-D; Anatyl; Avicid; Bestocid-O; Bestocid; Bipgel; Bluegel-O; Bluegel; Cadgil; Coligon-O; Depcid-O; Digiflux-A; Digirest; Domgel; Duogel; Elcid; Eldrate-S; Endcid; Fomacid; Forzole Gel; G-Gel; Gelone; Glocid; Graster; Hilcid; Icer-MS; Iceron; Kaicid-O; Kaicid; Madarat-S; Madrat-S; Magacone; Magel-MPS; Maglid; Magnadrox; Merigel-A; Merigel; Metadrate; Moska; NBCid; NCA; Netrocid; Neugel; Neutracaine; Nilcid-MPS; Normocid; Norper; Novagel-D; Nulasta; Numeg; Nutec MPS; Ocinil; pH4; Rolac Plus; Ulgel; *Indon.*: Asidrat†; Magalat; Nudramag; *Mex.*: Gex; Masedi; Riopan; *Turk.*: Asidopan Plus; Simelgat Plus; *UK*: Bisodol Extra; Bisodol Heartburn Relief; *USA*: Iosopan Plus†; Lowsium Plus; Riopan Plus; *Venez.*: Cremalon.

Pharmacopoeial Preparations

BP 2014: Magaldrate Oral Suspension;

USP 36: Magaldrate and Simethicone Oral Suspension; Magaldrate and Simethicone Tablets; Magaldrate Oral Suspension; Magaldrate Tablets.

Magnesium Carbonate

Bázisos magnézium-karbonát; E504; Magnesii Carbonas; Magnesii Subcarbonas; Magnesio, carbonato de; Magnésium, carbonate de; Magnesiumsubkarbonaatti; Magnesiumsubkarbonat; Magnezu węglan; Magnezyum Karbonat; Magnio subkarbonatas; Uhličitan hořečnatý zásaditý; Магния Карбонат.

CAS — 546-93-0 (anhydrous magnesium carbonate); 23389-33-5 (hydrated normal magnesium carbonate); 39409-82-0 (hydrated basic magnesium carbonate).

ATC — A02AA01; A06AD01.

ATC Vet — QA02AA01; QA06AD01.

UNII — 0E53J927NA.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.* Some pharmacopoeias include a single monograph that permits both the light and heavy varieties while some have 2 separate monographs for the 2 varieties.

Ph. Eur. 8: (Magnesium Carbonate, Heavy; Magnesii Subcarbonas Ponderosus). A hydrated basic magnesium carbonate containing the equivalent of 40 to 45% of MgO. A white or almost white powder. Practically insoluble in water; dissolves in dilute acids with strong effervescence.

Ph. Eur. 8: (Magnesium Carbonate, Light; Magnesii Subcarbonas Levis). A hydrated basic magnesium carbonate containing the equivalent of 40 to 45% of MgO. A white or almost white powder. Practically insoluble in water; dissolves in dilute acids with strong effervescence.

USP 36: (Magnesium Carbonate). A basic hydrated magnesium carbonate or a normal hydrated magnesium carbonate containing the equivalent of 40.0 to 43.5% of MgO. It is an odourless, bulky white powder or light, white, friable masses. Practically insoluble in water; insoluble in alcohol; dissolves in dilute acids with effervescence.

Profile

Magnesium carbonate is an antacid with general properties similar to those of magnesium hydroxide (p. 1857.2) that is given in oral doses of up to about 500 mg. When given orally, it reacts with gastric acid to form soluble magnesium chloride and carbon dioxide in the stomach; the carbon dioxide may cause flatulence and eructation. Magnesium carbonate is often given with aluminium-containing antacids such as aluminium hydroxide, which counteract its laxative effect.

Magnesium carbonate may be used as a magnesium supplement. It is also used as a food additive, and as a binder and diluent in tablet-making.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Polvo Roge; Total Magnesiano; *Austria*: Magnofit; OsvaRen; *Canad.*: Magmix II; *Fr.*: Mag 2 Junior†; Mag 2; Sargemag; *Ger.*: Biolectra Magnesium 365; OsvaRen; Palmicol†; *Gr.*: Limonata Citromagnes; *Hung.*: Magnosolv; *Ital.*: Magnofit; *Pol.*: Additiva Magnesium†; Magnezin; *S.Afr.*: Be-Lax; *Switz.*: Magnesium Nutrimed; *Turk.*: Magnesium Nutrimed; *USA*: Mag-Carb.

Multi-ingredient Preparations. *Arg.*: Acinat; Antiacid; Benitol; Calmose; Gastranil; Gastricur; Holomagnesio Vital; Magnesio + C/Mag-CE; Mucaine; Polper Calcio-Magnesio; Rennie; Rennie; Total Magnesiano E; Total Magnesiano Energizante; Total Magnesiano Fem; Total Magnesiano Sport; Total Magnesiano; *Austral.*: Antacid Chewable Tablets†; Cal Alkyline†; Degas Extra†; Rennie; *Austria*: Magnosolv; Rennie Digestif; Rennie; *Belg.*: Magnesie Plus; Neutroses; Rennie†; Rennie; *Braz.*: Gaviz; Magnesia Bisurada; *Canad.*: Calmax†; Dol-Mite†; Gaviscon Heartburn & Acid Reflux Relief; Gaviscon Maxrelief; Maalox HRF†; Mega Dole†; *Chile*: Algicote†; Nogastra; Peptinal Forte†; Peptinal†; Reflumox; *China*: JieAn (揭安); Rennie (罗内); *Cz.*: Digestif Rennie†; Gastal†; Magnosolv; OsvaRen; Rennie Duo†; Rennie; Tums†; *Denm.*: BiOrto Al-C; Novaluzid; OsvaRen; *Fin.*: Novaluzid; OsvaRen; Rennie; *Fr.*: Actigess†; Bouillet; Citrocholine†; Dops†; Gastropax; Ginvit; Hepatoum Brulures d'Estomac†; Kaobrol; Magnesie Composee†; Neutroses; Nutri Yin-Nutri Yang†; Pelvimag; Peptyl; Rennie Deflatine; Rennie; Renniechew†; Topaal; Topalkan†; Vascocitrol†; *Ger.*: Liquirit; Losnesium; Rennie; *Gr.*: Alcamex-Mg; Andrews Antacid; Conquista; Dyspagone; Elkopas; KH3; OsvaRen; Rennie; Tums; *Hong Kong*: Antacaine; Mucaine†; *Hung.*: Digestif Rennie†; Rennie; *India*: Almacarb; Diovol; Ossofez; *Indon.*: Minos†; Yanthi Baby & Bath Powder†; *Irl.*: Andrews Antacid†; Bisodol Extra Strong Mint Tablets; Bisodol†; Bisodol; OsvaRen; Rennie Deflatine; Rennie Dual Action; Rennie Peppermint; Rennie Spearmint; Rennie Sugar Free; Topaal; *Israel*: Fresco; Rekiv†; Rennie; *Ital.*: Citrato Espresso Gabbiani; Citromagnesiaca; Magnesia Bisurata Aromatic; Magnosol; Neutrose S Pellegrino; Rennie; *Jpn*: Cabe 2†; The Guard Seichojo; *Neth.*: Algicon; Algicon; OsvaRen; Rennie Deflatine; Rennie Duo; Rennie; Roteroblong Maagtabletten; *Norw.*: Novaluzid; OsvaRen; *NZ*: KH3; *Philipp.*: Algycon; Novaluzid†; Vita SL; *Pol.*: Dolomit; Gastal; Gastro†; Gastrofan†; Osteogel; Proacid†; Redinac†; Rennie; Ulgamax†; *Port.*: Bisodol†; OsvaRen; Rennie Digestif; *Rus.*: Inalan (Иналан); Magnesium Plus (Магний Плюс); Rennie (Ренни); Vicair (Викэир); Vicalin (Викалин); *S.Afr.*: Adcomag Trisil†; Be-Tabs Antacid†; Behoedmiddel vir Kinders; Bisodol†; Carminex†; Digestif Rennie; Gentrisil†; *Singapore*: Aromag; Baby Brand Antacid; Bismag†; Inon; Kaomix; Magtasil; Rennie Deflatine; Rennie; *Spain*: Bupeptina; Gelodrox; Hecteonona; Mabogastrol†; OsvaRen; Rennie; Sales Pruta Mag Viviar†; *Swed.*: Novaluzid; OsvaRen; Rennie; Samarin; *Switz.*: Neutroses; Rennie Deflatine; Rennie Ice; Rennie; *Thai.*: Algycon; Carbonpectate; KH3†; Mucaine†; *Turk.*: Bisman; Bismomagnesie†; Bismomagnesie; Calmy Plus; Calmy; Magcar; Rennie Duo; Rennie; *UAE*: JulMag; *UK*: Actonorm; Andrews Antacid; Birley's; Bisma-Rex; Bisodol Wind Relief; Bisodol; Bisodol; Calcium Clear; De Witt's Antacid; De Witt's Antacid; Moorland; Opas; OsvaRen; Rennie Deflatine; Rennie Duo†; Rennie; Topal; Uriflex R; Uro-Tainer Solution R; Valonorm; *Ukr.*: Remmax (Реммакс); Rennie (Ренни); Vicair (Викэир); Vicalin (Викалин); *USA*: Acid Gone; Alenic Alka; Extra Strength Genaton; Gaviscon Extra Strength Relief Formula; Gaviscon Extra Strength; Gaviscon; Genaton; MagneBind; Marblen; Mi-Acid Gelcaps; Mylagen; Renacidin; Tonsiline.

Used as an adjunct in:. *Arg.*: Dristan Compuesto; *Braz.*: Bufferin; Somalgin; *Canad.*: Aspirin with Stomach Guard; Bufferin; Tri-Buffered ASA†; *USA*: Adprin-B; Bufferin; Buffex; Extra Strength Bayer Plus.

Homoeopathic Preparations. *Canad.*: Homeo-Form CO†; Optalia†; Tyglan†; *Fr.*: Aftosium; Homeoptic; *Ger.*: Gastritis Complex; Prostata-Komplex L Ho-Pu-Complex; Prostata-Komplex N Ho-Pu-Complex†; *Neth.*: Homeoptic†; Kind 0-6 Kindival; *Rus.*:

Tabacum-Plus (Табакум-Плюс); *Switz.*: Regenaplex Nr. 88b; *Ukr.*: Dormikind (Дормикинд).

Pharmacopoeial Preparations
BP 2014: Aromatic Magnesium Carbonate Mixture; Chewable Calcium Carbonate and Heavy Magnesium Carbonate Tablets; Compound Magnesium Trisilicate Oral Powder; Kaolin Mixture; Magnesium Sulphate Mixture; Magnesium Trisilicate Mixture;
USP 36: Alumina and Magnesium Carbonate Oral Suspension; Alumina and Magnesium Carbonate Tablets; Alumina, Magnesium Carbonate, and Magnesium Oxide Tablets; Calcium and Magnesium Carbonates Oral Suspension; Calcium and Magnesium Carbonates Tablets; Magnesium Carbonate and Citric Acid for Oral Solution; Magnesium Carbonate and Sodium Bicarbonate for Oral Suspension; Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution; Magnesium Citrate Oral Solution.

Magnesium Citrate

Magnesii citras; Magnesio, citrato de; Magnésium, citrate de; Магний Цитрат.

$C_{12}H_{10}Mg_3O_{14}$=451.1

CAS — 3344-18-1 (anhydrous magnesium citrate); 153531-96-5 (magnesium citrate nonahydrate); 144-23-0 (dibasic magnesium citrate).

ATC — A06AD19; A12CC04; B05CB03.

ATC Vet — QA06AD19; QA12CC04; QB05CB03.

UNII — RHO26O1T9V.

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

Ph. Eur. 8: (Magnesium Citrate, Anhydrous). A white or almost white, fine, slightly hygroscopic powder. Soluble in water; practically insoluble in alcohol. It dissolves in dilute hydrochloric acid. Store in non-metallic, airtight containers.

Ph. Eur. 8: (Magnesium Citrate Dodecahydrate). A white or almost white, fine powder. Sparingly soluble in water; practically insoluble in alcohol; dissolves in dilute hydrochloric acid. A 5% solution in water has a pH of 6.0 to 8.5.

Ph. Eur. 8: (Magnesium Citrate Nonahydrate). A white or almost white, fine powder. Sparingly soluble in water; practically insoluble in alcohol; dissolves in dilute hydrochloric acid. A 5% solution in water has a pH of 6.0 to 8.5.

USP 36: (Magnesium Citrate). A 5% suspension in water has a pH of 5.0 to 9.0. Store in airtight containers.

Profile

Magnesium citrate is an osmotic laxative (p. 1804.1) used as a bowel evacuant before investigational procedures or surgery of the colon. Dosages have ranged from about 11 to 25 g of magnesium citrate. In the UK, an aqueous solution containing magnesium citrate is prepared from a sachet (*Citramag; Sanochemia, UK*) containing about 11.6 g of magnesium carbonate and about 17.8 g of anhydrous citric acid by mixing with 200 mL of hot water. After the solution has cooled, one dose (the contents of one sachet) is taken orally at 8 a.m. the day before the procedure, and a second dose between 2 and 4 p.m. For doses in children, see below. A high fluid intake and low residue diet are needed with such bowel preparations. Magnesium citrate is also used with sodium picosulfate, see p. 1887.2.

Magnesium citrate is given as a magnesium supplement in oral doses of up to about 1.9 g daily.

Dibasic magnesium citrate (magnesium hydrogen citrate) has also been used.

For the general properties of magnesium salts, see p. 1786.3.

References.
1. Hoy SM, *et al.* Sodium picosulfate/magnesium citrate: a review of its use as a colorectal cleanser. *Drugs* 2009; 69: 123–36.

Administration in children. The *BNFC* recommends the following oral doses of magnesium citrate (*Citramag; Sanochemia, UK*) for use as a bowel cleanser in children, to be taken on the day before the procedure:

- 5 to 10 years: of a sachet at 8 a.m. and of a sachet between 2 and 4 p.m.
- 10 to 18 years: ½ to 1 sachet at 8 a.m. and ½ to 1 sachet between 2 and 4 p.m.

For reconstitution directions, see above.

Migraine. For mention of the use of magnesium supplementation, including magnesium citrate, for the prophylaxis of migraine, see p. 1788.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Holomagnesio; Limonada Roge; Total Magnesiano; *Austria*: Magnesium Diasporal; Magnesium Verla; Magnofit; *Canad.*: Citro-Mag; Citrodan; Mag-Citrate; Magnesit; Royvac†; *Ger.*: Magnesium Diasporal; Magnesium Verla N; Magnesium-Sandoz forte†; *Israel*: Magnesium Diasporal; *Mon.*: Oromag; *Norw.*: Nycoplus Magnesium; *Pol.*: Magnesol; *Switz.*: Actimagon†; Magnegon; Magnesium Biomed; Magnesium Diasporal; Magnesium-Sandoz; *Turk.*: Magnezyum Diasporal; *UK*: Citramag; *USA*: Evac-Q-Mag.

Multi-ingredient Preparations. *Arg.*: Holomagnesio B6; Magnebe; Total Magnesiano B6; *Austral.*: Go Kit Plus; Go Kit; Magnesium Powder; *Belg.*: Carbobel; *Braz.*: Emidrat; *Canad.*: Bio-Gyn†; Cal-Mag Citrate with Zinc and Vitamin D; Femidause†; Royvac Kit†; *Chile*: Laxogeno; *Fr.*: Citrocholine†; Magnevie B6; *Ger.*: Biomagnesin; Magnerot N; *Gr.*: Magnesium Sandoz; *Hong Kong*: Active Calcium†; *Hung.*: Beres Magnezium + B_6; Magne-B_6 Extra; Pregmag†; *India*: Alkamax-MB6; Noculi; *Ital.*: Bionefrol; Litostop; Pomag; *Philipp.*: Nutrafem; *Pol.*: Aronomag†; *Port.*: Detoxergon; *Spain*: Salmagne; *UK*: CitraFleet; Picolax; *Ukr.*: Magne B6 Premium (Магне-В6 Премиум)†.

Pharmacopoeial Preparations
USP 36: Magnesium Citrate for Oral Solution.

Magnesium Hydroxide

E528; Hydroxid hořečnatý; Magnesii hydroxidum; Magnesio, hidróxido de; Magnésium-Hydrate; Magnésium, hydroxyde de; Magneslumhydroksidi; Magnesiumhydroxid; Magnézium-hidroxid; Magnezyum Hidroksit; Magnio hidroksidas; Магния Гидроксид.

$Mg(OH)_2$=58.32

CAS — 1309-42-8.

ATC — A02AA04; G04BX01.

ATC Vet — QA02AA04; QG04BX01.

UNII — NBZ3QY004S.

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

- Co-magaldrox *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of magnesium hydroxide and aluminium hydroxide respectively.

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

Ph. Eur. 8: (Magnesium Hydroxide). A fine white or almost white amorphous powder. Practically insoluble in water; dissolves in dilute acids. A solution in water is alkaline to phenolphthalein.

USP 36: (Magnesium Hydroxide). A bulky white powder. Practically insoluble in water, in alcohol, in chloroform, and in ether; soluble in dilute acids. Store in airtight containers.

Uses and Administration

Magnesium hydroxide is an antacid (see p. 1803.1) that is given in oral doses of up to about 1 g. It is often given with aluminium-containing antacids such as aluminium hydroxide which counteract its laxative effect.

Magnesium hydroxide is also given as an osmotic laxative (p. 1804.1) in oral doses of about 2 to 5 g.

Magnesium hydroxide has also been used as a food additive and as a magnesium supplement in deficiency states.

Adverse Effects, Treatment, and Precautions

As for magnesium salts in general, see p. 1789.3. Magnesium hydroxide may cause diarrhoea, an effect that is dose-dependent. Hypermagnesaemia may occur, usually in patients with renal impairment.

Hypermagnesaemia. There have been reports of hypermagnesaemia in infants given magnesium-containing antacids,[1-3] and in an adult patient with normal renal function but bowel obstruction.[4]

1. Brand JM, Greer FR. Hypermagnesemia and intestinal perforation following antacid administration in a premature infant. *Pediatrics* 1990; 85: 121–4.
2. Alison LH, Bulugahapitiya D. Laxative induced magnesium poisoning in a 6 week old infant. *BMJ* 1990; 300: 125.
3. Sullivan JE, Berman BW. Hypermagnesemia with lethargy and hypotonia due to administration of magnesium hydroxide to a 4-week-old infant. *Arch Pediatr Adolesc Med* 2000; 154: 1272–4.
4. Laughlin SA, McKinney PE. Antacid-induced hypermagnesemia in a patient with normal renal function and bowel obstruction. *Ann Pharmacother* 1998; 32: 312–15.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies magnesium hydroxide 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 03/10/11)

Interactions

As outlined on p. 1803.1, antacids, including magnesium salts, interact with many other drugs both by alterations in gastric pH and emptying, and by formation of complexes that are not absorbed. Interactions can be minimised by giving the antacid and any other medications 2 to 3 hours apart.

Pharmacokinetics

Magnesium hydroxide, given orally, reacts relatively rapidly with hydrochloric acid in the stomach to form magnesium chloride and water. About 30% of the magnesium ions are absorbed from the small intestine, as described for Magnesium Salts, p. 1790.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Leche de Magnesia Phillips; Magnesia San Pellegrino; *Braz.*: Leite de Magnesia de Phillips; Mylanta Plus; *Canad.*: Milk of Magnesia; Phillips' Magnesia Tablets; Phillips' Milk of Magnesia; *Chile*: Leche de Magnesia Phillips; Magnesia Pasteur; Tabletas Antiacidas; *Denm.*: Magnesia; *Fin.*: Emgesan; Magnesiamaito; *Fr.*: Magnesie San Pellegrino; *Gr.*: Milk of Magnesia; *Hong Kong*: Pedia-Lax; *Hung.*: Antagel M; *India*: Dey's Milk of Magnesia; Tricaine-MPS; *Indon.*: Laxasium; *Irl.*: Milk of Magnesia; *Israel*: Magnesia S Pellegrino; Milk of Magnesia; *Ital.*: Citrato Espresso S. Pellegrino; Magnesia S Pellegrino; *Mex.*: Agrulex†; Leche de Magnesia Normex; *Mon.*: Chlorumagene; *Port.*: Leite Magnesia Phillips; Magnesia San Pellegrino†; *S.Afr.*: Babys Own Tummy Tablets†; *Spain*: Magnesia San Pellegrino; Magnesia; *Swed.*: Emgesan; *Switz.*: Magnesia S Pellegrino; *Thai.*: Alumina-Magnesia; Emulax MOM; Mag-Mag; Magnesia; Milk of Magnesia; *Turk.*: Magcine; Magnesie Calcinee; Magnesium Naneli Lafar†; Magnokal; *UK*: Milk of Magnesia; *USA*: Dulcolax; Milk of Magnesia; Pedia-Lax; Phillips' Chewable; Phillips' Milk of Magnesia; *Venez.*: Magnesia San Pellegrino; Philips Leche de Magnesia.

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

Used as an adjunct in. *Denm.*: Kodamid; Kodimagnyl; Magnyl; *Gr.*: Ascriptin; *Indon.*: Naspro; Rheumapill†; *Ital.*: Ascriptin; Aspirina 03; *Mex.*: Ascriptin; *Rus.*: Cardiomagnyl (Кардиомагнил); *Ukr.*: Cardiomagnyl (Кардиомагнил); Combi-ASA (Комбя-АСК); Magnikor (Магникор); *USA*: Arthritis Pain Formula; Ascriptin; Cope; Vanquish; *Venez.*: Ascriptin.

Homoeopathic Preparations. *Ger.*: Hepar-Magnesium.

Pharmacopoeial Preparations
BP 2014: Co-magaldrox Oral Suspension; Co-magaldrox Tablets; Liquid Paraffin and Magnesium Hydroxide Oral Emulsion; Magnesium Hydroxide Mixture;
USP 36: Alumina and Magnesia Oral Suspension; Alumina and Magnesia Tablets; Alumina, Magnesia, and Calcium Carbonate Oral Suspension; Alumina, Magnesia, and Calcium Carbonate Tablets; Alumina, Magnesia, and Simethicone Oral Suspension; Alumina, Magnesia, and Simethicone Tablets; Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets; Aspirin, Alumina, and Magnesia Tablets; Calcium Carbonate and Magnesia Tablets; Calcium Carbonate, Magnesia, and Simethicone Tablets; Magnesia Tablets; Magnesium Hydroxide Paste; Milk of Magnesia.

Magnesium Oxide

E530; Magnesii Oxidum; Magnesio, óxido de; Magnésium, oxyde de; Magnesiumoksidi; Magnesiumoxid; Magnezu tlenek; Magnezyum Oksit; Magnio oksidas; Nehéz magnézium; Oxid hořečnatý; Магния Оксид.

MgO=40.30

CAS — 1309-48-4.

ATC — A02AA02; A06AD02; A12CC10.

ATC Vet — QA02AA02; QA06AD02; QA12CC10.

UNII — 3A3U0GI71G.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.* Some pharmacopoeias include a single monograph that permits both the light and heavy varieties while some have 2 separate monographs for the 2 varieties.

Ph. Eur. 8: (Magnesium Oxide, Heavy; Magnesii Oxidum Ponderosum). A fine, white or almost white powder. 15 g has an apparent volume before settling of not more than 60 mL. Practically insoluble in water; dissolves in dilute acids with at most slight effervescence.

Ph. Eur. 8: (Magnesium Oxide, Light; Magnesii Oxidum Leve). A fine, white or almost white, amorphous powder. 15 g has an apparent volume before settling of at least 100 mL. Practically insoluble in water; dissolves in dilute acids with at most slight effervescence.

USP 36: (Magnesium Oxide). A very bulky, white powder, or a relatively dense, white powder, or a granulated powder. Practically insoluble in water; insoluble in alcohol; soluble in dilute acids. Store in airtight containers.

Profile

Magnesium oxide is an antacid with general properties similar to those of magnesium hydroxide (above). It is given in usual oral doses of about 400 mg. It is often given with aluminium-containing antacids such as aluminium hydroxide, which counteract its laxative effect.

Magnesium oxide has been used for its osmotic laxative properties in bowel preparation; oral doses of 3.5 g are given for this purpose, combined with bisacodyl or sodium picosulfate.

Magnesium oxide is also used as a magnesium supplement in deficiency states in oral doses of up to 800 mg (20 mmol) daily. It is also used as a food additive.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies magnesium oxide 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 03/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Magnesio Vital; Polvo Roge; SG33; *Austria*: Magnonorm; *Canad.*: Urologic G; *Denm.*: Salilax†; *Fr.*: Easymagnevie; Mag 2 Junior†; MAG'Ocean†; Sargemag; Thalamag; *Ger.*: Biolectra Magnesium 240; Biolectra Magnesium 365; Magium†; Magnesium Diasporal; Magnesium Tonil†; Magnetrans extra; Magnetrans forte; Magno Sanol; *Hung.*: Magnosolv; *S.Afr.*: Solumag; *Swed.*: Salilax†; *Switz.*: Andreamag; Solmag; *Thai.*: Magoral; *Turk.*: Biolectra Magnesium; Magnezi Kalsine; *USA*: Mag-200; Mag-Ox; Maox; Uro-Mag.

Multi-ingredient Preparations. *Arg.*: Benitol; Chiafibra; Complex B Calcio Y Magnesio; Dafne; LX-30†; Total Magnesiano NF; *Austral.*: AB Extra Bone-Care +; Bio Magnesium; Bone Builder; Caltrate Plus; FAB Tri-Cal†; Machlor; Meno Support Plus; NA Neurocard; PicoPrep; *Austria*: Magnosolv; *Belg.*: Regla pH Forte; *Canad.*: Artechol†; Articho-Nat; Cal-Mag with Vitamin D & Zinc; Cal-Mag†; Caltrate Plus; Formula C 29†; Heparticaut†; Pico-Salax; Picodan; Purg-Odan; *Chile*: Berocca Plus; Calcio 520; Fercovit; Oblax A-1-1; Polvos Alcalinos; *China*: Piaojiamei (朴佳美); Cz.: Caltrate Plus; Magnesium Pharmavit; Magnosolv; Picoprep; *Denm.*: Alminox; CitraFleet; Picoprep; *Fin.*: CitraFleet; Picoprep; *Fr.*: Carbosymag; CitraFleet; Forcadion; Isudrine†; Kaologeais†; Karayal; Mutesa†; Picoprep; Sympathyl; Thalamag fer B_6; Verrulyse-Methionine; *Ger.*: CitraFleet; Losnesium; Magnesium-Plus-Hevert†; Mapurit†; Picoprep; Rabro N; Ventricon N†; *Gr.*: Aludrox; Novalox; Oxaine-M; *Hong Kong*: Active Calcium†; Epilon; Picolax; *Hung.*: Antagel; Beres Magnezium + B_6; Magnevital†; Nilacid; Picoprep; *India*: Bescal; Bonforte; Cavit-PM; Elcal-Cit; Enhance; Levicit; Literate-CT; Menosoft; Moxafav; Neuratab B6; Neurocit; Ostebon-M; *Indon.*: Aludonna; Day-Cal; Hical; Osfit; Vitacal-D; *Irl.*: Asilone†; CitraFleet; Picolax; *Israel*: Pico-Salax; *Ital.*: Carbonesia; Citrato Espresso Gabbiani; Magnosol; Vitreosan; *Malaysia*: Gerskin; Obical; Picoprep†; *Mex.*: Alfem; *Mon.*: Evestrel Jour Nuit†; *Neth.*: Picoprep; *Norw.*: CitraFleet; Picoprep; *NZ*: Picoprep; *Philipp.*: Lungcaire Plus; Sleepasil; *Pol.*: MBE; Naturapia Calcium Complex†; Naturapia Menopauza; Nervomag; Suplemag B_6; *Port.*: CitraFleet; *Rus.*: Altacid (Алтацид); Calcemin Advance (Кальцемин Адванс); Sympathyl (Симпатил); *S.Afr.*: Adco-Mayogel; Adco-Medigel; Adco-Neutragel D; Alkalite D†; Alumag D; Alumite D†; Aluspastyl†; Betaclomin; Co-Gel; Gelumen; Kolantyl†; Microgel†; Neuragel-D†; Pedimed†; Picoprep†; Propan Gel-S; Remotrox†; Spasmogel; *Singapore*: Gerskin; Obical; *Spain*: CitraFleet; Edigastrol†; Eupeptina; *Swed.*: CitraFleet; Picoprep; *Switz.*: Neurocalme; Picoprep; *Turk.*: Magnezinc; Seldiyet; *UK*: Asilone†; Kolanticon; Magnesium-OK; Uriflex G; Uro-Tainer Suby G; *Ukr.*: Altacid (Алтацид)†; Calcemin Advance (Кальцемин Адванс); Vimifor Multivitamin with Beta-Carotene (Вімівор Мультивітамін з Бета-каротином)†; Vitrum Osteomag (Витрум Остеомаг); *USA*: Beelith; Prepopik; RBQ49+; *Venez.*: Calcibon D Magnesio; Calcibon D Soya; Dicigel; Hepasil; Polantac.

Used as an adjunct in. *Arg.*: Aspirina; *Braz.*: Bufferin; *Canad.*: Aspirin with Stomach Guard; Bufferin; Tri-Buffered ASA†; *Pol.*: Aspimag; Cardiofil; *USA*: Adprin-B; Bufferin; Cama Arthritis Pain Reliever; Extra Strength Bayer Plus.

Pharmacopoeial Preparations

USP 36: Alumina, Magnesium Carbonate, and Magnesium Oxide Tablets; Aromatic Cascara Fluidextract; Aspirin, Alumina, and Magnesium Oxide Tablets; Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation; Magnesium Oxide Capsules; Magnesium Oxide Tablets.

Magnesium Trisilicate

E553(a); Magnesii trisilicas; Magnesio, trisilicato de; Magnésium, trisilicate de; Magnesiumtrisilicat; Magnesiumtrisilikaatti; Magnesiumtrisilikat; Magnézium-trisziliká; Magnezyum Trisilikat; Magnio trisilikatas; Trikřemičitan hořečnatý; Магния Трисиликат.

CAS — 14987-04-3 (anhydrous magnesium trisilicate); 39365-87-2 (magnesium trisilicate hydrate).

UNII — C2EIC501T.

Description. Magnesium trisilicate is a hydrated magnesium silicate. The code E553(a) has been applied to both magnesium silicate and to magnesium trisilicate.

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

Ph. Eur. 8: (Magnesium Trisilicate). It has a variable composition corresponding approximately to the formula $Mg_2Si_3O_8.xH_2O$ containing not less than 29% of magnesium oxide and not less than the equivalent of 65% of silicon dioxide, both calculated with reference to the ignited substance. A white or almost white powder. Practically insoluble in water and in alcohol.

USP 36: (Magnesium Trisilicate). A compound of magnesium oxide and silicon dioxide with varying proportions of water. It contains not less than 20% of magnesium oxide and not less than 45% of silicon dioxide. A fine, white, odourless, powder, free from grittiness. Insoluble in water and in alcohol. It is readily decomposed by mineral acids.

Profile

Magnesium trisilicate is a hydrated magnesium silicate. It is an antacid with general properties similar to those of magnesium hydroxide (p. 1857.2). It may be given in typical oral doses of up to about 500 mg as required, although higher doses have been given. When given orally it reacts more slowly with hydrochloric acid in the stomach than magnesium hydroxide. Magnesium trisilicate is often given with aluminium-containing antacids such as aluminium hydroxide, which counteract its laxative effect.

Magnesium trisilicate is also used as a food additive and as a pharmaceutical excipient.

Effects on the kidneys. The formation of renal calculi containing silica is unusual, but has been reported in a small number of patients. In most of these cases, stone formation was attributed to the prolonged, and sometimes excessive, intake of antacids that contained magnesium trisilicate.[1,2]

1. Haddad PS, Kouyoumdjian A. Silica stones in humans. *Urol Int* 1986; **41**: 70–6.
2. Lee M-H, *et al.* Silica stone—development due to long time oral trisilicate intake. *Scand J Urol Nephrol* 1993; **27**: 267–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Singapore*: Magsil.

Multi-ingredient Preparations. *Arg.*: Dosulfin Bronquial; Gastranil; Mylanta Reflux; *Austral.*: Gastrogel; Gastrogel; Gaviscon; *Austria*: Neoplex; *Belg.*: Alucid; Gaviscon; Neutroses; Syngel; *Braz.*: Gastrobene; Gastrobene; Gaviz; Kolantyl; *Canad.*: Gasulsol†; *Chile*: Gaviscon†; *China*: Aoweishu (澳谓舒); Rudd-U (立愉); Wei Tai Kang (谓泰康); *Fr.*: Gastropax; Magnesie Composee†; Neutroses; *Ger.*: Duoventrinetten N; Progastrit†; *Gr.*: Gaviscon; Neo-Elcosal; *Hong Kong*: Aluvit-U†; Antacin-D; Fedra-Gel-S†; Gastrogel†; Gastrogel; Gaviscon; Gelucom†; Gelumag†; Gelusil; Oxema Improved; Silox-50; Triloxane†; Uni-Magel-SM†; Uni-Magel†; *Hung.*: Nilacid; *India*: Acigon; Alupectin DGL; Alupectin; Ancid; Bestec; Briflam; Buwin Plus; Catoxymag; Dacron-Plus; Delcid; Densera-D; Don-MR; Don; Fitflam; Gastracid; Gaviscon; Gelusil; Ibumax; Ibupar-M; Larigox; Magnine; Minidolo; Neurophen; Raftace; Raftace; Solacid; *Indon.*: Biogastron†; Corsamag; Gastrinal; Gelusil†; Lexacrol; Methaphyllin†; Progastric; Sanmag; Sanmag; Stomagel; Tri Act†; *Irl.*: Gaviscon†; Pyrogastrone†; *Israel*: Fresco; *Ital.*: Gaviscon†; Merankol Pastiglie; Neutrolac; Neutrose S Pellegrino; *Malaysia*: Dhalumag; Gaviscon†; Gelusil; *Neth.*: Alcasedine†; Gaviscon Forte†; *NZ*: Gaviscon; *Philipp.*: Contylan; *Rus.*: Gestid (Гестид); *S.Afr.*: Aciban; Adcomag Trisil†; Alusil†; Be-Tabs Antacid†; Gaviscon; Gelacid; Gelusil; Gentrisil†; Infant Gaviscon; Kolantyl†; *Singapore*: Allumag M; Allumag MPS; Alumag Plus; Alumag; Cenvite; Dhalumag; Gastrogel; Gaviscon†; Gelumag; Guardian Antacid; Magtasil; Neutrazid; Polysilic; Semor Stomach; SP-Alusil; Suntacid; Vi-Ron; Vyling Gastric; Welusil; *Spain*: Dolcopin; Gelodrox; Meteoril; Secrepat; *Swed.*: Gastrosan; *Switz.*: Comprimes a croquer Estomac†; Drofaron†; Neutroses; *Thai.*: Admag-M; Airtab†; Alkamine†; Almag; Alumag; Alupep; Amacone; Amco; Amico; ANH Mat; Antacia; Conmag; Dissowel; Droximag-P; Gacida; Gelusil†; KB Alu; L-Dacin; Maalox; Machto; New Gel-D; RT Gen†; Siemag; Sinlumag; Stomact†; Ulcid†; *Turk.*: Gaviscon; *UK*: Actonorm; Birley's; Bisma-Rex; De Witt's Antacid; De Witt's Antacid; Gastrocote; Moorland; Opas; Pegina; Valonorm; *Ukr.*: Secrepat Forte (Секрепат Форте); *USA*: Alenic Alka; Gaviscon; Genaton; *Venez.*: Polantac.

Used as an adjunct in. *Hong Kong*: Artrolin-P†; *India*: IPM; Osyfen Plus; Oxyprem; *Swed.*: Deltison.

Pharmacopoeial Preparations

BP 2014: Chewable Compound Magnesium Trisilicate Tablets; Compound Magnesium Trisilicate Oral Powder; Magnesium Trisilicate Mixture;

USP 36: Alumina and Magnesium Trisilicate Oral Suspension; Alumina and Magnesium Trisilicate Tablets; Magnesium Trisilicate Tablets.

Manna

Maná; Manne en Larmes; Манна.

UNII — Q0MN98P9Q4.

Profile

Manna is the dried exudation from the bark of the European flowering ash, *Fraxinus ornus* (Oleaceae), containing about 40 to 60% of mannitol (p. 1427.3). It has been used as an osmotic laxative.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Pervivo; Cz.: Dr Theiss Schweden Krauter†; *Ger.*: florabio Manna-Feigen†; *Hung.*: Bittner; *Ital.*: Cumadren; *Pol.*: Pervivo.

Mebeverine Hydrochloride

(BANM, USAN, rINNM)

CSAG-144; Hidrocloruro de mebeverina; Mebeverina, hidrocloruro de; Mébévérine, Chlorhydrate de; Mebeverini Hydrochloridum; Мебеверина Гидрохлорид.

4-[Ethyl(4-methoxy-α-methylphenethyl)amino]butyl veratrate hydrochloride.

$C_{25}H_{35}NO_5HCl$=466.0

CAS — 3625-06-7 (mebeverine); 2753-45-9 (mebeverine hydrochloride).

ATC — A03AA04.

ATC Vet — QA03AA04.

UNII — 15VZSAL4JN.

Pharmacopoeias. In *Br.*

BP 2014: (Mebeverine Hydrochloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol; practically insoluble in ether. A 2% solution in water has a pH of 4.5 to 6.5. Store in airtight containers at a temperature not exceeding 30 degrees. Protect from light.

Uses and Administration

Mebeverine hydrochloride is an antispasmodic with a direct action on the smooth muscle of the gastrointestinal tract. It is used in conditions such as irritable bowel syndrome (p. 1810.3) in a usual oral dose of 135 mg three times daily before meals; 100 mg three times daily has also been used. A modified-release preparation is also available, taken as 200 mg twice daily. The embonate is also used for oral liquid preparations in a dose equivalent to 150 mg of the hydrochloride three times daily.

For doses in children, see below.

Administration in children. Mebeverine is used in children for the symptomatic relief of gastrointestinal smooth muscle spasm. The *BNFC* suggests the following oral doses, expressed as mebeverine hydrochloride, given three times daily, preferably 20 minutes before meals:

- 3 to 4 years: 25 mg
- 4 to 8 years: 50 mg
- 8 to 10 years: 100 mg
- 10 to 18 years: adult doses may be given, see above

A modified-release formulation is also available; children from 12 years of age may be given adult doses, see above.

Adverse Effects and Precautions

Although adverse effects appear rare, gastrointestinal disturbances, dizziness, headache, insomnia, anorexia, and decreased heart rate have been reported in patients receiving mebeverine. Cases of hypersensitivity, including erythematous rash, urticaria, and angioedema, have also been reported. Mebeverine should be avoided in patients with paralytic ileus. Based on theoretical concerns, it should be used with care in patients with marked hepatic or renal impairment, and those with cardiac disorders such as heart block.

Cystic fibrosis. A 24-year-old man with cystic fibrosis, given mebeverine hydrochloride for lower abdominal pain and constipation, was found to have a perforated stercoral ulcer with generalised peritonitis.[1] It was suggested that mebeverine produced colonic stasis, which predisposed the patient to ulceration,[1] but the manufacturers[2] considered that the development of constipation and distal intestinal syndrome (meconium ileus equivalent) in this patient precipitated the development of stercoral ulceration. It was recommended[1] that antispasmodics such as mebeverine should not be used for the symptomatic treatment of distal intestinal syndrome in cystic fibrosis.

1. Hassan W, Keaney N. Mebeverine-induced perforated colon in distal intestinal syndrome of cystic fibrosis. *Lancet* 1990; **335**: 1225.
2. Whitehead AM. Perforation of colon in distal intestinal syndrome of cystic fibrosis. *Lancet* 1990; **336**: 446.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mebeverine 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 07/10/11)

Pharmacokinetics

Mebeverine is rapidly absorbed after oral doses with peak plasma concentrations occurring in 1 to 3 hours. It is 75% bound to albumin in plasma. Mebeverine is completely metabolised by hydrolysis to veratric acid and mebeverine alcohol, the latter of which may then be conjugated. The metabolites are excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Duspatalin; *Austral.*: Colese; Colofac; *Austria*: Colofac; *Belg.*: Duspatalin; *Braz.*: Duspatalin; *Chile*: Doloverina; Duspatal; Evadol; Meditoina; *China*: Duspatalin (杜适林); *Cz.*: Duspatalin; *Denm.*: Duspatalin; *Fr.*: Colopriv†; Duspatalin; Spasmopriv†; *Ger.*: Duspatal; *Gr.*: Dolospasmo; Duspatalin; Gastromins; Trisolvetan; Yugorex; *Hong Kong*: Duspatalin; *Hung.*: Duspatalin; *India*: Colospa; Libure; Mebaspa; Mebiz; Mebrin; Meva; Morease; *Indon.*: Duspatalin; Irbosyd; *Irl.*: Colofac; Mebecon; *Israel*: Colotal; *Ital.*: Duspatal; Duspatalin; *Malaysia*: Duspatalin; Lezpain; Mebetin; *Mex.*: Arluy; Duspatalin; *Neth.*: Duspatal; Duspatalin; *NZ*: Colofac; *Philipp.*: Duspatalin; *Pol.*: Duspatalin; *Port.*: Duspatal; *Rus.*: Duspatalin (Дюспаталин); Sparex (Спарекс); *S.Afr.*: Bevispas; Colofac; *Singapore*: Duspatalin; Mebetin; *Spain*: Duspatalin; *Switz.*: Duspatalin; *Thai.*: Colofac; Duspatin; Parlotac; Menosor; *Turk.*: Duspatalin; Duspaverin; Spasflex; *UK*: Colofac; IBS Relief; *Ukr.*: Duspatalin (Дуспаталин); Mebsin (Мебсин); Meverin (Меверин).

Multi-ingredient Preparations. *India*: Mebasap-AL; Mebrin-AZ; Meva-C; Morease-I; *Irl.*: Fybogel Mebeverine; *UK*: Fybogel Mebeverine.

Pharmacopoeial Preparations
BP 2014: Mebeverine Tablets.

Mecloxamine Citrate *(rINNM)*

Citrato de mecloxamina; Mécloxamine, Citrate de; Mecloxamini Citras; Меклоксамина Цитрат.
2-[1-(4-Chlorophenyl)-1-phenylethoxy]-*N*,*N*-dimethyl-1-propanamine citrate.
$C_{19}H_{24}ClNO,C_6H_8O_7$=510.0
CAS — 5668-06-4 (mecloxamine); 56050-03-4 (mecloxamine citrate).
UNII — 26G46G752S.

Profile

Mecloxamine citrate is reported to have antimuscarinic properties and has been used for its antiemetic action in antimigraine preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Avamigran; *Turk.*: Avmigran; *Ukr.*: Nomigren (Номигрен).

Mepenzolate Bromide *(BAN, rINN)*

Bromuro de mepenzolato; Mepentsolaattibromidi; Mepenzolatbromid; Mépenzolate, Bromure de; Mepenzolate Methylbromide; Mepenzolati Bromidum; Mepenzolato, bromuro de; Mepenzolone Bromide; Мепензолата бромид.
3-Benziloyloxy-1,1-dimethylpiperidinium bromide.
$C_{21}H_{26}BrNO_3$=420.3
CAS — 25990-43-6 (mepenzolate); 76-90-4 (mepenzolate bromide).
ATC — A03AB12.
ATC Vet — QA03AB12.
UNII — APX8D32IX1.

Pharmacopoeias. In *Jpn.*

Profile

Mepenzolate bromide is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p. 1312.1). It has been used in the relief of gastrointestinal disorders associated with smooth muscle spasm and as an adjunct in the treatment of peptic ulcer disease. Up to 200 mg daily may be given orally in divided doses.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mepenzolate 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 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Trancolon; *USA*: Cantil.

Multi-ingredient Preparations. *Jpn*: Trancolon P.

Mesalazine *(BAN, rINN)*

5-Aminosalicylic Acid; 5-ASA; Fisalamine; Mesalamine (USAN); Mesalatsiini; Mesalazin; Mesalazina; Mesalazinas; Mésalazine; Mesalazinum; Месалазин.
5-Amino-2-salicylic acid.
$C_7H_7NO_3$=153.1.
CAS — 89-57-6.
ATC — A07EC02.
ATC Vet — QA07EC02.
UNII — 4Q81I59GXC.

NOTE. Distinguish from 4-aminosalicylic acid (Aminosalicylic Acid, p. 215.2) which is used in the treatment of tuberculosis.

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

Ph. Eur. 8: (Mesalazine). An almost white or light grey or light pink powder or crystals. Very slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute solutions of alkali hydroxides and in dilute hydrochloric acid. Store in airtight containers. Protect from light.

USP 36: (Mesalamine). Light tan to pink needle-shaped crystals, odourless or with a slight characteristic odour. The colour may darken on exposure to air. Slightly soluble in water; very slightly soluble in dehydrated alcohol, in acetone, and in methyl alcohol; practically insoluble in butyl alcohol, in chloroform, in dichloromethane, in ether, in ethyl acetate, in *n*-hexane, and in propyl alcohol; soluble in dilute hydrochloric acid and in dilute alkali hydroxides. A 2.5% suspension in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

Uses and Administration

Mesalazine is an anti-inflammatory drug structurally related to the salicylates and active in inflammatory bowel disease (p. 1808.3); it is considered to be the active moiety of sulfasalazine (p. 1890.1). Mesalazine is thought to act locally on the inflamed intestinal tissue, rather than systemically. Although its precise mechanism of action is uncertain, it may be due to inhibition of prostaglandin and leukotriene synthesis in the gastrointestinal mucosa.

Mesalazine is given orally or rectally in the treatment of *acute attacks* of mild to moderate ulcerative colitis, or the *maintenance of remission* of ulcerative colitis. Some products are also used for the *maintenance of remission* of Crohn's ileocolitis.

There are several differently formulated oral preparations of mesalazine available, and dosage recommendations vary. Recommended doses for some UK preparations are as follows:

- *Asacol 400 mg* tablets (*Warner Chilcott, UK*), *Ipocol* tablets (*Sandoz, UK*), *Mesren* tablets (*IVAX, UK*): acute attack, initially 2.4 g daily in divided doses; maintenance of remission, 1.2 to 2.4 g daily in divided doses.
- *Asacol 800 mg* tablets (*Warner Chilcott, UK*): mild acute exacerbations, 2.4 g daily in divided doses; moderate acute exacerbations, 4.8 g daily in divided doses; maintenance of remission, up to 2.4 g daily in divided doses
- *Mezavant* tablets (*Shire, UK*): acute attack, initially 2.4 to 4.8 g once daily; maintenance of remission, 2.4 g once daily
- *Pentasa* tablets (*Ferring, UK*): acute attack, initially up to 4 g daily in 2 or 3 divided doses; maintenance of remission, adjusted individually from an initial dose of 2 g once daily.
- *Pentasa* granules (*Ferring, UK*): acute attack, initially, up to 4 g daily in 2 to 4 divided doses; maintenance of remission, 2 g once daily.
- *Salofalk* tablets (*Falk, UK*): acute attack, initially 1.5 to 3 g daily in 3 divided doses; maintenance of remission, 1.5 g daily in 3 divided doses.
- *Salofalk* granules (*Falk, UK*): acute attack, initially 1.5 to 3 g daily, either once daily, or in 3 divided doses; maintenance of remission, 1.5 g daily in 3 divided doses.

Mesalazine may be given rectally, particularly when disease affects the sigmoid colon and rectum. Various formulations are available and the dose is usually given at night, but preparations do vary. Recommended doses for some UK preparations are as follows:

- *Asacol* suppositories (*Warner Chilcott, UK*): 0.75 to 1.5 g daily in divided doses
- *Asacol* foam enema (*Warner Chilcott, UK*): 1 g daily for disease affecting the rectosigmoid region; 2 g daily for disease involving the descending colon
- *Pentasa* suppositories and suspension enema (*Ferring, UK*): 1 g daily
- *Salofalk* suppositories (*Falk, UK*): 0.5 to 1 g given 2 or 3 times daily
- *Salofalk* foam enema and suspension enema (*Falk, UK*): 2 g daily

Similar preparations are available in other countries, and in the USA a suspension enema containing 4 g of mesalazine has been used.

For doses in children, see below.

References.

1. Clement D, Markham A. Prolonged-release mesalazine: a review of its therapeutic potential in ulcerative colitis and Crohn's disease. *Drugs* 2000; 59: 929–56.
2. Hanauer SB, Strömberg U. Oral Pentasa in the treatment of active Crohn's disease: a meta-analysis of double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol* 2004; 2: 379–88.
3. Akobeng AK, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's Disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 01/06/07).
4. Sutherland L, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 01/06/07).
5. Sutherland L, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 01/06/07).
6. Bergman R, Parkes M. Systematic review: the use of mesalazine in inflammatory bowel disease. *Aliment Pharmacol Ther* 2006; 23: 841–55.
7. van Bodegraven AA, Mulder CJ. Indications for 5-aminosalicylate in inflammatory bowel disease: is the body of evidence complete? *World J Gastroenterol* 2006; 12: 6115–23.
8. Anonymous. Once-daily mesalamine (Lialda) for ulcerative colitis. *Med Lett Drugs Ther* 2007; 49: 25–6.
9. McCormack PL, *et al.* Delayed-release Multi Matrix System (MMX) mesalazine: in ulcerative colitis. *Drugs* 2007; 67: 2635–42.
10. Kale-Pradhan PB, *et al.* Multi-Matrix System Mesalamine: to use or not to use. *Ann Pharmacother* 2008; 42: 265–9.

Administration. Because the release characteristics of different formulations of mesalazine vary, they should not be regarded as interchangeable.[1] This applies even to those formulations where the dosage is apparently similar.[2] However, a study in healthy subjects established that an oral once-daily regimen was bioequivalent to a twice-daily regimen of the same product (*Pentasa (Ferring, France)*),[3] and another study using a different product (*Salofalk granules (Falk, Germany)*) found that 8 weeks of once-daily dosing had similar safety and efficacy to a three-times daily regimen for inducing remission in patients with active ulcerative colitis.[4]

1. Forbes A, Chadwick C. Mesalazine preparations. *Lancet* 1997; 350: 1329.
2. Benbow AG, Gould L. Mesalazine preparations. *Lancet* 1998; 351: 68.
3. Gandia P, *et al.* Is once-daily mesalazine equivalent to the currently used twice-daily regimen? A study performed in 30 healthy volunteers. *J Clin Pharmacol* 2007; 47: 334–42.
4. Kruis W, *et al.* International Salofalk OD Study Group. Once daily versus three times daily mesalazine granules in active ulcerative colitis: a double-blind, double-dummy, randomised, non-inferiority trial. *Gut* 2009; 58: 233–40.

Administration in children. Mesalazine may be given orally or rectally to children in the treatment of *acute attacks* of mild to moderate ulcerative colitis, or the *maintenance of remission* of ulcerative colitis.

There are several differently formulated oral preparations of mesalazine available, and dosage recommendations vary. The *BNFC* suggests the following oral doses for some UK preparations when used in children:

- *Asacol 400 mg* tablets (*Warner Chilcott, UK*): children aged 12 to 18 years may be given similar doses to adults, see above.
- *Ipocol* tablets (*Sandoz, UK*): children aged 6 to 18 years and weighing 40 kg or more may be given similar doses to adults.
- *Pentasa* tablets and granules (*Ferring, UK*) and *Salofalk* tablets and granules (*Falk, UK*): children aged 5 to 18 years and under 40 kg: acute attack, 30 to 60 mg/kg daily in 3 divided doses; maintenance of remission, 15 to 30 mg/kg daily in 2 or 3 divided doses. Children aged 5 to 18 years and over 40 kg may be given similar doses to adults.

In addition, *Salofalk* granules may be given to children under 40 kg in a dose of 30 to 50 mg/kg once daily (preferably in the morning) for an acute attack.

Mesalazine may also be given rectally to children, particularly when disease affects the sigmoid colon and rectum. Various formulations are available and the dose is usually given at night, but preparations do vary. The *BNFC* suggests that children aged 12 to 18 years may be given similar doses to adults.

Diverticular disease. In a study involving 218 patients with a history of recurrent attacks of acute diverticulitis (p. 1806.2), half were assigned to treatment with oral

rifaximin 400 mg twice daily for 7 days, and half received rifaximin plus a modified-release formulation of mesalazine 800 mg three times daily, again for 7 days. Courses were then repeated, with rifaximin at the same dose and mesalazine at 800 mg twice daily, for 7 days in each month, and patients followed for 12 months. The combination of rifaximin and mesalazine was significantly more effective in reducing symptomatic episodes and normalisation of bowel habit than rifaximin alone: 89 of 107 patients given the combination were symptom-free at 12 months, compared with 44 of 105 given just the antibacterial.[1] Similarly, the same group found that in patients with uncomplicated diverticular disease given 10 days of treatment with rifaximin and mesalazine (*Pentacol; Sofar, Ital.*) in the doses above, followed by mesalazine 1.6 g daily for 8 weeks, 70 of 86 completing the study were completely asymptomatic, suggesting that daily mesalazine alone was an effective maintenance therapy, although longer-term studies were needed.[2] Mesalazine has also been investigated in combination with a probiotic preparation of lactic-acid-producing organisms.[3]

1. Tursi A, *et al.* Long-term treatment with mesalazine and rifaximin versus rifaximin alone for patients with recurrent attacks of acute diverticulitis of colon. *Dig Liver Dis* 2002; 34: 510–15.
2. Brandimarte G, Tursi A. Rifaximin plus mesalazine followed by mesalazine alone is highly effective in obtaining remission of symptomatic uncomplicated diverticular disease. *Med Sci Monit* 2004; 10: PI70–PI73.
3. Tursi A, *et al.* Mesalazine and/or Lactobacillus casei in preventing recurrence of symptomatic uncomplicated diverticular disease of the colon: a prospective, randomized, open-label study. *J Clin Gastroenterol* 2006; 40: 312–16.

Malignant neoplasms. The potential chemopreventive action of mesalazine against colorectal cancer, particularly in patients with inflammatory bowel disease, has been reviewed[1,2] but studies[3,4] have reached conflicting conclusions.

1. Stolfi C, *et al.* Molecular basis of the potential of mesalazine to prevent colorectal cancer. *World J Gastroenterol* 2008; 14: 4434–9.
2. Lyakhovich A, Gasche C. Systematic review: molecular chemoprevention of colorectal malignancy by mesalazine. *Aliment Pharmacol Ther* 2010; 31: 202–9.
3. Ullman T, *et al.* Progression to colorectal neoplasia in ulcerative colitis: effect of mesalamine. *Clin Gastroenterol Hepatol* 2008; 6: 1225–30.
4. Tang J, *et al.* Mesalamine protects against colorectal cancer in inflammatory bowel disease. *Dig Dis Sci* 2010; 55: 1696–1703.

Adverse Effects and Precautions

Mesalazine may cause headache and gastrointestinal disturbances, such as nausea, diarrhoea, and abdominal pain. Hypersensitivity reactions may occasionally occur. Some patients may experience exacerbation of symptoms of colitis. There are some reports of myocarditis, pericarditis, pancreatitis, interstitial nephritis, nephrotic syndrome, allergic lung reaction, increased liver enzyme values, hepatitis, lupus-like syndrome, skin reactions, alopecia, peripheral neuropathy, myalgia, and arthralgia. There have been rare reports of blood disorders including aplastic anaemia, agranulocytosis, leucopenia, neutropenia, thrombocytopenia, and methaemoglobinaemia.

Mesalazine should not be given to patients with severe renal or hepatic impairment, or salicylate hypersensitivity. It should be used with caution in the elderly, and in mild to moderate renal or hepatic impairment, active peptic ulceration, or sulfasalazine allergy.

If a blood dyscrasia is suspected treatment should be stopped immediately and a blood count performed. Patients or their carers should be told how to recognise signs of blood toxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop. It is recommended that renal function is monitored before and during therapy (see Effects on the Kidneys, below).

Many of the adverse effects associated with sulfasalazine (sulfapyridine linked to mesalazine) therapy have been attributed to the sulfapyridine moiety and most patients unable to tolerate sulfasalazine because of hypersensitivity or adverse reactions can be transferred to mesalazine without adverse effects occurring.[1-4] However, a small number of patients also have adverse effects while taking mesalazine and these are often very similar to those seen with sulfasalazine.[1-4] They may include nausea, abdominal discomfort or pain, exacerbation of diarrhoea, headache, fever, and rashes. Mesalazine is not generally associated with sulfasalazine's adverse effects on sperm (although there has been a case of reversible male infertility attributed to mesalazine—see under Sulfasalazine, p. 1891.2). An analysis of adverse reactions reported to the UK CSM between 1991 and 1998 found no evidence of a significant difference in the frequency of serious adverse effects for mesalazine and sulfasalazine in the treatment of inflammatory bowel disease.[5] Reports of pancreatitis and interstitial nephritis were more common with mesalazine (but see Effects on the Kidneys, below). However, it has been pointed out that 80% of patients intolerant to sulfasalazine will tolerate mesalazine without problems.[6]

Mesalazine therapy should be started cautiously in patients with a history of sulfasalazine hypersensitivity and it should be withdrawn if signs of sensitivity develop or if there is diarrhoea or rectal bleeding. It has been suggested[2] that patients with a history of sulfasalazine hypersensitivity should be given test doses of mesalazine before starting a full course.

1. Dew MJ, *et al.* Treatment of ulcerative colitis with oral 5-aminosalicylic acid in patients unable to take sulphasalazine. *Lancet* 1983; ii: 801.
2. Campieri M, *et al.* 5-Aminosalicylic acid as rectal enema in ulcerative colitis patients unable to take sulphasalazine. *Lancet* 1984; i: 403.
3. Donald IP, Wilkinson SP. The value of 5-aminosalicylic acid in inflammatory bowel disease for patients intolerant or allergic to sulphasalazine. *Postgrad Med J* 1985; 61: 1047–8.
4. Rao SS, *et al.* Clinical experience of the tolerance of mesalazine and olsalazine in patients intolerant of sulphasalazine. *Scand J Gastroenterol* 1987; 22: 332–6.
5. Ransford RAJ, Langman MJS. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. *Gut* 2002; 51: 536–9.
6. D'Haens G, van Bodegraven AA. Mesalazine is safe for the treatment of IBD. *Gut* 2004; 53: 155.

Breast feeding. The concentrations of mesalazine in maternal plasma and breast milk in a woman taking 500 mg three times daily, were 410 and 110 nanograms/mL respectively.[1] Although it was considered that the amount of mesalazine distributed into breast milk was small and that it was safe during breast feeding,[2,3] maternal use of mesalazine 500 mg suppositories twice daily has been associated with watery diarrhoea in a breast-fed infant[2] and for this reason the American Academy of Pediatrics considers that mesalazine should be given with caution to breast-feeding mothers.[4]

1. Jenss H, *et al.* 5-Aminosalicylic acid and its metabolite in breast milk during lactation. *Am J Gastroenterol* 1990; 85: 331.
2. Nells GF. Diarrhoea due to 5-aminosalicylic acid in breast milk. *Lancet* 1989; i: 383.
3. Klotz U, Harings-Kaim A. Negligible excretion of 5-aminosalicylic acid in breast milk. *Lancet* 1993; 342: 618–19.
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 28/02/06)

Effects on the blood. Although uncommon, mesalazine-associated adverse effects on the blood have been reported, including thrombocytopenia,[1,2] neutropenia,[3] severe aplastic anaemia,[4,5] and pancytopenia.[6] In July 1995 the UK CSM stated that it had been notified of 49 haematological reactions suspected of being associated with mesalazine,[7] including 5 reports of aplastic anaemia, 1 of agranulocytosis, 11 of leucopenia, and 17 of thrombocytopenia. There had been 3 fatalities. They recommended a blood count and immediate withdrawal of the drug if a dyscrasia was suspected. Intensive immunosuppressive treatment has been used in the management of mesalazine-associated aplastic anaemia.[5,8]

1. Daneshmend TK. Mesalazine-associated thrombocytopenia. *Lancet* 1991; 337: 1297–8.
2. Parrell RJ, *et al.* Mesalamine-associated thrombocytopenia. *Am J Gastroenterol* 1999; 94: 2304–6.
3. Wyatt S, *et al.* Filgrastim for mesalazine-associated neutropenia. *Lancet* 1993; 341: 1476.
4. Abboudi ZH, *et al.* Fatal aplastic anaemia after mesalazine. *Lancet* 1994; 343: 542.
5. Otsubo H, *et al.* Mesalazine-associated severe aplastic anemia successfully treated with antithymocyte globulin, cyclosporine and granulocyte colony-stimulating factor. *Int J Hematol* 1998; 68: 445–8.
6. Kotanagi H, *et al.* Pancytopenia associated with 5-aminosalicylic acid use in a patient with Crohn's disease. *J Gastroenterol* 1998; 33: 571–4.
7. CSM/MCA. Blood dyscrasias and mesalazine. *Current Problems* 1995; 21: 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE6-dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 15/06/06)
8. Laidlaw ST, Reilly JT. Antilymphocyte globulin for mesalazine-associated aplastic anaemia. *Lancet* 1994; 343: 981–2.

Effects on the cardiovascular system. Myocarditis associated with chest pain and ECG abnormalities has been reported[1,2] in 2 patients taking mesalazine; 1 patient died in cardiogenic shock.[2] It has been suggested that mesalazine or sulfasalazine should be replaced by glucocorticoids if cardiac symptoms arise during treatment.[2] Pericarditis[3,4] with fever, rash, dyspnoea, pleural and pericardial effusions, and arthritis, has been described, and is considered to constitute a drug-induced lupus-like syndrome. Constrictive pericarditis with an absence of other lupus-like symptoms developed in a patient taking mesalazine for inflammatory bowel disease.[5] Based on reported cases of mesalazine-induced pericarditis, symptoms of this potentially life-threatening adverse effect have tended to arise 2 to 4 weeks after starting mesalazine, although symptom onset may be delayed by concurrent corticosteroid treatment.[6] Mesalazine cardiotoxicity presenting as an acute coronary syndrome, without myocarditis or pericarditis, has also been reported.[7]

1. Agnholt J, *et al.* Cardiac hypersensitivity to 5-aminosalicylic acid. *Lancet* 1989; i: 1133.
2. Kristensen KS, *et al.* Fatal myocarditis associated with mesalazine. *Lancet* 1990; 335: 605.
3. Deni MT, *et al.* Mesalazine induced lupus-like syndrome. *BMJ* 1992; 305: 159.
4. Lim AG, Hine KR. Fever, vasculitic rash, arthritis, pericarditis, and pericardial effusion after mesalazine. *BMJ* 1994; 308: 113.
5. Oxentenko AS, *et al.* Constrictive pericarditis in chronic ulcerative colitis. *J Clin Gastroenterol* 2002; 34: 247–51.
6. Waite RA, Malinowski JM. Possible mesalamine-induced pericarditis: case report and literature review. *Pharmacotherapy* 2002; 22: 391–4.
7. Amin HR, *et al.* Mesalamine-induced chest pain: a case report. *Can J Cardiol* 2000; 16: 667–9.

Effects on fertility. For a report of reversible male infertility occurring with mesalazine, see under Sulfasalazine, p. 1891.2.

Effects on the hair. For a report of accelerated loss of scalp hair in 2 patients receiving mesalazine enemas, see under Sulfasalazine, p. 1891.3.

Effects on the kidneys. Between February 1988 and December 1990 the UK CSM[1] received 9 reports of serious nephrotoxic reactions associated with the use of *Asacol*, a modified-release mesalazine preparation. The reactions included 4 cases of interstitial nephritis, 3 of severe renal failure, and 2 cases of nephrotic syndrome. A subsequent case report[2] indicated that by September 1998 the number of such reports for mesalazine totalled 104, including 35 cases of interstitial nephritis. The authors considered that monitoring of renal function was required in patients receiving mesalazine. A protocol for such monitoring was subsequently suggested,[3] and a similar protocol has been adopted in UK licensing information for mesalazine, with serum creatinine being estimated:

- before treatment
- every 3 months for the first year
- every 6 months for the next 4 years
- annually thereafter

The nephrotic syndrome[4] and interstitial nephritis[5] have also been reported with sulfasalazine, and interstitial nephritis with olsalazine (see p. 1867.1). A large UK epidemiologic study found no difference in risk of renal disease between mesalazine and sulfasalazine. The study also concluded that the risk of renal disease associated with mesalazine and related compounds is low and may be partly attributable to the underlying disease.[6] Overall nephrotoxicity has been estimated to occur in about 1 in 4000 UK patients per year taking aminosalicylate-based therapy.[7]

1. CSM. Nephrotoxicity associated with mesalazine (Asacol). *Current Problems 30* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE6-dDocName=CON2024448&RevisionSelectionMethod=LatestReleased (accessed 02/07/08)
2. Popoola J, *et al.* Late onset interstitial nephritis associated with mesalazine treatment. *BMJ* 1998; 317: 795–7.
3. Corrigan G, Stevens PE. Review article: interstitial nephritis associated with the use of mesalazine in inflammatory bowel disease. *Aliment Pharmacol Ther* 2000; 14: 1–6.
4. Barbour VM, Williams PF. Nephrotic syndrome associated with sulphasalazine. *BMJ* 1990; 301: 818.
5. Dwarakanath AD, *et al.* Sulphasalazine induced renal failure. *Gut* 1992; 33: 1006–1007.
6. Van Staa TP, *et al.* Experience of 5-aminosalicylate nephrotoxicity in the United Kingdom. *Aliment Pharmacol Ther* 2003; 21: 1217–24.

Effects on the liver. A case of chronic hepatitis and liver fibrosis has been reported after prolonged use of mesalazine.[1] The authors considered that mesalazine should be stopped when liver dysfunction occurred.

1. Deltenre P, *et al.* Mesalazine (5-aminosalicylic acid) induced chronic hepatitis. *Gut* 1999; 44: 886–8.

Effects on the nervous system. Peripheral neuropathy,[1] mainly affecting the legs, has occurred during mesalazine treatment. The symptoms resolved on stopping the drug. Mononeuritis multiplex was part of the presentation of an eosinophilic reaction attributed to mesalazine in an asthmatic patient;[2] Churg-Strauss syndrome developed after withdrawal of mesalazine, but the patient subsequently recovered without sequelae.

1. Woodward DK. Peripheral neuropathy and mesalazine. *BMJ* 1989; 299: 1224.
2. Morice AH, *et al.* Mesalazine activation of eosinophil. *Lancet* 1997; 350: 1105.

Effects on the pancreas. Pancreatitis has been reported as an adverse effect of mesalazine.[1-4] In 2 patients,[1,2] with abdominal pain and raised amylase activity, this reaction to mesalazine was confirmed by rechallenge and symptoms resolved on mesalazine withdrawal. By February 1994 the UK CSM had received 15 reports[3] of pancreatitis associated with mesalazine therapy. However, a case control study suggested that inflammatory bowel disease, rather than the use of mesalazine, may be associated with an increased risk of acute pancreatitis (see under Sulfasalazine, p. 1891.3)

1. Sachedina B, *et al.* Acute pancreatitis due to 5-aminosalicylate. *Ann Intern Med* 1989; 110: 490–2.
2. Deprez P, *et al.* Pancreatitis induced by 5-aminosalicylic acid. *Lancet* 1989; ii: 445–6.
3. CSM. 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 02/07/08)

4. Adachi E, *et al.* Acute pancreatitis secondary to 5-aminosalicylic acid therapy in a patient with ulcerative colitis. *Int J Pancreatol* 1999; 25: 217–21.

Effects on the respiratory system. Pulmonary complications have been rarely reported with mesalazine. There have though been cases of interstitial lung disease, with features of hypersensitivity pneumonia.[1-3] Symptoms have included dyspnoea, cough, fever, and pleuritic chest pain, with the onset of symptoms varying from a few days to several years after starting mesalazine therapy. Although pulmonary complications can also be associated with inflammatory bowel disease itself, there has been a report[4] of eosinophilic pleural effusion in a patient who was given mesalazine in the absence of an established diagnosis of inflammatory bowel disease.

Pulmonary complications have also been reported with sulfasalazine (p. 1891.3), and pulmonary symptoms may also manifest as part of a broader lupus-like syndrome (see Effects on the Cardiovascular System, p. 1860.2).

1. Foster RA, *et al.* Mesalamine-related lung disease: clinical, radiographic, and pathologic manifestations. *Inflamm Bowel Dis* 2003; 9: 308–15.
2. Lamsiah T, *et al.* Pneumopathie interstitielle indulte par la mésalazine. *Gastroenterol Clin Biol* 2010; 34: 224–6.
3. Jain N, *et al.* Mesalamine lung toxicity. *Conn Med* 2010; 74: 265–7.
4. Trisolini R, *et al.* Eosinophilic pleural effusion due to mesalamine: report of a rare occurrence. *Sarcoidosis Vasc Diffuse Lung Dis* 2000; 17: 288–91.

Lupus. A lupus-like syndrome has been reported in 4 patients receiving mesalazine who developed antinuclear antibody (ANA)-positivity with at least one clinical feature of lupus, such as arthropathy, skin rashes, or acute inflammation unrelated to the underlying condition.[1] In all 4 cases symptoms resolved upon stopping mesalazine. For similar reports, see Effects on the Cardiovascular System, p. 1860.2.

1. Kirkpatrick AW, *et al.* Lupus-like syndrome caused by 5-aminosalicylic acid in patients with inflammatory bowel disease. *Can J Gastroenterol* 1999; 13: 159–62.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mesalazine 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 03/10/11)

Pregnancy. Renal insufficiency in a neonate whose mother received oral mesalazine 2 to 4 g daily during the second trimester of pregnancy was suggested to be due to the drug,[1] although the proposed mechanism, inhibition of prostaglandin synthesis in the neonatal kidney, has been questioned.[2] A subsequent case-control study[3] found that use of oral mesalazine in 165 pregnant women with inflammatory bowel disease was not associated with a greater incidence of malformations. However, women treated with mesalazine were more likely to have preterm deliveries and newborns with decreased birth-weights, although the disease may have been a factor in this finding. A commentator on this study,[4] considered that active inflammatory bowel disease was a greater risk to pregnancy than drug treatment. In a further cohort of 123 pregnancies,[5] oral mesalazine at doses of 3 g daily or less did not increase the risk of fetal malformations or affect pregnancy outcome. The researchers concluded that further information was required on doses higher than 3 g daily. In another study,[6] all of 19 pregnancies in women receiving rectal mesalazine were full-term with no fetal abnormalities. A Danish cohort study[7] found an increased risk of still-birth and preterm birth in women who had been prescribed mesalazine or olsalazine during pregnancy, but no significant increased risk of malformations. The risk of still-birth was greatest in women with ulcerative colitis who were prescribed corticosteroids and either mesalazine or olsalazine, and the risk of preterm birth was greatest in women with ulcerative colitis who were prescribed either mesalazine or olsalazine alone. The authors acknowledged that it was difficult to distinguish between the increase in risk due to disease state, and the increase in risk due to medication.[7] For a discussion of sulfasalazine in pregnancy, see p. 1892.1.

1. Colombel J-F, *et al.* Renal insufficiency in infant: side-effect of prenatal exposure to mesalazine? *Lancet* 1994; 344: 620–1.
2. Marteau P, Devaux CB. Mesalazine during pregnancy. *Lancet* 1994; 344: 1708–9.
3. Diav-Citrin O, *et al.* The safety of mesalamine in human pregnancy: a prospective controlled cohort study. *Gastroenterology* 1998; 114: 23–8.
4. Sachar D. Exposure to mesalamine during pregnancy increased preterm deliveries (but not birth defects) and decreased birth weight. *Gut* 1998; 43: 316.
5. Marteau P, *et al.* Foetal outcome in women with inflammatory bowel disease treated during pregnancy with oral mesalazine microgranules. *Aliment Pharmacol Ther* 1998; 12: 1101–8.
6. Bell CM, Habal FM. Safety of topical 5-aminosalicylic acid in pregnancy. *Am J Gastroenterol* 1997; 92: 2201–2.
7. Nørgård B, *et al.* Birth outcome in women exposed to 5-aminosalicylic acid during pregnancy: a Danish cohort study. *Gut* 2003; 52: 243–7.

Interactions

Preparations formulated to release mesalazine in the colon should not be given with drugs, such as lactulose, that lower colonic pH as they may prevent the release of mesalazine (but see Gastrointestinal Drugs below).

Anticoagulants. For reference to a case of mesalazine reducing the effect of *warfarin*, see Gastrointestinal Drugs, p. 1534.1.

Antineoplastics. For mention of 5-aminosalicylates such as mesalazine inhibiting the metabolism of thiopurine antineoplastics, and increasing their toxicity, see Gastrointestinal Drugs, p. 822.1.

Gastrointestinal drugs. Although it has been suggested that *lactulose* could delay the intestinal release of mesalazine from modified-release preparations, a study found no evidence that lactulose influenced the release or disposition of mesalazine.[1] Similarly, *omeprazole* did not appear to increase the likelihood of premature mesalazine release.

1. Hussain FN, *et al.* Mesalazine release from a pH dependent formulation: effects of omeprazole and lactulose co-administration. *Br J Clin Pharmacol* 1998; 46: 173–5.

Pharmacokinetics

If given orally as conventional formulations, mesalazine would be extensively absorbed from the upper gastrointestinal tract, with little of the drug reaching the colon. Oral preparations are therefore generally formulated to release the drug in the terminal ileum and colon, where it is thought to exert a mainly local action. The specific release characteristics differ somewhat between formulations and this, together with interindividual variation, makes comparison of pharmacokinetic data between studies difficult. Even with modified-release preparations some 30 to 50% of an oral dose is thought to be lost to absorption in healthy subjects. Absorption from rectal dosage forms has also varied widely, with factors such as the dose, the formulation, and the pH also playing a role, but mean absorption of around 10 to 30% of a rectal dose has been reported.

The absorbed portion of mesalazine is almost completely acetylated in the gut wall and in the liver to acetyl-5-aminosalicylic acid. The rate of acetylation, and hence the concentration of parent drug and metabolite in the systemic circulation, may be dose dependent and subject to saturation. The acetylated metabolite is excreted mainly in urine by tubular secretion, with traces of the parent compound.

The plasma half-life of mesalazine is reported to be about 40 minutes and it is 40 to 50% bound to plasma proteins; the acetylated metabolite has a plasma half-life of 70 minutes and is about 80% bound to plasma proteins.

Only negligible quantities of mesalazine cross the placenta. Amounts distributed into breast milk are very small.

Reviews.

1. De Vos M. Clinical pharmacokinetics of slow release mesalazine. *Clin Pharmacokinet* 2000; 39: 85–97.
2. Sandborn WJ, *et al.* Systematic review: the pharmacokinetic profiles of oral mesalazine formulations and mesalazine pro-drugs used in the management of ulcerative colitis. *Aliment Pharmacol Ther* 2003; 17: 29–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bufexan; Exotran; Mezavant; Pentasa; Rectocalm; Salofalk; Sekena; Suprimal; Xalazina; Yolecol; ***Austral.***: Mesasal; Mezavant; Pentasa; Salofalk; ***Austria***: Claversal; Mesagran; Mezavant; Pentasa; Salofalk; ***Belg.***: Claversal; Colitofalk; Mezavant; Pentasa: ***Braz.***: Asalit; Chron-ASA; Mesacol; ***Canad.***: Asacol; Mesasal; Mezavant; Pentasa; Salofalk; ***Chile***: Pentasa; Salofalk; ***China***: Anjiesha (安洁莎); Etiasa (艾迪莎); Pentasa (颇得斯安); Salofalk (莎尔福); ***Cz.***: Asacol; Pentasa; Salofalk; Samezil†; ***Denm.***: Asacol; Lixacol†; Mesasal; Mesavancol; Mezavant; Pentasa; Quintasa; Salofalk; ***Fin.***: Asacol; Mesasal; Mezavant; Pentasa; Salofalk; ***Fr.***: Fivasa; Pentasa; Rowasa; ***Ger.***: Asacol†; Asacolitin†; Claversal; Mezavant: Pentasa; Salofalk; ***Gr.***: Asacol; Asalazin; Crohnezine; Cronezil; Ectospasmol: Empenox; Enterin; Favorat; Laboxantryl; Mesagin; Mezavant: Pentasa; Prozylex; Salofalk; ***Hong Kong***: Asacol; Pentasa; Salofalk; ***Hung.***: Asacol†; Pentasa; Salofalk; Xalazin; ***India***: Asacol; Cosacol; Elmes; Etiasa; Mesacol; ***Indon.***: Midodrine; Salofalk; ***Irl.***: Asacolon; Mezavant; Pentasa; Salofalk; ***Israel***: Asacol; Pentasa; Rafassal; ***Ital.***: Asacol; Asalex; Asamax; Asavixin; Claversal; Enteraproct; Enterasin; Lextrasa; Mesaflor; Pentacol; Pentasa; Plimage; Proctasacol; ***Jpn***: Pentasa; ***Malaysia***: Pentasa; Salofalk; ***Mex.***: Asacol; Pentasa; Salofalk; Seramine; ***Neth.***: Asacol; Asamax†; Mesavancol; Mezavant; Pentasa; Salofalk; ***Norw.***: Asacol; Mesasal; Mezavant: Pentasa; Salofalk; ***NZ***: Asacol; Asamax; Pentasa; ***Philipp.***: Pentasa; Salofalk; ***Pol.***: Asamax; Colitan; Crohnax; Jucolon; Pentasa; Salofalk; ***Port.***: Asacol; Claversal; Pentasa; Salofalk; ***Rus.***: Asacol (Асакол); Mesacol (Месакол); Pentasa (Пентаса); Salofalk (Салофальк); Samezil (Самезил); ***S.Afr.***: Asacol; Mesasal†; Pentasa; ***Singapore***: Asacol; Pentasa; Salofalk; ***Spain***: Claversal; Lixacol; Mezavant; Pentasa; Salofalk; ***Swed.***: Asacol; Mesasal; Mezavant; Pentasa; Salofalk; ***Switz.***: Asacol; Asazine; Mesazine†; Pentasa; Salofalk; ***Thai.***: Mesacol; Pentasa; Salofalk; ***Turk.***: Asacol; Asocol; Pentasa; Salofalk; ***UK***: Asacol; Ipocol; Mesren†; Mezavant; Octasa; Pentasa; Salofalk; ***Ukr.***: Pentasa (Пентаса); Salofalk (Салофальк); ***USA***: Apriso; Asacol; Canasa; Delzicol; Lialda; Pentasa; Rowasa.

Pharmacopoeial Preparations

BP 2014: Gastro-resistant Mesalazine Tablets; Mesalazine Enema; Mesalazine Foam Enema; Mesalazine Suppositories; Prolonged-release Mesalazine Granules; Prolonged-release Mesalazine Tablets;

USP 36: Mesalamine Delayed-Release Tablets; Mesalamine Extended-Release Capsules; Mesalamine Rectal Suspension.

Methanthelinium Bromide *(BAN, pINN)*

Bromuro de metantelinio; Dixamonum Bromidum; Metantelinio, bromuro de; Methantheline Bromide; Methanthelinii Bromidum; Méthanthélinium, Bromure de; MTB-51; SC-2910; Метантеллиния бромид.

Diethylmethyl(2-(xanthen-9-ylcarbonyloxy)ethyl]ammonium bromide.

$C_{21}H_{26}BrNO_3$=420.3

CAS — 5818-17-7 (methanthelinium); 53-46-3 (methanthelinium bromide).

ATC — A03AB07.

ATC Vet — QA03AB07.

UNII — 090519SAPF.

Profile

Methanthelinium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been used as an adjunct in the treatment of peptic ulcer disease, in gastrointestinal disorders associated with smooth muscle spasm, and in the management of urinary incontinence. A usual oral dose in gastrointestinal disorders is 50 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Vagantin.

Methylbenactyzium Bromide *(rINN)*

Benactyzine Methobromide; Bromuro de metilbenacticio; Methylbenactyzii Bromidum; Méthylbénactyzium, Bromure de; Metilbenactício, bromuro de; Метилбенактизия бромид.

Diethyl(2-hydroxyethyl)methylammonium bromide benzilate.

$C_{21}H_{26}BrNO_3$=422.4

CAS — 3166-62-9.

UNII — M35Q3X4F69.

Pharmacopoeias. In *Jpn*.

Profile

Methylbenactyzium bromide, a derivative of benactyzine (p. 408.2), is an antimuscarinic with effects similar to those of atropine (p. 1312.1). It has been given orally for the treatment of gastrointestinal spasm and nocturnal enuresis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Yi Er Ning (益尔宁).

Multi-ingredient Preparations. ***Austria***: Anxiolit plus.

Methylnaltrexone Bromide *(BAN, USAN, rINN)*

Bromure de Méthylnaltrexone; Bromuro de metilnaltrexona; Methylnaltrexonii Bromidum; MRZ-2663BR; Naltrexone Methobromide; Метилнальтрексон бромид.

(17*RS*)-17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxy-17-methyl-6-oxomorphinanium bromide.

$C_{21}H_{26}BrNO_4$=436.3

CAS — 83387-25-1 (methylnaltrexone); 73232-52-7 (methylnaltrexone bromide).

ATC — A06AH01.

ATC Vet — QA06AH01.

UNII — RFO6IL3D3M.

Uses and Administration

Methylnaltrexone bromide is a selective peripherally acting antagonist of opioid μ-receptors that is used for the treatment of opioid-induced constipation in patients receiving palliative care for advanced illness, when response

The symbol † denotes a preparation no longer actively marketed

to usual laxative therapy is insufficient. It is also being studied for treatment of opioid-induced constipation in patients with chronic pain, as well as for opioid-induced urinary retention and postoperative ileus.

For the treatment of opioid-induced constipation methylnaltrexone bromide may be given by subcutaneous injection in the following doses according to body-weight:

- less than 38 kg: 150 micrograms/kg
- 38 to 62 kg: 8 mg
- 62 to 114 kg: 12 mg
- more than 114 kg: 150 micrograms/kg

Doses are usually given once every 48 hours as needed, but no more frequently than once in 24 hours. For doses in renal impairment, see Administration in Renal Impairment, below.

An oral formulation is under investigation.

References.
1. Yuan CS. Methylnaltrexone mechanisms of action and effects on opioid bowel dysfunction and other opioid adverse effects. *Ann Pharmacother* 2007; 41: 984–93.
2. Reichle FM, Conzen PF. Methylnaltrexone, a new peripheral μ-receptor antagonist for the prevention and treatment of opioid-induced extracerebral side effects. *Curr Opin Investig Drugs* 2008; 9: 90–100.
3. Thomas J, *et al.* Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med* 2008; 358: 2332–43.
4. Becker G, Blum HE. Novel opioid antagonists for opioid-induced bowel dysfunction and postoperative ileus. *Lancet* 2009; 373: 1198–1206.
5. Clemens KE, Klaschik E. Managing opioid-induced constipation in advanced illness: focus on methylnaltrexone bromide. *Ther Clin Risk Manag* 2010; 6: 77–82.
6. Garnock-Jones KP, McKeage K. Methylnaltrexone. *Drugs* 2010; 70: 919–28.

Administration in renal impairment. Renal impairment reduces the clearance of methylnaltrexone and increases exposure, and although the usual dose (see Uses and Administration, p. 1861.3) may be given to those with mild or moderate impairment (creatinine clearance 30 mL/minute and above), dose reductions are advised in those with severe impairment (creatinine clearance less than 30 mL/minute). UK licensed product information recommends the following subcutaneous doses, usually given once every 48 hours as needed (but no more often than once in 24 hours), according to weight:

- 62 to 114 kg: 8 mg
- less than 62 kg or above 114 kg: 75 micrograms/kg

Methylnaltrexone is not recommended in those with end-stage renal impairment requiring dialysis due to a lack of data.

Similarly, US licensed product information recommends halving the usual dose in severe renal impairment.

Adverse Effects and Precautions

The most common adverse effects in patients treated with methylnaltrexone bromide are gastrointestinal disorders such as abdominal pain, nausea, flatulence, and diarrhoea. If severe or persistent diarrhoea occurs, therapy should be stopped. Dizziness, hyperhidrosis, and injection site reactions are also reported commonly with methylnaltrexone.

Gastrointestinal perforation has been reported rarely and methylnaltrexone should not be used in patients with gastrointestinal obstruction or acute surgical abdomen. Caution is advised in patients with lesions that affect the structural integrity of the gastrointestinal tract such as cancer or peptic ulcer. Caution is also recommended in those with a peritoneal catheter, colostomy, active diverticular disease, or faecal impaction as methylnaltrexone use has not been studied in these patients.

Methylnaltrexone is not recommended in patients with severe hepatic impairment or with end-stage renal disease requiring dialysis, due to a lack of data.

Pharmacokinetics

After subcutaneous injection methylnaltrexone bromide is absorbed rapidly, with peak plasma concentrations occurring at about 0.5 hours. It is only minimally bound to plasma proteins. Methylnaltrexone is eliminated mostly as unchanged drug; metabolites include methylnaltrexone sulfate and methyl-6-naltrexol isomers. Methyl-6-naltrexol isomers have less antagonist activity than methylnaltrexone bromide; methylnaltrexone sulfate is inactive. N-demethylation of methylnaltrexone to naltrexone is not significant. About half of the dose is excreted in the urine and less in the faeces. The terminal half-life is about 8 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Relistor; *Austral.*: Relistor; *Austria*: Relistor; *Belg.*: Relistor; *Braz.*: Relistor; *Canad.*: Relistor; *Chile*: Relistor; *Cz.*: Relistor; *Denm.*: Relistor; *Fr.*: Relistor; *Ger.*: Relistor; *Gr.*: Relistor; *Hung.*: Relistor; *Irl.*: Relistor; *Ital.*: Relistor; *Neth.*: Relistor; *Norw.*: Relistor; *Pol.*: Relistor; *Port.*: Relistor; *Spain*: Relistor; *Swed.*: Relistor; *Switz.*: Relistor; *UK*: Relistor; *USA*: Relistor.

Metoclopramide *(BAN, rINN)*

Metoclopramid; Metoclopramida; Métoclopramide; Metoclopramidum; Metoklopramid; Metoklopramidas; Metoklopramidi; Метоклопрамид.

4-Amino-5-chloro-*N*-(2-diethylaminoethyl)-2-methoxybenzamide.

$C_{14}H_{22}ClN_3O_2$=299.8

CAS — 364-62-5.

ATC — A03FA01.

ATC Vet — QA03FA01.

UNII — L4YEB44I46.

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

Ph. Eur. 8: (Metoclopramide). A white or almost white, fine powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble to slightly soluble in alcohol; slightly soluble in dichloromethane.

Metoclopramide Hydrochloride

(BANM, USAN, rINNM)

AHR-3070-C; DEL-1267; Hidrocloruro de metoclopramida; Metoclopramida, hidrocloruro de; Métoclopramide, chlorhydrate de; Metoclopramidhydrochlorid; Metoclopramidi Hydrochloridum; Metoclopramidi Hydrochloridum Monohydricum; Metoklopramid Hidroklorür; Metoklopramidhidroklorid; Metoklopramid-hydrochlorid monohydrát; Metoklopramidhydroklorid; Metoklopramidihydroklorid; Metoklopramido hidrochloridas; Metoklopramidu chlorowodorek; MK-745; Метоклопрамида Гидрохлорид.

$C_{14}H_{22}ClN_3O_2$,HCl,H_2O=354.3

CAS — 7232-21-5 (anhydrous metoclopramide hydrochloride); 54143-57-6 (metoclopramide hydrochloride monohydrate); 2576-84-3 (anhydrous metoclopramide dihydrochloride).

ATC — A03FA01.

ATC Vet — QA03FA01.

UNII — 7B1QZY5SWZ (anhydrous metoclopramide hydrochloride); W1792A2RVD (metoclopramide hydrochloride monohydrate).

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

Ph. Eur. 8: (Metoclopramide Hydrochloride). A white or almost white, crystalline powder or crystals. Very soluble in water; freely soluble in alcohol; sparingly soluble in dichloromethane. A 10% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 36: (Metoclopramide Hydrochloride). A white or practically white, odourless or practically odourless, crystalline powder. Very soluble in water; freely soluble in alcohol; sparingly soluble in chloroform; practically insoluble in ether. Store in airtight containers. Protect from light.

Incompatibility. Proprietary preparations of metoclopramide hydrochloride are stated to be incompatible with cephalothin sodium, chloramphenicol sodium, and sodium bicarbonate.

Cisplatin, cyclophosphamide, doxorubicin hydrochloride, morphine hydrochloride, or diamorphine hydrochloride are stated to be compatible with metoclopramide hydrochloride but compatibility is dependent upon factors such as the particular formulation, drug concentration, and temperature.

Uses and Administration

Metoclopramide hydrochloride is a substituted benzamide used for its prokinetic and antiemetic properties. It stimulates the motility of the upper gastrointestinal tract without affecting gastric, biliary, or pancreatic secretion and increases gastric peristalsis, leading to accelerated gastric emptying and intestinal transit time. The resting tone of the gastro-oesophageal sphincter is increased and the pyloric sphincter is relaxed. Metoclopramide possesses parasympathomimetic activity as well as being a dopamine-receptor antagonist with a direct effect on the chemoreceptor trigger zone. It may have serotonin-receptor ($5\text{-}HT_3$) antagonist properties.

Metoclopramide is used in disorders of decreased gastrointestinal motility (p. 1805.2) such as gastroparesis or ileus; in gastro-oesophageal reflux disease (p. 1807.2) and dyspepsia (p. 1806.3); and in nausea and vomiting (p. 1811.3) associated with various gastrointestinal disorders, with migraine, after surgery, and with cancer therapy. It may be used to stimulate gastric emptying during radiographic examinations, to facilitate intubation of the small bowel, and in the management of aspiration syndromes (p. 1804.2).

In order to reduce the risks of neurological and other adverse effects, the EMA has restricted metoclopramide use to a maximum of 5 days and does not recommend its use for chronic conditions such as gastroparesis, dyspepsia, and gastro-oesophageal reflux disease, or as an adjunct in surgical or radiological procedures. The FDA also advises against chronic use unless the benefit of treatment outweighs the risk. The use of metoclopramide is restricted in children and young adults under 20 years of age (see Administration in Children, below).

It is usually given as the hydrochloride monohydrate with doses expressed as the anhydrous hydrochloride. In the USA, the strength of preparations of the hydrochloride monohydrate is usually expressed in terms of the base. Metoclopramide hydrochloride 10.5 mg is equivalent to about 10.0 mg of the anhydrous substance, which is equivalent to about 8.9 mg of the anhydrous base.

For most purposes the total daily dose should not exceed 500 micrograms/kg; dosage reduction is recommended in renal and perhaps hepatic impairment (see Administration in Hepatic or Renal Impairment, below).

- In the UK, the recommended dose, given orally, intramuscularly, or by slow intravenous injection (over at least 3 minutes), is 10 mg (expressed as anhydrous metoclopramide hydrochloride) three times daily.
- In the USA, the usual oral dose is 10 to 15 mg (expressed as the base) up to four times daily.
- Single doses of 10 to 20 mg (expressed as anhydrous base or anhydrous hydrochloride) may be given orally, intravenously, or intramuscularly when required, such as before a diagnostic procedure.

An intranasal formulation of metoclopramide is available in some countries.

The base, and salts including the dihydrochloride and the glycyrrhizate have also been used.

High-dose therapy. High doses of metoclopramide have been used, often with other drugs such as dexamethasone, in the treatment of the nausea and vomiting associated with cancer chemotherapy. In the UK, the loading dose of metoclopramide before cancer therapy is 2 to 4 mg/kg given as a continuous intravenous infusion over 15 to 20 minutes; it is followed by a maintenance dose of 3 to 5 mg/kg, again as a continuous intravenous infusion, given over 8 to 12 hours. Alternatively, initial doses of up to 2 mg/kg by intravenous infusion over at least 15 minutes may be given before cancer therapy and repeated every 2 hours. The total dosage by either continuous or intermittent infusion should not normally exceed 10 mg/kg in 24 hours. In the USA, dosing is started about 30 minutes before cancer chemotherapy; an initial dose of 2 mg/kg for highly emetogenic chemotherapy, or 1 mg/kg for less emetogenic chemotherapy, is given by intravenous infusion over at least 15 minutes. This dose is repeated every 2 hours for 2 doses, then every 3 hours for 3 doses.

Administration. INTRANASAL References.

1. Ormrod D, Goa KL. Intranasal metoclopramide. *Drugs* 1999; 58: 315–22. Commentaries. *ibid.*: 323–4.

Administration in children. In the EU the use of metoclopramide in children and young adults is restricted to a second-line option for prevention of delayed chemotherapy-induced nausea and vomiting and treatment of established postoperative nausea and vomiting. It may be used for up to 5 days in children aged 1 year and over. Usual oral and parenteral (intramuscular or intravenous) doses for all indications in the UK are:

- for those aged 15 to 19 years and weighing 60 kg and over: 10 mg three times daily
- 15 to 19 years (30 to 59 kg): 5 mg three times daily
- 9 to 14 years (30 kg and over): 5 mg three times daily
- 5 to 9 years (20 to 29 kg): 2.5 mg three times daily
- 3 to 5 years (15 to 19 kg): 2 mg two or three times daily
- 1 to 3 years (10 to 14 kg): 1 mg two or three times daily

An alternative dose for postoperative nausea and vomiting in those aged 1 to 20 years is 150 micrograms/kg given by slow intravenous injection. Further doses can be given 6 hours apart to a maximum of 500 micrograms/kg in 24 hours.

Where body-weight is below that specified for a given age group, the dose should reflect the weight rather than the age, so that a lower dose is chosen.

In the USA metoclopramide is licensed for use in children only to facilitate small bowel intubation in those resistant to conventional methods. A single intravenous dose, based on age, is recommended as follows:

- over 14 years: 10 mg
- 6 to 14 years: 2.5 to 5 mg
- under 6 years: 100 micrograms/kg

Administration in hepatic or renal impairment. Total clearance of metoclopramide is significantly reduced in patients with renal impairment[1-3] and the elimination half-life is prolonged to up to 19 hours.[2] This may be due to impaired metabolism[1,2] or to an alteration in enterohepatic circulation of metoclopramide.[1] Accumulation of metoclopramide could therefore occur in renal impairment with a possible increased risk of adverse effects. Dosage reductions of at least 50% have therefore been

recommended in patients with moderate to severe renal impairment.[1,2] US licensed product information recommends this dose reduction in those patients whose creatinine clearance is below 40 mL/minute; UK information advises dose reduction in significant renal impairment, but gives no guidance on appropriate doses.

Patients undergoing haemodialysis do not require dosage supplements since relatively little metoclopramide is cleared by this process.[2,3]

UK licensed product information also recommends that the dose of metoclopramide should be reduced in patients with clinically significant **hepatic impairment**, although again no recommendations on the size of the reduction are given; caution is advised in liver disease, due to loss of conjugation. The US product information notes that metoclopramide undergoes minimal hepatic metabolism and has been used safely in some patients with advanced liver disease (whose renal function was normal), and it makes no such recommendation for reduction of dose. Decreases in clearance and increases in half-life and area under the plasma concentration-time curve have been reported in patients with cirrhosis given metoclopramide.[4,5]

1. Bateman DN, *et al.* The pharmacokinetics of single doses of metoclopramide in renal failure. *Eur J Clin Pharmacol* 1981; 19: 437–41.
2. Lehmann CR, *et al.* Metoclopramide kinetics in patients with impaired renal function and clearance by haemodialysis. *Clin Pharmacol Ther* 1985; 37: 284–9.
3. Wright MR, *et al.* Effect of haemodialysis on metoclopramide kinetics in patients with severe renal failure. *Br J Clin Pharmacol* 1988; 26: 474–7.
4. Hellstern A, *et al.* Absolute bioavailability of metoclopramide given orally or by enema in patients with normal liver function or with cirrhosis of the liver. *Arzneimittelforschung* 1987; 37: 733–6.
5. Magueur E, *et al.* Pharmacokinetics of metoclopramide in patients with liver cirrhosis. *Br J Clin Pharmacol* 1991; 31: 185–7.

Blood disorders. Responses to treatment with metoclopramide have been reported in patients with Diamond-Blackfan anaemia, probably through induction of prolactin release, although the mechanism by which prolactin affects erythropoiesis is unclear.[1,2] In a pilot study, 3 out of 9 evaluable patients responded after 12 to 15 weeks of therapy; high serum ferritin, pituitary dysfunction, male sex, and younger age may have contributed to the poor response to metoclopramide in other patients.[1] In another case, response was seen by the fourth week of treatment; at the time of the report, the patient had remained asymptomatic and transfusion independent for 8 months.[2]

1. Abkowitz JL, *et al.* Response of Diamond-Blackfan anemia to metoclopramide: evidence for a role for prolactin in erythropoiesis. *Blood* 2002; 100: 2687–91.
2. Akiyama M, *et al.* Successful treatment of Diamond-Blackfan anemia with metoclopramide. *Am J Hematol* 2005; 78: 295–8.

Gastroenteritis. For mention of the use of antiemetics such as metoclopramide to reduce vomiting in acute gastroenteritis, see Ondansetron, p. 1873.1.

Hiccup. Metoclopramide has been used in the management of intractable hiccup. For a discussion of hiccup and its management see p. 1046.3.

Lactation induction. Metoclopramide has been used[1,2] in doses of 10 mg three times daily for its dopamine antagonist properties to stimulate lactation in women who wish to breast feed and in whom mechanical stimulation of the nipple alone is inadequate, including mothers of adopted babies or babies born to surrogates.[3,4] However, pharmacological lactation induction should be viewed as adjunctive to mechanical methods and the duration of therapy should probably be limited to 7 to 14 days.[1,2] In addition, the efficacy of metoclopramide in stimulating lactation in women with preterm deliveries has been questioned by a controlled study.[5] Young women are at increased risk of extrapyramidal effects from metoclopramide—see under Adverse Effects, p. 1864.1. There has also been concern about the presence of the drug in breast milk. For a discussion of lactation inhibition and induction, see p. 2130.1.

1. Anderson PO, Valdés V. Increasing breast milk supply. *Clin Pharm* 1993; 12: 479–80.
2. Gabay MP. Galactogogues: medications that induce lactation. *J Hum Lact* 2002; 18: 274–9.
3. Cheales-Siebenaler NJ. Induced lactation in an adoptive mother. *J Hum Lact* 1999; 15: 41–3.
4. Biervliet FP, *et al.* Induction of lactation in the intended mother of a surrogate pregnancy: case report. *Hum Reprod* 2001; 16: 581–3.
5. Hansen WF, *et al.* Metoclopramide effect on breastfeeding the preterm infant: a randomized trial. *Obstet Gynecol* 2005; 105: 383–9.

Migraine. Metoclopramide is used in the treatment of migraine (p. 670.3) to alleviate nausea and vomiting and gastric stasis, which commonly develop as a migraine attack progresses and can lead to poor absorption of oral antimigraine preparations. It may also be given to counteract nausea and vomiting from the use of ergotamine. Metoclopramide is included in some combination analgesic preparations for the treatment of acute attacks of migraine. In one study, oral lysine aspirin with metoclopramide was as effective as oral sumatriptan in the treatment of migraine.[1] However, a review of combinations of oral metoclopramide plus an analgesic for migraine suggested that they were likely to be less effective than triptan monotherapy, although they might be an option for patients in whom triptans are contra-indicated or who could not tolerate triptans.[2] Metoclopramide with sumatriptan may be effective in patients unresponsive to a triptan alone.[3]

Parenteral metoclopramide has also been shown to be an effective treatment for acute migraine; it reduces pain, and to some extent nausea (although other antiemetics may be more effective), and a systematic review concluded that it should be considered a first-line treatment for migraine in the emergency department.[4] A later study found intravenous metoclopramide (with intermittent doses of diphenhydramine) to be comparable to subcutaneous sumatriptan in terms of pain relief at both 2 and 24 hours after treatment.[5]

1. Tfelt-Hansen P, *et al.* The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. *Lancet* 1995; 346: 923–6.
2. Azzopardi TD, Brooks NA. Oral metoclopramide as an adjunct to analgesics for the outpatient treatment of acute migraine. *Ann Pharmacother* 2008; 42: 397–402.
3. Schulman EA, Dermott KF. Sumatriptan plus metoclopramide in triptan-nonresponsive migraineurs. *Headache* 2003; 43: 729–33.
4. Colman I, *et al.* Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials. *BMJ* 2004; 329: 1369–72.
5. Friedman BW, *et al.* A trial of metoclopramide vs sumatriptan for the emergency department treatment of migraines. *Neurology* 2005; 64: 463–8.

Orthostatic hypotension. Metoclopramide has been tried in the management of some patients with orthostatic hypotension, as mentioned on p. 1634.3.

Tourette's syndrome. A small, short-term study in children and adolescents with Tourette's syndrome (see Tics, p. 1030.1) or chronic tic disorders found that treatment with oral metoclopramide (up to 40 mg daily) significantly reduced tic score and severity compared with placebo.[1]

1. Nicolson R, *et al.* A randomized, double-blind, placebo-controlled trial of metoclopramide for the treatment of Tourette's disorder. *J Am Acad Child Adolesc Psychiatry* 2005; 44: 640–6.

Variceal haemorrhage. Metoclopramide 20 mg intravenously controlled bleeding from oesophageal varices within 15 minutes in 10 of 11 patients compared with 4 of 11 patients given placebo; all patients were treated by sclerotherapy.[1] Lower oesophageal sphincter pressure is increased by metoclopramide, thus reducing blood flow to varices and achieving haemostasis; another study[2] found use of metoclopramide with intravenous glyceryl trinitrate to be more effective than glyceryl trinitrate alone in reducing intravariceal pressure.

For a discussion of variceal haemorrhage and its management, see p. 2563.1.

1. Hosking SW, *et al.* Pharmacological constriction of the lower oesophageal sphincter: a simple method of arresting variceal haemorrhage. *Gut* 1988; 29: 1098–1102.
2. Sarin SK, Saraya A. Effects of intravenous nitroglycerin and nitroglycerin and metoclopramide on intravariceal pressure: a double blind, randomized study. *Am J Gastroenterol* 1995; 90: 48–53.

Adverse Effects

Metoclopramide is a dopamine antagonist and may cause extrapyramidal symptoms (usually acute dystonic reactions); these are more common in children and young adults, and at daily doses above 500 micrograms/kg. Parkinsonism and tardive dyskinesia have occasionally occurred, usually during prolonged treatment in elderly patients.

Other adverse effects affecting the CNS include restlessness, drowsiness, dizziness, anxiety, confusion, and tremor; hallucinations have been reported rarely. Depression has occurred and can be severe, with suicidal ideation and suicide reported. Hypotension, hypertension, gastrointestinal disturbances, dyspnoea, visual disturbances, urinary frequency and incontinence, and headache may also occur and there are isolated reports of blood disorders, hypersensitivity reactions (rash, bronchospasm, angioedema), and neuroleptic malignant syndrome. Disorders of cardiac conduction have been reported with intravenous metoclopramide and transient flushing of the face and upper body has followed high intravenous doses.

Metoclopramide stimulates prolactin secretion and may cause galactorrhoea or related disorders. Transient increases in plasma-aldosterone concentrations have been reported.

Effects on the blood. Agranulocytosis was associated with use of metoclopramide on 2 separate occasions.[1] Both episodes resolved within 2 to 3 weeks of withdrawing metoclopramide. Methaemoglobinaemia[2-4] and sulfhaemoglobinaemia[5,6] have also been reported. Methaemoglobinaemia (p. 1559.3) may be treated with methylthioninium chloride. In one case,[3] the patient died despite such treatment; blood samples taken before death were found to be haemolysed, and assays showed deficiency in G6PD activity (methylthioninium chloride should not be used in G6PD-deficient patients, see Adverse Effects of Methylthioninium Chloride, p. 1560.2).

1. Harvey RL, Luzar MJ. Metoclopramide-induced agranulocytosis. *Ann Intern Med* 1988; 108: 214–15.
2. Grant SCD, *et al.* Methaemoglobinaemia produced by metoclopramide in an adult. *Eur J Clin Pharmacol* 1994; 47: 89.
3. Karadsheh NS, *et al.* Metoclopramide-induced methemoglobinemia in a patient with co-existing deficiency of glucose-6-phosphate dehydrogenase and NADH-cytochrome b5 reductase: failure of methylene blue treatment. *Haematologica* 2001; 86: 659–60.
4. Mérieau E, *et al.* Métoclopramide et méthémoglobinémie néonatale. *Arch Pediatr* 2005; 12: 438–41.
5. Van Veldhuizen PJ, Wyatt A. Metoclopramide-induced sulfhemoglobinemia. *Am J Gastroenterol* 1995; 90: 1010–11.
6. Aravindhan N, Chisholm DG. Sulfhemoglobinemia presenting as pulse oximetry desaturation. *Anesthesiology* 2000; 93: 883–4.

Effects on the cardiovascular system. There have been reports of hypotension,[1] hypertension,[2,3] and supraventricular tachycardia[4] associated with metoclopramide. Bradycardia followed by total heart block,[5] and sinus arrest,[6] have also been reported. It was suggested that metoclopramide may have contributed to a prolonged QT interval and torsade de pointes in a patient with heart failure and renal impairment.[7]

1. Park GR. Hypotension following metoclopramide administration during hypotensive anaesthesia for intracranial aneurysm. *Br J Anaesth* 1978; 50: 1268–9.
2. Sheridan C, *et al.* Transient hypertension after high doses of metoclopramide. *N Engl J Med* 1982; 307: 1346.
3. Fillbeck DJ, *et al.* Metoclopramide-induced hypertensive crisis. *Clin Pharm* 1984; 3: 548–9.
4. Bevacqua BK. Supraventricular tachycardia associated with postpartum metoclopramide administration. *Anesthesiology* 1988; 68: 124–5.
5. Midttun M, Øberg B. Total heart block after intravenous metoclopramide. *Lancet* 1994; 343: 182–3.
6. Malkoff MD, *et al.* Sinus arrest after administration of intravenous metoclopramide. *Ann Pharmacother* 1995; 29: 381–3.
7. Siddique SM, *et al.* Metoclopramide as a possible cause of prolonged QT syndrome and torsade de pointes in a patient with heart failure and renal insufficiency. *Ann Intern Med* 2009; 150: 502–4.

Effects on the endocrine system. *ALDOSTERONISM.* Metoclopramide has been reported to increase plasma-aldosterone concentrations in healthy individuals[1] and in patients with liver cirrhosis and ascites associated with secondary hyperaldosteronism.[2] Increased plasma aldosterone after metoclopramide use has also been associated with the development of oedema in a patient with congestive heart failure.[3] The metoclopramide-induced aldosterone response was blunted by giving neostigmine beforehand.[1]

1. Sommers DK, *et al.* Effect of neostigmine on metoclopramide-induced aldosterone secretion in man. *Eur J Clin Pharmacol* 1989; 36: 411–13.
2. Mazzacca G, *et al.* Metoclopramide and secondary hyperaldosteronism. *Ann Intern Med* 1983; 98: 1024–5.
3. Zumoff B. Metoclopramide and edema. *Ann Intern Med* 1983; 98: 557.

HYPERPROLACTINAEMIA. Hyperprolactinaemia, galactorrhoea, and pituitary adenoma occurred in a 49-year-old woman with reflux oesophagitis who had received metoclopramide for 3 months.[1] Her plasma-prolactin concentrations fell to normal and her symptoms resolved over 4 months after withdrawal of metoclopramide. The pituitary tumour was considered to be incidental to, and not caused by, metoclopramide therapy. A 21-year-old female developed mastodynia, galactorrhoea, and hyperprolactinaemia after 2 days of treatment with metoclopramide;[2] she had previously taken domperidone intermittently without any problems. Her symptoms resolved rapidly on stopping therapy. Galactorrhoea has also been reported[3] in a neonate given metoclopramide.

1. Cooper BT, *et al.* Galactorrhoea, hyperprolactinaemia, and pituitary adenoma presenting during metoclopramide therapy. *Postgrad Med J* 1982; 58: 314–15.
2. Bozzolo M, *et al.* Medikamentös induzierte Hyperprolaktinämie und Galaktorrhöe. *Schweiz Rundsch Med Prax* 1992; 81: 1511–13.
3. Paturi B, *et al.* Galactorrhea with metoclopramide use in the neonatal unit. *J Perinatol* 2009; 29: 391–2.

Effects on mental state. There are isolated reports of dose-related delirium, depression, and uncontrollable crying in patients treated with metoclopramide in doses of 40 to 80 mg daily.[1-3] Symptoms resolved on reducing the dose or withdrawing metoclopramide, and tolerance could be achieved by gradually increasing the dose. In another report,[4] a patient developed acute akathisia (see Extrapyramidal Effects p. 1864.1) shortly after starting metoclopramide 10 mg four times daily; this was accompanied by restlessness, anxiety, and irritability. Despite stopping the drug after 2 days, and treatment with paroxetine and lorazepam, the patient started to have panic attacks, which increased in frequency and severity; he also developed agoraphobia. Two months after taking metoclopramide he was diagnosed with major depressive disorder, which included intermittent suicidal ideation. Following aggressive therapy and hospitalisation, his symptoms gradually resolved.

Encephalopathy has been associated with intravenous metoclopramide in a patient with Parkinson's disease.[5]

Insomnia, with or without daytime drowsiness, has also been reported in patients taking metoclopramide 40 mg daily.[6]

Hypersensitivity psychosis has also been reported, shortly after stopping metoclopramide.[7] Symptoms included hallucinations, delusional experiences, anxiety, restlessness, and sleep disturbances; improvement and gradual resolution were noted after treatment with risperidone.

1. Bottner RK, Tullio CJ. Metoclopramide and depression. *Ann Intern Med* 1985; 103: 482.
2. Adams CD. Metoclopramide and depression. *Ann Intern Med* 1985; 103: 960.
3. Fishbain DA, Rogers A. Delirium secondary to metoclopramide hydrochloride. *J Clin Psychopharmacol* 1987; 7: 281–2.
4. Anfinson TJ. Akathisia, panic, agoraphobia, and major depression following brief exposure to metoclopramide. *Psychopharmacol Bull* 2002; 36: 82–93.
5. Messerschmidt KA, *et al.* Encephalopathy associated with metoclopramide use in a patient with Parkinson's disease. *Am J Health-Syst Pharm* 2012; 69: 1303–6.
6. Saxe TG. Metoclopramide side effects. *Ann Intern Med* 1983; 98: 674.
7. Lu M-L, *et al.* Metoclopramide-induced supersensitivity psychosis. *Ann Pharmacother* 2002; 36: 1387–90.

Extrapyramidal effects. The Adverse Reactions Register of the UK CSM for the years 1967 to 1982 contained 479 reports of extrapyramidal reactions in which metoclopramide was the suspected drug: 455 were for dystonic-dyskinetic reactions, 20 for parkinsonism, and 4 for tardive dyskinesia.[1]

Acute **dystonic-dyskinetic** reactions occur most commonly in children and young adults[1-3] and about 70% of reactions are in females;[1,3] many are associated with doses above those recommended by the manufacturers.[1,3,4] Symptoms reported include oculogyric crisis,[4,5] opisthotonus,[6] torticollis,[5,7] trismus,[5,7] a tetanus-like reaction,[8] and blue coloration of the tongue;[6] akathisia after the use of metoclopramide alone,[9] or with droperidol[10] or haloperidol[9] has been reported (see also Effects on Mental State, p. 1863.3).

These effects usually occur within 72 hours of starting treatment[1] but have been reported within 30 minutes of receiving metoclopramide.[4] When metoclopramide is given intravenously, the rate may be important in determining the incidence of acute extrapyramidal reactions: a study indicated that akathisia was less frequent when the same dose was given as a 15-minute infusion rather than a 2-minute bolus injection.[11] Acute effects can occur in patients who have previously taken metoclopramide without complications[5,6,10] and may be precipitated by other drugs. Although generally self-limiting, deaths have occurred.[1,5] The reactions are readily reversed by an antihistamine such as diphenhydramine,[7] or an antimuscarinic such as benzatropine;[4,6] prophylactic use of diphenhydramine has been suggested for patients with a history of extrapyramidal reactions and in those less than 30 years of age.[7,8]

Metoclopramide-associated **parkinsonism** is thought to occur less commonly than the acute dystonias and is seen mainly in older patients. Symptoms usually appear several months after starting metoclopramide, but may occur within days or not for several years. Withdrawal of metoclopramide usually results in resolution of symptoms, although it may take several months.[1] A study has suggested that metoclopramide-induced parkinsonism (misdiagnosed as idiopathic Parkinson's disease) may be more common in the elderly than generally realised.[12]

Tardive dyskinesia may rarely be associated with use of metoclopramide. Development of this condition is directly related to the length of treatment with metoclopramide and the number of doses taken.[13] The reaction is usually confined to elderly patients after prolonged oral use,[14,15] but it has been reported with short-term high-dose parenteral use as an antiemetic in cancer chemotherapy,[16] and a case has been reported in an 8-year-old child treated with metoclopramide for gastro-oesophageal reflux disease in usual doses.[17] The average duration of treatment before the onset of symptoms was 14 months (range 4 to 44 months) in a report of 11 cases[15] and 26 months (range 8 to 60 months) in a report of 12 cases;[18] some patients did not have symptoms until after withdrawal of metoclopramide. Tardive dyskinesia is potentially irreversible and its management is difficult.[18] Some patients improve after withdrawal of metoclopramide but symptoms persisting during follow-up periods of up to 3 years have been reported.[14,15] The emphasis must be on prevention, hence the recommendation that metoclopramide should not be prescribed for the long-term treatment of minor symptoms, especially in elderly patients.[18] After analyses suggested that metoclopramide was the most common cause of drug-induced movement disorders and that about 20% of patients who used metoclopramide used it for longer than 3 months, the FDA recommended that chronic use of metoclopramide should be avoided in all patients unless the benefit of treatment is believed to outweigh the risk.[13] The EMA[19] has also restricted metoclopramide use to a maximum of five days and does not recommend its use for chronic conditions or as an adjunct in surgical or radiological procedures; its use in children is also restricted (see Administration in Children, p. 1862.3).

1. Bateman DN, *et al.* Extrapyramidal reactions with metoclopramide. *BMJ* 1985; 291: 930–2.
2. Anonymous. Measuring therapeutic risk. *Lancet* 1989; ii: 139–40.
3. Adverse Drug Reactions Advisory Committee. Metoclopramide—choose the dose carefully. *Aust Adverse Drug React Bull* 1990; Feb.
4. Tait P, *et al.* Metoclopramide side effects in children. *Med J Aust* 1990; 152: 387.
5. Pollera CF, *et al.* Sudden death after acute dystonic reaction to high-dose metoclopramide. *Lancet* 1984; ii: 460–1.
6. Alroe C, Bowen P. Metoclopramide and prochlorperazine: "the blue-tongue sign". *Med J Aust* 1989; 150: 724–5.
7. Kris MG, *et al.* Extrapyramidal reactions with high-dose metoclopramide. *N Engl J Med* 1983; 309: 433–4.
8. Della Valle R, *et al.* Metoclopramide-induced tetanus-like dystonic reaction. *Clin Pharm* 1985; 4: 102–3.
9. Akagi H, Kumar TM. Akathisia: overlooked at a cost. *BMJ* 2002; 324: 1506–7.
10. Barnes TRE, *et al.* Acute akathisia after oral droperidol and metoclopramide preoperative medication. *Lancet* 1982; ii: 48–9.
11. Regan LA, *et al.* Slower infusion of metoclopramide decreases the rate of akathisia. *Am J Emerg Med* 2009; 27: 475–80.
12. Avorn J, *et al.* Increased incidence of levodopa therapy following metoclopramide use. *JAMA* 1995; 274: 1780–2.
13. FDA. FDA requires boxed warning and risk mitigation strategy for metoclopramide-containing drugs (issued 26th February, 2009). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm149533.htm (accessed 15/07/10)
14. Grimes JD, *et al.* Long-term follow-up of tardive dyskinesia due to metoclopramide. *Lancet* 1982; ii: 563.
15. Wiholm B-E, *et al.* Tardive dyskinesia associated with metoclopramide. *BMJ* 1984; 288: 545–7.
16. Breitbart W. Tardive dyskinesia associated with high-dose intravenous metoclopramide. *N Engl J Med* 1986; 315: 518.
17. Putnam PE, *et al.* Tardive dyskinesia associated with use of metoclopramide in a child. *J Pediatr* 1992; 121: 983–5.
18. Orme ML'E, Tallis RC. Metoclopramide and tardive dyskinesia in the elderly. *BMJ* 1984; 289: 397–8.
19. EMA. European Medicines Agency recommends changes to the use of metoclopramide: changes aim mainly to reduce the risk of neurological side effects (issued 26 July, 2013). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Metoclopramide_31/WC500146610.pdf (accessed 02/10/13)

Hypersensitivity. A patient given intravenous metoclopramide and butylhyoscine for gastrointestinal disturbances developed pruritus, generalised urticaria, hypotension, and loss of consciousness. She was treated with intravenous fluid, antihistamines, and corticosteroids. Skin prick tests revealed a response to metoclopramide, suggesting an IgE-mediated allergic reaction.[1]

1. Kerstan A, *et al.* Anaphylaxis during treatment of nausea and vomiting: IgE-mediated metoclopramide allergy. *Ann Pharmacother* 2006; 40: 1889–90.

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome (NMS, p. 1050.2) has occurred very rarely with metoclopramide. In a report of a case with a fatal outcome, it was noted that 17 additional cases had been published in the years 1978 to 1998, three of which resulted in death.[1] A case report in a 6-month-old female with Freeman-Sheldon syndrome[2] given metoclopramide suggested that pre-existing fever and myopathy may be predisposing factors. In another case,[3] a burns patient, there was some suggestion that the patient may have been susceptible to neuroleptic hyperthermic syndromes such as NMS and malignant hyperthermia. Metoclopramide should be stopped immediately if NMS occurs, and the patient treated urgently with bromocriptine.

1. Nonino F, Campomori A. Neuroleptic malignant syndrome associated with metoclopramide. *Ann Pharmacother* 1999; 33: 644–5.
2. Stein ML, *et al.* Neuroleptic malignant syndrome induced by metoclopramide in an infant with Freeman-Sheldon syndrome. *Anesth Analg* 2006; 103: 786–7.
3. Nachreiner R, *et al.* Neuroleptic malignant syndrome associated with metoclopramide in a burn patient. *J Burn Care Res* 2006; 27: 237–41.

Precautions

Metoclopramide should not be used when stimulation of muscular contractions might adversely affect gastrointestinal conditions, as in gastrointestinal haemorrhage, obstruction, perforation, or for a few days after surgery. There have been reports of hypertensive crises in patients with phaeochromocytoma given metoclopramide, thus its use is not recommended in such patients; caution is advised in patients with hypertension. Metoclopramide is also not recommended for use in patients with epilepsy as the frequency and severity of seizures may be increased.

Children, young adults, and the elderly should be treated with care as they are at increased risk of extrapyramidal reactions; the use of metoclopramide is restricted in children and young adults under 20 years (see Administration in Children, p. 1862.3). Prolonged therapy should generally be avoided (see Extrapyramidal Effects, above). Care should also be taken when metoclopramide is given to patients with renal or hepatic impairment, Parkinson's disease, or a history of depression, atopy (including asthma), or porphyria. Intravenous metoclopramide should be given with caution to patients at increased risk of cardiovascular reactions, including those with cardiac conduction abnormalities such as sick sinus syndrome.

Metoclopramide may cause drowsiness or impaired reactions; patients so affected should not drive or operate machinery.

Breast feeding. Metoclopramide is excreted into breast milk. The American Academy of Pediatrics[1] considers that the use of metoclopramide by mothers during breast feeding may be of concern, owing to its dopamine-receptor blocking activity. UK licensed product information states that problems in humans have not been reported.

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 07/05/04)

Porphyria. Metoclopramide has been used successfully in the management of acute attacks of porphyria.[1] The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies metoclopramide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[2]

1. Elder GH, *et al.* Metoclopramide and acute porphyria. *Lancet* 1997; 350: 1104.
2. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/11/11)

Pregnancy. Metoclopramide is often used to treat nausea and vomiting in pregnancy. A large retrospective cohort study confirmed that exposure to metoclopramide in the first trimester was not associated with adverse effects on the fetus including congenital malformations, perinatal death, and low birth-weight.[1]

1. Matok I, *et al.* The safety of metoclopramide use in the first trimester of pregnancy. *N Engl J Med* 2009; 360: 2528–35.

Interactions

Increased toxicity may occur if metoclopramide is given with other centrally active drugs. Metoclopramide should be used with caution in patients taking other drugs that can also cause extrapyramidal reactions, such as the phenothiazines. It should also be used with care with other drugs acting at central dopamine receptors, such as pergolide. Combining metoclopramide with CNS depressant drugs can lead to increased sedative effects. Antimuscarinics and opioid analgesics antagonise the gastrointestinal effects of metoclopramide.

The absorption of other drugs may be affected by metoclopramide; it may either diminish absorption from the stomach (as with digoxin) or enhance absorption from the small intestine (for example, with alcohol, ciclosporin, levodopa, aspirin, or paracetamol). The absorption of food may be affected requiring adjustment of the insulin regimen in diabetic patients. Metoclopramide inhibits serum cholinesterase and may prolong neuromuscular blockade produced by suxamethonium (see p. 2040.1) and mivacurium (p. 2035.1). Metoclopramide may also increase prolactin blood concentrations and therefore interfere with drugs which have a hypoprolactinaemic effect such as bromocriptine (but see p. 899.1). The response to gonadorelin may be altered by metoclopramide, see p. 2282.2. Caution is required if metoclopramide must be given to patients receiving MAOIs and care is required when metoclopramide is given with drugs that affect cardiac conduction.

Antidepressants. For reference to extrapyramidal effects and other adverse effects suggestive of serotonin syndrome in patients taking metoclopramide with SSRIs or venlafaxine, see Gastrointestinal Drugs under Interactions for Fluoxetine (p. 424.3) and Venlafaxine (p. 457.1) respectively.

Carbamazepine. For a report of neurotoxicity associated with the use of metoclopramide with carbamazepine, see p. 517.3.

Hydroxyzine. Acute anxiety, rigidity, generalised tremor, opisthotonus, and hypertension developed in a 20-year-old man given metoclopramide 10 mg intravenously and hydroxyzine 100 mg intramuscularly.[1] The adverse effects occurred 30 minutes after giving hydroxyzine and it was suggested that hydroxyzine potentiated the onset of the reaction.

1. Fouilladieu JL, *et al.* Possible potentiation by hydroxyzine of metoclopramide's undesirable side effects. *Anesth Analg* 1985; 64: 1227–8.

Pharmacokinetics

Metoclopramide is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses, although conditions such as vomiting or impaired gastric motility may reduce absorption. However, it undergoes hepatic first-pass metabolism, which varies considerably between subjects, and hence absolute bioavailability and plasma concentrations are subject to wide interindividual variation. On average, the bioavailability of oral metoclopramide is about 80%, but it varies between about 30 and 100%. Peak plasma concentrations of metoclopramide occur about 1 to 2 hours after an oral dose. Bioavailability is equally variable after rectal or intranasal doses, although it may be somewhat better if the drug is given intramuscularly.

Metoclopramide is weakly bound to plasma proteins (13 to 30%).

Metoclopramide is widely distributed in the body, and readily crosses the blood-brain barrier into the CNS. It also freely crosses the placenta, and has been reported to attain concentrations in fetal plasma about 60 to 70% of those in maternal plasma. Concentrations in breast milk may be higher than those in maternal plasma, particularly in the early puerperium, although concentrations decrease somewhat in the late puerperium.

Elimination of metoclopramide is biphasic, with a terminal elimination half-life of about 4 to 6 hours, although this may be prolonged in renal impairment, with consequent elevation of plasma concentrations. It is excreted in the urine, about 85% of a dose being eliminated in 72 hours, 20% as unchanged metoclopramide and the remainder as sulfate or glucuronide conjugates, or as metabolites. About 5% of a dose is excreted in faeces via the bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Disgradon†; Ponderyl; Gastrocalm; Lizarona; Metoc; Midatenk; Novomit; Praux; Primavera-N; Primperil; Reliveran; Rilaquin; Rupemet; Saften; Sintegran; *Austral.*: Maxolon; Pramin; *Austria*: Gastrosil; Metogastron; Paspertin; *Belg.*: Dibertil; Docmetoclo†; Primperan; *Braz.*: Aristopramida; Emetic†; Eucil; Fluccil; Metoclosan; Metoclosantisa; Metoplamin†; Neolasil; No-Vomit†; Plabel; Plagex; Plamida†; Plamidasil; Plamivon; Plasil; Pramil; *Canad.*: Apo-Metoclop; *Chile*: Hemibe; Itan; *Cz.*: Cerucal; Degan; MCP; *Denm.*: Emperal; Gastro-Timelets; Primperan; *Fin.*: Primperan; *Fr.*: Anausin; Primperan; *Ger.*: Cerucal; Gastronerton; MCP; Paspertin; *Gr.*: Gaspalon; Geneprami-D; Lumania; Luv; Pharmyork; Primperan; *Hong Kong*: Emeliv†; Maril; Martomide†; Maxolon†; Metolon†; Metomide†; Metram†; Pramin†; Primperan; Syntomide†; *Hung.*: Cerucal; *India*: Bacnorm; Donmet; Emenil; Emenorm; Labmet; Maxeron; Maxinorm; Metajex; Metamin; Metoclop; Metocontin; Perinorm; Reglan; Tomid; Vominorm; *Indon.*: Clopramel; Damaben; Emeran; Ethiferan; Gavistal; Lexapram; Meclam; Mepramide; Metolon†; Nilatika; Nofoklam; Normastin†; Obteran†; Opram; Piralen; Plasil; Praminal†; Primperan; Raclonid; Reguloop†; Sotatic; Tivomit; Tomit; Vertivom; Vilapon; Vomidex†; Vomipram; Vomitrol; Zumatrol†; *Irl.*: Antimet†; Gastrobid Continus†; Maxolon; Metocyl†; *Israel*: Pramin; *Ital.*: Delipramil; Digestivo S Pellegrino; Isaprandil; Plasil; Pramidin; Randum; *Jpn*: Primperan; *Malaysia*: Malon; Maril; Maxolon†; Mexomide; Primperan; Pulin; *Mex.*: Biopram; Carnotprim; Cirulan; Clorimet-Z; Conysmin; Dolmisin; Eudiges; Gigemet; Hopram; Meclomid; Midetol; Mipramid; Plasil; Polcotec; Pradex; Pramilem†; Primperan†; Propace; Raamfen; Synespramid; *Mon.*: Prokinyl; *Neth.*: Primperan; *Norw.*: Afipran; *NZ*: Maxolon; Metamide; *Philipp.*: Biclomet; Clometide; Clomitene; Clozil; Metsil; Novom†; Plasil; Reglomar; Vitamet; Vomaine; *Pol.*: Pramidin†; *Port.*: Primperan; *Rus.*: Apo-Metoclop (Апометоклоп)†; Cerucal (Церукал); Ceruglan (Церуглан); Cerulan (Церулан); Metamol (Метамол); Perinorm (Перинорм); *S.Afr.*: Acumet†; Adco-Contromet; Betaclopramide; Clopamon; Maxolon; Metalon†; Perinorm†; Pramalon†; Setin; *Singapore*: Apo-Metoclop; Emeliv; Maril; Metolon; Primperan; Pulin; Syntomide; *Spain*: Primperan; *Swed.*: Primperan; *Switz.*: Paspertin; Primperan; *Thai.*: Emetal; Gensil†; H-Peran; Hawkperan; KB Meta; Manosil; Maril; Met-Sil; Metoclor; Nausil; Nausin†; Plamide; Plamine; Plasil; R-J; Vomesea; *Turk.*: Emoject; Metoklamide; Metpamid; Primperan; *UAE*: Premosan; *UK*: Maxolon; Primperan; *Ukr.*: Cerucal (Церукал); Metucal (Метукал)†; *USA*: Metozolv; Octamide†; Reclomide; Reglan; *Venez.*: Clodoxin; Irtopan; Mepramida; Pramide; Primperan.

Multi-ingredient Preparations. *Arg.*: Bil 13 Enzimatico; Bitecain AA; Digesplen; Facilgest; Factorine; Paradil Enzimatico†; Paradil; Migral Compositum; Pakinase; Pankreon Total; Tetralgin; Vacuobil Plus; *Austral.*: Anagraine; Metomax; *Austria*: Ceolat Compositum; *Belg.*: Migpriv; *Braz.*: Cefalium; Digeplus; Essen; Plagon†; Plasil Enzimatico; Sintozima†; *Chile*: Aero Itan; Aerogastrol; Digespar; Garceptol; No-Ref; Pangastren; *Cz.*: Migranerton; *Fin.*: Migpriv†; *Fr.*: Migpriv; *Ger.*: Migraeflux MCP; Migralave + MCP; Migrane-Neuridal; Migranerton; *Gr.*: Egityl; Premig; *Hung.*: Migpriv; *India*: Copar; Metadrate; Metoclop-P; Metopar; Metpar; Nausifar MPS; Okanorm Plus; Pacimol-M; Paramet; Paranorm; *Indon.*: Primadol; Primperan Compositum; *Irl.*: Paramax; *Ital.*: Geffer; Migpriv; Migraprim; *Mex.*: Antigram; Digenor Plus; Digenor; Espaven MD; Espraden; Plasil Enzimatico; Pramigel; Primpesasy†; *Neth.*: Migrafin; *NZ*: Paramax; *Pol.*: Migpriv; *Spain*: Aeroflat; Anti-Anorex Triple; Suxidina; *Swed.*: Migpriv†; *Switz.*: Migpriv†; *Turk.*: Migprin; *UK*: Migramax; Paramax.

Pharmacopoeial Preparations

BP 2014: Metoclopramide Injection; Metoclopramide Oral Solution; Metoclopramide Tablets;

USP 36: Metoclopramide Injection; Metoclopramide Oral Solution; Metoclopramide Tablets.

Metopimazine *(BAN, USAN, rINN)*

EXP-999; Metopimazina; Métopimazine; Metopimazinum; RP-9965; Метопимазин.

1-[3-(2-Methylsulphonylphenothiazin-10-yl)propyl]piperidine-4-carboxamide.

$C_{22}H_{27}N_3O_3S_2$=445.6

CAS — 14008-44-7.

ATC — A04AD05.

ATC Vet — QA04AD05.

UNII — 238575V9AV.

Pharmacopoeias. In *Fr.*

Profile

Metopimazine, a phenothiazine dopamine antagonist, is an antiemetic with general properties similar to those of chlorpromazine (p. 1045.2). It is used in the management of nausea and vomiting, including that associated with cancer chemotherapy (p. 1811.3). It is given in usual oral doses of 15 to 30 mg daily, in up to 4 divided doses; similar daily doses have been given rectally in 3 divided doses. It has also been given by injection in a dose of 10 to 20 mg daily, usually intramuscularly but occasionally by the intravenous route. Higher doses of 30 to 50 mg daily in divided doses by intramuscular injection or intravenous infusion have been given for chemotherapy-induced nausea and vomiting; the first dose is given before chemotherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Vogalene; Vogalib; *Gr.*: Vogalene.

Mosapride Citrate *(rINNM)*

AS-4370; Citrato de mosaprida; Mosaprida, citrato de; Mosapride, Citrate de; Mosapridi Citras; Rimopride Citrate; Мозаприда Цитрат.

(±)-4-Amino-5-chloro-2-ethoxy-*N*-[(4-(*p*-fluorobenzyl)-2-morpholinyl)methyl]benzamide citrate dihydrate.

$C_{21}H_{25}ClFN_3O_3,C_6H_8O_7,2H_2O$=650.1

CAS — 112885-41-3 (mosapride); 112885-42-4 (mosapride citrate).

UNII — MF497J489P (mosapride citrate); 73033I28Y6 (mosapride citrate dihydrate).

Profile

Mosapride is a substituted benzamide used for its prokinetic properties. It is reported to be an agonist at 5-HT_4 receptors, increasing acetylcholine release and stimulating gastrointestinal motility (see also Cisapride, p. 1832.1), as well as having 5-HT_3 antagonist properties. It is given orally as the citrate dihydrate, but doses are expressed as the anhydrous citrate, and are 5 mg three times daily before or after meals.

References.

1. Sakashita M, *et al.* Pharmacokinetics of the gastrokinetic agent mosapride citrate after single and multiple oral administrations in healthy subjects. *Arzneimittelforschung* 1993; 43: 867–72.
2. Ruth M, *et al.* The effect of mosapride, a novel prokinetic, on acid reflux variables in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1998; 12: 35–40.
3. Ruth M, *et al.* The effect of mosapride on oesophageal motor function and acid reflux in patients with gastro-oesophageal reflux disease. *Eur J Gastroenterol Hepatol* 2003; 15: 1115–21.
4. Asakawa H, *et al.* Effect of mosapride on glycemic control and gastric emptying in type 2 diabetes mellitus patients with gastropathy. *Diabetes Res Clin Pract* 2003; 61: 175–82.
5. Liu Z, *et al.* Mosapride citrate, a novel 5-HT4 agonist and partial 5-HT3 antagonist, ameliorates constipation in parkinsonian patients. *Mov Disord* 2005; 20: 680–6.
6. He M, *et al.* Mosapride citrate prolongs survival in stroke patients with gastrostomy. *J Am Geriatr Soc* 2007; 55: 142–4.
7. Curran MP, Robinson DM. Mosapride: in gastrointestinal disorders. *Drugs* 2008; 68: 981–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alprida†; Galopran; Gastrokin; Intesul; Levusid; Lostapride; Mosar; Vagantyl; *China*: Bei Luo Na (贝络纳); Gasmotin (加斯清); Kuai Li (快力); Mei Wei Ning (美唯宁); RuiQi (瑞琪); Xinluona (新络纳); *India*: Kinetix; M-Pride; Mic; Mopride; Mosadec; Mosafe; Mosakind; Mosap; Mosapid; Mosart; Mosiba; Mosid-MT; Mosid-OD; Moten Instab; Moza; Mozasef; Mozatone; Mozax; Musapro; Muzic; Normagut; Peripride†; *Jpn*: Gasmotin; *Mex.*: Dosier; *Philipp.*: Gasmotin; *Thai.*: Gasmotin.

Multi-ingredient Preparations. *Arg.*: Mosar Enzimatico; Mosar Plus; *India*: M-Pride-MPS; Mosid-MPS; Moza MPS; Moza Plus; Mozax-MPS; Pantec Plus.

Nabilone *(BAN, USAN, rINN)* ⊗

Compound 109514; Lilly-109514; Nabilon; Nabilona; Nabiloni; Nabilonum; Набилон.

(±)-(6a*R*,10a*R*)-3-(1,1-Dimethylheptyl)-6a,7,8,9,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-6*H*-benzo[c]chromen-9-one.

$C_{24}H_{36}O_3$=372.5

CAS — 51022-71-0.

ATC — A04AD11.

ATC Vet — QA04AD11.

UNII — 2N4O9L084N.

Uses and Administration

Nabilone, a synthetic cannabinoid with antiemetic properties, is used for the control of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetics (p. 1811.3).

The usual initial oral dose is 1 mg twice daily, increased to 2 mg twice daily if necessary. The first dose should be given the evening before starting chemotherapy, and the second dose 1 to 3 hours before the first dose of antineoplastic. Nabilone may be given throughout each cycle of chemotherapy and for 48 hours after the last dose of chemotherapy, if required. The dose of nabilone should not exceed 6 mg daily, given in 3 divided doses.

Reviews.

1. Tramer MR, *et al.* Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ* 2001; 323: 16–21.
2. Davis MP. Oral nabilone capsules in the treatment of chemotherapy-induced nausea and vomiting and pain. *Expert Opin Invest Drugs* 2008; 17: 85–95.

Multiple sclerosis. There is a report of reduction in spasticity and nocturia, and improvement in mood and well-being, in a patient with multiple sclerosis (p. 996.3) who received nabilone 1 mg every second day.[1] A subsequent small crossover study[2] in patients with chronic upper motor neurone syndrome found that oral nabilone 1 mg daily reduced spasticity-related pain in this group. There are also anecdotal reports of improvement in symptoms in patients with multiple sclerosis who took cannabis, however, a review[3] considered evidence of efficacy to be lacking.

1. Martyn CN, *et al.* Nabilone in the treatment of multiple sclerosis. *Lancet* 1995; 345: 579.
2. Wissel J, *et al.* Low dose treatment with the synthetic cannabinoid nabilone significantly reduces spasticity-related pain: a double-blind placebo-controlled cross-over trial. *J Neurol* 2006; 253: 1337–41.
3. Killestein J, *et al.* Cannabinoids in multiple sclerosis: do they have a therapeutic role? *Drugs* 2004; 64: 1–11.

Adverse Effects

Nabilone may produce adverse effects similar to those of cannabis (see p. 2468.2). The most common adverse effects are drowsiness, vertigo, and dry mouth. Neurological effects have included ataxia, confusion, disorientation, dizziness, euphoria, dysphoria, hallucinations, psychosis, depression, headache, decreased coordination, and tremors. Adverse cardiovascular reactions including hypotension, orthostatic hypotension, and tachycardia have occurred. Gastrointestinal disturbances, decreased appetite, and abdominal pain have also been reported.

Precautions

Nabilone is extensively metabolised and largely excreted in bile, and therefore is not recommended in patients with severe hepatic impairment. It should be used with caution in patients with a history of psychiatric disorders or depression, or those with hypertension or heart disease.

Because of the possibility of CNS depression, patients should be warned not to drive or operate machinery.

The possibility of dependence similar to that of cannabis should be borne in mind.

Interactions

Nabilone has been shown to have an additive CNS depressant effect when given with alcohol, codeine, diazepam, or other CNS depressants.

Pharmacokinetics

Nabilone is well absorbed from the gastrointestinal tract and is rapidly and extensively metabolised; one or more of the metabolites may be active. The major excretory pathway is the biliary system; about 65% of a dose is excreted in the faeces and about 20% in the urine. The elimination half-life of nabilone is about 2 hours, but the half-life of its combined metabolites is about 35 hours after an oral dose.

References.

1. Rubin A, *et al.* Physiologic disposition of nabilone, a cannabinol derivative, in man. *Clin Pharmacol Ther* 1977; 22: 85–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cesamet; *Canad.*: Cesamet; *Mex.*: Cesamet; *USA*: Cesamet.

Nizatidine *(BAN, USAN, rINN)*

LY-139037; Nitsatidiini; Nizatidin; Nizatidina; Nizatidinas; Nizatidinum; ZL-101; Низатидин.

4-[2-(1-Methylamino-2-nitrovinylamino)ethylthiomethyl] thiazol-2-ylmethyl(dimethyl)amine; *N*-[2-(2-Dimethylaminomethylthiazol-4-ylmethylthio)ethyl]-*N'*-methyl-2-nitrovinylidenediamine.

$C_{12}H_{21}N_5O_2S_2$=331.5

CAS — 76963-41-2.

ATC — A02BA04.

ATC Vet — QA02BA04.

UNII — P41PML4GHR.

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

Ph. Eur. 8: (Nizatidine). An almost white or slightly brownish, crystalline powder. Sparingly soluble in water; soluble in methyl alcohol. A 1% solution in water has a pH of 8.5 to 10.0.

USP 36: (Nizatidine). An off-white to buff crystalline solid. Sparingly soluble in water; freely soluble in chloroform; soluble in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Nizatidine is a histamine H_2-antagonist with actions and uses similar to those of cimetidine (see p. 1827.2).

In the management of benign **gastric and duodenal ulceration** (p. 1813.2), and NSAID-associated ulceration, a daily oral dose of nizatidine 300 mg is given either as a single dose at bedtime or in 2 divided doses, for 4 to 8 weeks. Where appropriate a maintenance dose of 150 mg daily may be given at night.

In **gastro-oesophageal reflux disease** (p. 1807.2) an oral dose of 150 to 300 mg twice daily is recommended for up to 12 weeks.

For the short-term symptomatic relief of **dyspepsia** an oral dose of 75 mg, repeated if necessary, up to a maximum of 150 mg daily may be taken for up to 14 days.

Nizatidine has also been given intravenously by continuous or intermittent infusion.

Doses of nizatidine should be reduced in patients with renal impairment (see below). For doses in children, see below.

Administration in children. Nizatidine is given to children for oesophagitis and gastro-oesophageal reflux disease in the USA; an oral dose of 150 mg twice daily for up to 8 weeks is licensed in those 12 years of age or over.

Administration in renal impairment. The dosage of nizatidine should be reduced in patients with renal impairment according to creatinine clearance (CC). Licensed product information recommends the following oral doses in renal impairment:

- CC 20 to 50 mL/minute: doses should be reduced by 50%, *or* where the standard dose would be 150 mg daily, 150 mg may be given on alternate days
- CC less than 20 mL/minute: doses should be reduced by 75%, *or* where the standard dose would be 300 mg daily, 150 mg may be given on alternate days, and where the standard dose would be 150 mg daily, 150 mg may be given every third day

Adverse Effects

As for Cimetidine, p. 1828.3. Some patients taking nizatidine may experience excessive sweating and urticaria; anaemia may also occur.

Nizatidine is considered to have no anti-androgenic activity although there are isolated reports of gynaecomastia and impotence.

Precautions

As for Cimetidine, p. 1830.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nizatidine 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 07/10/11)

Interactions

Unlike cimetidine (p. 1830.3) nizatidine does not inhibit cytochrome P450 isoenzymes, and therefore is considered to have little effect on drugs metabolised by this route. However, like other H_2-antagonists its effects on gastric pH may affect the absorption of drugs whose absorption is dependent on an acid gastric pH.

Alcohol. Any interaction between H_2-antagonists and alcohol is generally thought unlikely to be clinically significant (see p. 1735.2).

Antacids. For discussion of the effect of antacids on the bioavailability of H_2-antagonists, see Cimetidine, p. 1831.1.

Sucralfate. For information on the effect of sucralfate on the bioavailability of H_2-antagonists, see Cimetidine, p. 1831.1.

Pharmacokinetics

Nizatidine is readily absorbed from the gastrointestinal tract with peak plasma concentrations about 0.5 to 3 hours after an oral dose. The bioavailability of nizatidine exceeds 70% and may be slightly increased by the presence of food. It is widely distributed and is about 35% bound to plasma proteins.

The elimination half-life of nizatidine is 1 to 2 hours and is prolonged in renal impairment. A small amount is metabolised in the liver: nizatidine *N*-2-oxide, nizatidine *S*-oxide, and *N*-2-monodesmethylnizatidine have been identified, the latter having about 60% of the activity of nizatidine.

More than 90% of a dose of nizatidine is excreted in the urine, in part by active tubular secretion, within 12 hours, about 60% as unchanged drug. Less than 6% is excreted in the faeces. Nizatidine is distributed into breast milk.

References.
1. Callaghan JT, *et al.* A pharmacokinetic profile of nizatidine in man. *Scand J Gastroenterol* 1987; **22** (suppl 136): 9–17.
2. Abdel-Rahman SM, *et al.* Single-dose pharmacokinetics of nizatidine (Axid) in children. *J Clin Pharmacol* 2002; **42**: 1089–96.
3. Blum RA, *et al.* Pharmacokinetics and pharmacodynamics of a novel nizatidine controlled-release formulation in healthy subjects. *J Clin Pharmacol* 2003; **43**: 74–83.
4. Abdel-Rahman SM, *et al.* Developmental pharmacokinetics and pharmacodynamics of nizatidine. *J Pediatr Gastroenterol Nutr* 2004; **38**: 442–51.

Bioavailability. The bioequivalence of 3 oral liquid formulations of nizatidine was investigated relative to a commercially available nizatidine capsule. Of the 3 liquid formulations, one was a commercially available oral syrup (15 mg/mL), and 2 others were extemporaneously prepared, one as a solution in apple juice (1.2 mg/mL) and another as a suspension in an infant formula (*Enfamil; Ross, USA*; 15 mg/mL). Nizatidine in apple juice showed markedly less bioavailability, whereas the other 2 formulations were considered to be bioequivalent to the reference capsule.[1]

1. Abdel-Rahman SM, *et al.* The bioequivalence of nizatidine (Axid) in two extemporaneously and one commercially prepared oral liquid formulations compared with capsule. *J Clin Pharmacol* 2003; **43**: 148–53.

Distribution into breast milk. About 0.1% of an oral dose of nizatidine was secreted in breast milk in a study in lactating women.[1] The milk to serum ratio varied (from 1:1 to 4.9:1) with the time of samples.

1. Obermeyer BD, *et al.* Secretion of nizatidine into human breast milk after single and multiple doses. *Clin Pharmacol Ther* 1990; **47**: 724–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Nizac; Tacidine; Tazac; *Braz.*: Axid; *Canad.*: Axid; *Chile*: Nizaxid; *China*: Axid (爱希); Ni Ting (妮停); Sai Fa Lei (赛法雷); *Fr.*: Nizaxid; *Gr.*: Axid; Elkofen; Flectar; Flexidon; Pterosan; Ozeltan; Peptodin; Ulcogastrin; *Hung.*: Naxidin; *Indon.*: Axid†; *Irl.*: Axid; *Ital.*: Cronizat; Nizax; *Mex.*: Axid†; *Neth.*: Axid; *Philipp.*: Axid†; Nolcer; *Port.*: Nizaxid†; Prospaxid; *S.Afr.*: Antizid†; *Spain*: Distaxid†; *Thai.*: Axid; *Turk.*: Axid; *UK*: Axid†; *USA*: Axid†; Axid; Axid.

Pharmacopoeial Preparations
BP 2014: Nizatidine Infusion;
USP 36: Nizatidine Capsules.

Octatropine Methylbromide *(BAN, rINN)*

Anisotropine Methobromide; Anisotropine Methylbromide (USAN); Metilbromuro de octatropina; Octatropina, metilbromuro de; Octatropine, Méthylbromure d'; Octatropini Methylbromidum; Октатропина Метилбромид.

(1*R*,3*r*,5*S*)-8-Methyl-3-(2-propylvaleryloxy)tropanium bromide.

$C_{17}H_{32}BrNO_2$=362.4

CAS — 80-50-2.

UNII — 62M960DHIL.

Pharmacopoeias. In *It.*

Profile

Octatropine methylbromide is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p. 1312.1). It has been used as an adjunct in the treatment of peptic ulcer disease and to relieve visceral spasms.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Espasmo Dioxadol; *Chile*: Bufacyl; Valpin; *Ital.*: Valpinax.

Olsalazine Sodium *(BANM, USAN, rINNM)*

Azodisal Sodium; CI Mordant Yellow 5; CI-91B; Colour Index No. 14130; Natrii Olsalazinum; Olsalatsiininatrium; Olsalazin disodná sůl; Olsalazin-Natrium; Olsalazin Sodyum; Olsalazina sódica; Olsalazine Sodique; Olsalazinnatrium; Olsalazino natrio druska; Olsalazinum Dinatricum; Olsalazinum natricum; Olszalazin-nátrium; Sodium Azodisalicylate; Натрий Ольсалазин.

Disodium 5,5'-azodisalicylate.

$C_{14}H_8N_2Na_2O_6$=346.2

CAS — 6054-98-4.

ATC — A07EC03.

ATC Vet — QA07EC03.

UNII — Y7JEW0XG7L.

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

Ph. Eur. 8: (Olsalazine Sodium). A yellow, fine, crystalline powder; it exhibits polymorphism. Sparingly soluble in water; soluble in dimethyl sulfoxide; very slightly soluble in methyl alcohol.

Uses and Administration

Olsalazine consists of two molecules of mesalazine (p. 1859.2) linked with an azo bond. It is activated in the colon where the active mesalazine is released. It is given orally as the sodium salt in the management of acute mild ulcerative colitis and for the maintenance of remission (see Inflammatory Bowel Disease, p. 1808.3). The usual initial dose of olsalazine sodium is 1 g daily in divided doses and this is gradually increased, if necessary, over one week, to a maximum dose of 3 g daily. The usual dose for the maintenance of remission is 500 mg twice daily. Doses should be taken after meals and a single dose should not exceed 1 g. For doses in children, see below.

Administration in children. Although not licensed in the UK for use in children under 12 years, the *BNFC* suggests an oral dose of olsalazine for children aged 2 years and over; the adult dose may be given for an acute attack of mild ulcerative colitis (see Uses and Administration, above), and for maintenance of remission, a dose of 250 to 500 mg may be given twice daily, after food.

Adverse Effects and Precautions

As for Mesalazine, p. 1860.1. The most common adverse effects associated with olsalazine sodium are diarrhoea, arthralgia, and skin rashes. Diarrhoea may be watery in some patients; it may resolve with dosage reduction but can be severe enough to require withdrawal of treatment. Diarrhoea is less likely if the drug is taken after meals. There have been a few reports of blood dyscrasias. If a blood dyscrasia is suspected treatment should be stopped immediately and a blood count performed. Patients or their carers should be told how to recognise signs of haematotoxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop.

Incidence of adverse effects. In an open study[1] of oral olsalazine 1 g daily involving 160 patients with active ulcerative colitis and a history of sulfasalazine intolerance, 103 (64.4%) patients had no adverse effects; 29 patients reported only minor adverse effects: gastrointestinal disturbances in 22 patients, transient skin rash in 3, and headache, increased salivation, cough, and irritability each in one patient. The most common adverse effect was frequent loose stools which affected 25 patients, 20 of whom had to stop treatment. This adverse effect occurred early in treatment, within 10 hours of the first dose in 13 patients. Severe diarrhoea was more frequent in patients with widespread disease, but the incidence of diarrhoea did not correlate with disease severity.

A subsequent study[2] in healthy subjects has shown that olsalazine has a significant inhibitory effect on water and electrolyte absorption in the small intestine, which may account, at least in part, for the induction of diarrhoea. Patients with extensive colitis have reduced colonic absorptive function and may be less able to assimilate the increased colonic inflow volumes.

1. Sandberg-Gertzén H, *et al.* Azodisal sodium in the treatment of ulcerative colitis: a study of tolerance and relapse-prevention properties. *Gastroenterology* 1986; 90: 1024–30.
2. Raimundo AH, *et al.* Effects of olsalazine and sulphasalazine on jejunal and ileal water and electrolyte absorption in normal human subjects. *Gut* 1991; 32: 270–4.

Breast feeding. A study[1] involving a 39-year-old woman with Crohn's disease found that olsalazine did not appear to present a clinically significant risk to the breast-fed infant. Olsalazine was undetectable in the breast milk for 48 hours after a single oral 500-mg dose, and although small amounts of the metabolite acetylated 5-aminosalicylic acid were detected in breast milk the infant showed no adverse effects during the 3 weeks afterwards in which the mother continued taking olsalazine.

1. Miller LG, *et al.* Disposition of olsalazine and metabolites in breast milk. *J Clin Pharmacol* 1993; 33: 703–6.

Effects on the blood. As of July 1995, the UK CSM had received 4 reports of blood dyscrasias associated with olsalazine, none of them fatal.[1] It was recommended that a blood count be performed and the drug stopped immediately if there was suspicion of a dyscrasia. See also under Mesalazine, p. 1860.2.

1. CSM/MCA. Blood dyscrasias and mesalazine. *Current Problems* 1995; 21: 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 15/06/06)

Effects on the kidneys. A report of nephrotoxicity, characterised by interstitial nephritis, was associated with the use of olsalazine.[1] Symptoms resolved on stopping of the drug. See also under Mesalazine, p. 1860.3.

1. Wilcox GM, *et al.* Nephrotoxicity associated with olsalazine. *Am J Med* 1996; 100: 238–40.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies olsalazine 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 03/10/11)

Interactions

Antineoplastics. For mention of 5-aminosalicylates such as olsalazine inhibiting the metabolism of thiopurine antineoplastics, and increasing their toxicity, see Gastrointestinal Drugs, p. 822.1.

Pharmacokinetics

Very little of an oral dose of olsalazine is absorbed via the upper gastrointestinal tract, and almost the entire dose reaches its site of action in the colon intact. It is broken down by the colonic bacterial flora into 2 molecules of 5-aminosalicylic acid (mesalazine). Some mesalazine is absorbed and acetylated (see p. 1861.2) but systemic concentrations of mesalazine and its metabolite are lower than after comparable oral doses of mesalazine, perhaps because there is less release of mesalazine in the small intestine, where absorption is better. Mesalazine concentrations in the colon after a dose of olsalazine are stated to be about 1000 times greater than systemic concentrations.

The small amounts (1 to 2% of the dose or less) of intact olsalazine that are absorbed are excreted mainly in urine; the elimination half-life after an intravenous dose has been calculated at about 1 hour. Some olsalazine is metabolised by sulfate conjugation in the liver: the elimination half-life of the metabolite is reported to be about 7 days.

References.

1. Ryde EM. Pharmacokinetic aspects of drugs targeted for the colon, with special reference to olsalazine. *Acta Pharm Suec* 1988; 25: 327–8.
2. Laursen LS, *et al.* Disposition of 5-aminosalicylic acid by olsalazine and three mesalazine preparations in patients with ulcerative colitis: comparison of intraluminal colonic concentrations, serum values, and urinary excretion. *Gut* 1990; 31: 1271–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Dipentum; *Austria*: Dipentum; *Canad.*: Dipentum; *Chile*: Dipentum†; *China*: Chang Mei (畅美); *Denm.*: Dipentum; *Fin.*: Dipentum; *Fr.*: Dipentum; *Ger.*: Dipentum; *Gr.*: Dipentum; *Hong Kong*: Dipentum; *Irl.*: Dipentum; *Neth.*: Dipentum; *Norw.*: Dipentum; *NZ*: Dipentum; *Port.*: Dipentum†; *S.Afr.*: Dipentum; *Swed.*: Dipentum; *Switz.*: Dipentum†; *Turk.*: Dipentum†; *UK*: Dipentum; *USA*: Dipentum.

Omeprazole *(BAN, USAN, rINN)*

H-168/68; Omepratsoli; Omeprazol; Omeprazolas; Oméprazole; Omeprazolo; Omeprazolum; Omenpasoн.

(*RS*)-5-Methoxy-2-(4-methoxy-3,5-dimethyl-2-pyridylmethylsulphinyl)benzimidazole.

$C_{17}H_{19}N_3O_3S$=345.4

CAS — 73590-58-6.

ATC — *A02BC01.*

ATC Vet — *QA02BC01.*

UNII — *KG60484QX9.*

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

Ph. Eur. 8: (Omeprazole). A white or almost white powder. It exhibits polymorphism. Very slightly soluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers at a temperature between 2 degrees and 8 degrees. Protect from light.

USP 36: (Omeprazole). A white to off-white powder. Very slightly soluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in dichloromethane. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from moisture.

Omeprazole Magnesium *(BANM, USAN, rINNM)*

Magnesii Omeprazolum; Omeprazol magnésico; Omeprazol-Magnesium; Oméprazole Magnesique; Oméprazole magnésique; Omeprazolum magnesicum; Магния Омепразол.

$C_{34}H_{36}MgN_6O_6S_2$=713.1.

CAS — 95382-33-5.

ATC — *A02BC01.*

ATC Vet — *QA02BC01.*

UNII — *426QFE7XLK.*

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

Ph. Eur. 8: (Omeprazole Magnesium). A white or almost white, hygroscopic powder. Very slightly soluble in water; sparingly soluble in methyl alcohol; practically insoluble in heptane. Store in airtight containers. Protect from light.

USP 36: (Omeprazole Magnesium). A white to off-white powder. Very soluble in water and in dichloromethane; slightly soluble in alcohol; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Omeprazole Sodium *(BANM, USAN, rINNM)*

Natrii Omeprazolum; Omepratsolinatrium; Omeprazol-Natrium; Omeprazol sódico; Omeprazol sódná sůl monohydrát; Oméprazole sodique; Omeprazolnatrium; Omeprazol-nátrium; Omeprazolo natrio druska; Omeprazolum natricum; Omeprazolum Natricum Monohydricum; Натрий Омепразол.

$C_{17}H_{18}N_3NaO_3S$=367.4

CAS — 95510-70-6.

ATC — *A02BC01.*

ATC Vet — *QA02BC01.*

UNII — *KV03YZ6QLW.*

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

Ph. Eur. 8: (Omeprazole Sodium). A white or almost white, hygroscopic powder. Freely soluble in water and in alcohol; very slightly soluble in dichloromethane; soluble in propylene glycol. The pH of a 2% solution in water is 10.3 to 11.3. Store in airtight containers. Protect from light.

Uses and Administration

Omeprazole is a proton pump inhibitor. It suppresses secretion of gastric acid by inhibiting the enzyme system of hydrogen/potassium adenosine triphosphatase (H^+/K^+ ATPase), the 'proton pump' of the gastric parietal cell. It is used in conditions where inhibition of gastric acid secretion may be beneficial, including aspiration syndromes (p. 1804.2), dyspepsia (p. 1868.1), gastro-oesophageal reflux disease (p. 1807.2), peptic ulcer disease (p. 1813.2), and the Zollinger-Ellison syndrome (p. 1814.3).

Esomeprazole (p. 1841.1), an isomer of omeprazole, is also used.

Omeprazole may be given orally as the base or magnesium salt, or intravenously as the sodium salt. Doses are expressed in terms of the base. Omeprazole magnesium 10.32 mg and omeprazole sodium 10.64 mg are each equivalent to about 10 mg of omeprazole.

For the relief of acid-related **dyspepsia** omeprazole is given in usual doses of 10 or 20 mg daily orally for 2 to 4 weeks.

The usual dose for the treatment of **gastro-oesophageal reflux disease** is 20 mg orally once daily for 4 weeks, followed by a further 4 to 8 weeks if not fully healed. In refractory oesophagitis, a dose of 40 mg daily may be used. Maintenance therapy after healing of oesophagitis is 20 mg once daily, and for acid reflux is 10 mg daily. For dosage in children see below.

In the management of **peptic ulcer disease** a single daily dose of 20 mg orally, or 40 mg in severe cases, is given. Treatment is usually continued for 4 weeks for duodenal ulcer and 8 weeks for gastric ulcer. Where appropriate, a dose of 10 to 20 mg once daily may be given for maintenance.

For the eradication of *Helicobacter pylori* in peptic ulceration omeprazole may be combined with antibacterials in dual or triple therapy. Effective **triple therapy** regimens include omeprazole 20 mg twice daily or 40 mg once daily combined with: amoxicillin 500 mg and metronidazole 400 mg, both three times daily; clarithromycin 250 mg and metronidazole 400 mg (or tinidazole 500 mg) both twice daily; or with amoxicillin 1 g and clarithromycin 500 mg, both twice daily. These regimens are given for 7 or 10 days. **Dual therapy** regimens such as omeprazole 40 mg daily with clarithromycin 500 mg three times daily are licensed but are much less effective and must be given for 2 weeks. Omeprazole monotherapy may be continued after dual or triple therapy in patients with ulceration at the start of therapy; antisecretory therapy can be continued after triple therapy in those with large ulcers or complications.

Doses of 20 mg daily orally are used in the treatment of **NSAID-associated ulceration**; a dose of 20 mg daily may also be used for prophylaxis in patients with a history of gastroduodenal lesions who require continued NSAID treatment.

The initial recommended dosage for patients with the **Zollinger-Ellison syndrome** is 60 mg orally once daily, adjusted as required. The majority of patients are effectively controlled by doses in the range 20 to 120 mg daily, but doses up to 120 mg three times daily have been used. Daily doses above 80 mg should be given as divided doses (usually 2).

Omeprazole is also used for the prophylaxis of **acid aspiration** during general anaesthesia, in a dose of 40 mg the evening before surgery and a further 40 mg two to six hours before the procedure.

The dose of omeprazole may need to be reduced in patients with hepatic impairment (see p. 1868.1).

PARENTERAL DOSAGE.

In patients who are unsuited to receive oral therapy omeprazole sodium may be given on a short-term basis by intravenous infusion, in a usual dose equivalent to 40 mg of the base over a period of 20 to 30 minutes in 100 mL of sodium chloride 0.9% or glucose 5%. It may also be given by slow intravenous injection. Higher intravenous doses have been given to patients with Zollinger-Ellison syndrome, with a usual initial dose of 60 mg daily.

Although unlicensed in the UK for major peptic bleeding after endoscopy, the *BNF* suggests that omeprazole 80 mg can be infused intravenously over 40 to 60 minutes, followed by a continuous infusion of 8 mg/hour for 72 hours; treatment can then be continued orally.

General reviews.

1. Langtry HD, Wilde MI. Omeprazole: a review of its use in Helicobacter pylori infection, gastro-oesophageal reflux disease and peptic ulcers induced by nonsteroidal anti-inflammatory drugs. *Drugs* 1998; 56: 447–86.
2. Berardi RR, Welage LS. Proton-pump inhibitors in acid-related diseases. *Am J Health-Syst Pharm* 1998; 55: 2289–98.
3. Erstad BL. Proton-pump inhibitors for acute peptic ulcer bleeding. *Ann Pharmacother* 2001; 35: 730–40.
4. Robinson M, Horn J. Clinical pharmacology of proton pump inhibitors: what the practising physician needs to know. *Drugs* 2003; 63: 2739–54.
5. Dekel R, *et al.* The role of proton pump inhibitors in gastro-oesophageal reflux disease. *Drugs* 2004; 64: 277–95.
6. Anonymous. Proton pump inhibitors for GERD in children. *Med Lett Drugs Ther* 2007; 49: 17–18.
7. Boparai V, *et al.* Guide to the use of proton pump inhibitors in adult patients. *Drugs* 2008; 68: 925–47.
8. Lazzaroni M, Porro GB. Management of NSAID-induced gastrointestinal toxicity: focus on proton pump inhibitors. *Drugs* 2009; 69: 51–69.
9. Bardou M, *et al.* Intravenous proton pump inhibitors: an evidence-based review of their use in gastrointestinal disorders. *Drugs* 2009; 69: 435–48.

Administration. Omeprazole is given orally as tablets or capsules containing enteric-coated pellets or granules, which should be swallowed whole and not crushed or chewed. In children or patients with swallowing difficulties, UK licensed product information (*Losec; AstraZeneca*) states that the tablet be dispersed in water and then mixed with fruit juice (with a pH less than 5) or yogurt before swallowing without chewing. Similarly the contents of the capsules can be mixed with water, fruit juice (with a pH less than 5) or yogurt and swallowed without chewing. An oral suspension is available in some countries.

Administration in children. Licensed UK *oral* doses of omeprazole for the treatment of gastro-oesophageal reflux disease or reflux oesophagitis in children 1 year of age and over are determined by body-weight as follows:

- 10 to 20 kg: 10 mg once daily
- over 20 kg: 20 mg once daily

These doses may be doubled if necessary. Treatment may be given for 2 to 4 weeks for gastro-oesophageal reflux disease and for 4 to 8 weeks for reflux oesophagitis. Similar doses

are licensed in the USA, where an oral dose of 5 mg daily is included for children weighing from 5 kg up to 10 kg.

For gastro-oesophageal reflux disease, acid-related dyspepsia, treatment of duodenal and benign gastric ulcers including NSAID-associated ulceration, prophylaxis of acid aspiration, Zollinger-Ellison syndrome, and to reduce the degradation of pancreatic enzyme supplements in children with cystic fibrosis, the *BNFC* recommends an oral dose of 700 micrograms/kg once daily in neonates and children 1 month to 2 years of age. If needed, doses may be increased in neonates after 7 to 14 days, to 1.4 mg/kg once daily; some neonates may require up to 2.8 mg/kg once daily. In children up to 2 years of age, doses may be increased up to 3 mg/kg (to a maximum of 20 mg) once daily.

For *parenteral* dosage in children the *BNFC* recommends an intravenous dose of 500 micrograms/kg (to a maximum of 20 mg) once daily in children aged 1 month to 12 years; this may be increased to 2 mg/kg (to a maximum of 40 mg) once daily if needed.

For the eradication of *Helicobacter pylori* licensed oral doses in the UK for children from 4 years of age are omeprazole 10 mg in those weighing 15 to 30 kg or omeprazole 20 mg in those weighing over 30 kg, given twice daily with amoxicillin and clarithromycin for 1 week. In children from 1 to 12 years of age, the *BNFC* recommends an oral dose of omeprazole 1 to 2 mg/kg (to a maximum dose of 40 mg) once daily. This is given with antibacterial therapy under specialist supervision.

For administration of the tablets or capsules to children, see Administration, p. 1867.3.

A systematic review found that evidence was insufficient to support the efficacy and safety of proton pump inhibitors for the treatment of gastro-oesophageal disease in children and adolescents, although short-term use was well tolerated; proton pump inhibitors were found to be ineffective for infants.[1]

1. van der Pol RJ, *et al.* Efficacy of proton-pump inhibitors in children with gastroesophageal reflux disease: a systematic review. *Pediatrics* 2011; 127: 925–35.

Administration in hepatic impairment. Bioavailability and half-life of omeprazole can increase in patients with hepatic impairment. UK licensed product information suggests that a daily oral or intravenous dose of 10 to 20 mg may be sufficient for these patients.

Dyspepsia. Although earlier UK guidelines on the use of proton pump inhibitors in dyspepsia (p. 1806.3) suggested that they should not be used routinely in non-ulcer dyspepsia,[1] subsequent guidelines on its general management in both the UK[2] and the USA[3] consider that a 1-month empirical course in patients aged under 55 without symptoms suggestive of more serious disease is a valid first-line treatment.

1. NICE. Guidance on the use of proton pump inhibitors in the treatment of dyspepsia (issued July 2000). Available at: http://www.nice.org.uk/nicemedia/pdf/proton.pdf (accessed 11/02/08)
2. NICE. Dyspepsia: management of dyspepsia in adults in primary care (Clinical Guideline 17: issued August 2004, updated June 2005). Available at: http://www.nice.org.uk/nicemedia/pdf/CG017NICEguideline.pdf (accessed 11/02/08)
3. American Gastroenterological Association. American Gastroenterological Association medical position statement: evaluation of dyspepsia. *Gastroenterology* 2005; 129: 1753–5. Also available at: http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508505018172.pdf (accessed 11/02/08)

Inflammatory bowel disease. There are a few reports[1-3] of responses to omeprazole in patients with inflammatory bowel disease (p. 1808.3). Combination of omeprazole with mesalazine has also been tried.[2]

1. Reinstow U, Schlegelberger T. Omeprazole in ulcerative colitis. *Lancet* 1994; 343: 477.
2. Dickinson JB. Is omeprazole helpful in inflammatory bowel disease? *J Clin Gastroenterol* 1994; 18: 317–19.
3. Guslandi M, Tittobello A. Symptomatic response to omeprazole in inflammatory bowel disease. *J Clin Gastroenterol* 1996; 22: 159–60.

Scleroderma. Gastro-oesophageal reflux is one of the gastrointestinal manifestations of systemic sclerosis, and proton pump inhibitors such as omeprazole play a major role in the management of such gastrointestinal disease.[1] For a discussion of the broader management of the condition see p. 1938.3.

1. Williamson DJ. Update on scleroderma. *Med J Aust* 1995; 162: 599–601.

Adverse Effects

Proton pump inhibitors are generally well tolerated, and adverse effects are relatively infrequent. The adverse effects reported most often with omeprazole and other proton pump inhibitors have been headache, gastrointestinal disturbances, and rash; they have sometimes been severe enough to require stopping treatment.

Other effects include pruritus, dizziness, fatigue, cough, back or abdominal pain, arthralgia and myalgia, urticaria, and dry mouth. Isolated cases of photosensitivity, bullous eruption, erythema multiforme, and Stevens-Johnson syndrome have occurred; toxic epidermal necrolysis has sometimes been fatal. Systemic hypersensitivity reactions, including fever, bronchospasm, angioedema, and anaphylaxis have been reported. Effects on the CNS include occasional insomnia, somnolence, aggression, and vertigo; reversible confusional states, agitation, depression, and hallucinations have occurred in severely ill patients. Raised liver enzymes, and isolated cases of hepatitis, jaundice, and hepatic encephalopathy have been reported; fatalities have occurred from hepatic failure or necrosis.

Other adverse effects reported rarely include gastrointestinal (including oesophageal) candidiasis, muscular weakness, paraesthesia, blurred vision, alopecia, stomatitis, increased sweating, taste disturbances, peripheral oedema, malaise, hyponatraemia, hypomagnesaemia, blood disorders (including agranulocytosis, leucopenia, and thrombocytopenia), gynaecomastia, impotence, and interstitial nephritis. Cardiovascular effects may occur, including angina, tachycardia or bradycardia. Pancreatitis (sometimes fatal) has been reported, as have tinnitus, urinary disorders, and eye disorders.

Proton pump inhibitors may increase the risk of gastrointestinal infections because of their acid suppressive effects. The absorption of some vitamins and minerals may be reduced.

Early toxicological studies identified carcinoid-like tumours of the gastric mucosa in *rats* given very high doses of omeprazole over long periods (see under Gastrointestinal Tumours, p. 1869.3).

References.

1. Yang Y-X, Metz DC. Safety of proton pump inhibitor exposure. *Gastroenterology* 2010; 139: 1115–27.
2. Sheen E, Triadafilopoulos G. Adverse effects of long-term proton pump inhibitor therapy. *Dig Dis Sci* 2011; 56: 931–50.
3. Abraham NS. Proton pump inhibitors: potential adverse effects. *Curr Opin Gastroenterol* 2012; 28: 615–20.

Incidence of adverse effects. Prescription-event monitoring for 16 205 patients prescribed omeprazole, 17 329 prescribed lansoprazole, and 11 541 prescribed pantoprazole indicated that adverse events were reported infrequently, with the most common being gastrointestinal disturbances and headache. The incidences of diarrhoea, the most commonly reported event, per 1000 days of exposure, were 0.18 for omeprazole, 0.39 for lansoprazole, and 0.23 for pantoprazole. Despite the inherent biases of such a cohort study, there did seem to be some evidence that lansoprazole might be associated with a somewhat greater risk of diarrhoea, particularly in the elderly.[1]

1. Martin RM, *et al.* The rates of common adverse events reported during treatment with proton pump inhibitors used in general practice in England: cohort studies. *Br J Clin Pharmacol* 2000; 50: 366–72.

Effects on the blood. There have been rare cases of leucopenia, agranulocytosis, thrombocytopenia, and pancytopenia, with omeprazole and other proton pump inhibitors such as lansoprazole and pantoprazole.[1-4] Auto-immune haemolytic anaemia has also been reported with omeprazole.[5]

1. Holt TL, *et al.* Neutropenia associated with omeprazole. *Med J Aust* 1999; 170: 141–2.
2. Zlabek JA, Anderson CG. Lansoprazole-induced thrombocytopenia. *Ann Pharmacother* 2002; 36: 809–11.
3. Watson TD, *et al.* Pantoprazole-induced thrombocytopenia. *Ann Pharmacother* 2006; 40: 758–61.
4. Thakor AS, *et al.* Toxic epidermal necrolysis and neutropaenia: complications of omeprazole. *Australas J Dermatol* 2009; 50: 207–10.
5. Burt ML *et al.* Autoimmune haemolytic anaemia associated with use of omeprazole. *Br J Hosp Med* 2007; 68: 108.

Effects on the cardiovascular system. Results and preliminary analyses from 2 studies raised concerns about a possible increased risk of myocardial infarction, cardiac failure, and cardiac-related sudden death in patients taking *omeprazole* or *esomeprazole* compared with patients who had surgery for gastro-oesophageal reflux disease.[1,2] However, an FDA safety review found that patients who had surgery tended to be younger and less likely to have a history of cardiac problems or cardiac risk factors than those given such drugs.[2] The FDA concluded that long-term use of these drugs is not likely to be associated with an increased risk of cardiac problems.[3] However, while Health Canada[4] considered that there was no evidence to support such an increased risk with long-term use of esomeprazole they were unable to make such a definitive conclusion for omeprazole.

There is a possible increased risk of cardiovascular events when proton pump inhibitors are used with clopidogrel, see Proton Pump Inhibitors, under Interactions of Clopidogrel, p. 1344.2. However, patients given proton pump inhibitors after myocardial infarction were found to have an increased risk for adverse cardiovascular outcomes in a retrospective cohort study,[5] an effect which was independent of clopidogrel use.

1. FDA. Early communication about an ongoing safety review: omeprazole (Prilosec) esomeprazole (Nexium) (issued 9th August 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm072497.htm (accessed 15/07/10)
2. FDA. Follow-up to the August 9, 2007, communication about the ongoing safety review of omeprazole and esomeprazole (issued 10th December 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm143258.htm (accessed 15/07/10)
3. FDA. FDA's safety reviews of Prilosec and Nexium find no evidence of increased rates of cardiac events (issued 10th December 2007). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm109037.htm (accessed 15/07/10)
4. Health Canada. Health Canada completes safety review of Losec (omeprazole) and Nexium (esomeprazole) (issued 27 February 2008). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_34-eng.php (accessed 09/07/08)
5. Charlot M, *et al.* Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study. *Ann Intern Med* 2010; 153: 378–86.

Effects on electrolytes. Electrolyte disturbances have been reported with proton pump inhibitors, including hyponatraemia, with *omeprazole*,[1] *esomeprazole*,[2] *lansoprazole*,[3] and *pantoprazole*.[4] Refractory hypomagnesaemia with hypocalcaemia and hypokalaemia has been reported in 2 patients given omeprazole. Both patients were also taking other medicines that can affect electrolyte balance; however all abnormalities resolved when omeprazole was stopped.[5] In another case, severe hypomagnesaemia with hypocalcaemia and hypokalaemia occurred after prolonged treatment with omeprazole; electrolytes recovered when treatment with ranitidine was substituted, but fell again when pantoprazole and then lansoprazole therapy were tried.[6] The FDA reviewed 61 reports of hypomagnesaemia associated with proton pump inhibitors when used for at least 3 months and generally for more than 1 year. Serious adverse events included tetany, arrhythmias, and seizures. In about a quarter of cases, magnesium supplementation did not improve concentrations and the proton pump inhibitor had to be stopped. The mechanism responsible for proton pump inhibitors causing hypomagnesaemia is unknown; however, long-term use of proton pump inhibitors may cause changes in intestinal absorption of magnesium. Measurement of magnesium concentrations should be considered in patients starting long-term proton pump inhibitor treatment, those taking digoxin, or those taking other medicines which may cause hypomagnesaemia.[7]

1. Colli BM, Menzies OH. Hyponatraemia, fever, vomiting, severe abdominal pain, and weight loss associated with omeprazole. *N Z Med J* 2005; 118: U1263.
2. Mennecier D, *et al.* Hyponatremia with consciousness disturbance associated with esomeprazole. *Ann Pharmacother* 2005; 39: 774–5.
3. Fort E, *et al.* Hyponatrémie sous lansoprazole. *Gastroenterol Clin Biol* 2000; 24: 686.
4. Hamilton DV, Lewis HRA. A rare cause of hyponatraemia? *Br J Hosp Med* 2009; 70: 663.
5. Shabajee N, *et al.* Omeprazole and refractory hypomagnesaemia. Abridged version: *BMJ* 2008; 337: 173–5. Full version: http://www.bmj.com/cgi/content/full/337/jul10_3/a425 (accessed 17/06/09)
6. Broeren MAC, *et al.* Hypomagnesemia induced by several proton-pump inhibitors. *Ann Intern Med* 2009; 151: 755–6. Correction. *ibid.* 2010; 152: 268.
7. FDA. Low magnesium levels can be associated with long-term use of proton pump inhibitor drugs (PPIs) (issued 2nd March 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm (accessed 26/09/11)

Effects on the endocrine system. Up to December 1991, WHO had received 30 reports of impotence or gynaecomastia which might have been due to omeprazole;[1] of these reports 15 were of impotence, 13 of gynaecomastia in men, and 2 of breast enlargement in women. The Spanish Pharmacovigilance System reported 24 cases of gynaecomastia associated with the use of proton pump inhibitors, including lansoprazole and rabeprazole, between January 1982 and July 2006. In most of the cases, gynaecomastia improved after stopping the drug.[2] For reference to a case-control study showing no statistical link between gynaecomastia and omeprazole, see under Cimetidine, p. 1829.2.

1. Lindquist M, Edwards IR. Endocrine adverse effects of omeprazole. *BMJ* 1992; 305: 451–2.
2. Carvajal A, *et al.* Gynaecomastia associated with proton pump inhibitors: a case series from the Spanish Pharmacovigilance System. *Drug Safety* 2007; 30: 527–31.

Effects on the eyes. Visual disturbances associated with the use of omeprazole have included 6 cases of irreversible blindness or visual impairment in severely ill patients given the drug intravenously, and 13 cases of visual disturbances associated with oral use.[1] As a result of concern about these effects the availability of intravenous omeprazole was restricted in Germany; however, the consensus appears to be that a causal link has not been established. Suggestions that visual (and also auditory[2]) impairment could follow drug-induced vasculitis[2-4] appear to be contentious.[1,5-7] A cohort study involving 140 128 patients given antisecretory therapy, 33 988 of whom received omeprazole, found no evidence that any of the drugs used was associated with a major increase in risk of vascular or inflammatory disorders of the eye;[8] however, the statistical power of this study was not high.[9]

1. Creutzfeldt WC, Blum AL. Safety of omeprazole. *Lancet* 1994; 343: 1098.
2. Schönhöfer PS. Intravenous omeprazole and blindness. *Lancet* 1994; 343: 665.

3. Schönhöfer PS. Safety of omeprazole and lansoprazole. *Lancet* 1994; 343: 1369–70.
4. Schönhöfer PS, *et al.* Ocular damage associated with proton pump inhibitors. *BMJ* 1997; 314: 1805.
5. Colin-Jones D. Safety of omeprazole and lansoprazole. *Lancet* 1994; 343: 1369.
6. Lessell S. Omeprazole and ocular damage. *BMJ* 1998; 316: 67.
7. Sachs G. Omeprazole and ocular damage. *BMJ* 1998; 316: 67–8.
8. García Rodríguez LA, *et al.* A cohort study of the ocular safety of anti-ulcer drugs. *Br J Clin Pharmacol* 1996; 42: 213–16.
9. Merlo J, Ranstam J. Ocular safety of anti-ulcer drugs. *Br J Clin Pharmacol* 1997; 43: 449.

Effects on the gastrointestinal tract. Treatment with a proton pump inhibitor has been associated with rebound acid hypersecretion on withdrawal. In healthy subjects without gastric acid-related disease or symptoms, withdrawal of oral esomeprazole after 8 weeks treatment induced acid-related symptoms such as heartburn, acid regurgitation, and dyspepsia.[1]

1. Reimer C, *et al.* Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. *Gastroenterology* 2009; 137: 80–7.

Effects on the kidneys. A systematic review of proton pump inhibitor-associated interstitial nephritis included 47 cases with omeprazole, 6 with pantoprazole, 3 with esomeprazole, 2 with lansoprazole, and 2 with rabeprazole. Although there was insufficient evidence to conclude that proton pump inhibitors caused this reaction, there was a low-prevalence association between their use and the development of interstitial nephritis.[1]

A 2011 report by the Australian Therapeutic Goods Administration[2] stated that acute interstitial nephritis should be considered a class effect of proton pump inhibitors. There have been reports associated with all the proton pump inhibitors, although the incidence is unknown and may vary between individual drugs. Patients had usually presented with non-specific symptoms such as fever, anorexia, weight loss, fatigue, nausea, and vomiting; pyuria, proteinuria, and/or haematuria may also be noted. In some reports[3,4] of interstitial nephritis with omeprazole the condition was associated with rash and eosinophilia, and an allergic mechanism has been postulated.[4]

1. Sierra F, *et al.* Systematic review: proton pump inhibitor-associated acute interstitial nephritis. *Aliment Pharmacol Ther* 2007; 26: 545–53.
2. Anonymous. Proton pump inhibitors and acute interstitial nephritis. *Aust Prescriber* 2011; 34: 190. Also available at: http://www.tga.gov.au/pdf/msu-2011-06.pdf (accessed 10/09/13)
3. Ruffenach SJ, *et al.* Acute interstitial nephritis due to omeprazole. *Am J Med* 1992; 93: 472–3.
4. Christensen PB, *et al.* Renal failure after omeprazole. *Lancet* 1993; 341: 55.

Effects on the liver. Raised liver enzymes have occurred with omeprazole and other proton pump inhibitors, and there have been isolated cases of hepatotoxicity. For a study comparing the incidence of acute liver injury in patients receiving omeprazole or histamine H_2-antagonists, see Cimetidine, p. 1829.3.

References.

1. Jochem V, *et al.* Fulminant hepatic failure related to omeprazole. *Am J Gastroenterol* 1992; 87: 523–5.
2. Kourg SI, *et al.* Omeprazole and the development of acute hepatitis. *Eur J Emerg Med* 1998; 5: 467–9.

Effects on the musculoskeletal system. Progressive muscular weakness suggestive of *myopathy* developed in a 78-year-old patient given oral omeprazole.[1] After 4 weeks of treatment the patient required assistance in walking and rising from squatting. Weakness resolved on withdrawal of the drug, but returned on rechallenge. Acute myopathy has also been reported after a single infusion of omeprazole.[2] Analysis of the WHO adverse drug reaction database in March 2005 revealed 868 reports associating proton pump inhibitors with *myalgia*, of which 292 cases had symptoms indicative of muscle disorders including *polymyositis* and *rhabdomyolysis*.[3] Reports implicated omeprazole, pantoprazole, lansoprazole, esomeprazole, and rabeprazole, and it was suggested that myopathy was probably a class effect. The mechanism might involve induction of auto-immune antibodies.

A report of 5 cases of *arthralgia*, sometimes associated with swelling of the affected joints, in patients receiving omeprazole,[4] also noted that some reported cases of omeprazole-associated headache were accompanied by arthralgia or myalgia. In another case[5] arthralgia in a patient with a hereditary myopathy receiving omeprazole appeared to represent one aspect of a drug-induced *lupus* syndrome, being accompanied by malaise, fever, Raynaud's phenomenon, raised antinuclear antibody titres, and anticardiolipin and antihistone antibodies. Symptoms resolved on withdrawal of the drug.

A case of *eosinophilia* and myalgia related to lansoprazole treatment has been reported.[6]

There has also been a report of 2 cases of acute *gout* associated with omeprazole;[7] in one patient symptoms, which resolved on withdrawal, recurred on rechallenge. However, case control studies have failed to show an increased risk of polyarthralgia[8] or gout[9] associated with omeprazole use.

An FDA review[10] found an increased risk of *fractures* of the hip, wrist, or spine in 6 out of 7 epidemiological studies, in which patients took proton pump inhibitors for 1 to 12 years; the one study that did not find an association limited the study population to those without major risk factors for fracture. Patients in most studies were 50 years of age or older, and the increased risk was mainly in this age group, with treatment for one year or more. Two studies reported an increase in fractures with higher doses, and 2 reported an increase with longer duration of use. These data suggest patients taking proton pump inhibitors may be at an increased risk of fractures. However, factors that might influence this conclusion such as history of osteoporosis, smoking status, alcohol use, and BMI cannot be accounted for in epidemiological studies and 3 studies found no consistent association between chronic proton pump inhibitor use and bone mineral density; it is therefore unclear if proton pump inhibitor use causes an increased risk of fractures. A subsequent meta-analysis[11] of 11 observational studies (including 6 of the studies in the above FDA review) found that proton pump inhibitors modestly increased the risk of hip, spine, and fractures at any site. The MHRA[12] has also reported that meta-analyses of epidemiological studies suggest the risk of fracture is increased by 10 to 40% above baseline, although the studies varied in the extent to which they adjusted for confounders. It has been suggested that calcium malabsorption secondary to acid suppression may explain the association.[13]

1. Garrote FJ, *et al.* Subacute myopathy during omeprazole therapy. *Lancet* 1992; 340: 672.
2. Tuccori M, *et al.* Acute severe myopathy following a single infusion of omeprazole. *Ann Pharmacother* 2006; 40: 352–3.
3. Clark DWJ, Strandell J. Myopathy including polymyositis: a likely class adverse effect of proton pump inhibitors? *Eur J Clin Pharmacol* 2006; 62: 473–9.
4. Beutler M, *et al.* Arthralgias and omeprazole. *BMJ* 1994; 309: 1620.
5. Sivakumar K, Dalakas MC. Autoimmune syndrome induced by omeprazole. *Lancet* 1994; 344: 619–20.
6. Smith JD, *et al.* Possible lansoprazole-induced eosinophilic syndrome. *Ann Pharmacother* 1998; 32: 196–200.
7. Kraus A, Flores-Suárez LF. Acute gout associated with omeprazole. *Lancet* 1995; 345: 461–2.
8. Meier CR, Jick H. Omeprazole, H_2 blockers, and polyarthralgia: case-control study. *BMJ* 1997; 315: 1283.
9. Meier CR, Jick H. Omeprazole, other antiulcer drugs and newly diagnosed gout. *Br J Clin Pharmacol* 1997; 44: 175–8.
10. FDA. FDA drug safety communication: possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors (issued 25th May, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm (accessed 26/09/11)
11. Yu EW, *et al.* Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies. *Am J Med* 2011; 124: 519–26.
12. MHRA. Proton pump inhibitors in long-term use: recent epidemiological evidence of increased risk of fracture. *Drug Saf Update* 2012; 5 9: A2. Also available at: http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con149785.pdf (accessed 10/09/13)
13. Yang Y-X, *et al.* Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006; 296: 2947–53. Correction. *ibid.* 2007; 297: 470.

Effects on the nervous system. Ataxia has been reported in a patient given omeprazole;[1] symptoms resolved on stopping the drug. A patient given rabeprazole developed marked anxiety with panic attacks, episodic night terrors, confusion, and attention deficit.[2] Her symptoms resolved 2 days after stopping therapy. A month later, she was given esomeprazole, with no adverse neuropsychiatric symptoms. The authors hypothesised that rabeprazole use had resulted in significantly greater plasma gastrin concentrations than esomeprazole, which may have affected gastrin receptors in the brain.

1. Varona L, *et al.* Gait ataxia during omeprazole therapy. *Ann Pharmacother* 1996; 30: 192.
2. Polimeni G, *et al.* Rabeprazole and psychiatric symptoms. *Ann Pharmacother* 2007; 41: 1315–17.

Effects on the respiratory system. An intractable, dry, non-productive cough started abruptly in a 42-year-old non-smoker given omeprazole for gastro-oesophageal reflux disease (GORD). The cough was initially thought to be related to the GORD and treatment was continued for 4 months, without any cessation in the cough. Omeprazole was stopped, and the cough ceased abruptly, with no recurrence during a 2-year follow-up.[1]

For discussion of a possible increased risk of respiratory infection and pneumonia in patients taking proton pump inhibitors see Infection, p. 1870.1.

1. Howaizi M, Delafosse C. Omeprazole-induced intractable cough. *Ann Pharmacother* 2003; 37: 1607–9.

Effects on the skin. An extensive blistering erythematous rash in an elderly woman given omeprazole[1] was characteristic of acute disseminated epidermal necrosis. The UK CSM had received 223 reports of cutaneous reactions to omeprazole up to August 1992, including 6 of erythema multiforme, but none of this severity. Other severe reactions that have subsequently been reported include a toxic bullous skin reaction,[2] exfoliative dermatitis,[3,4] erythema multiforme,[4] toxic erythema,[4] and dermatomyositis.[5] One patient developed exfoliative dermatitis with both omeprazole and lansoprazole.[4] The authors of this report noted that by January 1998 a total of 1296 skin reactions to omeprazole, 500 to lansoprazole, and 44 to pantoprazole, had been reported to the CSM. Most were non-specific rashes, pruritus, urticaria, erythematous rashes, and photosensitive eruptions. A lichenoid reaction that occurred in a patient taking omeprazole cleared after ceasing the drug, but recurred during treatment with both lansoprazole and pantoprazole.[6] Proton pump inhibitors, including esomeprazole, have been reported to worsen vitiligo.[7]

For a report of urticaria and angioedema possibly associated with the formulation of omeprazole see Hypersensitivity, p. 1870.1. For the association of rash with interstitial nephritis, see Effects on the Kidneys, above.

1. Cox NH. Acute disseminated epidermal necrosis due to omeprazole. *Lancet* 1992; 340: 857.
2. Stenier C, *et al.* Bullous skin reaction induced by omeprazole. *Br J Dermatol* 1995; 133: 343–4.
3. Epelde Gonzalo FD, *et al.* Exfoliative dermatitis related to omeprazole. *Ann Pharmacother* 1995; 29: 82–3.
4. Cockayne SE, *et al.* Severe erythrodermic reactions to the proton pump inhibitors omeprazole and lansoprazole. *Br J Dermatol* 1999; 141: 173–5.
5. Pan Y, *et al.* Omeprazole-induced dermatomyositis. *Br J Dermatol* 2006; 154: 557–8.
6. Bong JL, *et al.* Lichenoid drug eruption with proton pump inhibitors. *BMJ* 2000; 320: 283.
7. Schallreuter KU, Rokos H. From the bench to the bedside: proton pump inhibitors can worsen vitiligo. *Br J Dermatol* 2007; 156: 1371–3.

Fever. Fever, associated with severe myalgia and headache, was seen in a 64-year-old man on 2 occasions, several hours after taking a dose of esomeprazole.[1] Although it was suggested[2] that the patient's hyperpyrexia was due to a hypersensitivity reaction, the authors argued[3] that esomeprazole may have interfered with the hypothalamic regulatory centres of body temperature.[1,3]

1. Grattagliano I, *et al.* Esomeprazole-induced central fever with severe myalgia. *Ann Pharmacother* 2005; 39: 757–60.
2. Su SS, *et al.* Comment: esomeprazole-induced central fever with severe myalgia. *Ann Pharmacother* 2005; 39: 1764.
3. Grattagliano I. Comment: esomeprazole-induced central fever with severe myalgia. *Ann Pharmacother* 2005; 39: 1765.

Gastrointestinal tumours. Early toxicological studies in *rats* given high doses of omeprazole over 2 years identified carcinoid tumours of the gastric mucosa associated with complete block of gastric acid secretion leading to *hypergastrinaemia and hyperplasia of enterochromaffin-like cells*.[1] This has been the main issue concerning the safety of omeprazole and other proton pump inhibitors and initially led to restrictions in use and duration of treatment. A drug manufacturer, *Glaxo*, developed a new test to detect genotoxicity of antisecretory drugs which indicated that a genotoxic effect of omeprazole could not be discounted.[2] This study was heavily criticised; more established genotoxicity tests have been reported to be negative for omeprazole,[3-5] and other groups have not been able to replicate the findings with the new test.[6] The lowest doses at which *Glaxo* found[2] a genotoxic effect of omeprazole were 10 to 20 mg/kg and the clinical significance of their results was questioned.[3] Long-term studies of omeprazole in patients with Zollinger-Ellison syndrome have found no increase in fasting serum-gastrin concentrations and no evidence of gastric carcinoid tumours.[7,8] For mention of the risk of proton pump inhibitors delaying the diagnosis of gastric carcinoma, see under Precautions, p. 1870.2. Hypergastrinaemia can occur with both short- and long-term omeprazole therapy,[9] and may be higher in patients with *Helicobacter pylori* infection.[10,11] Patients who had *H. pylori* eradicated before long-term omeprazole treatment had lower gastrin concentrations than those who did not, since *H. pylori* eradication reduced the pretreatment gastrin concentrations.[12]

H. pylori is also a cause of *atrophic gastritis*, another risk factor for stomach cancer, and one study found that omeprazole increased the risk of atrophic gastritis in *H. pylori*-positive patients with gastro-oesophageal reflux disease.[13] However, the results of this study require confirmation since it was nonrandomised and retrospective. Nevertheless, some have suggested that it may be appropriate to eradicate *H. pylori* before long-term treatment with a proton pump inhibitor.[12,13] Conversely, there is some evidence that *H. pylori* may be protective in gastro-oesophageal reflux disease.[14]

There has been a report of *gastric polyps* developing in 3 of 8 patients after receiving omeprazole 20 or 40 mg daily for one year.[15] In a subsequent report it was noted that these omeprazole-induced fundic gland polyps had remained asymptomatic and non-malignant for up to five years after their onset.[16]

The possible association between acid suppressing drugs and risk of gastric cancer has been studied (see also Cimetidine, under Carcinogenicity, p. 1828.3). A small increase in the risk of gastric cancer has been reported with the use of proton pump inhibitors, although the authors of this case control study suggested that confounding by indication was the most likely explanation.[17]

Further long-term studies of omeprazole may be needed before a realistic risk assessment can be made.

1. Ekman L, *et al.* Toxicological studies on omeprazole. *Scand J Gastroenterol* 1985; 20 (suppl 108): 53–69.
2. Burlinson B, *et al.* Genotoxicity studies of gastric acid inhibiting drugs. *Lancet* 1990; 335: 419.
3. Ekman L, *et al.* Genotoxicity studies of gastric acid inhibiting drugs. *Lancet* 1990; 335: 419–20.
4. Wright NA, Goodlad RA. Omeprazole and genotoxicity. *Lancet* 1990; 335: 909–10.
5. Helander HF, *et al.* Omeprazole and genotoxicity. *Lancet* 1990; 335: 910–11.
6. Goodlad RA. Acid suppression and claims of genotoxicity: what have we learned? *Drug Safety* 1994; 10: 413–19.
7. Lloyd-Davies KA, *et al.* Omeprazole in the treatment of Zollinger-Ellison syndrome: a 4-year international study. *Aliment Pharmacol Ther* 1988; 2: 13–32.
8. Maton PN, *et al.* Long-term efficacy and safety of omeprazole in patients with Zollinger-Ellison syndrome: a prospective study. *Gastroenterology* 1989; 97: 827–36.
9. Koop H, *et al.* Serum gastrin levels during long-term omeprazole treatment. *Aliment Pharmacol Ther* 1990; 4: 131–8.
10. Sanduleanu S, *et al.* Serum gastrin and chromogranin A during medium- and long-term acid suppressive therapy: a case-control study. *Aliment Pharmacol Ther* 1999; 13: 145–53.
11. Kuipers EJ. Proton pump inhibitors and gastric neoplasia. *Gut* 2006; 55: 1217–21.
12. El-Nujumi A, *et al.* Eradicating Helicobacter pylori reduces hypergastrinaemia during long term omeprazole treatment. *Gut* 1998; 42: 159–65.
13. Kuipers EJ, *et al.* Atrophic gastritis and Helicobacter pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med* 1996; 334: 1018–22.
14. Labenz J, Malfertheiner P. Helicobacter pylori in gastro-oesophageal reflux disease: causal agent, independent or protective factor? *Gut* 1997; 41: 277–80.
15. Graham JR. Gastric polyposis: onset during long-term therapy with omeprazole. *Med J Aust* 1992; 157: 287–8.
16. Graham JR. Gastric acne: omeprazole-induced fundic gland polyposis. *Med J Aust* 1998; 168: 93.
17. Tamim H, *et al.* Association between use of acid-suppressive drugs and risk of gastric cancer: a nested case-control study. *Drug Safety* 2008; 31: 675–84.

Hypersensitivity. Cases of anaphylactic reactions after treatment with omeprazole, lansoprazole, and pantoprazole, have been reported in the literature and to WHO.[1] Cross-sensitivity to pantoprazole was reported[2] on skin-testing in 4 of 9 patients sensitive to omeprazole; oral challenge tests with pantoprazole in 3 patients, 2 of whom were negative on skin testing, produced pruritus and urticaria in all 3. However, none of the patients had a reaction to skin tests with lansoprazole, and 8 of the 9 tolerated oral challenge with lansoprazole without problems; the other developed widespread urticaria one hour after a therapeutic dose was reached.

Urticaria, facial angioedema, and bronchospasm in a patient given omeprazole capsules did not recur when the patient was given omeprazole granules and the reaction might have been precipitated by the ingredients of the capsule shell.[3]

See also under Effects on the Kidney and Effects on the Musculoskeletal System, p. 1869.1.

1. Natsch S, *et al.* Anaphylactic reactions to proton-pump inhibitors. *Ann Pharmacother* 2000; 34: 474–6.
2. Lobera T, *et al.* Nine cases of omeprazole allergy: cross-reactivity between proton pump inhibitors. *J Investig Allergol Clin Immunol* 2009; 19: 57–60.
3. Heeney MR. Angio-oedema and urticaria associated with omeprazole. *BMJ* 1992; 305: 870.

Infection. Gastric-acid suppressing drugs such as proton pump inhibitors and H_2-antagonists have been linked to an increased risk of infection. A systematic review[1] found an increased risk of enteric infections such as *Salmonella, Campylobacter, Shigella,* or *Clostridium difficile* in patients taking acid suppressing drugs, although there was considerable heterogeneity between studies. Increased rates of sepsis[2] and necrotising enterocolitis[3] have also been reported in infants given H_2-antagonists. It has been suggested that the increased rate of infection could be due to the rise in gastric pH after acid suppressive treatment, resulting in increased microbial colonisation of the upper gastrointestinal tract.[1-3]

Results from studies into the risk of developing community-acquired pneumonia with the use of acid suppressants have been inconsistent. Increased rates of pneumonia have been reported with current use of acid suppressants in case-control and cohort studies,[4-7] whereas an industry-sponsored analysis of pooled adverse effect data on esomeprazole did not support an association between its use and respiratory-tract infections, including pneumonia.[8] A case control study found no overall increase in the risk of community-acquired pneumonia with current use of proton pump inhibitors, although unexpectedly, an increased risk was noted when proton pump inhibitors had been started in the previous month.[9] A systematic review also failed to find an association between use of proton pump inhibitors (esomeprazole, rabeprazole, pantoprazole and omeprazole) and respiratory infections, although it noted a trend towards an association.[10]

1. Leonard J, *et al.* Systematic review of the risk of enteric infection in patients taking acid suppression. *Am J Gastroenterol* 2007; 102: 2047–56.
2. Bianconi S, *et al.* Ranitidine and late-onset sepsis in the neonatal intensive care unit. *J Perinat Med* 2007; 35: 147–50.
3. Guillet R, *et al.* National Institute of Child Health and Human Development Neonatal Research Network. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2006; 117: e137–e142. Also available at: http://pediatrics.aappublications.org/cgi/reprint/117/2/e137 (accessed 09/04/08)
4. Laheij RJF, *et al.* Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004; 292: 1955–60.
5. Canani RB, *et al.* Working Group on Intestinal Infections of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP). Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics* 2006; 117: e817–e820. Available at: http://pediatrics.aappublications.org/cgi/reprint/117/5/e817 (accessed 01/04/09)
6. Herzig SJ, *et al.* Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA* 2009; 301: 2120–8.
7. Eurich DT, *et al.* Recurrent community-acquired pneumonia in patients starting acid-suppressing drugs. *Am J Med* 2010; 123: 47–53.
8. Ruben L, Joelson S. Occurrence of community-acquired respiratory tract infection in patients receiving esomeprazole: retrospective analysis of adverse events in 31 clinical trials. *Drug Safety* 2008; 31: 627–36.
9. Sarkar M, *et al.* Proton-pump inhibitor use and the risk for community-acquired pneumonia. *Ann Intern Med* 2008; 149: 391–8.
10. Sultan N, *et al.* Association between proton pump inhibitors and respiratory infections: a systematic review and meta-analysis of clinical trials. *Can J Gastroenterol* 2008; 22: 761–6.

Lupus syndrome. For a report of drug-induced lupus syndrome associated with omeprazole therapy, see Effects on the Musculoskeletal System, p. 1869.1.

Malabsorption. Omeprazole has been reported to result in a substantial reduction in *cyanocobalamin* (vitamin B_{12}) absorption,[1] probably related to the increase in gastric pH, and indicating a potential risk of vitamin deficiency with long-term therapy.[2] UK licensed product information recommends that severely ill children, who may have borderline body stores of cyanocobalamin, should have serum vitamin B_{12} concentrations monitored if they require long-term therapy. Omeprazole has also been reported to impair the bioavailability of dietary *vitamin C*.[3] *Fat* malabsorption, secondary to increased deconjugation of bile acids caused by bacterial overgrowth in the jejunum, has also been reported with omeprazole treatment.[4] For the suggestion that proton pump inhibitors can cause *calcium* malabsorption, see Effects on the Musculoskeletal System, p. 1869.1.

1. Marcuard SP, *et al.* Omeprazole therapy causes malabsorption of cyanocobalamin (vitamin B_{12}). *Ann Intern Med* 1994; 120: 211–15.
2. Termanini B, *et al.* Effect of long-term gastric acid suppressive therapy on serum vitamin B_{12} levels in patients with Zollinger-Ellison syndrome. *Am J Med* 1998; 104: 422–30.
3. Henry EB, *et al.* Proton pump inhibitors reduce the bioavailability of dietary vitamin C. *Aliment Pharmacol Ther* 2005; 22: 539–45.
4. Shindo K, *et al.* Omeprazole induces altered bile acid metabolism. *Gut* 1998; 42: 266–71.

Overdosage. A report of 2 cases of overdosage with omeprazole.[1] The major clinical features were drowsiness, headache (possibly due to a metabolite), and tachycardia. Both patients recovered uneventfully without specific treatment.

1. Ferner RE, Allison TR. Omeprazole overdose. *Hum Exp Toxicol* 1993; 12: 541–2.

Precautions

Before giving omeprazole or other proton pump inhibitors to patients with gastric ulcers the possibility of malignancy should be excluded since these drugs may mask symptoms and delay diagnosis. Omeprazole and other proton pump inhibitors should be used with caution in hepatic impairment and dose adjustment may be required.

Breast feeding. Omeprazole is excreted in human milk. After a single oral dose, peak concentrations of omeprazole in breast milk were reported to be less than 7% of the peak serum concentration.[1]

1. Marshall JK, *et al.* Omeprazole for refractory gastroesophageal reflux disease during pregnancy and lactation. *Can J Gastroenterol* 1998; 12: 225–7.

Gastric carcinoma. Proton pump inhibitors relieve dyspeptic symptoms associated with gastric carcinoma and can therefore delay its diagnosis. In addition, there is some evidence that they may also endoscopically 'heal' early gastric carcinoma so that the diagnosis is missed.[1] Consequently, some commentators recommend that proton pump inhibitors should not be prescribed for symptom control before endoscopy in patients at risk for gastric carcinoma.[2]

1. Wayman J, *et al.* The response of early gastric cancer to proton-pump inhibitors. *N Engl J Med* 1998; 338: 1924–5.
2. Griffin SM, Raimes SA. Proton pump inhibitors may mask early gastric cancer: dyspeptic patients over 45 should undergo endoscopy before these drugs are started. *BMJ* 1998; 317: 1606–7.

Helicobacter infection. Treatment with proton pump inhibitors may cause false-negative results in the urea breath test for *Helicobacter pylori* infection. In one study in patients with *H. pylori* infection, lansoprazole 30 mg daily for 4 weeks caused 33% of patients to have negative urea breath tests.[1] The breath test became positive again in all patients within 2 weeks of stopping lansoprazole therapy. In a similar study, 52% of patients had negative urea breath tests for *H. pylori* while receiving omeprazole 20 mg daily, and the breath test became positive again in all patients within 2 to 6 days of stopping treatment.[2] The manufacturers of the urea breath test for *H. pylori* recommend that it should not be performed for at least 2 weeks after stopping treatment with an antisecretory drug.

For a discussion of the link between proton pump inhibitors, *H. pylori*, and gastritis, see under Gastrointestinal Tumours p. 1869.3.

1. Laine L, *et al.* Effect of proton-pump inhibitor therapy on diagnostic testing for Helicobacter pylori. *Ann Intern Med* 1998; 129: 547–50.
2. Connor SJ, *et al.* The effect of dosing with omeprazole on the accuracy of the ^{13}C-urea breath test in Helicobacter pylori-infected subjects. *Aliment Pharmacol Ther* 1999; 13: 1287–93.

Hepatic impairment. In patients with cirrhosis an increase in omeprazole bioavailability, and elimination half-life has been reported.[1] For dosage adjustment in hepatic impairment see Administration in Hepatic Impairment, p. 1868.1.

1. Andersson T, *et al.* Pharmacokinetics of [^{14}C]omeprazole in patients with liver cirrhosis. *Clin Pharmacokinet* 1993; 24: 71–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies omeprazole 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 03/10/11)

Pregnancy. Proton pump inhibitors are not generally licensed for use during pregnancy (although the UK has licensed omeprazole for such use), but a meta-analysis[1] of 5 studies of exposure to proton pump inhibitors during the first trimester, involving 593 exposed infants, found the relative risk of major abnormalities associated with such exposure to be only 1.18, with a 95% confidence interval ranging from 0.72 to 1.94. Meta-analysis of exposures to omeprazole (from 4 studies only) gave a relative risk of 1.05 (95% confidence interval 0.59 to 1.85). It was concluded that exposure to proton pump inhibitors, and omeprazole in particular, did not pose an important teratogenic risk. A retrospective epidemiological study of data from the Swedish Medical Birth Registry, which identified 955 exposed infants, also found no evidence of significant risk after exposure to omeprazole during pregnancy,[2] a finding confirmed by a subsequent meta-analysis.[3] Additionally, a cohort study[4] into the use of proton pump inhibitors in the first trimester did not find an increased risk of major birth defects.

1. Nikfar S, *et al.* Use of proton pump inhibitors during pregnancy and rates of major malformations: a meta-analysis. *Dig Dis Sci* 2002; 47: 1526–9.
2. Källén BAJ. Use of omeprazole during pregnancy—no hazard demonstrated in 955 infants exposed during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2001; 96: 63–8.
3. Gill SK, *et al.* The safety of proton pump inhibitors (PPIs) in pregnancy: a meta-analysis. *Am J Gastroenterol* 2009; 104: 1541–5.
4. Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. *N Engl J Med* 2010; 363: 2114–23.

Interactions

Omeprazole and other proton pump inhibitors are metabolised by the cytochrome P450 system, mainly by isoenzyme CYP2C19, and to a smaller extent by CYP3A4. Inhibitors or inducers of these isoenzymes may affect exposure to omeprazole and other proton pump inhibitors. In turn, proton pump inhibitors may alter the metabolism of some drugs metabolised by these enzymes. Omeprazole also inhibits CYP2C19 and may prolong the elimination of cilostazol, diazepam, phenytoin, and warfarin (but see below). Omeprazole and other proton pump inhibitors can affect the absorption of drugs such as dasatinib, erlotinib, posaconazole, ketoconazole, and itraconazole, whose absorption is dependent on an acid gastric pH. With voriconazole, the plasma concentration of both drugs may be increased (for further information, see p. 1871.1). Other proton pump inhibitors may be similarly affected by voriconazole. Omeprazole and other proton pump inhibitors should not be used with atazanavir or nelfinavir, as it substantially reduces exposure to the HIV-protease inhibitor.

The decrease in gastric activity with proton pump inhibitors may give false positive results in diagnostic investigations for neuroendocrine tumours and treatment should be stopped before such investigations.

Omeprazole is mainly metabolised by the cytochrome P450 isoenzyme CYP2C19 (see Metabolism, p. 1871.2) and therefore may interact with diazepam (see under Gastrointestinal Drugs, p. 1069.3). Some metabolism of phenytoin (see p. 544.3), tolbutamide, and the *R*-enantiomer of warfarin (see p. 1534.1) also takes place by CYP2C19, but the effects seen have been minor.[1] Although some induction of CYP1A2, which metabolises caffeine and

theophylline (p. 1236.1), has been reported this does not appear to be clinically significant.[2] While some consider the effect of omeprazole on CYP3A4 activity to be insignificant,[3] others have noted increasing evidence that competitive inhibition of intestinal CYP3A4 by omeprazole may affect the first-pass metabolism of several drugs.[4] A review concluded that, while omeprazole and possibly esomeprazole have a considerable potential for drug interactions, lansoprazole, pantoprazole and rabeprazole are associated with a lower incidence of drug interactions.[4]

For a study *in vitro* suggesting that omeprazole affected CYP3A4 metabolism of tacrolimus, see under Interactions of Tacrolimus, p. 1972.3. For more on the effect of proton pump inhibitors on tacrolimus, see Gastrointestinal Drugs, p. 1973.3. Proton pump inhibitors, including omeprazole, may also affect exposure to mycophenolate, see p. 1965.1.

For reference to the possibility of enhanced digoxin absorption with omeprazole, see p. 1357.3. For a study suggesting that omeprazole reduces the absorption of cyanocobalamin and vitamin C, see Malabsorption, p. 1870.2, and for its effect on calcium absorption see p. 1825.1. For reference to possible interactions between methotrexate and omeprazole, see p. 828.1.

1. Andersson T. Pharmacokinetics, metabolism and interactions of acid pump inhibitors: focus on omeprazole, lansoprazole and pantoprazole. *Clin Pharmacokinet* 1996; 31: 9–28.
2. Rizzo N, *et al.* Omeprazole and lansoprazole are not inducers of cytochrome P4501A2 under conventional therapeutic conditions. *Eur J Clin Pharmacol* 1996; 49: 491–5.
3. Tateishi T, *et al.* Omeprazole does not affect measured CYP3A4 activity using the erythromycin breath test. *Br J Clin Pharmacol* 1995; 40: 411–12.
4. Blume H, *et al.* Pharmacokinetic drug interaction profiles of proton pump inhibitors. *Drug Safety* 2006; 29: 769–84.

Clarithromycin. Studies in healthy subjects have indicated that use of omeprazole with clarithromycin results in an approximate 30% increase in peak plasma concentrations of omeprazole, and an increase in its mean half-life from 1.2 to 1.6 hours.[1] At the same time, plasma concentrations of clarithromycin were also modestly increased, as were local concentrations in gastric tissue and mucus.[1] Clarithromycin inhibits[2] the metabolism of omeprazole mediated by the cytochrome P450 isoenzyme CYP3A4. The interaction may contribute to the benefits of combined therapy for *Helicobacter pylori* infection.

1. Gustavson LE, *et al.* Effect of omeprazole on concentrations of clarithromycin in plasma and gastric tissue at steady state. *Antimicrob Agents Chemother* 1995; 39: 2078–83.
2. Furuta T, *et al.* Effects of clarithromycin on the metabolism of omeprazole in relation to CYP2C19 genotype status in humans. *Clin Pharmacol Ther* 1999; 66: 265–74.

Clopidogrel. For recommendations that the use of proton pump inhibitors such as omeprazole with clopidogrel should be discouraged, see p. 1344.2.

Fluvoxamine. Omeprazole and other proton pump inhibitors are metabolised mainly by cytochrome P450 isoenzyme CYP2C19, which shows genetically determined polymorphism, yielding extensive metabolisers and poor metabolisers. Fluvoxamine increased exposure to omeprazole, lansoprazole, and rabeprazole in patients who were extensive metabolisers, but had no effect on pharmacokinetic parameters in poor metabolisers.[1-3] Dose reductions may need to be considered in patients treated with fluvoxamine and proton pump inhibitors.

1. Yasui-Furukori N, *et al.* Different inhibitory effect of fluvoxamine on omeprazole metabolism between CYP2C19 genotypes. *Br J Clin Pharmacol* 2004; 57: 487–94.
2. Yasui-Furukori N, *et al.* Effects of fluvoxamine on lansoprazole pharmacokinetics in relation to CYP2C19 genotypes. *J Clin Pharmacol* 2004; 44: 1223–9.
3. Uno T, *et al.* Different effects of fluvoxamine on rabeprazole pharmacokinetics in relation to CYP2C19 genotype status. *Br J Clin Pharmacol* 2006; 61: 309–14.

Voriconazole. When omeprazole is given with voriconazole, exposure to both drugs is increased. UK licensed product information for omeprazole states that a dose adjustment of omeprazole is not routinely indicated, unless patients have severe hepatic impairment and long-term therapy is indicated. However, UK licensed product information for voriconazole states that, while no dosage adjustment is considered necessary for voriconazole, when patients already receiving omeprazole are started on voriconazole, the dose of omeprazole should be halved. Other proton pump inhibitors may be similarly affected by voriconazole.

Pharmacokinetics

Omeprazole is rapidly but variably absorbed after oral doses. Absorption is not significantly affected by food. Omeprazole is acid-labile and the pharmacokinetics of the various formulations developed to improve oral bioavailability may vary. The absorption of omeprazole also appears to be dose-dependent; increasing the dosage above 40 mg has been reported to increase the plasma concentrations in a non-linear fashion because of saturable first-pass hepatic metabolism. In addition, bioavailability is higher after long-term use.

Bioavailability of omeprazole may be increased in elderly patients, in some ethnic groups such as Chinese, and in patients with hepatic impairment, but is not markedly affected in patients with renal impairment.

On absorption, omeprazole is almost completely metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP2C19 to form hydroxy-omeprazole, and to a small extent by CYP3A4 to form omeprazole sulfone. The metabolites are inactive, and are excreted mostly in the urine and to a lesser extent in bile. The elimination half-life from plasma is reported to be about 0.5 to 3 hours. Omeprazole is about 95% bound to plasma proteins.

References.
1. Andersson T, *et al.* Pharmacokinetics of various single intravenous and oral doses of omeprazole. *Eur J Clin Pharmacol* 1990; 39: 195–7.
2. Andersson T, Regårdh C-G. Pharmacokinetics of omeprazole and metabolites following single intravenous and oral doses of 40 and 80 mg. *Drug Invest* 1990; 2: 255–63.
3. Ching MS, *et al.* Oral bioavailability of omeprazole before and after chronic therapy in patients with duodenal ulcer. *Br J Clin Pharmacol* 1991; 31: 166–70.
4. Landahl S, *et al.* Pharmacokinetic study of omeprazole in elderly healthy volunteers. *Clin Pharmacokinet* 1992; 23: 469–76.
5. Andersson T, *et al.* Pharmacokinetics of [^{14}C]omeprazole in patients with liver cirrhosis. *Clin Pharmacokinet* 1993; 24: 71–8.
6. Jacqz-Aigrain E, *et al.* Pharmacokinetics of intravenous omeprazole in children. *Eur J Clin Pharmacol* 1994; 47: 181–5.
7. Litalien C, *et al.* Pharmacokinetics of proton pump inhibitors in children. *Clin Pharmacokinet* 2005; 44: 441–66.
8. Fock KM, *et al.* Proton pump inhibitors: do differences in pharmacokinetics translate into differences in clinical outcomes? *Clin Pharmacokinet* 2008; 47: 1–6.

Metabolism. The major enzyme involved in omeprazole metabolism is cytochrome P450 isoenzyme CYP2C19. This enzyme is polymorphically expressed, and individuals who are deficient in the enzyme are poor metabolisers of omeprazole. This occurs in about 3% of Caucasians and 15% of Chinese, Japanese, and Koreans. These individuals have markedly higher plasma concentrations of omeprazole, and they may require dosage adjustment. Some omeprazole is metabolised by CYP3A4, and some by CYP2D6 to form desmethylomeprazole.

References.
1. Andersson T, *et al.* Identification of human liver cytochrome P450 isoforms mediating omeprazole metabolism. *Br J Clin Pharmacol* 1993; 36: 521–30.
2. Cavco Y, *et al.* Ethnic and genetic determinants of omeprazole disposition and effect. *Clin Pharmacol Ther* 1996; 60: 157–67.
3. Karam WG, *et al.* Human CYP2C19 is a major omeprazole 5-hydroxylase, as demonstrated with recombinant cytochrome P450 enzymes. *Drug Metab Dispos* 1996; 24: 1081–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acimed; Aziatop; Brux; Buscasan; Danlox; Faboacid Plus; Fabrazol; Fendiprazol; Gastec; Gastroprazol; Gastrotem; Klomeprax; Lafeprazol; Losec; Lyncis 24; Mucoxol; Nexoprazol; Oblisec; Omefar; Omeprasec; Pepticus; Pravil; Procelac; Prysma; Regulacid; Sedigastrol; Stomacine; Timezol; Ulcozol; Ulsanol†; Veroprazol; Zoltenk; *Austral.*: Acimax; Losec; Maxor; Meprazol; Omepral; Ozmep; Pemzo; Probitor; *Austria*: Gastrobene; Gastroplex†; Losec; Omec; Omepralan; *Belg.*: Docomepra†; Logastric†; Losec; Sedacid; *Braz.*: Estomepe; Eupept; Gasec†; Gaspiren; Gastrium; Gastrocimet; Gastrozol; Klispel; Loprazol; Losec; Lozeprel; Meprazan; Mesopran; Neoprazol; Neprazol; Omegastrol; Omenax; Omep; Omepramed; Omeprazin; Omeprotec; Omezolon; Omoprel; Oprazon; Peprazol; Pepsicaps†; Prazolex; Prazolol; Prazonil†; Ulcefor†; Uniprazol; Victrix; *Canad.*: Losec; *Chile*: Lomex; Losec; Micromex; Omeprax; Togran; Ulc-Out; Ulcelac†; Ulcizole; Ulcrux; Zatrol; Zomepral; *China*: Ai Ni (爱尼); Ao Ke (奥克); Ao Li Ya (奥立雅); Ao Si Tan (奥斯坦); Ao Wei Kang (奥韦康); Aomeizhen (奥美真); Aoqi (奥齐); Aoxikang (奥西康); Haibaike (海百克); Ji Li (吉立); Jin Ao Kang (金奥康); Ke Di Sheng (克迪圣); Kun Li Yu (坤丽雨); Ledi (乐迪); Li Ao Jia (丽奥佳); Li Wei Ting (利韦廷); Losec (洛赛克); Luodan (罗丹); Luokai (洛凯); Novek (礼先); Pi Si Ke (彼司克); Ping Fang Shu (平芳淑); Ramezol; Sai Ao (赛奥); Shenliyu (绅丽雨); Tianlong Taike (天龙泰克); Cz.: Apo-Ome; Asilar; Gasec; Helicid; Lomac; Losec†; LosecPro; Loseprazol; Omepirex†; Omeprol†; Omolin†; Onprelen; Ortanol; Sinomenorm; Tulzol; Ultop; *Denm.*: Losec; Omelix†; Omestad; Ortanol; *Fin.*: Gastrostad; Losec; Omestad; *Fr.*: Mopral; Mopralpro; Omediprol; Zoltum; *Ger.*: Antra; Buscogast; Gastracid†; Ome TAD†; Ome-nerton; Ome-Puren†; Ome-Q†; Omebeta; Omedoc†; Omegamma†; OmeHennig†; OmeLich†; Omep†; Ulcozol; Ulnor†; *Gr.*: Acromon; Alcerelief; Alevior; Assoprol; Belifax; Benzol; Candazol; Comoprazol; Diorium; Efrozin; Elcodrop; Elcofar; Elcontrol; Elibactin; Elkostop; Elkotheran; Eselan; Esopraz; Ezipol; Flusal; Gastronorm; Gertalgin; Gerxus; Glaveral; Inhiplex; Keriofin; Lanex; Lenar; Lexigor; Lodrec; Lomezec; Loproc; Lordin; Losec; Lozaprin; Lyopraz; Malortil; Meprolen; Nedopron; Novek; Odamesol; Odasol; Ofnimarex; Olark; Omeprol; Omerane; Omezalin; Oprazium; Ortanol; Palser; Penrazol; Pip Acid; Prazolin; Probitor; Rukuz; Rythmogastryl; Sedacid; Sieral; Silato; Sodeprol; Spezato; Ufonitren; Vamac; Veralox; Zolandil; Zolelcon; Zolidenol; Zolmach; *Hong Kong*: Losec; *Hung.*: Losec; Ludea; Omegen; Omep; Omeprawin†; Ulzol†; *India*: Abcid; Acichek; Acidof; Acigone; Aciom; Acitec; Adprazole; Adzole; Atozol; Avizol; Azol; Biocid; Biomac; Brocid; C-Praz; Capcid; Capocid; CG Mez; CGMag; Cinom; Coszol; Coz; Cozep; Cucid; Cuzole; DGR; Diocid; Dorcan; E-Zole; Elome; Elpra; Ezol; Forzole; Hariom; Hocid; Icer; Jotac; Lexcid; Litom; Lokit; Lomac; Lomecid; Lopra; Loress; Losec; Lupome; Menzol; Nilsec; Niszol; Nitpep; Nogacid; Novacid; O-Bit; Ocid; Ocimax; Ocinil; Odizol; Ogestrel; Okacid; Olicap; Olit; Olla-MT; Omag; Omalcer; Omapin; Ombel; Ombest; Omcare; Omcid; Omcure; Ome-PPI; Omecer; Omecid; Omecip; Omecos; Omega; Omegold; Omegord; Omejel; Omel; Omelax; Omen; Omenat; Omep; Omeplus; Omepral; Omepraz; Omepren; Omepromp; Omeraze; Omeris; Omesun; Omesym; Ometab; Omevar; Omey; Omez-FF; Omez; Omezol; Omezole; Omfact; Omicap; Omicas; Omicool; Omig; Omilee; Omind; Omitive; Omizac; Omizol; Omkair; Omlink; Omlo; Ommac; Omnilup; Omore; Ompep; Ompirol; Ompli; Ompraz; Omracap; Omriz; Omsy; Omtec; Omven; Omzee; Onazole; Op-Zole; Opaz; Opel; Opep; Opera; Oraz; Orole; Osec; Oskar; Ospicid; Ossum; OTG; Otto; Ozed; OZL; Ozo-D; Ozo; Ozol; Promisec; Ulzol; *Indon.*: Contral; Dudencer; Inhipump; Lokev; Loklor†; Losec; Meisec; Norsec; Omevell; OMZ; Onic; Opm; Oprezol; Ozid; Prilos; Prohibit; Promezol; Protop; Pumpitor; Redusec; Regasec; Rindopump; Rocer; Socid; Stomacer; Ulpraz; Ulzol; Zepral; Zeprazol; Zolacap; Zollocid; *Irl.*: Bentomet†; BySec; Davliet†; Kalgriff†; Lopraz; Losamel; Losapol†; Losec; Losepine; Mylcer†; Pugritex; Romep; Sedacid; Tulzol†; Ulcid; *Israel*: Losec; Omepra; Omepradex; Omeprix; *Ital.*: Alsidol; Anadlr; Antra; Arpezol; Cletus; Ibimezolo; Komezol; Kruxagon; Limnos; Losec; Maricrio; Mepral; Nansen; Omeprazen; Omolin; Protec; Ulcezol; Zaprol; *Jpn*: Omepral; *Malaysia*: Gasec; Losec; Medoprazole; Omelon; Omesec; Omez; Omezol; Omezole; Probitor; Risek; Romesec; Zenpro; Zimor; *Mex.*: Albor; Aleprozil; Apopraza; Azoran†; Danovag; Domer; Gerdex; Grizol; Haitrax; Hitrax†; Ibax; Ibemiral; Inhibitron; Logazil; Lopram; Losec; Medral; Melet; Mopral; Mornin; Olexin; Omecaps; Ometec; Opramid; Osiren; Ozoken; Panzer; Pastrizol; Pentren; Prazidec; Prazolit; Promezal; Reux; Sarox; Silopral; Solcer; Suifac; Tarzol; Ucetal; Ulsen; Ultizol; Ultromep†; Usaltron; Vulcasid; Zolufen; Zoral; Zulmedx; *Neth.*: Buscozol; Ipegen; Itomed†; Kruidvat maagzuuremmer Omeprazole; Loprilin; Losec; Losecosan; Moprilic; Novek†; Omolin; Omoquis; Prazigast†; Romisan; *Norw.*: Losec; *NZ*: Losec; Omezol; *Philipp.*: Acifre; Acipres; Aizole; Farmazol; Flazomel; Frazole; Gastriloc; Hovizol; Hycid; Lokit; Lomezek; Lopep; Loprezol; Losec; Megaprazt; Mepracid; Mepralin; Mepraz; Nocid; Omebloc; Omed; Omelon; Omenole; Omepron; Ometas; Omez; Omizac; Omlek; OMZ; Opehex†; Opraz; Peptisolv; Perazole; Pleom; Plosek; Pramiz; Premio; Prexon; Promesec†; Prosec; Protonix; Puroxel; Risek; Somecid; Sydenprazole; Tansinel; Ulsek; Viprazo; Wilom; Zefxon; Zegacid; Zolmep; Zomep; Zosec; Zyom; *Pol.*: Agastin; Bioprazol; Gasec; Helicid; Losec; Loseprazol; Notis; Omar†; Ortanol; Polprazol; Prazigast; Prazol; Progastim; Tulzol; Ultop; Ulzol†; *Port.*: Albosan; Balzoprem; Belmazol; Bloprazol†; Eczop†; Eugastrim; Gasec; Losec; Luzina; Megazol†; Mepraz; Nems; Novek†; Omegrim†; Omepra; Omeratio†; Omerax; Ometon; Omezolan; Prazentol; Prazex; Prazolene; Procior; Proton; *Rus.*: Cisagast (Цисагаст); Gastrozol (Гастрозол); Helicid (Хеликид); Helol (Хелол); Lomac (Ломак); Losec (Лосек); Ocid (Оцид); Omecaps (Омекапс); Omez (Омез); Omipix (Омипикс); Omitox (Омитокс); Omizac (Омизак); Pleom (Плеом); Promes (Промез); Romesec (Ромесек); Sopral (Сопрал); Ulcozol (Улкозол); Ultop (Ультоп); Ulzol (Улзол)†; Zerocid (Зероцид); *S.Afr.*: Altosec; Lokit; Losec; Nozer; Omez; Omiloc†; Ulzec†; *Singapore*: Gasec; Losec; Ocid; Olit; Omesec; Omezol; Omezole; Omicap; Opizole; Penrazole; Proceptin; Pumpitor; Ramezol; Romesec; Zefxon; Zenpro; Zimor; *Spain*: Arapride; Audazol; Aulcer; Belmazol; Ceprandal; Dolintol; Elgam†; Emeproton; Gastrimut; Indurgan†; Ipirasa†; Losec; Miol; Norpramin†; Novek; Nuclosina; Omapren; Ompranyt; Parizac; Pepticum; Prazipar†; Prysma; Sanamidol†; Ulceral; Ulcesep; Zimor; *Swed.*: Losec; Omecat; *Switz.*: Antra†; Antramups; AntraPro; Omed; Omeprax; Omezol; Oprazol†; *Thai.*: Airomet; Amnopra; Desec; Dosate; Duogas; Duosolin; Eselan; Eucid; Gaster; Gomec; Lokit; Lomac; Lomicid; Losec; Madiprazole; Meiceral†; Metsec; Miracid; Moprix; Mosec; Nocid; O-Sid; Ocid; Olit†; Omeman; Omepac; Omeprol; Omesec; Omez†; Omezol; Omezole; Omicap†; Omlek; Opramed; Oprazole†; Prazole; Probitor†; Sanosec; Seto-o; Stomec; Ulpracid; Ulprazole; Zecid†; Zefxon; Zigacap; *Turk.*: Demeprazol; Erbolin; Eselan; Gastromax; Losec; Omegast; Omeprazid; Omeprol; Omesek; Prosek; *UAE*: Risek; *UK*: Heartburn Relief; Losec; Mezzopram; Zanprol; *Ukr.*: Cerol (Церол)†; Gasec (Гасек); Loseprazol (Лосепразол); Omep (Омеп); Omez (Омез); Oprazol (Опразол); Ultop (Ультоп); *USA*: Prilosec; *Venez.*: Fordex; Gastronol; Losec; Omebloc; Omevax; Omezul; Parsolen; Probitor; Promezol.

Multi-ingredient Preparations. *Arg.*: Danlox Rapido; Gastec Rapido; *Austral.*: Klacid HP 7; Losec Hp 7†; Probitor Hp7; *Braz.*: Erradic Omepramix; *Canad.*: Losec 1-2-3 A; Losec 1-2-3 M; *India*: Abcid-D; Abcool-D; Acio; Acitec-D; Adprazole-D; Adzole-DM; Atozol-D; Avizol-D; Azinorm O; Azo-O; Bemez-D; Biomac-D; Brozol-D; C-Praz-D; Capcid-D; Capocid-DM; Cool Zone D; Coszol-D; Coz-D; Cucid-DM; Cuzole-D; Demo D; DGR-Plus; Dic-OM; Diocid-D; Diopra; Domcl; Domepraz; Domeway; Domezol; Domizol-DS; Domocid; Domped-OZ; Domperon-O; Dompra; Domsin-O; Domstal-O; Domstal-RD; Domz; Dorcan-D; Drag-D; E-Zole-D; Elpra-D; Emidon-OM; Emopaz-D; Forzole-D; GI Kit; Ginac; GR8; Helibact; Helikit; Helipac HP Kit; Icer-D; Jotac-D; L-Cot; Lexcid-DM; Litom-D; Lokit-Kit; Lomecid-D; Lopra-D; Lupome-D; Miliom-D; Minisec-AR; Netom-D; Neutral-O; Nitpep-D; Nogacid D; Novacid-D; O & D; O-Bit-DM; Ocid-D; Ocinil-D; Od; Odoman; Ogestrel-D; Okacid D; Olicap-D; Olla-D; Ombel-D; Ombest-D; Omcare-D; Omcure-D;

Omdom; Omecer-D; Omecid-D; Omecid-RD; Omecip-D; Omecos-D; Omeezol-D; Omejel-DM; Omelax-D; Omen-D; Omepraz-HP Kit; Omeraze-D; Omeris-D; Omesun-D; Omesym-D; Omevar-D; Omez Insta; Omex-D; Omfact-D; Omibase-D; Omic-D; Omicas-D; Omicool-D; Omidec; Omidip; Omidom; Omiflux; Omig-DM; Omilee-D; Omitive-D; Omitop-DM; Omitop; Omizol-D; Omkair-D; Omlink-D; Omlo-D; Ommac Plus; Omore-D; Omoxitin; Ompil-D; Ompraz-D; Omprest-D; Omracap-DM; Omriz-D; Omven-D; Omzee-D; Onazole-DP; Onazole-RD; Oned; Onto-D; Op-Zole D; Opaz-DM; Opel-D; Opera-D; Oraz-D; Orole-D; Ospicid-D; Ossum-D; OTC HP Kit; OTG-D; Otto-D; Ozed-D; Ozodom; Ozol-D; Pacidom-O; *Malaysia:* Pylobact Combi; *Mex.:* Pridamiral Pack; *NZ:* Losec Hp7; *Philipp.:* OAC Hp7+; *Rus.:* Domstal-O (Домстал-О); Omez D (Омез Д); Pylobact (Пилобакт); *Ukr.:* Linzer (Линцер); Omez-D (Омез-Д); Pylobact Neo (Пилобакт Нео); *USA:* Omeclamox-Pak; Zegerid.

Used as an adjunct in: *Arg.:* Dioxaflex Protect; *Philipp.:* Skelan Protect; *UK:* Axorid.

Pharmacopoeial Preparations

BP 2014: Gastro-resistant Omeprazole Capsules; Gastro-resistant Omeprazole Tablets; Omeprazole Oral Suspension;
USP 36: Omeprazole Delayed-Release Capsules; Omeprazole Oral Suspension.

Ondansetron *(BAN, rINN)*

GR-38032; Ondansetrón; Ondansétron; Ondansetroni; Ondansetronum; Ондансетрон.

(±)-1,2,3,9-Tetrahydro-9-methyl-3-(2-methylimidazol-1-ylmethyl)-carbazol-4(9*H*)-one.

$C_{18}H_{19}N_3O$=293.4

CAS — 99614-02-5; 116002-70-1.

ATC — A04AA01.

ATC Vet — QA04AA01.

UNII — 4AF302ESOS.

Pharmacopoeias. In *US.*

USP 36: (Ondansetron). A white to off-white powder. Sparingly soluble in water; very soluble in acid solutions. Store in airtight containers. Protect from light.

Ondansetron Hydrochloride

(BANM, USAN, rINNM)

GR-38032F; GR-C507-75; GR-C507/75; Hidrocloruro de ondansetrón; Odanserin; Ondansétron, chlorhydrate d'; Ondansetrón, hidrocloruro de; Ondansetron hydrochlorid; Ondansetronhydroklorid; Ondansetroni hydrochloridum; Ondansetronihydroklorid; Ondansetrono hidrochloridas; Ondanstroni Hydrochloridum; Ondánszetronhidroklorid; SN-307; Ондансетрона Гидрохлорид.

$C_{18}H_{19}N_3O.HCl.2H_2O$=365.9

CAS — 99614-01-4; 103639-04-9.

ATC — A04AA01.

ATC Vet — QA04AA01.

UNII — NMH84OZK2B.

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

Ph. Eur. 8: (Ondansetron Hydrochloride Dihydrate). A white or almost white powder. Sparingly soluble in water and in alcohol; slightly soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

USP 36: (Ondansetron Hydrochloride). A white to off-white powder. Sparingly soluble in water and in alcohol; very slightly soluble in acetone, in chloroform, and in ethyl acetate; slightly soluble in dichloromethane and in isopropyl alcohol; soluble in methyl alcohol. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Ondansetron hydrochloride and dexamethasone sodium phosphate were not compatible when high concentrations were combined in polypropylene syringes.[1] Lower concentrations (up to 640 micrograms/mL of ondansetron and 400 micrograms/mL of dexamethasone phosphate) were stable in 50 mL containers of infusion fluid for 30 days under refrigeration. Compatibility has been reported for 24 hours in plastic syringes at 4 degrees or 23 degrees with a variety of other drugs,[2] and with several antineoplastics (cytarabine, dacarbazine, doxorubicin, etoposide, or methotrexate) in PVC infusion bags for 48 hours at room temperature.[3]

1. Hagan RL, *et al.* Stability of ondansetron hydrochloride and dexamethasone sodium phosphate in infusion bags and syringes for 32 days. *Am J Health-Syst Pharm* 1996; 53: 1431–5.
2. Stewart JT, *et al.* Stability of ondansetron hydrochloride and 12 medications in plastic syringes. *Am J Health-Syst Pharm* 1998; 55: 2630–4.
3. Stewart JT, *et al.* Stability of ondansetron hydrochloride and five antineoplastic medications. *Am J Health-Syst Pharm* 1996; 53: 1297–1300.

Uses and Administration

Ondansetron is a 5-HT_3 antagonist (5-HT_3-receptor antagonist) with antiemetic activity. It is used in the management of **nausea and vomiting** induced by cytotoxic chemotherapy and radiotherapy. It is also used for the prevention and treatment of postoperative nausea and vomiting. For the management of nausea and vomiting, and the important role of 5-HT_3 antagonists, see p. 1811.3.

Ondansetron is given by intramuscular or slow intravenous injection or infusion as the hydrochloride, orally as the hydrochloride or base, or rectally as the base. Doses are expressed in terms of the base. Ondansetron hydrochloride 4.99 mg is equivalent to about 4 mg of ondansetron base.

Numerous dosing schedules of ondansetron have been used; some typical examples are cited below.

For *highly emetogenic* **chemotherapy** the following dose schedules appear to be equally effective in *preventing* acute emesis:

- a single dose of 8 mg by slow intravenous or intramuscular injection immediately before treatment

or

- 8 mg by slow intravenous or intramuscular injection immediately before treatment, either followed by a continuous intravenous infusion of 1 mg/hour for up to 24 hours, or by a further two doses of 8 mg two to four hours apart

or

- a single dose of 16 mg given by intravenous infusion over at least 15 minutes immediately before treatment, which can be followed by a further 2 doses of 8 mg by slow intravenous or intramuscular injection four hours apart

or

- 150 micrograms/kg (maximum 16 mg) by intravenous infusion over 15 minutes, beginning 30 minutes before chemotherapy, followed by a further 2 doses four hours apart

or

- a 16-mg suppository rectally, given 1 to 2 hours before treatment

or

- a single oral dose of 24 mg taken 30 minutes before the start of single-day chemotherapy

The efficacy of ondansetron in highly emetogenic chemotherapy may be enhanced by giving intravenous dexamethasone sodium phosphate 20 mg before chemotherapy.

Similar regimens to those given above are used for preventing acute emesis with *less emetogenic chemotherapy* and/or **radiotherapy** and also include:

- 8 mg given orally or by slow intravenous injection up to 2 hours before treatment, followed by an oral dose of 8 mg given 8 to 12 hours later

To protect against delayed emesis these regimens are followed by oral ondansetron 8 mg twice daily, or 16 mg rectally once daily, for up to 5 days after the end of a course of chemotherapy.

To *prevent* **postoperative nausea and vomiting** the following doses may be given:

- 16 mg orally an hour before anaesthesia

or

- 8 mg orally an hour before anaesthesia followed by 2 further doses of 8 mg at 8-hour intervals

or

- a single dose of 4 mg by slow intravenous or intramuscular injection at induction of anaesthesia

For the *treatment* of postoperative nausea and vomiting a single dose of 4 mg by intramuscular or slow intravenous injection is recommended.

For dosing in children, elderly patients, or those with hepatic impairment, see below.

Reviews.

1. Perez EA. A risk-benefit assessment of serotonin 5-HT_3 receptor antagonists in antineoplastic therapy-induced emesis. *Drug Safety* 1998; 18: 43–56.
2. Gregory RE, Ettinger DS. 5-HT_3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting: a comparison of their pharmacology and clinical efficacy. *Drugs* 1998; 55: 173–89.
3. Lindley C, Blower P. Oral serotonin type 3-receptor antagonists for prevention of chemotherapy-induced emesis. *Am J Health-Syst Pharm* 2000; 57: 1685–97.
4. Culy CR, *et al.* Ondansetron: a review of its use as an antiemetic in children. *Paediatr Drugs* 2001; 3: 441–79.
5. Gridelli C. 5-HT_3-receptor antagonists in the control of delayed-onset emesis. *Anticancer Res* 2003; 23: 2773–82.
6. Constenla M. 5-HT_3 receptor antagonists for prevention of late acute-onset emesis. *Ann Pharmacother* 2004; 38: 1683–91.
7. Aapro M. 5-HT_3-receptor antagonists in the management of nausea and vomiting in cancer and cancer treatment. *Oncology* 2005; 69: 97–109.
8. Anonymous. 5HT_3-receptor antagonists as antiemetics in cancer. *Drug Ther Bull* 2005; 43: 57–62.

Administration. Ondansetron has been successfully used by continuous *subcutaneous* infusion to control intractable nausea and vomiting.[1] Despite concern about the low pH of ondansetron injection there was no problem with the skin at the infusion site. An *oral* protocol for chemotherapy-induced emesis in children has been described;[2] efficacy was similar to intravenous use.

1. Mulvenna PM, Regnard CFB. Subcutaneous ondansetron. *Lancet* 1992; 339: 1059.
2. Walker PC, *et al.* Promoting the use of oral ondansetron in children receiving cancer chemotherapy. *Am J Health-Syst Pharm* 2001; 58: 598–602.

Administration in children. Ondansetron is used in children for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. It is also used for the prevention and treatment of postoperative nausea and vomiting. Ondansetron is given by slow intravenous injection or infusion as the hydrochloride, or orally as the hydrochloride or base. Doses are expressed in terms of the base.

In the USA a licensed regimen for **chemotherapy**-induced nausea and vomiting in children over 6 months of age is ondansetron 150 micrograms/kg by intravenous infusion 30 minutes before moderately to highly emetogenic chemotherapy, repeated 4 and 8 hours after the first dose. Alternatively, for children aged 4 to 11 years, an oral dose of 4 mg may be given 30 minutes before the start of moderately emetogenic chemotherapy, with subsequent 4-mg doses given 4 and 8 hours thereafter. An oral dose of 4 mg three times daily may be given for 1 to 2 days after the end of chemotherapy.

In the UK, ondansetron is licensed for use in children aged from 6 months and doses are calculated using body-weight or body-surface; weight-based dosing results in higher daily doses compared with those based on body-surface. In a typical regimen based on body-surface, an intravenous dose of ondansetron 5 mg/m^2 (maximum 8 mg) is infused (over at least 15 minutes) immediately before chemotherapy and followed after 12 hours by oral dosing for up to 5 days:

- children aged from 6 months and less than 0.6 m^2 body-surface: 2 mg every 12 hours
- from 6 months and 0.6 m^2 and over: 4 mg every 12 hours

When using body-weight, an intravenous dose of ondansetron 150 micrograms/kg (maximum 8 mg) is given immediately before chemotherapy and repeated every 4 hours for up to 3 doses. This is followed after 12 hours by oral dosing for up to 5 days:

- body-weight 10 kg and less: 2 mg every 12 hours
- over 10 kg: 4 mg every 12 hours

The daily dose of ondansetron by any route should not exceed 32 mg.

While ondansetron is not licensed in the UK for **radiotherapy**-induced nausea and vomiting in children the *BNFC* recommends the same doses as those used for chemotherapy-induced nausea and vomiting (above).

A protocol for oral ondansetron dosage, with similar efficacy to intravenous use, has also been described, see Administration, above.

For the prevention and treatment of **postoperative nausea and vomiting** in children aged from 1 month 100 micrograms/kg may be given by slow intravenous injection, up to a maximum dose of 4 mg.

Administration in the elderly. Most licensed product information for ondansetron states that dose adjustments for patients over 65 years of age are not necessary. However the product information for one preparation (*Zofran; GSK UK*) recommends that patients over 75 years of age are given an initial dose of 8 mg by intravenous infusion over 15 minutes for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy; this may be followed by a further 2 infusions of 8 mg given at least four hours apart.

Administration in hepatic impairment. Licensed product information recommends that the dose of ondansetron should not exceed 8 mg daily in patients with moderate or severe hepatic impairment. When this dose was given intravenously to patients with hepatic impairment, those with severe impairment showed an increase in the area under the plasma concentration/time curve and in the terminal plasma half-life, and a decrease in plasma clearance.[1] The authors of this study, some of whom worked for the manufacturers (*Glaxo*), considered that ondansetron should be restricted to once daily dosage in severe hepatic impairment.

1. Blake JC, *et al.* The pharmacokinetics of intravenous ondansetron in patients with hepatic impairment. *Br J Clin Pharmacol* 1993; 35: 441–3.

Bulimia nervosa. A combination of counselling, supportive psychotherapy, and antidepressants is the usual treatment of bulimia nervosa. Preliminary reports have indicated

that ondansetron may be of benefit in the treatment of this disorder.[1,2]

1. Faris PL, *et al.* Effect of decreasing afferent vagal activity with ondansetron on symptoms of bulimia nervosa: a randomised, double-blind trial. *Lancet* 2000; 355: 792–7.
2. Pung SM, Ferrill MJ. Treatment of bulimia nervosa with ondansetron. *Ann Pharmacother* 2001; 35: 1270–3.

Fatigue. Preliminary results indicated that treatment with 5-HT_3 antagonists such as ondansetron and tropisetron may be of benefit in patients with chronic fatigue.[1] Oral ondansetron 4 mg twice daily was reported[2] to resolve fatigue in a woman with chronic hepatitis C. In a randomised study in 36 patients with chronic hepatitis C, this dose of ondansetron given for 1 month significantly improved fatigue scores at day 15 and day 60 (beyond the treatment period) when compared with placebo.[3] The authors noted that patient awareness that constipation was a possible effect of active treatment may have potentially unblinded the study. Further confirmation by larger studies is needed.

1. Späth M, *et al.* Treatment of chronic fatigue syndrome with 5-HT_3 receptor antagonists—preliminary results. *Scand J Rheumatol* 2000; 113 (suppl): 72–7.
2. Jones EA. Relief from profound fatigue associated with chronic liver disease by long-term ondansetron therapy. *Lancet* 1999; 354: 397.
3. Piche T, *et al.* Effect of ondansetron, a 5-HT_3 receptor antagonist, on fatigue in chronic hepatitis C: a randomised, double blind, placebo controlled study. *Gut* 2005; 54: 1169–73.

Gastroenteritis. Antiemetics such as ondansetron have been tried to reduce vomiting during acute gastroenteritis in children. Reviews[1-3] have found that ondansetron (given orally or intravenously) reduces the risk of persistent vomiting, the need for intravenous fluids, and hospital admissions; an increased incidence of diarrhoea was seen, but further research was considered necessary to determine its clinical significance.[2] Metoclopramide was also effective in reducing the number of vomiting episodes and hospital admissions, although it was less often used because of its potentially serious adverse effects.[3]

1. DeCamp LR, *et al.* Use of antiemetic agents in acute gastroenteritis: a systematic review and meta-analysis. *Arch Pediatr Adolesc Med* 2008; 162: 858–65.
2. Phillips B. Towards evidence based medicine for paediatricians. *Arch Dis Child* 2010; 95: 945–7.
3. Fedorowicz Z, *et al.* Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 9. Chichester: John Wiley; 2011 (accessed 05/10/11).

Pain. Preliminary results from a small crossover study[1] indicated that oral ondansetron was more effective than paracetamol in relieving the pain of fibromyalgia, a chronic disorder that responds poorly to conventional analgesics. A single bolus of ondansetron given to patients with chronic neuropathic pain significantly reduced pain scores 2 hours after injection in a placebo-controlled study;[2] this effect may be due to an action on 5-HT_3 receptors in the spinal cord.

Other 5-HT_3 antagonists such as granisetron[3-5] and tropisetron[6-8] have also been investigated in various painful syndromes.

1. Hrycaj P, *et al.* Pathogenetic aspects of responsiveness to ondansetron (5-hydroxytryptamine type 3 receptor antagonist) in patients with primary fibromyalgia syndrome—a preliminary study. *J Rheumatol* 1996; 23: 1418–23.
2. McCleane GJ, *et al.* Does a single intravenous injection of the 5HT3 receptor antagonist ondansetron have an analgesic effect in neuropathic pain? A double-blinded, placebo-controlled cross-over study. *Anesth Analg* 2003; 97: 1474–8.
3. Voog O, *et al.* Immediate effects of the serotonin antagonist granisetron on temporomandibular joint pain in patients with systemic inflammatory disorders. *Life Sci* 2000; 68: 591–602.
4. Dubey PK, Prasad SS. Pain on injection of propofol: the effect of granisetron pretreatment. *Clin J Pain* 2003; 19: 121–4.
5. Ernberg M, *et al.* Effects on muscle pain by intramuscular injection of granisetron in patients with fibromyalgia. *Pain* 2003; 101: 275–82.
6. Farber L, *et al.* Short-term treatment of primary fibromyalgia with the 5-HT3-receptor antagonist tropisetron: results of a randomized, double-blind, placebo-controlled multicenter trial in 418 patients. *Int J Clin Pharmacol Res* 2001; 21: 1–13.
7. Stratz T, *et al.* Local treatment of tendinopathies: a comparison between tropisetron and depot corticosteroids combined with local anesthetics. *Scand J Rheumatol* 2002; 31: 366–70.
8. Spath M, *et al.* Efficacy and tolerability of intravenous tropisetron in the treatment of fibromyalgia. *Scand J Rheumatol* 2004; 33: 267–70.

Pruritus. There are several case reports[1,2] of cholestatic pruritus (p. 1687.3) responding to intravenous or oral ondansetron, including one in pregnancy.[3] However, results from controlled studies[4-6] have been mixed. It is similarly unclear if ondansetron is of benefit in pruritus due to renal failure,[7-9] and results have been conflicting from controlled studies evaluating its use in opioid-induced pruritus.[10-15] There are reports of ondansetron ameliorating the pruritus associated with some skin disorders.[16] Other 5-HT_3 antagonists such as tropisetron[9] and dolasetron[14] have also been investigated.

1. Schwörer H, Ramadori G. Improvement of cholestatic pruritus by ondansetron. *Lancet* 1993; 341: 1277.
2. Raderer M, *et al.* Ondansetron for pruritus due to cholestasis. *N Engl J Med* 1994; 330: 1540.
3. Schumann R, Hudcova J. Cholestasis of pregnancy, pruritus and 5-hydroxytryptamine 3 receptor antagonists. *Acta Obstet Gynecol Scand* 2004; 83: 861–2.
4. Müller C, *et al.* Treatment of pruritus in chronic liver disease with the 5-hydroxytryptamine receptor type 3 antagonist ondansetron: a randomized, placebo-controlled, double-blind cross-over trial. *Eur J Gastroenterol Hepatol* 1998; 10: 865–70.
5. O'Donohue JW, *et al.* A controlled trial of ondansetron in the pruritus of cholestasis. *Aliment Pharmacol Ther* 2005; 21: 1041–5.
6. Jones EA, *et al.* Ondansetron and pruritus in chronic liver disease: a controlled study. *Hepatogastroenterology* 2007; 54: 1196–9.
7. Balaskas EV, *et al.* Histamine and serotonin in uremic pruritus: effect of ondansetron in CAPD-pruritic patients. *Nephron* 1998; 78: 395–402.
8. Murphy M, *et al.* A randomized, placebo-controlled, double-blind trial of ondansetron in renal itch. *Br J Dermatol* 2003; 148: 314–7.
9. Weisshaar E, *et al.* Antipruritic effects of two different 5-HT3 receptor antagonists and an antihistamine in haemodialysis patients. *Exp Dermatol* 2004; 13: 298–304.
10. Borgeat A, Stirnemann H-R. Ondansetron is effective to treat spinal or epidural morphine-induced pruritus. *Anesthesiology* 1999; 90: 432–6.
11. Korhonen AM, *et al.* Ondansetron does not prevent pruritus induced by low-dose intrathecal fentanyl. *Acta Anaesthesiol Scand* 2003; 47: 1292–7.
12. Wells J, *et al.* Intrathecal fentanyl-induced pruritus during labour: the effect of prophylactic ondansetron. *Int J Obstet Anesth* 2004; 13: 35–9.
13. Waxler B, *et al.* Prophylactic ondansetron does not reduce the incidence of itching induced by intrathecal sufentanil. *Can J Anesth* 2004; 51: 685–9.
14. Iatrou CA, *et al.* Prophylactic intravenous ondansetron and dolasetron in intrathecal morphine-induced pruritus: a randomized, double-blinded, placebo-controlled study. *Anesth Analg* 2005; 101: 1516–20.
15. Siddik-Sayyid SM, *et al.* Does ondansetron or granisetron prevent subarachnoid morphine-induced pruritus after cesarean delivery? *Anesth Analg* 2007; 104: 421–4.
16. Zenker S, *et al.* Behandlung von Pruritus als Symptom von Hauterkrankungen mit dem Serotonin-Rezeptorantagonisten Ondansetron. *J Dtsch Dermatol Ges* 2003; 1: 705–10.

Psychiatric disorders. Ondansetron has been tried experimentally in several psychiatric disorders including schizophrenia,[1-3] and psychosis in patients with parkinsonism,[4] and may be of value in moderating tardive dyskinesia.[5] A reduction in tic severity in Tourette's syndrome (see Tics, p. 1030.1) has been reported,[6] and preliminary results have suggested benefit in obsessive-compulsive disorder,[7] and bulimia nervosa (see p. 1872.3). It is also reported to be under investigation in the management of panic attacks (p. 1029.1). For the more conventional management of schizophrenia, parkinsonism, and obsessive-compulsive disorder see p. 1031.3, p. 889.1, and p. 1028.2, respectively.

1. White A, *et al.* Ondansetron in the treatment of schizophrenia. *Lancet* 1991; 337: 1173.
2. Adler LE, *et al.* Improved P50 auditory gating with ondansetron in medicated schizophrenia patients. *Am J Psychiatry* 2005; 162: 386–8.
3. Levkovitz Y, *et al.* The effect of ondansetron on memory in schizophrenic patients. *Brain Res Bull* 2005; 65: 291–5.
4. Zoldan J, *et al.* Psychosis in advanced Parkinson's disease: treatment with ondansetron, a 5-HT_3 receptor antagonist. *Neurology* 1995; 45: 1305–8.
5. Sirota P, *et al.* Use of the selective serotonin 3 receptor antagonist ondansetron in the treatment of neuroleptic-induced tardive dyskinesia. *Am J Psychiatry* 2000; 157: 287–9.
6. Toren P, *et al.* Ondansetron treatment in Tourette's disorder: a 3-week, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2005; 66: 499–503.
7. Pallanti S, *et al.* Ondansetron augmentation in treatment-resistant obsessive-compulsive disorder: a preliminary, single-blind, prospective study. *CNS Drugs* 2009; 23: 1047–55.

Substance dependence. Ondansetron is being studied in the management of alcohol dependence (p. 1734.1). However, in one study[1] a significant reduction in alcohol consumption was found only in lighter drinkers after subgroup analysis. Another study[2] found a reduction in alcohol consumption by patients with early-onset alcoholism (onset before age 25) who took ondansetron compared with placebo. No such effect was seen, however, in patients with late-onset alcoholism. Further study found that ondansetron also effectively ameliorated mood disturbances including symptoms of depression, anxiety, and hostility, in early-onset alcoholics.[3] Self-reported alcohol consumption also reduced in adolescents (between ages 14 and 20) with alcohol dependence who were given ondansetron in an open study.[4]

1. Sellers EM, *et al.* Clinical efficacy of the 5-HT_3 antagonist ondansetron in alcohol abuse and dependence. *Alcohol Clin Exp Res* 1994; 18: 879–85.
2. Johnson BA, *et al.* Ondansetron for reduction of drinking among biologically predisposed alcoholic patients. *JAMA* 2000; 284: 963–71.
3. Johnson BA, *et al.* Ondansetron reduces mood disturbance among biologically predisposed, alcohol-dependent individuals. *Alcohol Clin Exp Res* 2003; 27: 1773–9.
4. Dawes MA, *et al.* A prospective, open-label trial of ondansetron in adolescents with alcohol dependence. *Addict Behav* 2005; 30: 1077–85.

Adverse Effects and Precautions

Ondansetron and other 5-HT_3 antagonists may cause headache, a sensation of flushing or warmth, hiccups, and constipation. A transient rise in liver enzymes has occasionally occurred. There have been rare reports of immediate hypersensitivity reactions, including anaphylaxis. Chest pain, arrhythmias, hypotension, tachycardia, and bradycardia have been reported rarely. Dizziness and transient visual disturbances such as blurred vision (or very rarely, transient blindness) have been reported during rapid intravenous injection. Transient ECG changes including QT interval prolongation have occurred very rarely, mainly with intravenous ondansetron. Seizures and movement disorders, including extrapyramidal reactions such as dystonia, dyskinesia, and oculogyric crisis have been reported. Rashes and urticaria have also occurred. Injection site reactions may develop, and local burning sensations are common after insertion of suppositories.

5-HT_3 antagonists should generally not be used in patients who have had a hypersensitivity reaction to a member of this drug class. They should be used with care in patients with signs of subacute intestinal obstruction or ileus. Ondansetron should be given in reduced doses to patients with moderate to severe hepatic impairment.

Effects on carbohydrate metabolism. Hypoglycaemia associated with dystonia and seizures developed in a four-year-old child after ondansetron treatment for vomiting.[1] Blood glucose concentrations returned to normal with intravenous glucose. Indirect inhibition of stress-induced corticotropin and cortisol secretion via the effects of ondansetron on serotonergic pathways was suggested as a possible cause for the hypoglycaemia. For more reports of extrapyramidal effects and seizures, see Effects on the Nervous System, p. 1874.1.

1. Patel A, *et al.* Ondansetron-induced dystonia, hypoglycemia, and seizures in a child. *Ann Pharmacother* 2011; 45: e7.

Effects on the cardiovascular system. In 1992 chest pain and/or cardiac arrhythmias that might have been associated with ondansetron were reported[1] in 4 patients, 2 of whom died. In 3 subsequent patients who developed severe chest or anginal pain, treatment with ondansetron was stopped.

The manufacturers (*Glaxo*) had at that time no evidence of a causal relationship between ondansetron and episodes of chest pain and cardiac abnormalities.[2] Giving ondansetron or granisetron intravenously produced no clinically important cardiovascular changes in a study in 12 healthy subjects.[3] Since then, however, hypotension, coronary vasospasm, and atrial fibrillation have been reported with ondansetron,[4] and myocardial ischaemia has been reported with both ondansetron[5] and dolasetron;[6] in the latter case this led to an acute myocardial infarction. Supraventricular tachycardia reported with dolasetron was attributed to an interaction with sevoflurane.[7] Dolasetron-induced torsade de pointes has also occurred,[8] and overdose of dolasetron has produced prolongation of the QT_c interval and hypotension.[9] Another study in healthy subjects found that dolasetron mainly altered ECG parameters indicative of ventricular depolarisation, whereas ondansetron affected mainly ventricular repolarisation.[10] However, ECG changes were transient and asymptomatic. Studies of high-dose intravenous granisetron[11-13] found no significant adverse effects on pulse, blood pressure, or ECG measurements. A review[14] of the electrocardiographic and cardiovascular effects of the 5-HT_3 antagonists concluded that although this class of drugs may cause small, transient ECG changes, the clinical benefits of the drugs outweighed the small theoretical risk of any clinically significant cardiovascular events. Nonetheless, the use of dolasetron in children has been contra-indicated in some countries (see Administration in Children, p. 1837.3).

1. Ballard HS, *et al.* Ondansetron and chest pain. *Lancet* 1992; 340: 1107.
2. Palmer JBD, Greenstreet YL. Ondansetron and chest pain. *Lancet* 1992; 340: 1410.
3. Boike SC, *et al.* Cardiovascular effects of i.v. granisetron at two administration rates and of ondansetron in healthy adults. *Am J Health-Syst Pharm* 1997; 54: 1172–6.
4. Havrilla PL, *et al.* Coronary vasospasm and atrial fibrillation associated with ondansetron therapy. *Ann Pharmacother* 2009; 43: 532–6.
5. Bosek V, *et al.* Acute myocardial ischemia after administration of ondansetron hydrochloride. *Anesthesiology* 2000; 92: 885–7.
6. Arole A, *et al.* Coronary vasospasm leading to an acute myocardial infarction after the administration of dolasetron. *J Clin Anesth* 2005; 17: 72–4.
7. Higgins DJ, Bunker NJ. Dolasetron and peri-operative cardiac arrhythmia. *Anaesthesia* 2005; 60: 936–7.
8. Turner S, *et al.* Dolasetron-induced torsades de pointes. *J Clin Anesth* 2007; 19: 622–5.
9. Rochford M, *et al.* Dolasetron overdose resulting in prolonged QTc interval and severe hypotension: a case report and literature review. *Emerg Med J* 2007; 24: 515–7.
10. Benedict CR, *et al.* Single-blind study of the effects of intravenous dolasetron mesylate versus ondansetron on electrocardiographic parameters in normal volunteers. *J Cardiovasc Pharmacol* 1996; 28: 53–9.
11. Carmichael J, Harris AL. High-dose i.v. granisetron for the prevention of chemotherapy-induced emesis: cardiac safety and tolerability. *Anticancer Drugs* 2003; 14: 739–44.
12. Carmichael J, Harris AL. The cardiovascular safety of high-dose intravenous granisetron in cancer patients receiving highly emetogenic chemotherapy. *Cancer Chemother Pharmacol* 2004; 53: 123–8.
13. Aapro M, Bourke JP. Rapid intravenous administration of granisetron prior to chemotherapy is not arythmogenic [sic]: results of a pilot study. *Eur J Cancer* 2003; 39: 927–31.
14. Navari RM, Koeller JM. Electrocardiographic and cardiovascular effects of the 5-hydroxytryptamine$_3$ receptor antagonists. *Ann Pharmacother* 2003; 37: 1276–86.

Effects on the eyes. Blurring followed by transient loss of vision has been reported after rapid intravenous injection of ondansetron.[1] Oculogyric crisis may occur as part of

extrapyramidal reactions seen with ondansetron, see Effects on the Nervous System, below.

1. Cherian A, Maguire M. Transient blindness following intravenous ondansetron. *Anesthesia* 2005; 60: 938–9.

Effects on the liver. Although disturbances in liver enzyme values have been reported in patients given ondansetron,[1] more severe symptoms of liver disorder appear to be very rare; however, there is a report of severe jaundice associated with ondansetron as an antiemetic for chemotherapy.[2] Symptoms did not recur when the patient received granisetron.

1. Lewandowski MJ, Chapman SA. Ondansetron-induced aminotransferase level elevation: case report and review of the literature. *Pharmacotherapy* 2008; 28: 1542–6.
2. Verrill M, Judson I. Jaundice with ondansetron. *Lancet* 1994; 344: 190–1.

Effects on the nervous system. Tonic-clonic movements and frothing at the mouth occurred in a patient 90 minutes after an infusion of ondansetron;[1] the patient responded to diazepam intravenously. The manufacturers had seen 10 patients who developed *seizures* during initial clinical studies, but considered that, unlike this case, all these patients had predisposing factors. Hypotension and generalised tonic-clonic seizures were reported in a patient with metastatic breast cancer given ondansetron as an intravenous bolus.[2] Although seizures might have been due to brain metastases, the authors concluded that ondansetron had been the likely cause, since the patient had no further problems when antiemetic therapy was changed to metoclopramide. A seizure associated with palonosetron therapy has also been reported.[3] *Extrapyramidal reactions* in patients given ondansetron as part of a chemotherapy regimen[4,5] and for postoperative nausea and vomiting[6–8] have also been reported. In one case,[8] transient multifocal encephalopathy developed. Clinical manifestations such as clonus, oculogyric crisis, and oromandibular and limb dystonia resembled those of structural brain injury, and response to diphenhydramine was poor; despite this, the patient made a full neurological recovery over the course of 12 hours. For reference to seizures and dystonia associated with hypoglycaemia in an ondansetron-treated child see Effects on Carbohydrate Metabolism, p. 1873.3. Ondansetron and related drugs can induce *headache*; it has sometimes been confused with post-dural puncture headache.[9]

1. Sargent AL *et al.* Seizure associated with ondansetron. *Clin Pharm* 1993; 12: 613–15.
2. Sharma A, Raina V. Generalised seizures following ondansetron. *Ann Oncol* 2001; 12: 131–2.
3. Zambelli A, *et al.* Seizure associated with palonosetron. *Support Care Cancer* 2009; 17: 217.
4. Krstenansky PM, *et al.* Extrapyramidal reaction caused by ondansetron. *Ann Pharmacother* 1994; 28: 280.
5. Mathews HG, Tancil CG. Extrapyramidal reaction caused by ondansetron. *Ann Pharmacother* 1996; 30: 196.
6. Stonell C. An extrapyramidal reaction to ondansetron. *Br J Anaesth* 1998; 81: 658.
7. Tolan MM, *et al.* Perioperative extrapyramidal reactions associated with ondansetron. *Anesthesiology* 1999; 90: 340–1.
8. Ritter MJ, *et al.* Ondansetron-induced multifocal encephalopathy. *Mayo Clin Proc* 2003; 78: 1150–2.
9. Sharma R, Panda A. Ondansetron-induced headache in a parturient mimicking postdural puncture headache. *Can J Anaesth* 2010; 57: 187–8.

Hypersensitivity. Anaphylactoid reactions have been reported in patients given ondansetron injections. The FDA stated in October 1993 that it had received 24 reports of such reactions,[1] mostly occurring after the first ondansetron dose of the second or third chemotherapy cycle, and characterised by urticaria, angioedema, hypotension, bronchospasm, and dyspnoea. Similar effects have been reported in a patient with no prior exposure to ondansetron.[2] A protocol for skin testing has been documented.[3]

Cross-sensitivity between 5-HT_3 antagonists has been reported;[4] 2 patients who had had a mild hypersensitivity reaction to one 5-HT_3 antagonist developed a more severe reaction after exposure to another. In the first case severe acute asthma, cyanosis, and loss of consciousness developed after ondansetron in a patient who had previously had an asthmatic reaction after tropisetron. The second patient had developed pruritus after a tropisetron injection and urticaria after ondansetron, and subsequently developed anaphylactic shock 5 minutes after a further dose of tropisetron. It was recommended that another 5-HT_3 antagonist should not be given as a replacement to patients who developed a hypersensitivity reaction to a drug of this class. However, there are reports of the successful use of granisetron in patients sensitive to ondansetron[5] and vice versa.[6]

1. Chen M, *et al.* Anaphylactoid-anaphylactic reactions associated with ondansetron. *Ann Intern Med* 1993; 119: 862.
2. Weiss KS. Anaphylactic reaction to ondansetron. *Arch Intern Med* 2001; 161: 2263.
3. Fernando SL, Broadfoot AJ. Ondansetron anaphylaxis: a case report and protocol for skin testing. *Br J Anaesth* 2009; 102: 285–6.
4. Kataja V, de Bruijn KM. Hypersensitivity reactions associated with 5-hydroxytryptamine$_3$-receptor antagonists: a class effect? *Lancet* 1996; 347: 584–5.
5. Bousquet PJ, *et al.* Isolated urticaria to ondansetron and successful treatment with granisetron. *Allergy* 2005; 60: 543–4.
6. Kanny G, *et al.* IgE-mediated allergy to granisetron and safe use of ondansetron. *J Allergy Clin Immunol* 2001; 108: 1059–60.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ondansetron 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 07/10/11)

Interactions

Ondansetron does not appear to induce or inhibit the cytochrome P450 isoenzyme system, but it is itself metabolised by multiple hepatic isoenzymes, including CYP3A4, CYP2D6, and CYP1A2. US licensed product information states that inducers or inhibitors of these isoenzymes may change the clearance and half-life of ondansetron, but that on the basis of available data, no dose adjustments are recommended. UK licensed product information states that enzyme inhibition of one isoenzyme is usually compensated for by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement. Potent inducers of CYP3A4, such as phenytoin, carbamazepine, and rifampicin, have been reported to increase ondansetron clearance and reduce ondansetron plasma concentrations.

Because of the reports of transient ECG changes in some patients taking 5-HT_3 antagonists (see p. 1873.3), there is a theoretical need for caution if given with drugs that prolong QT-interval or cardiotoxic drugs such as anthracyclines; however, clinical evidence of a significant interaction seems to be mostly lacking.

Analgesics. For evidence of reduced analgesic efficacy of *tramadol* in patients also given 5-HT_3-receptor antagonists, such as ondansetron, see p. 140.3.

Antibacterials. *Rifampicin* pretreatment reduced the area under the plasma concentration-time curve of oral ondansetron by 65% and of intravenous ondansetron by 48% in healthy subjects.[1] Use of rifampicin, or other potent inducers of cytochrome P450 isoenzyme CYP3A4, with ondansetron may reduce antiemetic efficacy.

1. Villikka K, *et al.* The effect of rifampin on the pharmacokinetics of oral and intravenous ondansetron. *Clin Pharmacol Ther* 1999; 65: 377–81.

Antineoplastics. For mention of retrospective studies suggesting a change of pharmacokinetic parameters of high-dose cyclophosphamide and cisplatin when given with an ondansetron-containing antiemetic regimen, see Gastrointestinal Drugs, p. 773.3.

Pharmacokinetics

Peak plasma concentrations of ondansetron occur about 1.5 hours after an oral dose of 8 mg, and about 6 hours after a rectal dose. The absolute bioavailability is about 60%, mainly because of hepatic first-pass metabolism. In elderly subjects, bioavailability may be somewhat higher (65%) and clearance lower, presumably due to reduced hepatic first-pass metabolism.

Ondansetron is extensively distributed in the body; about 70 to 75% of the drug in plasma is protein bound. It is metabolised in the liver through multiple enzymatic pathways; ondansetron is a substrate for cytochrome P450 isoenzymes, primarily CYP3A4, but also CYP1A2 and CYP2D6. Less than 5% of a dose is excreted unchanged in the urine.

The terminal elimination half-life is about 3 hours after oral or parenteral doses, and about 6 hours after rectal use. The terminal elimination half-life is prolonged to about 5 hours in the elderly and in those with renal impairment. These differences are not considered sufficient to warrant dosage adjustment. However, in patients with severe hepatic impairment, bioavailability may approach 100% and clearance is markedly reduced, with elimination half-lives of 15 to 32 hours; dosage restriction is advisable (see Administration in Hepatic Impairment, p. 1872.3). In general, children have a higher clearance than adults, although age-related reductions in clearance have also been reported, with younger children having lower clearances. Use of weight-based doses compensates for these changes and normalises exposure in paediatric patients.

References.
1. Rolia F, Del Favero A. Ondansetron clinical pharmacokinetics. *Clin Pharmacokinet* 1995; 29: 95–109.
2. Figg WD, *et al.* Pharmacokinetics of ondansetron in patients with hepatic insufficiency. *J Clin Pharmacol* 1996; 36: 206–15.
3. Van Den Berg CM, *et al.* Pharmacokinetics of three formulations of ondansetron hydrochloride in healthy volunteers: 24-mg oral tablet, rectal suppository, and iv infusion. *Am J Health-Syst Pharm* 2000; 57: 1046–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cetron; Dantenk; Dismolan; Espasevit; Finaber; Finoxi†; Tiosalis; Zofran; ***Austral.***: Ondaz; Onsetron; Zofran; ***Austria.***: Ondensan; Zofran; Zotrix†; ***Belg.***: Avessa†; Avessaron; Zofran; ***Braz.***: Ansentron; Injectra; Modifical; Nausedron; Ondantril; Ontrax; Vonau; Zofrar; ***Canad.***: Zofran; ***Chile.***: Amilene; Gardoton; Izofran; Levro; Odanex†; Oncoemet†; Trorix†; ***China.***: An Si Xin (安斯欣; Aoyimai (奥一麦); Di Li Xin (地力昕); En Pu De (恩复德); En Nuo Ping (恩诺平); Fu Mi Ting (富米汀); Kang Da Li Te (康达立特); Lu Wei Sen (路维森); Ou Bei (欧贝); Shi Tai (时泰); Wei Ze (维泽); Yi Feng (奕丰); Yi Shu Ning (益舒宁); Zofran (枢复宁; Zudan (枢丹); Cz.: Danemet†; Emeset; Novetron; Ondemet; Setronon†; Zofran; ***Denm.***: Setofilm; Setrogen; Zofran; Zotrix†; ***Fin.***: Zofran; ***Fr.***: Setofilm; Zophren; ***Ger.***: Axisetron; cellondar; Zofran; ***Gr.***: Biosetron; Cruzafen; Dentron; Fedral; Jodol; Nofai; Odasen; Odnatron; Onda; Ondameton; Ondaren; Ondasepro; Ondeton; Otredil; Setrodan; Trondamet; Vefron; Zetron; Zodatron; Zofron; Zophralen; ***Hong Kong***: Zofran; ***Hung.***: Antivom; Emetron; Ondagen; Zofran; ***India***: Adom-O; Afon MD; Anse care; Anset; Back2Norm; C-Tron; Danset; Dasin; Dentron Doin; Domi-Up; Donset; Donsetron; Doran-O; Dotson; Dutron E-On; Eldon; Emeran; Emeset; Emestal-O; Emestop; Emigo Emitino; Emitus; Emnil; Emsetron; Emstal; Emtron; Flatron Flexi; Fodino; Gendem-MD; Glendan; Glotron; K-Tron; Kansei Keron; Lupisetron; Monda; Myset; Mytic; Naucet; Naucid; Neomit; Nitron; Nosirid; Novatron; Nuset; O-Set; Odanse; Olex Tab Ominil; Omit; Onbit; Oncare; Oncoden; Oncon; Ond; Ondace Ondai; Ondansetran; Ondanz; Ondar; Ondarom; Ondas; Ondavom; Ondax; Ondem; Ondemet-MD; Ondet; Ondigo; Onditron Ondocil; Ondocos; Ondorise; Ondosia; Ondosym; Ondot Ondrea; Ondron; Ondrovit; Onest; Ongone; Oniz; Onkam Onlex; Ono; Onriz; Onsat; Onset; Onsett; Onstal; Onstar Ontek; Ontic; Ontil; Ontiz; Ontome; Onv; Onvin; Onzy; Oralis Orio-DT; Oset; Osetron; Otron; Periset; Vomiof; ***Indon.***: Cedantron; Ceteron; Dantroxal; Entron; Frazon; Invomit; Kliran Lametic; Narfoz; Odanostin; Ondavell; Onetic; Trovensis; Vomceran; Vometraz; Vometron; Zantron; Zofran; ***Irl.***: Emital† Emizof; Ondatab; Ondran; Setofilm; Zofran; ***Israel***: Zofran ***Ital.***: Zofran; ***Malaysia***: Osetron; Setronax; Zofran; ***Mex.***: Danac Dosatron; Modifical; Nalisen; Nodanton†; Onancen; Ondal; Precirux; Vosrym; Zofran; ***Neth.***: Setofilm; Zofran; ***Norw.***: Zofran ***NZ***: Ondanaccord; Onsetron†; Zofran; ***Philipp.***: Emistop; Emodan; Nozuca; Onset; Vometron; Zofran; ***Pol.***: Atossa; Emetron Ondagen; OndaLEK; Setronon; Zofran; ***Port.***: Emetron; Morpar Nausiend†; Olmar; Otobrol; Zofran; ***Rus.***: Domegan (Домеган) Emeset (Эмесет); Emetron (Эметрон); Latran (Латран); Ondaso (Ондасол); Osetron (Осетрон); Setronon (Сетронон); Zofrar (Зофрар); ***S.Afr.***: Alepet; Danset; Dantron; Nausetron; Vomiz Zofer; Zofran; ***Singapore***: Osetron; Setronax; Zofran; ***Spain*** Carvyx†; Setofilm; Yatrox; Zofran; ***Swed.***: Zofran; Zotrix† ***Switz.***: Zofran; ***Thai.***: Dantron; Emeset; Emistop; Ondavell Onsia; Zetron; Zofran; ***Turk.***: Zofer; Zofran; Zoltem; Zontron Zophralen; ***UK***: Ondemet; Setofilm; Zofran; ***Ukr.***: Emetror (Эметрон); Osetron (Осетрон); Setronon (Сетронон); Zofrar (Зофрар); Zoltem (Золтем); ***USA***: Zofran; Zuplenz; ***Venez.***: Dismolan; Emeset; Tructum; Zofran.

Multi-ingredient Preparations. *India*: Acidom-O; Alcirid-O; Alotac; Doran-O; Lupisetron Plus; Ond-R.

Pharmacopoeial Preparations

BP 2014: Ondansetron Injection; Ondansetron Tablets;

USP 36: Ondansetron Hydrochloride Oral Suspension; Ondansetron Injection; Ondansetron Oral Solution; Ondansetron Orally Disintegrating Tablets; Ondansetron Tablets.

Oxapium Iodide *(rINN)*

Ciclonium Iodide; Cyclonium Iodide; Ioduro de oxapio; Oxapii Iodidum; Oxapium, Iodure d'; SH-100; Оксапия Йодид.

1-(2-Cyclohexyl-2-phenyl-1,3-dioxolan-4-ylmethyl)-1-methylpiperidinium iodide.

$C_{27}H_{34}INO_2$=471.4

CAS — 6577-41-9.

UNII — 682380CG4N.

NOTE. Distinguish from Ciclonium Bromide, p. 1827.1, an unrelated antispasmodic.

Pharmacopoeias. In *Jpn.*

Profile

Oxapium iodide is an antimuscarinic that has been used as an antispasmodic in the treatment of gastrointestinal disorders and renal calculi.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Esperan.

Oxyphencyclimine Hydrochloride

(BANM, rINNM)

Hidrocloruro de oxifenciclimina; Oksifensiklimin Hidroklorür; Oxifenciclimina, hidrocloruro de; Oxyphencyclimine, Chlorhydrate d'; Oxyphencyclimini Hydrochloridum; Оксифенциклимина Гидрохлорид.

1,4,5,6-Tetrahydro-1-methylpyrimidin-2-ylmethyl α-cyclohexylmandelate hydrochloride.

$C_{20}H_{28}N_2O_3$,HCl=380.9

CAS — 125-53-1 (oxyphencyclimine); 125-52-0 (oxyphencyclimine hydrochloride).

ATC — A03AA01.

ATC Vet — QA03AA01.

UNII — GWO1432WOU.

Profile

Oxyphencyclimine hydrochloride is a tertiary amine antimuscarinic with effects similar to those of atropine (p. 1312.1). It has been used as an adjunct in the treatment of peptic ulcer disease and for the relief of smooth muscle spasms in gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hong Kong***: Daricon; ***Thai.***: KB Duode; Oxynot†; Proclimine; Weicon.

Multi-ingredient Preparations. ***China***: Rudd-U (立愉); ***Hong Kong***: Aluvit-U†; ***Thai.***: Bismocane; ***Turk.***: Spazmo-Valibrin.

Oxyphenonium Bromide *(BAN, rINN)*

Bromuro de oxifenonio; Oksyfenoniowy bromek; Oxifenonio, bromuro de; Oxphenonii Bromidum; Oxyphenonil Bromidum; Oxyphenonium Bromatum; Oxyphénonium, Bromure d'; Оксифенония Бромид.

2-(α-Cyclohexylmandeloyloxy)ethyldiethylmethylammonium bromide.

$C_{21}H_{34}BrNO_3$=428.4

CAS — 14214-84-7 (oxyphenonium); 50-10-2 (oxyphenonium bromide).

ATC — A03AB03.

ATC Vet — QA03AB03.

UNII — S9421HWB3Z.

Pharmacopoeias. In *Pol.*

Profile

Oxyphenonium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been given orally in a usual dose of 5 to 10 mg three or four times daily to relieve visceral spasms.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Antrenyl; ***Pol.***: Spasmophen†.

Palonosetron Hydrochloride

(USAN, rINNM)

Hidrocloruro de palonosetrón; Palonosétron, Chlorhydrate de; Palonosetrón, hidrocloruro de; Palonosetroni Hydrochloridum; RS-25259-197; Палоносетрона Гидрохлорид.

(3a*S*)-2,3,3a,4,5,6-Hexahydro-2-[(3*S*)-3-quinuclidinyl]-1*H*-benz[*de*]isoquinolin-1-one hydrochloride.

$C_{19}H_{24}N_2O$,HCl=332.9

CAS — 135729-56-5 (palonosetron); 135729-55-4 (palonosetron hydrochloride); 135729-62-3 (palonosetron hydrochloride).

ATC — A04AA05.

ATC Vet — QA04AA05.

UNII — 233100D4I19.

Stability. The stability of palonosetron hydrochloride at concentrations of 5 and 30 micrograms/mL was assessed in PVC bags of the following 4 infusion solutions: glucose 5%, sodium chloride 0.9%, glucose 5% in sodium chloride 0.45%, and glucose 5% in lactated Ringer's solution. All solutions were considered to be physically and chemically stable for at least 48 hours at room temperature exposed to light, and for 14 days under refrigeration.[1]

Palonosetron 50 micrograms/mL (as palonosetron hydrochloride) was found to be physically and chemically stable during simulated Y-site administration with the following drugs:[2,3]

- atropine sulfate 400 micrograms/mL
- famotidine 2 mg/mL
- fentanyl citrate 50 micrograms/mL
- heparin sodium 100 units/mL
- hydromorphone hydrochloride 500 micrograms/mL
- lidocaine hydrochloride 10 mg/mL
- morphine sulfate 15 mg/mL
- pethidine hydrochloride 10 mg/mL
- potassium chloride 100 mmol/litre
- sufentanil 12.5 micrograms/mL (as sufentanil citrate)

1. Trissel LA, Xu QA. Physical and chemical stability of palonosetron HCl in 4 infusion solutions. *Ann Pharmacother* 2004; 38: 1608–11.
2. Trissel LA, *et al.* Physical and chemical stability of palonosetron hydrochloride with five opiate agonists during simulated Y-site administration. *Am J Health-Syst Pharm* 2007; 64: 1209–13.
3. Kupiec TC, *et al.* Physical and chemical stability of palonosetron hydrochloride with five common parenteral drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 2008; 65: 1735–9.

Uses and Administration

Palonosetron is a 5-HT_3 antagonist used in the prevention of nausea and vomiting induced by cytotoxic chemotherapy and for the prevention of postoperative nausea and vomiting. Palonosetron is given as the hydrochloride but doses are expressed in terms of the base; 280.8 micrograms of palonosetron hydrochloride is equivalent to about 250 micrograms of palonosetron.

For the prevention of acute and delayed **nausea and vomiting** associated with initial and repeat courses of moderately or highly emetogenic cancer **chemotherapy**, a dose of 250 micrograms is given intravenously over 30 seconds about 30 minutes before chemotherapy. Palonosetron can also be given orally to prevent acute nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy. A dose of 500 micrograms is given about 1 hour before the start of chemotherapy.

For the prevention of **postoperative** nausea and vomiting, for up to 24 hours after surgery, a single dose of 75 micrograms is given intravenously over 10 seconds immediately before the induction of anaesthesia. Efficacy beyond 24 hours has not been shown.

Reviews

1. Siddiqui MAA, Scott LJ. Palonosetron. *Drugs* 2004; 64: 1125–32.
2. Tonini G, *et al.* New drugs for chemotherapy-induced nausea and vomiting: focus on palonosetron. *Expert Opin Drug Metab Toxicol* 2005; 1: 143–9.
3. Celio L, *et al.* Clinical update on palonosetron in the management of chemotherapy-induced nausea and vomiting. *Tumori* 2008; 94: 447–52.
4. Yang LPH, Scott LJ. Palonosetron: in the prevention of nausea and vomiting. *Drugs* 2009; 69: 2257–78.
5. Navari RM. Palonosetron: a second generation 5-hydroxytryptamine 3 receptor antagonist. *Expert Opin Drug Metab Toxicol* 2009; 5: 1577–86.
6. Ruhlmann C, Herrstedt J. Palonosetron hydrochloride for the prevention of chemotherapy-induced nausea and vomiting. *Expert Rev Anticancer Ther* 2010; 10: 137–48.
7. Saito M, Tsukuda M. Review of palonosetron: emerging data distinguishing it as a novel 5-HT_3 receptor antagonist for chemotherapy-induced nausea and vomiting. *Expert Opin Pharmacother* 2010; 11: 1003–14. Correction. *ibid.*; 1231.

Adverse Effects and Precautions

As for Ondansetron, p. 1873.2, although no dosage reduction is considered necessary in hepatic impairment. Diarrhoea, fatigue, and abdominal pain may also occur. Patients with a history of constipation or signs of subacute intestinal obstruction should be monitored if given palonosetron.

Effects on the cardiovascular system. For a discussion of the effects of 5-HT_3 antagonists on the cardiovascular system, see under Ondansetron, p. 1873.3.

Effects on the nervous system. For mention of a seizure associated with palonosetron see under Ondansetron, p. 1874.1.

Interactions

As for Ondansetron, p. 1874.2.

Pharmacokinetics

Palonosetron is well absorbed after oral dosing, with an absolute bioavailability of about 97%. Peak plasma concentrations occur about 5 hours after an oral dose. Palonosetron has a volume of distribution of around 7 to 8 litres/kg; plasma protein binding is about 62%. About 50% of a dose is metabolised in the liver by cytochrome P450 isoenzymes (notably CYP2D6, but also CYP3A4 and CYP1A2). About 80% of a dose is recovered in the urine within 144 hours, as palonosetron and its metabolites. The mean terminal elimination half-life is reported to be about 40 hours.

References.

1. Hunt TL, *et al.* Evaluation of safety and pharmacokinetics of consecutive multiple-day dosing of palonosetron in healthy subjects. *J Clin Pharmacol* 2005; 45: 589–96.
2. Shah A, *et al.* Pharmacokinetic evaluation and safety profile of a 15-minute versus 30-second infusion of palonosetron in healthy subjects. *J Clin Pharmacol* 2006; 46: 1139–45.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Aloxi; ***Belg.***: Aloxi; ***Braz.***: Onicit; ***Chile***: Onicit; ***China***: Jiouting (吉欧停); Zhiruo (止若); ***Cz.***: Aloxi; ***Denm.***: Aloxi; ***Ger.***: Aloxi; ***Gr.***: Aloxi; ***Hung.***: Aloxi; ***India***: Palnox; Palonew; Palzen; ***Indon.***: Paloxi; ***Irl.***: Aloxi; ***Israel***: Paloxi; ***Ital.***: Aloxi; ***Jpn***: Aloxi; ***Mex.***: Onicit; ***Neth.***: Aloxi; ***Norw.***: Aloxi; ***Pol.***: Aloxi; ***Port.***: Aloxi; ***S.Afr.***: Onicit; ***Singapore***: Aloxi; ***Spain***: Aloxi; ***Swed.***: Aloxi; ***Switz.***: Aloxi; ***Thai.***: Aloxi; ***Turk.***: Aloxi; ***UK***: Aloxi; ***USA***: Aloxi; ***Venez.***: Onicit.

Pantoprazole *(BAN, USAN, rINN)*

BY-1023; Pantopratsoli; Pantoprazol; Pantoprazolum; SKF-96022; Пантопразол.

5-Difluoromethoxybenzimidazol-2-yl 3,4-dimethoxy-2-pyridylmethyl sulphoxide.

$C_{16}H_{15}F_2N_3O_4S$=383.4

CAS — 102625-70-7.

ATC — A02BC02.

ATC Vet — QA02BC02.

UNII — D8TST4O562.

Pantoprazole Sodium *(BANM, USAN, rINNM)*

Natrii Pantoprazolum; Pantoprazol sódico; Pantoprazole Sodique; Pantoprazolum natricum; Натрий Пантопразол.

Pantoprazole sodium sesquihydrate.

$C_{16}H_{14}F_2N_3NaO_4S$,1½H_2O=432.4

CAS — 138786-67-1 (anhydrous pantoprazole sodium); 164579-32-2 (pantoprazole sodium sesquihydrate).

ATC — A02BC02.

ATC Vet — QA02BC02.

UNII — 6871619Q5X.

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

Ph. Eur. 8: (Pantoprazole Sodium Sesquihydrate). A white or almost white powder. Freely soluble in water and in alcohol; practically insoluble in hexane. Protect from light.

USP 36: (Pantoprazole Sodium). A white to off-white powder. Freely soluble in water, in dehydrated alcohol, and in methyl alcohol; practically insoluble in dichloromethane and in hexane. Protect from light.

Stability. A suspension of pantoprazole 2 mg/mL in sterile water and sodium bicarbonate was deemed to be physically and chemically stable[1] in amber polyethylene terephthalate bottles for 62 days at 2 degrees to 8 degrees.

1. Dentinger PJ, *et al.* Stability of pantoprazole in an extemporaneously compounded oral liquid. *Am J Health-Syst Pharm* 2002; 59: 953–6.

Uses and Administration

Pantoprazole is a proton pump inhibitor with actions and uses similar to those of omeprazole (p. 1867.2). It is given as the sodium salt but doses are expressed in terms of the base. Pantoprazole sodium 11.28 mg is equivalent to about 10 mg of pantoprazole.

In the treatment of **gastro-oesophageal reflux disease** (p. 1807.2), the usual oral dose is 20 to 40 mg once daily, which may be increased up to 80 mg daily. Treatment is usually given for 4 weeks, increased to 8 weeks if necessary; in the USA, up to 16 weeks of therapy is permitted for healing of erosive oesophagitis. For maintenance therapy, treatment can be continued with 20 to 40 mg daily. Alternatively, for recurring symptoms, an on-demand regimen of 20 mg daily may be given.

The usual dose for the treatment of **peptic ulcer disease** (p. 1813.2) is 40 mg once daily, increased up to 80 mg daily if needed. Treatment is usually given for 2 to 4 weeks for duodenal ulceration, or 4 to 8 weeks for benign gastric ulceration. For the eradication of *Helicobacter pylori* pantoprazole may be combined with two antibacterials in a 1-week **triple therapy** regimen. Effective regimens include pantoprazole 40 mg twice daily combined with clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily, or combined with clarithromycin 250 mg twice daily and metronidazole 400 mg twice daily.

Patients who require prophylaxis for **NSAID-associated ulceration** may take 20 mg daily.

In the treatment of pathological hypersecretory states such as the **Zollinger-Ellison syndrome** (p. 1814.3), the initial dose is 80 mg daily in a single dose or 2 divided doses, adjusted as required; up to 240 mg daily has been used. Daily doses greater than 80 mg should be given in 2 divided doses.

PARENTERAL DOSAGE.

Pantoprazole may also be given intravenously, as the sodium salt, over 2 to 15 minutes, either as a slow injection or a short-term infusion. For peptic ulceration or gastro-oesophageal reflux disease, the recommended dose is 40 mg

daily. A dose of 80 mg once or twice daily may be used for Zollinger-Ellison syndrome; up to 240 mg daily may be given in divided doses. Patients should be switched to oral therapy as soon as possible.

For use in children, see below. Doses of pantoprazole may need to be reduced in patients with hepatic impairment (see below).

The magnesium salt and *S*-isomer of pantoprazole have also been used.

Reviews.

1. Anonymous. Pantoprazole—a third proton pump inhibitor. *Drug Ther Bull* 1997; 35: 93–4.
2. Poole P. Pantoprazole. *Am J Health-Syst Pharm* 2001; 58: 999–1008.
3. Cheer SM, *et al.* Pantoprazole: an update of its pharmacological properties and therapeutic use in the management of acid-related disorders. *Drugs* 2003; 63: 101–32.
4. Gisbert JP, *et al.* Pantoprazole based therapies in Helicobacter pylori eradication: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2004; 16: 89–99.
5. Lehmann FS, Beglinger C. Role of pantoprazole in the treatment of gastro-oesophageal reflux disease. *Expert Opin Pharmacother* 2005; 6: 93–104.

Administration. Bioequivalence has been shown for pantoprazole granules (*Protonix, Wyeth*) given *orally* mixed with either apple juice or apple sauce, or when mixed with apple juice and given through a size 16 French nasogastric tube.[1]

The safety and tolerability profiles of *intravenous* pantoprazole given in 10 mL of sodium chloride 0.9% over 2 minutes were similar to those given over 15 minutes in 100 mL.[2]

A study[3] comparing two different infusion regimens of adjunctive pantoprazole for peptic ulcer bleeding found that clinical outcomes were similar if an intravenous bolus injection of pantoprazole 80 mg was followed by either a continuous intravenous infusion of 192 mg daily (given at 8 mg/hour which is usual practice), or 160 mg daily (given as 40 mg every 6 hours), both for 3 days.

1. Tammara B, *et al.* Bioequivalence among three methods of administering pantoprazole granules in healthy subjects. *Am J Health-Syst Pharm* 2009; 66: 1923–8.
2. Micalizzi M, *et al.* Comparative tolerability of 2-and 15-minute intravenous infusions of pantoprazole. *Am J Health-Syst Pharm* 2007; 64: 1822–6.
3. Hsu Y-C, *et al.* A randomized controlled trial comparing two different dosages of infusional pantoprazole in peptic ulcer bleeding. *Br J Clin Pharmacol* 2010; 69: 245–51.

Administration in children. Pantoprazole is licensed in the USA for oral use in children from 5 years of age with gastro-oesophageal reflux disease. Children weighing 15 kg up to 40 kg are given 20 mg once daily, and those weighing 40 kg and over are given 40 mg once daily, for up to 8 weeks for erosive oesophagitis.

For findings from a review regarding the efficacy and safety of proton pump inhibitors in infants, children, and adolescents, see Administration in Children, under Omeprazole, p. 1867.3.

Administration in hepatic impairment. Dosage of pantoprazole may need to be reduced in severe hepatic impairment. UK licensed product information recommends a maximum dose of 20 mg daily orally or intravenously; however, US licensed product information suggests that doses up to 40 mg daily can be used. Doses above 40 mg daily have not been studied in patients with hepatic impairment. Liver enzymes should be monitored during therapy, and pantoprazole should be stopped if elevations occur.

Administration in renal impairment. Most studies have not found the pharmacokinetics of pantoprazole to be altered in patients with renal impairment[1] and licensed product information in the UK and USA generally does not recommend dosage adjustment in this group; however some UK sources, including the *BNF*, suggest that a maximum oral dose of 40 mg daily should be observed.

1. Cheer SM, *et al.* Pantoprazole: an update of its pharmacological properties and therapeutic use in the management of acid-related disorders. *Drugs* 2003; 63: 101–132.

Adverse Effects and Precautions

As for Omeprazole, p. 1868.1. Dosage may need to be reduced in severe hepatic impairment; liver function should be monitored regularly, and therapy stopped if liver enzymes are elevated.

Incidence of adverse effects. In a postmarketing surveillance study of the 6-month period after the launch of pantoprazole in England (UK), the adverse effects reported most frequently were diarrhoea, nausea, and headache. Other effects included malaise or lassitude, rash, other gastrointestinal disturbances, myalgia, and oedema.[1]

1. Wilton LV, *et al.* The pharmacovigilance of pantoprazole: the results of postmarketing surveillance on 11 541 patients in England. *Drug Safety* 2003; 26: 121–32.

Effects on the blood. For a report of thrombocytopenia with pantoprazole, see under Omeprazole, p. 1868.2.

Effects on electrolytes. For mention of a fall in blood-electrolytes during treatment with proton pump inhibitors including pantoprazole, see Omeprazole, p. 1868.3.

Effects on the kidneys. For reports of interstitial nephritis associated with pantoprazole see p. 1869.1.

Effects on the skin. For mention of skin reactions to pantoprazole, see p. 1869.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pantoprazole 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 03/10/11)

Interactions

As for Omeprazole, p. 1870.3.

For reference to a lack of effect of pantoprazole on diazepam, see Gastrointestinal Drugs, p. 1069.3, and for a lack of effect on theophylline, see p. 1236.1. Licensed product information states that there are reports of increased prothrombin time in patients taking pantoprazole and warfarin, but for reports suggesting a lack of effect on warfarin, see p. 1534.1. For a report of severe generalised myalgia and bone pain attributed to the use of methotrexate with pantoprazole, see Gastrointestinal Drugs, p. 828.1. Proton pump inhibitors, including pantoprazole, may affect exposure to mycophenolate, see p. 1965.1.

Pharmacokinetics

Pantoprazole is rapidly absorbed and peak plasma-pantoprazole concentrations occur about 2 to 2.5 hours after an oral dose. The oral bioavailability is about 77% with the enteric-coated tablet formulation, and does not vary after single or multiple doses. Pantoprazole is about 98% bound to plasma proteins. It is extensively metabolised in the liver, primarily by the cytochrome P450 isoenzyme CYP2C19, to desmethylpantoprazole; small amounts are also metabolised by CYP3A4, CYP2D6, and CYP2C9. Metabolites are excreted mainly (about 80%) in the urine, with the remainder being excreted in faeces via the bile. The terminal elimination half-life is about 1 hour, and is prolonged in hepatic impairment; the half-life in patients with cirrhosis was 3 to 6 hours. Although the elimination half-life has been reported to be 3.5 to 10 hours in slow metabolisers (see also Metabolism under Omeprazole, p. 1871.2), minimal accumulation occurs with once-daily dosing.

References.

1. Pue MA, *et al.* Pharmacokinetics of pantoprazole following single intravenous and oral administration to healthy male subjects. *Eur J Clin Pharmacol* 1993; 44: 575–8.
2. Kearns GL, *et al.* Single-dose pharmacokinetics of oral and intravenous pantoprazole in children and adolescents. *J Clin Pharmacol* 2008; 48: 1356–65.
3. Pettersen G, *et al.* Population pharmacokinetics of intravenous pantoprazole in paediatric intensive care patients. *Br J Clin Pharmacol* 2009; 67: 216–27.
4. Knebel W, *et al.* Population pharmacokinetic modeling of pantoprazole in pediatric patients from birth to 16 years. *J Clin Pharmacol* 2011; 51: 333–45.
5. Ward RM, *et al.* A multicenter, randomized, open-label, pharmacokinetics and safety study of pantoprazole tablets in children and adolescents aged 6 through 16 years with gastroesophageal reflux disease. *J Clin Pharmacol* 2011; 51: 876–87.

Bioavailability. A suspension of pantoprazole in sodium bicarbonate solution was rapidly absorbed, and peak plasma concentrations were comparable to that of the tablet. However, bioavailability of the suspension was about 25% lower than that of the tablet; the amount of sodium bicarbonate used may affect the bioavailability.[1]

1. Ferron GM, *et al.* Oral bioavailability of pantoprazole suspended in sodium bicarbonate solution. *Am J Health-Syst Pharm* 2003; 60: 1324–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Gastromax; Pampar; Pangest; Pantaltius†; Pantocas; Pantomed; Pantop; Pantus; Peptazol; Sipar; Supracam; Uldoral; *Austral.*: Ozpan; Salpraz; Somac; Sozol; *Austria*: Azidex; Gastroloc Gastrozol; Genepan; Panprabene; Pantip; Pantoloc; Pantozol; Prazopant; Zurcal; *Belg.*: Pantomed; Pantozol; Zurcale; Zurcamed; *Braz.*: Gastropan; Pantasun; Pantocal; Pantopaz; Pantox; Pantozol; Pantrat; Tecta; Ziprol; Zurcal; *Canad.*: Panto; Pantoloc; Tecta; *Chile*: Ulcemex; Zurcal; *China*: Pu Shi Tan (普诗坦); Jian Lang Chen (健朗晨); Luoxu (罗旭); Nuosen (诺森); Panlisu (泮立苏); Panmeilu (潘美路); Pantoloc Tai Mei Ni Ke (泰美尼克); Wei Di (韦迪); Wei Ke An (卫可安); Cz.: Adozole; Apo-Panto; Controloc; Gastrolan; Gastronorm; Loxanto; Nolpaza; Panogastin; Pantecta; Pantoloc; Pantomyl; Pantozol; Pantul; Somac; Supracid; Ulprix; *Denm.*: Contracid†; Magamyl; Olypan†; Panrazol; Pantelke†; Pantoloc; Pantomyl†; PantoNyco; PantoNycomed; Prazomyl; Sigilamyl†; Ulprix; Zanlytab; Zaprym†; *Fin.*: Giasemin; Panzor; Somac; *Fr.*: Eupantol; Inipepsia; Inipomp; Ipraalox; Pantopan†; Pantozol; *Ger.*: Gastrozol; Pantoprem; Pantozol; Rifun; *Gr.*: Controloc; Gastroprozal; Noxadif; Ozepran; Pantium; Pantosec; Praz-Up; Roxitrol; Ulcened; Ulceron; Verneg; Zurcazol; *Hong Kong*: Panrazol; Pantoloc; *Hung.*: Controloc; Gerprazol; Noacid; Nolpaza; Pafenon; Panogastin; Pantacid; Pantomed†; Pazolexa; Zeladrol; Zimpax; *India*: Achpilori; Aciban; Acidopent; Acihalt; Ampen; Anzop; Apanta; Apentral; Aripan; Arloc; Asipan; Avopan; Bus; Canozol; Caspan; CGPan; Concid; Controsec; Cool Pan; Culex; Cupan; Cypan; Digene Total; Domocid-PX; Dupent; E-Pento; Eracid; Fozole; Pulpan; Gasopep; Genpen; Gerdopan; Glopan; Hypa; Hyzole-P; Inpan; Intapan; Ipant; Isopan; Kapyl; Kenta; Klenz; Kurepane; Leetop; Lupipan; Medipent; Newpan; Nexpan; Nitzole; Normocid; Nupan; Omentum; Orapan; Oritop; Oxypan; Pacid; Pagero; Palgic; Palin; Palio; Pan-OD; Pan; Panbloc; Pancas; Pandat; Pandon; Pandosun; Pandry; Panfast; Pangy; Pankai; Panloc; Panmint; Pano; Panocid; Panopaz; Panor; Panpac; Panpari; Panpra; Panpro; Panprozole; Panpure; Pansa; Pansafe; Pansaul; Pansoft; Panstrike; Pansure; Pantab; Pantabit; Pantacin; Pantact; Pantadal; Pantagon; Pantakind; Pantamax; Pantamep; Pantanib; Pantaz; Pantazol; Pantec; Pantest; Pantif; Pantin-RD; Pantin; Pantium; Panto; Pantocaf; Pantocar; Pantocid; Pantocip; Pantocos; Pantodac; Pantoday; Pantofer; Pantofin; Pantol; Pantolex; Pantoloc; Pantolup; Pantom; Pantomas; Pantomax; Pantomore; Pantonid; Pantonis; Pantop; Pantopan; Pantopep; Pantopik; Pantopril; Pantosec; Pantosh; Pantosig; Pantosol; Pantotab; Pantotive; Pantovar; Pantox; Pantoz; Pantozol; Pantra; Pantric; Pantroz; Pantry; Pantz; Panum; Panwell; Panz; Panzac; Pentaloc; Praize; *Indon.*: Caprol; Panso; Pantozol; Pepzol; *Irl.*: Controloc Control; Freestom; Gastrolief; Nolpaza; Pantecta; Pantium; Pantoflux; Pantoloc; Pantosec; Pantozol Control; Pantup; Protium; Protizole; Somac; Zolepant; *Israel*: Controloc; Pantoavenir; *Ital.*: Pantecta; Pantopan; Pantorc; Peptazol; *Malaysia*: Controloc; Toprazole; *Mex.*: Panmicid; Pantozol; Peucetol; Prazolan; Protocord; Supacid; Tecta; Tevozol; Zolpeptid; Zolpra; Zoltum; Zurcal; *Neth.*: Controloc Control; Empaflun; Ipraalox; Nolpaza†; Panore; Pantecta; Pantogerolan; Pantoloc Control; Pantorc†; Pantozol; Previfect; Somac Control; *Norw.*: Pantoloc Control; Somac; *NZ*: Pantocid; Somac†; *Philipp.*: Domelong; Pantazol; Pantocar; Pantoloc; Pantopraz; Pantoprix; Pantor; Pantozim; Pantozol; Pentowin; Ulcepraz; *Pol.*: Anesteloc; Contix; Contracid; Controloc; IPP; Noacid; Nolpaza; Panogastin; Panprazox; Pantecta; Pantogen; Pantozol Control; Panzol; Ranloc; Somac Control; Xotepic; *Port.*: Apton; Controloc Control; Panbrabene; Panrazol; Pantecta; Pantoc; Panzat; Pranzol; Praoz†; Prazomyl†; Rarozol†; Somac Control; Zamol; Zamotil; Zipantol; Zurcal; *Rus.*: Controloc (Контролок); Nolpaza (Нольпаза); Panum (Панум); Peptazol (Пептазол); Sunpraz (Санпраз); Zipantola (Зипантола); *S.Afr.*: Conoran; Controloc†; Gastriwin; Pantocid; Pantoloc; Pentoz; Peploc; Topzole; *Singapore*: Controloc; Peptazol; *Spain*: Alapanzol; Anagastra; Citrel; Nolpaza; Normogastrol; Panproton; Pantecta; Pantoloc; Ulcotenal; *Swed.*: Pantoloc; *Switz.*: Contraflux; Gastrowell†; Panprax; Pantozol; Zurcal; *Thai.*: Controloc; Pantocid; Pantoprol; *Turk.*: Gastrazol; Pandev; Panref; Panthec; Panto; Pantpas; Protech; Protinum; Protonex; Pulcet; Ulcoreks; *UK*: Pantoloc Control; Protium; *Ukr.*: Controloc (Контролок); Nolpaza (Нольпаза); Pantokar (Пантокар); Pantosandoz (Пантосандоз)†; Penta (Пента)†; Proxium (Проксиум); Pulcet (Пульцет); Tecta Control (Текта Контрол); Ultera (Ультера)†; *USA*: Protonix; *Venez.*: Pantop.

Multi-ingredient Preparations. *Austral.*: Somac-MA†; *Ger.*: Zac-Pac; *India*: Achpilori-D; Aciban-DSR; Acidopent-DSR; Aldepraz-D; Alizole-DSR; Anzop-D; Apentral-D; Aripan-D; Arloc-D; Armcid D; Asipan-D; Avopan-D; Bus-D; Canozol-D; Cazole-D; Concid-DM; Concid-DSR; Cupan-DSR; Cypan-D; Dazole-D; Deepen-D; Depam; Domocid-PX; Dompan; Domtac; Domtec-P; Dufex; Dupent-D; Dyoflux; E-Pento-D; Eracid-D; Eupanta D; FB; Fozole-D; Pulpan-D; Ganaton Total; Genpen-D; Gerdom; Gi-Pri; Glopan-D; GR8-OD; Hypa-D; Hyzole-DP; Inpan-D; Intapan-D; IPD; Kapyl-D; Kenta-D; Klenz-D; Kurepane-D; Latop-D; Leetop-D; Medipent-D; Moza Plus; Multipan-D; Nitzole-D; Nupan-D; Odipan-D; Odipep; Omentum-D; Orapan-D; Oritop-D; Oxypan-D; Paleo-ISR; Palgic-D; Palin-D; Palio-D; Palzic-D; Pan-D; Pancas-D; Pandat-D; Pandiff; Pandom; Pandostal; Pandosun-D; Pandry D; Panfast-D; Pangy-DM; Pankai-D; Panlee-D; Panmint-D; Pano-D; Panopaz-D; Panor-D; Panpac-D; Panpari-D; Panpra-D; Panpro-D; Panrole-D; Pansa-D; Pansafe-D; Pansaul-D; Pansi-SD; Pansoft-D; Panstrike-D; Pantabit-D; Pantabol-D; Pantact-D; Pantadal-D; Pantadom; Pantagon-DM; Pantamep-D; Pantanib-D; Pantanib-IT; Pantapil-D; Pantec Plus; Pantec-D; Pantest-D; Pantin-D; Pantium-D; Panto-D; Pantocar-D; Pantocid-D; Pantocid-HP; Pantocid-IT; Pantocos-D; Pantodac-D; Pantoday-D; Pantofer-D; Pantoflux; Pantol-D; Pantolex-D; Pantom-D; Pantomas-D; Pantomed-D; Pantomore-D; Pantonid-D; Pantop-D; Pantop-HP Kit; Pantop-HP; Pantopik-D; Pantosec D; Pantosh D; Pantosig-D; Pantosym-D; Pantotive-D; Pantovar-D; Pantovom; Pantox-D; Pantoz-D; Pantozol-D; Pantra-D; Pantry-D; Pantz-D; Pantz-DM; Panum-D; Panz-D; Panz-SR; Panzac-D; Panzo-D; Praize-D; *Malaysia*: Klacid HP 7; *Neth.*: PantoPAC; *Switz.*: GastroPant; *Ukr.*: β-Klatinol (β-КЛАТИНОЛ).

Pharmacopoeial Preparations

USP 36: Pantoprazole Oral Suspension; Pantoprazole Sodium Delayed-Release Tablets.

Pargeverine Hydrochloride *(rINNM)*

Pargeverina, hidrocloruro de; Pargévérine, Chlorhydrate de; Pargeverini Hydrochloridum; Propinox Hydrochloride; Парговерина Гидрохлорид.

2-(Dimethylamino)ethyldiphenyl(2-propynyloxy)acetate hydrochloride.

$C_{21}H_{23}NO_3$,HCl=373.9

CAS — 13479-13-5 (pargeverine); 2765-97-1 (pargeverine hydrochloride).

UNII — XT63P694CJ.

Profile

Pargeverine is reported to possess antimuscarinic and smooth-muscle relaxant properties and has been used in the treatment of gastrointestinal and smooth muscle spasm.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Becebuen Gotas; Nova Paratropina; Sertal; *Chile*: Bevitex; Bramedil; Plazolit; Viadil; Viplan; Viproxil; *Mex.*: Bipasmin; Plidan; *Port.*: Vagopax; *Venez.*: Plidan.

Multi-ingredient Preparations. *Arg.*: Antispasmina Compuesto; Apasmo Compuesto; Becebuen Compuesto; Binvex; Espasmo Dolex; Nova Paratropina Compositum; Propalgin; Sertal Compuesto; *Chile*: Bramedil Compuesto; Scopanil; Viadil Compuesto; Viplan Compuesto; Viproxil Compuesto; *Mex.*: Firac Plus; Plidan Compuesto; *Venez.*: Dologinex; Plidan Compuesto.

Pentaerythritol

Pentaeritritol; Tetramethylolmethane; Пентаэритритол.

2,2-Bis(hydroxymethyl)propane-1,3-diol.

$C_5H_{12}O_4$=136.1

CAS — 115-77-5.

ATC Vet — QA06AD14.

UNII — SU420W1S6N.

Profile

Pentaerythritol is an osmotic laxative used in the treatment of constipation (p. 1804.3) in oral doses of 5 to 15 g daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Auxitrans.

Peppermint Leaf

Black Mint; Borsosmentalevél; Hoja de Menta; Hortelã-Pimenta; List máty peprné; Liść mięty pieprzowej; Menta piperita, hoja de; Menth. Pip.; Mentha Piperita; Menthae Piperitae Folium; Menthe Poivrée; Menthe poivrée, feuille de; Pepparmyntblad; Peppermint; Pfefferminzblätter; Piparmintunlehti; Pipirmėčių lapai; White Mint; Листья Мяты Перечной.

ATC Herb — HA03AW5039 (Mentha x piperita: leaf).

UNII — A389O33LX6.

Pharmacopoeias. In *Eur.* (see p. vii), which also includes the dry extract. Also in *USNF.*

Ph. Eur. 8: (Peppermint Leaf). The whole or cut dried leaves of *Mentha X piperita*, containing not less than 1.2% v/w of essential oil if whole, or not less than 0.9% v/w if cut. It has a characteristic and penetrating odour and a characteristic aromatic taste. Protect from light.

USNF 31: (Peppermint). The dried leaf and flowering top of *Mentha piperita* (Labiatae). It has an aromatic, characteristic odour and a pungent taste, and produces a cooling sensation in the mouth.

Peppermint Oil

Aceite esencial de menta; Borsosmentaolaj; Essence de Menthe, Poivrée; Essência de Hortelã-Pimenta; Menta piperita, aceite esencial de; Menthae Piperitae Aetheroleum; Menthae Piperitae Etheroleum; Menthe poivrée, huile essentielle de; Minzöl; Nane Yağı; Ol. Menth. Pip.; Olejek miętowy; Oleum Menthae Piperitae; Pepparmyntolja; Pfefferminzöl; Piparminttuöljy; Pipirmėčių eterinis aliejus; Silice máty pepmé; Масло Мяты Перечной.

CAS — 8006-90-4.

ATC Herb — HD04AW5002 (Mentha x piperita: essential oil); HA03AW5038 (Mentha x piperita: essential oil).

UNII — AV092KU4JH.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Peppermint Oil). It is obtained by steam distillation from the fresh overground parts of the flowering plant of *Mentha X piperita*. It contains 30.0 to 55.0% menthol, 14.0 to 32.0% menthone, and 2.8 to 10.0% menthyl acetate, 3.5 to 8.0% 1,8-cineole, 1.5 to 10.0% isomenthone, 1.0 to 8.0% menthofuran, 1.0 to 3.5% limonene, not more than 3.0% pulegone, and not more than 1.0% carvone; the ratio of 1,8-cineole content to limonene content is not less than two.

It is a colourless, pale yellow, or pale greenish-yellow liquid with a characteristic odour and taste followed by a sensation of cold. Miscible with alcohol and with dichloromethane. Store in well-filled, airtight containers at a temperature not exceeding 25 degrees.

USNF 31: (Peppermint Oil). The volatile oil distilled with steam from the fresh overground parts of the flowering plant *Mentha piperita* (Labiatae), rectified by distillation, and neither partially nor wholly dementholised. It yields not less than 5% of esters calculated as menthyl acetate and not less than 50% of total menthol, free and as esters.

It is a colourless or pale yellow liquid with a strong, penetrating, characteristic odour and a pungent taste, followed by a sensation of cold when air is drawn into the mouth. Soluble 1 in 3 of alcohol (70%) with not more than slight opalescence. Store in airtight containers at a temperature not exceeding 40 degrees.

Storage. The Pharmaceutical Society of Great Britain's Department of Pharmaceutical Sciences found that PVC bottles softened and distorted fairly rapidly in the presence of peppermint oil, which should not be stored or dispensed in such bottles.[1]

1. Department of Pharmaceutical Sciences of the Pharmaceutical Society of Great Britain. Plastic medicine bottles of rigid PVC. *Pharm J* 1973; 210: 100.

Uses and Administration

Peppermint oil is an aromatic carminative that relaxes gastrointestinal smooth muscle and relieves flatulence and colic. Enteric-coated capsules containing peppermint oil are used for the relief of symptoms of the irritable bowel syndrome or gastrointestinal spasm secondary to other disorders. Usual oral doses are 0.2 mL three times daily, (increased to 0.4 mL three times daily if necessary) for up to 2 to 3 months. The capsules should be taken before food and swallowed whole, not chewed.

Peppermint oil is used as a flavour and with other volatile agents in preparations for respiratory-tract disorders. It is also used in aromatherapy.

Peppermint leaf, the source of the oil, has also been used for its carminative and flavouring properties.

Gastrointestinal disorders. Menthol (p. 2553.2), the major constituent of peppermint oil, has properties similar to those of calcium-channel blockers on smooth muscle such as that in the human gut.[1] *Reviews*[2,3] of the use of peppermint oil in irritable bowel syndrome (p. 1810.3) concluded that there was some evidence of its benefit.

The relaxant effect of peppermint oil on the gastrointestinal tract has been used to reduce spasm during endoscopy by giving solubilised peppermint oil directly into the lumen, through the accessory channel of the endoscope. It has been described as effective during colonoscopy[4] and may be more effective than intramuscular hyoscine butylbromide during upper gastrointestinal endoscopy.[5] Addition of peppermint oil to barium enema has also been tried and appears to reduce spasm[6,7] and the need for intravenous antispasmodics.[6]

1. Grigoleit H-G, Grigoleit P. Pharmacology and preclinical pharmacokinetics of peppermint oil. *Phytomedicine* 2005; 12: 612–16.
2. Pittler MH, Ernst E. Peppermint oil for irritable bowel syndrome: a critical review and meta-analysis. *Am J Gastroenterol* 1998; 93: 1131–5.
3. Grigoleit H-G, Grigoleit P. Peppermint oil in irritable bowel syndrome. *Phytomedicine* 2005; 12: 601–6.
4. Asao T, *et al.* An easy method for the intraluminal administration of peppermint oil before colonoscopy and its effectiveness in reducing colonic spasm. *Gastrointest Endosc* 2001; 53: 172–7.
5. Hiki N, *et al.* Peppermint oil reduces gastric spasm during upper endoscopy: a randomized, double-blind, double-dummy controlled trial. *Gastrointest Endosc* 2003; 57: 475–82.
6. Sparks MJW, *et al.* Does peppermint oil relieve spasm during barium enema? *Br J Radiol* 1995; 68: 841–3.
7. Asao T, *et al.* Spasmolytic effect of peppermint oil in barium during double-contrast barium enema compared with Buscopan. *Clin Radiol* 2003; 58: 301–5.

Sore nipples. There is some evidence[1] that topical application of peppermint water after each feed may help prevent nipple cracks and soreness in breast-feeding mothers.

1. Sayyah Melli M, *et al.* Effect of peppermint water on prevention of nipple cracks in lactating primiparous women: a randomized controlled trial. *Int Breastfeed J* 2007; 2: 7.

Adverse Effects and Precautions

Peppermint oil can be irritant and may rarely cause hypersensitivity reactions. Reported reactions include erythematous skin rash, headache, bradycardia, muscle tremor, and ataxia. Heartburn has also been reported.

Effects on the cardiovascular system. Idiopathic atrial fibrillation occurred in 2 patients addicted to 'peppermints'. Normal rhythm was restored when peppermint-sucking ceased.[1]

1. Thomas JG. Peppermint fibrillation. *Lancet* 1962; i: 222.

Hypersensitivity. Exacerbation of asthma, with wheezing and dyspnoea, was associated with the use of paste-based toothpastes containing peppermint or wintergreen as a flavouring.[1]

1. Spurlock BW, Dailey TM. Shortness of (fresh) breath—toothpaste-induced bronchospasm. *N Engl J Med* 1990; 323: 1845–6.

Interactions

Adverse effects may be more likely if peppermint oil is taken with alcohol. Enteric-coated capsules containing peppermint oil should not be taken immediately after food or with antacids. There is some evidence that peppermint oil can inhibit the cytochrome P450 isoenzyme CYP3A4, and may affect the clearance of drugs whose metabolism is mediated by this enzyme.

References.

1. Dresser GK, *et al.* Evaluation of peppermint oil and ascorbyl palmitate as inhibitors of cytochrome P4503A4 activity in vitro and in vivo. *Clin Pharmacol Ther* 2002; 72: 247–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Mintec; Origins IBS Relief; *Austria*: Colpermin; Medicalm; *Braz.*: Mentaliv; *Cz.*: Colpermin; Matovy; Nat Maty Peprne†; *Fr.*: Locabiotal; *Ger.*: Euminz; Inspirol Heilpflanzenol†; spasmo gallo sanol N; Wildkrauterol spezial N; *Gr.*: Colpermin; *Hong Kong*: Colpermin; *Hung.*: China-Oil; Mentil; *Irl.*: Colpermin; *Israel*: China Oel; Colpermin; Po Sum On Medicated Oil†; *Ital.*: Carmint; Mintoil; *Neth.*: Tempocol; *Norw.*: Chiana; *NZ*: Mintec; *Port.*: Colominte; *S.Afr.*: Pepermentdruppels†; *Singapore*: Colpermin; *Switz.*: Colpermin; *Thai.*: Colpermin; Sahakarn Peppermint; *Turk.*: China Oel†; Colpermin; *UK*: Apercap; Colpermin; Equilon Herbal; Mintec; Obbekjaers.

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

Homoeopathic Preparations. *Canad.*: Cynara Complex†; Lemon Balm†; *Fr.*: Carominthe; Poconeol no 59†; *UK*: Catarrh Cream; Laxadoron; Medicinal Gargle; Oleum Rhinale.

Pharmacopoeial Preparations

BP 2014: Concentrated Peppermint Emulsion; Gastro-resistant Peppermint Oil Capsules; Peppermint Spirit;
USNF 31: Peppermint Water;
USP 36: Peppermint Spirit.

Phenolphthalein *(BAN, rINN)*

Dihydroxyphthalophenone; Fenolftalein; Fenolftaleína; Fenolftaleinas; Fenoliftaleiini; Fenoloftaleína; Phénolphtaléine; Phenolphtaleinum; Phenolphthaleinum; Фенолфталеин.

3,3-Bis(4-hydroxyphenyl)phthalide.

$C_{20}H_{14}O_4$=318.3

CAS — 77-09-8.

ATC — A06AB04.

ATC Vet — QA06AB04.

UNII — 6QK969R2IF.

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

Ph. Eur. 8: (Phenolphthalein). A white or almost white powder. Practically insoluble in water; soluble in alcohol. Protect from light.

Uses and Administration

Phenolphthalein is a diphenylmethane stimulant laxative that has been used for the treatment of constipation (p. 1804.3) and for bowel evacuation before investigational procedures or surgery. It has been withdrawn in many countries because of concern over its carcinogenic potential after reports of tumours in *rodents*.

It has been given in pills or tablets, and as an emulsion with liquid paraffin. Yellow phenolphthalein, an impure form, has been used similarly.

Adverse Effects and Precautions

As for Bisacodyl, p. 1821.2. Hypersensitivity reactions, usually as skin rashes or eruptions, have occurred with phenolphthalein. Phenolphthalein may cause pink discoloration of alkaline urine.

Tumours have occurred in *rats* and *mice* given very high doses of phenolphthalein; there does not appear to be evidence of carcinogenicity in humans, but phenolphthalein-containing products have been withdrawn in many countries because of concerns about long-term safety.

Effects on the skin. Reports of skin reactions associated with phenolphthalein include fixed drug eruptions,[1,2] erythema multiforme reactions,[1,3] and toxic epidermal necrolysis.[4,5]

1. Baer RL, Harris H. Types of cutaneous reactions to drugs. *JAMA* 1967; 202: 710–13.
2. Savin JA. Current causes of fixed drug eruptions. *Br J Dermatol* 1970; 83: 546–9.
3. Shelley WB, *et al.* Demonstration of intercellular immunofluorescence and epidermal hysteresis in bullous fixed drug eruption due to phenolphthalein. *Br J Dermatol* 1972; 86: 118–25.
4. Kar PK, *et al.* Toxic epidermal necrolysis in a patient induced by phenolphthalein. *J Indian Med Assoc* 1986; 84: 189–93.
5. Artymowicz RJ, *et al.* Phenolphthalein-induced toxic epidermal necrolysis. *Ann Pharmacother* 1997; 31: 1157–9.

Overdosage. The most likely consequence of phenolphthalein overdosage is excessive purgation, which may require fluid and electrolyte replacement. However, a possible association with acute pancreatitis occurred in a 34-year-old man who inadvertently ingested phenolphthalein 2 g. There was complete recovery with no sequelae from the pancreatitis.[1] Widespread organ failure with disseminated intravascular coagulation, massive liver damage, pulmonary oedema, renal failure, and myocardial damage in a second patient[2] were attributed to self-poisoning with an unknown quantity of phenolphthalein-containing laxative, although the diagnosis was problematic. The patient died despite intensive support.

1. Lambrianides AL, Rosin RD. Acute pancreatitis complicating excessive intake of phenolphthalein. *Postgrad Med J* 1984; 60: 491–2.
2. Sidhu PS, *et al.* Fatal phenolphthalein poisoning with fulminant hepatic failure and disseminated intravascular coagulation. *Hum Toxicol* 1989; 8: 381–4.

Pharmacokinetics

Up to 15% of phenolphthalein given orally is subsequently excreted in the urine. Enterohepatic circulation occurs and the glucuronide is excreted in the bile. Elimination may take several days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fructines; *India*: Jaglax; *Israel*: Easylax; *S.Afr.*: Brooklax†; Dr Mackenzies Veinoids†; Laxador†; Laxene†; SB Strong-Lax†; Super-Tabs†; Surge†; *Thai.*: Phenolax; Regulim†; *Turk.*: Alin; Laksafenol.

Multi-ingredient Preparations. *Arg.*: Cascara Sagrada Bouzen; Cascara Sagrada Puler; Genolaxante; Veracolate†; *Austral.*: Ford Pills†; *Austria*: Waldheim Abfuhrdragees forte†; *Chile*: Agarol†; Bulgarolax†; Fenokomp 39; Oblax A-1-1; *India*: Coslax; Jetomisol-P; *Indon.*: Laxadine; *Israel*: Laxative Compound; *Port.*: Doce Alivio; *S.Afr.*: Brooklax Pills†; SB 3 Triple Action Pills†; *Singapore*: Beagarol; *Spain*: Laxante Bescansa Aloico†; *Switz.*: Paragar; *Thai.*: Anson Emulax; Heroanson; Patarcolate; Taeniacide; Veracolate†; Zenda; *Turk.*: Fenolaks; Karboseptin; Musilaks; *UK*: Pam-Lax; *USA*: Agoral.

Pipenzolate Bromide *(BAN, rINN)*

Bromuro de pipenzolato; Pipenzolat Bromür; Pipenzolate, Bromure de; Pipenzolate Methylbromide; Pipenzolati Bromidum; Pipenzolato, bromuro de; Пипензолата бромид.

3-Benziloyloxy-1-ethyl-1-methylpiperidinium bromide.

$C_{22}H_{28}BrNO_3$=434.4

CAS — 13473-38-6 (pipenzolate); 125-51-9 (pipenzolate bromide).

ATC — A03AB14.

ATC Vet — QA03AB14.

UNII — JPX41OUS2B.

Profile

Pipenzolate bromide is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p. 1312.1). It has been used as an adjunct in the treatment of gastrointestinal disorders characterised by smooth muscle spasm.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Cholspas†; *Hong Kong*: Uni-Zolate†; *Mex.*: Expal†; Pipzen; *Turk.*: Piptalin.

Multi-ingredient Preparations. *Chile*: Baldmin; Gasorbol; Sinpasmon; *Hong Kong*: Infant-Sed†; *Indon.*: Piptal; *Mex.*: Espasal; Expal Compuesto; Finprob; *Turk.*: Asilon; Libkol.

Piperidolate Hydrochloride *(BANM, rINNM)*

Hidrocloruro de piperidolato; Pipéridolate, Chlorhydrate de; Piperidolati Hydrochloridum; Piperidolato, hidrocloruro de; Пиперидолата гидрохлорид.

1-Ethyl-3-piperidyl diphenylacetate hydrochloride.

$C_{21}H_{25}NO_2$,HCl=359.9

CAS — 82-98-4 (piperidolate); 129-77-1 (piperidolate hydrochloride).

ATC — A03AA30.

ATC Vet — QA03AA30.

UNII — 57UA660ILV.

Profile

Piperidolate hydrochloride is a tertiary amine antimuscarinic with effects similar to those of atropine (p. 1312.1). It has been given in the symptomatic treatment of smooth muscle spasm associated with gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Dactiran; *Mex.*: Dactil OB.

Multi-ingredient Preparations. *Braz.*: Dactil OB.

Pipethanate Ethobromide *(rINNM)*

Ethylpipethaniate Bromide; Etobromuro de pipetanato; Piperilate Ethobromide; Pipetanato, etobromuro de; Pipéthanate, Ethobromure de; Pipethanati Ethobromidum; Пипетаната этобромид.

1-(2-Benziloyloxyethyl)-1-ethylpiperidinium bromide.

$C_{23}H_{30}BrNO_3$=448.4

CAS — 4546-39-8 (pipethanate); 23182-46-9 (pipethanate ethobromide).

Profile

Pipethanate ethobromide is an antimuscarinic with actions similar to those of atropine (p. 1312.1). It has been used in the symptomatic treatment of visceral spasms in oral doses of up to 160 mg daily in divided doses. Pipethanate ethobromide has been given intramuscularly or intravenously in doses of 10 to 20 mg daily; it has also been given rectally.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Nospasmin; *Ital.*: Spasmodil; *Venez.*: Flespan.

Multi-ingredient Preparations. *Chile*: Nospasmin Compuesto.

Pirenzepine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de pirenzepina; LS-519 (pirenzepine); LS-519-Cl2; Pirentsepiinidihydrokloridimonohydraatti; Pirenzepina, hidrocloruro de; Pirenzepin-dihidrokloridmonohidrát; Pirenzepin-dihydrochlorid monohydrát; Pirenzepindihydrokloridmonohydrat; Pirenzépine, Chlorhydrate de; Pirenzépine (dichlorhydrate de) monohydraté; Pirenzepini dihydrochloridum monohydricum; Pirenzepini Hydrochloridum; Pirenzepino dihidrochloridas monohidratas; Пирензепина гидрохлорид.

5,11-Dihydro-11-(4-methylpiperazin-1-ylacetyl)pyrido[2,3-*b*][1,4]benzodiazepin-6-one dihydrochloride monohydrate.

$C_{19}H_{21}N_5O_2$,2HCl,H_2O=442.3

CAS — 28797-61-7 (pirenzepine); 29868-97-1 (pirenzepine hydrochloride).

ATC — A02BX03.

ATC Vet — QA02BX03.

UNII — 10YM403FLS.

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

Ph. Eur. 8: (Pirenzepine Dihydrochloride Monohydrate; Pirenzepine Hydrochloride BP 2014). A white or yellowish crystalline powder. Freely soluble in water; very slightly soluble in dehydrated alcohol; practically insoluble in dichloromethane; slightly soluble in methyl alcohol. A 10% solution in water has a pH of 1.0 to 2.0. Protect from light.

Uses and Administration

Pirenzepine is a selective M_1 tertiary amine antimuscarinic that displays a preferential action on the gastric mucosa thus causing a reduction in the secretion of gastric acid; it also reduces the secretion of pepsin. At therapeutic doses it has few other antimuscarinic actions.

Pirenzepine hydrochloride has been used in the management of peptic ulcer disease (p. 1813.2) in a usual oral dose of 50 mg two or three times daily for 4 to 6 weeks. It has also been given by slow intravenous or intramuscular injection in a dose of 10 mg every 12 hours.

Myopia. Pirenzepine ophthalmic gel has been investigated[1-4] in children for its potential in slowing the progression of myopia. In a study[3] involving 353 children with myopia, pirenzepine 2% gel given once or twice daily into the lower eyelid for 1 year was associated with reduced progression: at 12 months myopia had progressed by a mean of 0.7 and 0.47 dioptres in children assigned to once and twice daily dosage respectively, compared with 0.84 dioptres in those given placebo. The gel was generally well tolerated, the most frequent adverse effects being development of papillae or follicles, or abnormalities of accommodation such as mydriasis or cycloplegia. Of 55 patients who failed to complete the study, 31 did so as a result of adverse effects.

1. Bartlett JD, *et al.* A tolerability study of pirenzepine ophthalmic gel in myopic children. *J Ocul Pharmacol Ther* 2003; 19: 271–9.
2. Siatkowski RM, *et al.* US Pirenzepine Study Group. Safety and efficacy of 2% pirenzepine ophthalmic gel in children with myopia: a 1-year, multicenter, double-masked, placebo-controlled parallel study. *Arch Ophthalmol* 2004; 122: 1667–74.
3. Tan DTH, *et al.* Asian Pirenzepine Study Group. One-year multicenter, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. *Ophthalmology* 2005; 112: 84–91.
4. Siatkowski RM, *et al.* U.S. Pirenzepine Study Group. Two-year multicenter, randomized, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. *J AAPOS* 2008; 12: 332–9.

Adverse Effects and Precautions

Antimuscarinic adverse effects such as dry mouth and blurred vision have been reported but are less common with pirenzepine than with atropine (see p. 1312.1). Pirenzepine should be used with caution in patients with renal impairment, particularly those with end-stage renal failure.

Effects on the blood. Thrombocytopenia in one patient and agranulocytosis in another was probably associated with the use of pirenzepine.[1]

1. Stricker BHC, *et al.* Blood disorders associated with pirenzepine. *BMJ* 1986; 293: 1074.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Pharmacokinetics

Pirenzepine is absorbed from the gastrointestinal tract but the bioavailability is reported to be only about 20 to 30%, and is decreased to about 10 to 20% when taken with food. Very little pirenzepine is metabolised. About 10% of an oral dose is excreted unchanged in the urine, the remainder being excreted in the faeces.

Pirenzepine has an elimination half-life of about 12 hours and is about 12% bound to plasma proteins. Diffusion across the blood-brain barrier is poor and only minimal amounts are present in breast milk.

Renal impairment. The renal clearance and total plasma clearance of pirenzepine may be significantly reduced in patients with renal impairment,[1,2] with clearance decreasing proportionately with the degree of renal impairment. The half-life of pirenzepine is increased with reported values ranging from 14 to 20 hours.[1-3] Plasma concentrations of pirenzepine may be reduced by up to about 50% during haemodialysis.[2,3]

1. Krakamp B, *et al.* Steady-state intravenous pharmacokinetics of pirenzepine in patients with hepatic insufficiency and combined renal- and hepatic insufficiency. *Eur J Clin Pharmacol* 1989; 36: 71–3.
2. Krakamp B, *et al.* Steady-state intravenous pharmacokinetics of pirenzepine in patients with differing degrees of renal dysfunction. *Eur J Clin Pharmacol* 1989; 36: 75–8.
3. MacGregor T, *et al.* Oral pharmacokinetics of pirenzepine in patients with chronic renal insufficiency, failure, and maintenance haemodialysis. *Eur J Clin Pharmacol* 1990; 38: 405–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Gastrozepin; *Ger.*: Gastrozepin; *Gr.*: Gastrozepin; Threptin; *Jpn*: Gastrozepin; *Rus.*: Gastrozepin (Гастроцепин); *Thai.*: Cevanil; *Ukr.*: Gastrozepin (Гастроцепин).

Platyphylline Acid Tartrate

Platyphylline Bitartrate; Platyphyllini Hydrotartras; Платифиллина битартрат.

1,2-Dihydro-12-hydroxysenecionan-11,16-dione hydrogen tartrate.

$C_{18}H_{27}NO_5$,$C_4H_6O_6$=487.5

CAS — 480-78-4 (platyphylline); 1257-59-6 (platyphylline acid tartrate).

UNII — 6SXK0Y9D98.

Profile

Platyphylline acid tartrate is a pyrrolizidine alkaloid occurring in *Senecio platyphyllus* and other *Senecio* spp. It has antimuscarinic actions and has been given alone or with papaverine in antispasmodic preparations.

Plaunotol (rINN)

CS-684; Plaunotolum; Плаунотол.
(2*Z*,6*E*)-2-[(3*E*)-4,8-Dimethyl-3,7-nonadienyl]-6-methyl-2,6-octadiene-1,8-diol.
$C_{20}H_{34}O_2$=306.5
CAS — 64218-02-6.
UNII — MV715X4634.

Profile

Plaunotol is a complex aliphatic alcohol extracted from the Thai medicinal plant plau-noi (*Croton sublyratus* (Euphorbiaceae)). It is reported to possess cytoprotective properties and has been used in the treatment of gastritis and peptic ulcer disease in an oral dose of 80 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Kelnac; *Thai.*: Kelnac†.

Polaprezinc (rINN)

Polaprézinc; Polaprezincum; Z-103; Zinc-L-carnosine; Полапрезинк.
catena-Poly[zinc-μ-[β-alanyl-L-histidinato(2-)-*N*,*N*$^{\pi}$,*O*:*N*$^{\tau}$]].
$(C_9H_{12}N_4O_3Zn)_n$
CAS — 107667-60-7.

Profile

Polaprezinc is a cytoprotective agent used in the treatment of peptic ulcer disease and as a zinc supplement. It is under investigation as a treatment for taste disorders.

Poldine Metilsulfate (BAN, pINN)

IS-499; McN-R-726-47; Metilsulfato de poldina; Poldina, metilsulfato de; Poldine Methosulphate; Poldine Methylsulfate (USAN); Poldine Methylsulphate; Poldine, Métilsulfate de; Poldini Metilsulfas; Польдина Метилсульфат.
(*RS*)-2-Benziloyloxymethyl-1,1-dimethylpyrrolidinium methylsulphate.
$C_{21}H_{26}NO_3.CH_3O_4S$=451.5
CAS — 596-50-9 (poldine); 545-80-2 (poldine metilsulfate).
ATC — A03AB11.
ATC Vet — QA03AB11.
UNII — 564C0W9848.

Pharmacopoeias. In *Br.*

BP 2014: (Poldine Metilsulfate). A white odourless or almost odourless crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in chloroform. A 1% solution in water has a pH of 5.0 to 7.0.

Profile

Poldine metilsulfate is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p. 1312.1) and has been used in the management of gastrointestinal disorders, including peptic ulcer disease.

Preparations

Pharmacopoeial Preparations
BP 2014: Poldine Tablets.

Polycarbophil (BAN, rINN)

Policarbofilo; Polycarbophile; Polycarbophilum; Поликарбофил.
CAS — 9003-97-8.
UNII — W25LM17A4W.

Pharmacopoeias. In *US.*

USP 36: (Polycarbophil). It is polyacrylic acid cross-linked with divinyl glycol. White to creamy-white granules, with a characteristic, ester-like odour. Swells in water to a range of volumes, depending primarily on the pH. Insoluble in water, in common organic solvents, and in dilute acids and alkalis. A 1% mixture in water has a pH of not more than 4.0. Store in airtight containers.

Polycarbophil Calcium (BANM, rINNM)

AHR-3260B; Calcii Polycarbophilum; Calcium Polycarbophil (USAN); HSR-237; Policarbofilo cálcico; Polycarbophile Calcique; Polycarbophilum Calcii; Polykarbofiilikalsium; Polykarbofilkalcium; Polykarbophilum Calcicum; WI-140; Кальций Поликарбофил.
CAS — 126040-58-2.
ATC — A06AC08.
ATC Vet — QA06AC08.
UNII — 8F049NKY49.

Pharmacopoeias. In *US.*

USP 36: (Calcium Polycarbophil). A white to creamy-white powder. Insoluble in water, in common organic solvents, and in dilute acids and alkalis. It loses not more than 10% of its weight on drying and contains not less than 18% and not more than 22% of calcium, calculated on the dried basis. Store in airtight containers.

Uses and Administration

Polycarbophil calcium has similar properties to ispaghula (p. 1849.2) and is used as a bulk laxative and for adjusting faecal consistency. After ingestion calcium ions are replaced by hydrogen ions from gastric acid and the resultant polycarbophil exerts a hydrophilic effect in the intestines.

It is given orally in a usual dose equivalent to 1 g of polycarbophil up to four times daily, as necessary. Doses should be taken with at least 250 mL of water.

Polycarbophil is used topically as a vaginal moisturiser and as an ocular lubricant.

References.

1. Danhof IE. Pharmacology, toxicology, clinical efficacy, and adverse effects of calcium polycarbophil, an enteral hydrosorptive agent. *Pharmacotherapy* 1982; 2: 18–28.
2. Toskes PP, *et al.* Calcium polycarbophil compared with placebo in irritable bowel syndrome. *Aliment Pharmacol Ther* 1993; 7: 87–92.
3. Chiba T, *et al.* Colonic transit, bowel movements, stool form, and abdominal pain in irritable bowel syndrome by treatments with calcium polycarbophil. *Hepatogastroenterology* 2005; 52: 1416–20.

Adverse Effects and Precautions

As for Ispaghula, p. 1849.2. Polycarbophil calcium releases calcium ions in the gastrointestinal tract and should be avoided by patients who must restrict their calcium intake.

There is a risk of intestinal or oesophageal obstruction and faecal impaction, especially if such bulk laxatives are swallowed dry. Therefore, they should always be taken with sufficient fluid and should not be taken immediately before going to bed. They should be avoided by patients who have difficulty swallowing.

Interactions

The calcium component of polycarbophil calcium may produce interactions typical of calcium salts (p. 1786.1), such as reducing the absorption of tetracyclines from the gastrointestinal tract; it should not be taken within 2 hours of the antibacterial. Polycarbophil calcium has also been reported to decrease the absorption of ciprofloxacin and mycophenolate mofetil.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Replens; *Braz.*: Benestare; Muvinor; *Canad.*: Equalactin†; Fiber-on-Tablet; Fibre Laxative; Prodiem Bulk Fibre; Replens; *Chile*: Edubel; Hidrogel; *Ger.*: Rephresh; Replens; *Gr.*: Fibercon; *India*: Calibs; Fibotab; *Ital.*: Modula; Replens; *Jpn*: Colonel; *Mex.*: Replens; *Singapore*: RepHresh; Replens†; *Swed.*: Replens; *USA*: Equalactin; FiberLax; Fibercon; FiberNorm†; Replens.

Multi-ingredient Preparations. *Philipp.*: Mithra-Intim; *UK*: Feminesse.

Potassium Acid Tartrate

E336; Hydrogenvinan draselný; Kalii Hydrogenotartras; Kaliovandenilio tartratas; Kalium Hydrotartaricum; Káliumhidrogén-tartarát; Kaliumhydrogentartrat; Kaliumvätetartrat; Kaliumvetytartraatti; Potassium Bitartrate (USAN); Potassium Hydrogen Tartrate; Potassium, hydrogénotartrate de; Potasu wodorowinian; Purified Cream of Tartar; Tartarus Depuratus; Tartrato ácido de potasio; Weinstein; Кислый Виннокислый Калий.
$C_4H_5KO_6$=188.2
CAS — 868-14-4.
ATC — A12BA03.
ATC Vet — QA12BA03.
UNII — NPT6P8P3UU.

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

Ph. Eur. 8: (Potassium Hydrogen Tartrate). A white or almost white, crystalline powder or colourless crystals. Slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute solutions of mineral acids and alkali hydroxides.

USP 36: (Potassium Bitartrate). Colourless or slightly opaque crystals or a white, crystalline powder. Slightly soluble in water; soluble in boiling water; very slightly soluble in alcohol. A saturated solution is acid to litmus. Store in airtight containers.

Profile

Potassium acid tartrate is given with sodium bicarbonate as a suppository for the treatment of constipation (p. 1804.3) and for bowel evacuation before investigational procedures or surgery. Carbon dioxide gas is produced in the rectum, which stimulates defaecation within 5 to 30 minutes.

Potassium acid tartrate is used as a food additive and pharmaceutical aid.

Potassium acid tartrate has been used as an ingredient of preparations for potassium supplementation, although other potassium salts are usually preferred. For the general properties of potassium salts, see p. 1793.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Lecicarbon; *Ital.*: Potassion; *Jpn*: Circanetten; *Mon.*: Eductyl; *Swed.*: Relaxit; *Thai.*: Circanetten; *USA*: Ceo-Two.

Homoeopathic Preparations. *Ger.*: Phonix Silybum spag; Phonix Urtica-Arsenicum spag.

Pharmacopoeial Preparations
BPC 1968: Effervescent Potassium Tablets.

Potassium Sodium Tartrate

E337; Kalii Natrii Tartras; Kalio-natrio tartratas; Kalium Natrium Tartaricum; Kálium-nátrium-tartarát; Kaliumnatriumtartraatti; Kaliumnatriumtartrat; Potassium et de sodium, tartrate de; Rochelle Salt; Seignette Salt; Sodii et Potassii Tartras; Sodium Potassium Tartrate; Sodu potasu winian; Tartarus Natronatus; Tartrato de potasio y de sodio; Vinan draselno-sodný; Виннокислый Калий-натрий.
$C_4H_4KNaO_6.4H_2O$=282.2
CAS — 304-59-6 (anhydrous sodium potassium tartrate); 6381-59-5 (sodium potassium tartrate tetrahydrate); 6100-16-9 (sodium potassium tartrate tetrahydrate).
UNII — QH257BPV3J.

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

Ph. Eur. 8: (Potassium Sodium Tartrate Tetrahydrate). A white or almost white, crystalline powder or colourless transparent crystals. Very soluble in water; practically insoluble in alcohol.

USP 36: (Potassium Sodium Tartrate). Colourless crystals or a white, crystalline powder, with a cooling, saline taste. It effloresces slightly in warm dry air, the crystals often being coated with a white powder. Soluble 1 in 1 of water; practically insoluble in alcohol. Store in airtight containers.

Profile

Potassium sodium tartrate has been used as an osmotic laxative (p. 1804.1). It is also used as a food additive.

For the general properties of potassium salts, see p. 1793.1, and of sodium salts, see p. 1795.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Trigolax; Trilax.

Multi-ingredient Preparations. *Austria*: Laxalpin†; *Denm.*: Samarin; *Fr.*: Romarene†; *Hung.*: Samarin; *Philipp.*: Castoria; *Swed.*: Samarin; Samarin; *UK*: Jaaps Health Salt.

Pharmacopoeial Preparations
BPC 1973: Compound Effervescent Powder.

Prifinium Bromide (rINN)

Bromuro de prifinio; PDB; Prifinii Bromidum; Prifinio, bromuro de; Prifinium, Bromure de; Pyrodifenium Bromide; Прифиния Бромид.
3-Diphenylmethylene-1,1-diethyl-2-methylpyrrolidinium bromide.
$C_{22}H_{28}BrN$=386.4
CAS — 10236-81-4 (prifinium); 4630-95-9 (prifinium bromide).
ATC — A03AB18.
ATC Vet — QA03AB18.
UNII — 3B7O9ZC520.

Profile

Prifinium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It is structurally related to diphemanil metilsulfate (p. 2494.3).

Prifinium bromide is used to relieve smooth muscle spasms. Oral doses usually range from 90 to 180 mg daily in 3 divided doses. It can also be given by subcutaneous, intramuscular, or intravenous injection in a dose of 15 mg given 2 to 4 times daily. It has been given rectally.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Riabal; *Jpn*: Padrin; *Mex.*: Anespas†; *Rus.*: Riabal (Рябал); *Ukr.*: Riabal (Рябал).

Proglumide *(BAN, USAN, rINN)*

CR-242; Proglumida; Proglumidum; W-5219; Xylamide; Проглумид.

(±)-4-Benzamido-*N*,*N*-dipropylglutaramic acid.

$C_{18}H_{26}N_2O_4$=334.4

CAS — 6620-60-6.

ATC — A02BX06.

ATC Vet — QA02BX06.

UNII — EPL8W5565D.

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Proglumide is a cholecystokinin antagonist with an inhibitory effect on gastric secretion. It has been given orally or by intramuscular or intravenous injection in the treatment of peptic ulcer disease (p. 1813.2) and other gastrointestinal disorders.

Propantheline Bromide *(BAN, rINN)*

Bromuro de propantelina; Propantelinibromidi; Propantelin Brom ür; Propantelina, bromuro de; Propantelinbromid; Propantelin-bromid; Propantelino bromidas; Propanthelin-bromid; Propanthéline, Bromure de; Propanthelini bromidum; Propanthelinii Bromidum; Propanthelinium-bromid; Пропантелина Бромид.

Di-isopropylmethyl[2-(xanthen-9-ylcarbonyloxy)ethyl] ammonium bromide.

$C_{23}H_{30}BrNO_3$=448.4

CAS — 298-50-0 (propantheline); 50-34-0 (propantheline bromide).

ATC — A03AB05.

ATC Vet — QA03AB05.

UNII — UX9Z118X9F.

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

Ph. Eur. 8: (Propantheline Bromide). A white or yellowish-white, slightly hygroscopic powder. Very soluble in water, in alcohol, and in dichloromethane. Store in airtight containers.

USP 36: (Propantheline Bromide). White or practically white, odourless, crystals. Very soluble in water, in alcohol, and in chloroform; practically insoluble in ether and in benzene.

Uses and Administration

Propantheline bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been used as an antispasmodic (p. 1803.3) for conditions associated with gastrointestinal spasm, and as an adjunct in the treatment of peptic ulcer disease (p. 1813.2). The usual initial oral dose is 15 mg three times daily, 30 to 60 minutes before meals, and 30 mg at bedtime; doses of up to 120 mg daily may be needed in some patients. In elderly patients, doses of 7.5 mg three times daily may be sufficient. For doses in children, see below.

Propantheline bromide has been used in the treatment of adult enuresis or urinary incontinence, and in hyperhidrosis (see below), in doses similar to those given above.

Administration in children. Propantheline bromide is used in children for the symptomatic relief of gastrointestinal smooth muscle spasm. The *BNPC* suggests children from 1 month to 12 years may be given an oral dose of 300 micrograms/kg (maximum 15 mg) three or four times daily, at least 1 hour before food. Older children may be given the adult dose, see above.

Hyperhidrosis. Some antimuscarinics, including propantheline, have been applied topically in the treatment of hyperhidrosis (p. 1685.1). Adverse effects of antimuscarinics given orally generally preclude their use by this route, although oral propantheline was used successfully to control excessive sweating in 2 patients with spinal cord injuries,[1] and it is sometimes used in palliative care to control night sweats. The *BNF* notes that propantheline may be used for gustatory sweating in patients with diabetic neuropathy.

1. **Canaday BR, Stanford RH.** Propantheline bromide in the management of hyperhidrosis associated with spinal cord injury. *Ann Pharmacother* 1995; 29: 489–92.

Urinary incontinence. In the UK, guidelines issued by NICE suggest that propantheline should not be recommended for the treatment of urinary incontinence (p. 2349.2) or overactive bladder in women; other antimuscarinics are preferred.[1]

1. **NICE.** Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40fullguideline.pdf (accessed 03/07/08)

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1 and p. 1312.2. Contact dermatitis has been reported after topical application of propantheline bromide.

Buccal and oesophageal ulceration. Severe buccal mucosal ulceration has been reported[1] in a 95-year-old woman as a result of retaining emepronium bromide tablets in her mouth, and recurred on giving propantheline bromide tablets.

1. **Buston GJ, *et al.*** Anticholinergic drugs, buccal ulceration and mucosal potential difference. *Postgrad Med J* 1978; 54: 331–2.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Pharmacokinetics

Propantheline bromide is incompletely absorbed from the gastrointestinal tract and bioavailability is reported to be reduced by food; it is extensively metabolised in the small intestine before absorption. The plasma elimination half-life after a single oral dose has been reported to be about 2 to 3 hours. Propantheline is eliminated mainly in the urine as metabolites and less than 10% as unchanged drug. The duration of action is about 6 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Pro-Banthine; *Canad.*: Pro-Banthine†; *Denm.*: Ercoril; *Gr.*: Pro-Banthine; *Hong Kong*: Panbro†; *India*: Pro-Banthine; *Indon.*: Pro-Banthine†; *Irl.*: Pro-Banthine; *NZ*: Pro-Banthine; *S.Afr.*: Pro-Banthine; *Singapore*: Panbro; Pro-Banthine; *UK*: Pro-Banthine; *USA*: Pro-Banthine†.

Multi-ingredient Preparations. *Gr.*: Pro-Alusin-L; *Indon.*: Methaphyllin†; *Ital.*: Lexil.

Pharmacopoeial Preparations
BP 2014: Propantheline Tablets;
USP 36: Propantheline Bromide Tablets.

Prucalopride *(BAN, USAN, rINN)*

Prucaloprida; Prucalopridum; R-093877 (prucalopride or prucalopride hydrochloride); Прукалоприд.

4-Amino-5-chloro-2,3-dihydro-*N*-[1-(3-methoxypropyl)-4-piperidyl]-7-benzofurancarboxamide.

$C_{18}H_{26}ClN_3O_3$=367.9

CAS — 179474-81-8.

ATC — A06AX05.

ATC Vet — QA06AX05.

UNII — 0A09IUW5TP.

Prucalopride Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de prucalopride; Prucalopride, Chlorhydrate de; Prucalopridi Hydrochloridum; R-093877 (prucalopride or prucalopride hydrochloride); R-93877; Прукалоприда Гидрохлорид.

4-Amino-5-chloro-2,3-dihydro-*N*-[1-(3-methoxypropyl)-4-piperidyl]-7-benzofurancarboxamide hydrochloride.

$C_{18}H_{26}ClN_3O_3$,HCl=404.3

CAS — 179474-80-7.

ATC — A06AX05.

ATC Vet — QA06AX05.

UNII — M8IYX9Z79V.

Prucalopride Succinate *(BAN, USAN, rINNM)*

Prucalopride, Succinate de; Prucalopridi Succinas; R-108512; Succinato de prucalopride; Прукалоприда Сукцинат.

4-Amino-5-chloro-2,3-dihydro-*N*-[1-(3-methoxypropyl)-4-piperidyl]-7-benzofurancarboxamide succinate (1:1).

$C_{18}H_{26}ClN_3O_3$,$C_4H_6O_4$=486.0

CAS — 179474-85-2.

ATC — A06AX05.

ATC Vet — QA06AX05.

UNII — 4V2G75E1CK.

Uses and Administration

Prucalopride is a selective 5-HT$_4$ receptor agonist with prokinetic properties that is used in the treatment of women with chronic constipation where laxatives have failed to provide relief; efficacy in men has not been established. It is given as the succinate but doses are expressed as the base prucalopride succinate 1.32 mg is equivalent to about 1 mg of prucalopride. The usual oral dose in women aged over 18 years is prucalopride 2 mg once daily. In elderly patients aged over 65 years, an initial dose of 1 mg once daily can be given, increased up to 2 mg once daily if required. For doses of prucalopride in hepatic and renal impairment, see below.

References.

1. **Camilleri M, *et al.*** A placebo-controlled trial of prucalopride for severe chronic constipation. *N Engl J Med* 2008; 358: 2344–54.
2. **Quigley EM, *et al.*** Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation—a 12-week, randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2009; 29: 315–28.
3. **Tack J, *et al.*** Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. *Gut* 2009; 58: 357–65.
4. **Frampton JE.** Prucalopride. *Drugs* 2009; 69: 2463–76.
5. **Camilleri M, Deiteren A.** Prucalopride for constipation. *Expert Opin Pharmacother* 2010; 11: 451–61.

Administration in hepatic impairment. Due to a lack of data in patients with hepatic impairment, licensed product information for prucalopride recommends a reduced oral dose of 1 mg once daily in those with severe impairment (defined as Child-Pugh class C); no dose adjustments are considered necessary for those with mild to moderate impairment.

Administration in renal impairment. The main route of excretion of prucalopride is renal. Although no dosage adjustments are considered necessary in patients with mild to moderate renal impairment, licensed product information recommends a reduced oral dose of prucalopride 1 mg once daily in those with severe impairment (defined as a glomerular filtration rate of less than 30 mL/minute per 1.73 m^2). Prucalopride is not recommended for those on dialysis.

Adverse Effects and Precautions

The most frequently reported adverse effects during prucalopride treatment are headache and gastrointestinal disturbances such as abdominal pain, nausea, or diarrhoea. These usually occur at the start of therapy and resolve within a few days of continued treatment. Other common adverse effects include dizziness, pollakiuria (the frequent passing of small quantities of urine), and fatigue. Tremors, palpitations, anorexia, and fever have also been reported.

Due to a lack of study data, prucalopride should be used cautiously in patients with significant unstable comorbidities, particularly arrhythmias or ischaemic heart disease. It is not recommended in those with intestinal perforation or obstruction.

Interactions

In vitro data indicate that prucalopride does not affect the cytochrome P450 isoenzyme system, but may be a weak substrate of P-glycoprotein; ketoconazole, a potent P-glycoprotein inhibitor, increases exposure to prucalopride by about 40%, although this is not considered clinically relevant.

Pharmacokinetics

Oral prucalopride is rapidly absorbed and peak plasma concentrations occur after 2 to 3 hours. Absolute bioavailability is greater than 90%, and is not affected by food. Prucalopride is extensively distributed with low plasma-protein binding (about 30%). Metabolism in the liver is very slow and the main metabolite accounts for less than 4% of an excreted dose. Renal excretion of unchanged drug involves both passive filtration and active secretion. About 60% of a dose is excreted as unchanged drug via the urine and at least 6% via the faeces. Terminal elimination half-life is about 1 day. Prucalopride is excreted into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Resolor; *Canad.*: Resotran; *Cz.*: Resolor; *Denm.*: Resolor; *Fr.*: Resolor; *Ger.*: Resolor; *Gr.*: Resolor; *Irl.*: Resolor; *Neth.*: Resolor; *Pol.*: Resolor; *Port.*: Resolor; *Singapore*: Resolor; *Spain*: Resolor; *Switz.*: Resolor; *Thai.*: Resolor; *UK*: Resolor.

Prune

Ameixa; Ciruela; Prunus; Слива Домашняя (*Prunus domestica*).

UNII — S8O0119YLZ

Profile

Prune is the dried ripe fruits of the plum *Prunus domestica* and some other species of *Prunus* (Rosaceae). It has laxative and demulcent properties.

References.
1. Stacewicz-Sapuntzakis M, *et al.* Chemical composition and potential health effects of prunes: a functional food? *Crit Rev Food Sci Nutr* 2001; 41: 251–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Cirulaxia; Laxiruela; Mermelax; *Austral.*: Neo-Cleanse; *Chile*: Tamarine; *Fr.*: Complexe Assistance†; Resource Prunogil†; Transifine; *Ital.*: Fibranorm; *Mex.*: Ciruelax Jalea; Laxacaps; *UK*: Pure Plan.

Rabeprazole Sodium

(BANM, USAN, rINNM)

E-3810; LY-307640; Natrii Rabeprazolum; Rabeprazol sódico; Rabeprazol Sodyum; Rabéprazole Sodique; Rabeprazolum natricum; Sodium Pariprazole; Натрий Рабепразол.

2-({[4-(3-Methoxypropoxy)-3-methyl-2-pyridyl]methyl}sulfinyl)-1*H*-benzimidazole sodium.

$C_{18}H_{20}N_3NaO_3S$=381.4

CAS — 117976-89-3 (rabeprazole); 117976-90-6 (rabeprazole sodium).

ATC — A02BC04.

ATC Vet — QA02BC04.

UNII — 3L36P16U4R.

Uses and Administration

Rabeprazole is a proton pump inhibitor with actions and uses similar to those of omeprazole (p. 1867.2). It is given orally as rabeprazole sodium in the form of enteric-coated tablets. It is normally taken in the morning.

In the treatment of severe (erosive or ulcerative) **gastro-oesophageal reflux disease** (p. 1807.2), the usual dose of rabeprazole sodium is 20 mg once daily for 4 to 8 weeks; in the USA, a further 8-week course is permitted for healing of erosive oesophagitis. Thereafter, maintenance therapy can be continued with 10 or 20 mg daily depending on the response. For symptomatic disease without erosive or ulcerative oesophagitis a dose of 10 or 20 mg may be given once daily for 4 weeks; in the USA, a further 4-week course is permitted. Once symptoms have resolved, a dose of 10 mg once daily may be given as necessary.

For the treatment of active **peptic ulcer disease** (p. 1813.2), 20 mg daily is given for 4 to 8 weeks for duodenal ulcer and 6 to 12 weeks for gastric ulcer. For the eradication of *Helicobacter pylori* rabeprazole sodium may be combined with two antibacterials in a 1-week **triple therapy** regimen. Effective regimens include 20 mg twice daily combined with clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily, or combined with clarithromycin 250 mg twice daily and metronidazole 400 mg twice daily.

For **Zollinger-Ellison syndrome** (p. 1814.3), the starting dose is 60 mg once daily, adjusted according to response. Doses up to 120 mg daily have been given; when the daily dose is more than 100 mg it should be given in 2 divided doses.

For doses in children, see below.

Dexrabeprazole, the dextrorotatory isomer of rabeprazole, and its sodium salt have also been used.

Reviews.
1. Prakash A, Faulds D. Rabeprazole. *Drugs* 1998; 55: 261–7.
2. Anonymous. Rabeprazole. *Med Lett Drug Ther* 1999; 41: 110–12.
3. Carswell CI, Goa KL. Rabeprazole: an update of its use in acid-related disorders. *Drugs* 2001; 61: 2327–2356.
4. Pace F, *et al.* A review of rabeprazole in the treatment of acid-related diseases. *Ther Clin Risk Manag* 2007; 3: 363–79.
5. Pallotta S, *et al.* Rabeprazole: a second-generation proton pump inhibitor in the treatment of acid-related disease. *Expert Rev Gastroenterol Hepatol* 2008; 2: 509–22.
6. Dadabhai A, Friedenberg FK. Rabeprazole: a pharmacologic and clinical review for acid-related disorders. *Expert Opin Drug Safety* 2009; 8: 119–26.
7. Baldwin CM, Keam SJ. Rabeprazole: a review of its use in the management of gastric acid-related diseases in adults. *Drugs* 2009; 69: 1373–1401.

Administration in children. Rabeprazole sodium is licensed for use in children in the USA. For short-term treatment of gastro-oesophageal reflux disease, oral doses are given according to age and weight:

- 1 to 11 years and < 15 kg: 5 mg once daily, increased up to 10 mg once daily if needed, for up to 12 weeks
- 1 to 11 years and ≥ 15 kg: 10 mg once daily for up to 12 weeks
- 12 years and older: 20 mg once daily for up to 8 weeks

Adverse Effects and Precautions

As for Omeprazole, p. 1868.1.

Effects on the endocrine system. For cases of gynaecomastia associated with rabeprazole see Omeprazole, p. 1868.3.

Effects on the kidneys. For reports of interstitial nephritis associated with rabeprazole see p. 1869.1.

Effects on the nervous system. For a report of neuropsychiatric symptoms associated with rabeprazole, see p. 1869.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rabeprazole 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 03/10/11)

Interactions

As for Omeprazole (p. 1870.3) but because the cytochrome P450 isoenzyme system is a minor route of metabolism for rabeprazole, clinically significant interactions with diazepam, phenytoin, theophylline, or warfarin have not been found in healthy subjects.

Pharmacokinetics

Rabeprazole is rapidly absorbed and peak plasma concentrations occur about 3.5 hours after an oral dose. The oral bioavailability is about 52% with the enteric-coated tablet formulation, because of first-pass metabolism, and does not appear to vary after single or repeated doses. Rabeprazole is about 97% bound to plasma proteins. It is mainly metabolised via nonenzymatic reduction and, to a lesser extent, via the cytochrome P450 isoenzymes CYP2C19 and CYP3A4. Metabolites are excreted principally in the urine (about 90%) with the remainder in the faeces. The plasma half-life is about 1 to 2 hours, increased at least two to threefold in hepatic impairment, 1.6 times in CYP2C19 slow metabolisers (see also Metabolism under Omeprazole, p. 1871.2), and by 30% in the elderly.

References.
1. Yasuda S, *et al.* Comparison of the kinetic disposition and metabolism of E3810, a new proton pump inhibitor, and omeprazole in relation to S-mephenytoin 4-hydroxylation status. *Clin Pharmacol Ther* 1995; 58: 143–54.
2. Keane WF, *et al.* Rabeprazole: pharmacokinetics and tolerability in patients with stable, end-stage renal failure. *J Clin Pharmacol* 1999; 39: 927–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Pariet; Rabec; *Austral.*: Pariet; *Austria*: Pariet; *Belg.*: Pariet; *Braz.*: Pariet; *Canad.*: Pariet; *Chile*: Gastrodine; *China*: An Si Fei (安斯菲); Pariet (波利特); Rui Bo Te (瑞波特); Xin Wei An (信卫安); Yu Tian Qing (雨田青); *Cz.*: Rabebir; Rabecole; Rapoxol; Zulbex; *Denm.*: Pariet; *Fin.*: Pariet; *Fr.*: Pariet; *Ger.*: Pariet; *Gr.*: Pariet; *Hong Kong*: Pariet; *Hung.*: Pariet; Rabeman; RabirEP; Rabyprex; *India*: Abra; Acistal; Affirab; Albera; Algibra; Antuc; Aribzol; Asalt; Asirab; B-Joy; Bizo; Brazo; Cinrab; Coolx; Cyra; D-Rabibit; Depump; Desprazole; Dexicool; Dexpure; Dirab; Durab; Elrab; Furab-IT; Furab; Gasorab; Gastrazole; Genrab; Happi; Helirab; Hirabezole; Jeprab; Konzol; Koolzon; Mepraz; Nicid; Novorab; Nura; Odirab; Once; Oppi-R; Orpro; Rabeloc; Rabicip; *Indon.*: Pariet; *Irl.*: Pariet; Rabiclon; Razole; *Ital.*: Pariet; *Jpn*: Pariet; *Malaysia*: Pariet; *Mex.*: Pariet; *Neth.*: Berizar; Beryx; Fardole; Jelgrad; Pariet; Praber; Prabexol; Rapespes; Rodesa; *Philipp.*: Pariet; *Pol.*: Pariet; *Port.*: Pariet; *Rus.*: Pariet (Париет); *S.Afr.*: Pariet; *Singapore*: Pariet; *Spain*: Aciphex; Gelbra; Pariet; *Swed.*: Pariet; *Switz.*: Pariet; *Thai.*: Pariet; *Turk.*: Pariet; Prabex; Raneks; *UK*: Pariet; *Ukr.*: Barol (Барол); Razo (Разо)†; *USA*: Aciphex; *Venez.*: Pariet.

Multi-ingredient Preparations. *India*: Abra-D; Ace-Proxyvon; Acera; Acistal-D; Adec; Affirab-D; Antuc DSR; Antuc-IT; Aptase-DSR HG; Aribzol-D; Asalt-D; Asirab-D; B-Joy Plus; Bizo-D; Bizo-IT; Brazo-D; Brazo-IT; Brozole-D; Cidrid; Comvine; Cool Rab-It; Curab-D; Cyclochek; Cyra-D; D-Kool; D-Rabibit-D; Degurge-D; Dexrobel-D; Digerab-D; Dirab-D; Domrab; Domzole-R; Dorafem; Drab; Dynapar PPI; Elrab-D; Esoga-RD; Furab-D; Gasorab-D; Gasorab-T; Gastrazole-D; Genrab-D; Happi-D; Helirab-D; Hurtiz-DSR; Itoplus; Itopraz; Itorab; Itorbe; Jeprab-D; Konzol-D; Kurab-D; Kurab; Mac-IT; Mac-RD; Mepraz-D; Novorab-D; Nucid-D; Nuloc-D; Nura-D; Nura-IT; Once-D; Ond-R; Oshzol-D; *Ukr.*: Onristat (Орністат)†; Rabiril (Рабирил).

Racecadotril *(BAN, rINN)*

Acetorphan; Racécadotril; Racecadotrilo; Racecadotrilum; Рацекадотрил.

(±)-*N*-(2-[(Acetylthio)methyl]-1-oxo-3-phenylpropyl)glycine phenylmethyl ester; *N*-[(*R,S*)-3-acetylthio-2-benzylpropanoyl]glycine benzyl ester; (±)-*N*-[α-(Mercaptomethyl)hydrocinnamoyl]glycine benzyl ester acetate.

$C_{23}H_{25}NO_4S$=385.5

CAS — 81110-73-8.

ATC — A07XA04.

ATC Vet — QA07XA04.

UNII — 76K53XP4TO.

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

Ph. Eur. 8: (Racecadotril). A white or almost white powder. Practically insoluble in water; freely soluble in methyl alcohol and in dichloromethane.

Profile

Racecadotril is an enkephalinase inhibitor that inhibits the breakdown of endogenous opioids, thus reducing intestinal secretions. It is given orally in doses of 100 mg three times daily before meals for up to 7 days for the symptomatic management of acute diarrhoea (p. 1805.2).

The *S*-form of racecadotril (sinorphan, ecadotril—see Natriuretic Peptides, p. 1444.1) has been investigated for hypertension and heart failure.

References.
1. Baumer P, *et al.* Effects of acetorphan, an enkephalinase inhibitor, on experimental and acute diarrhoea. *Gut* 1992; 33: 753–8.
2. Roge J, *et al.* The enkephalinase inhibitor, acetorphan, in acute diarrhoea: a double-blind, controlled clinical trial versus Loperamide. *Scand J Gastroenterol* 1993; 28: 352–4.
3. Beaugerie L, *et al.* Treatment of refractory diarrhoea in AIDS with acetorphan and octreotide: a randomized crossover study. *Eur J Gastroenterol Hepatol* 1996; 8: 485–9.
4. Salazar-Lindo E, *et al.* Racecadotril in the treatment of acute watery diarrhea in children. *N Engl J Med* 2000; 343: 463–7.
5. Matheson AJ, Noble S. Racecadotril. *Drugs* 2000; 59: 829–35.
6. Alam NH, *et al.* Efficacy and tolerability of racecadotril in the treatment of cholera in adults: a double blind, randomised, controlled clinical trial. *Gut* 2003; 52: 1419–23.
7. Wang H-H, *et al.* A blind, randomized comparison of racecadotril and loperamide for stopping acute diarrhea in adults. *World J Gastroenterol* 2005; 11: 1540–3.
8. Szajewska H, *et al.* Systematic review: racecadotril in the treatment of acute diarrhoea in children. *Aliment Pharmacol Ther* 2007; 26: 807–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Tiorfix; *Braz.*: Tiorfan; *Chile*: Hidrasec; Resorcal; *China*: Du La Bao (杜拉宝); Feng Hai Ting (丰海停); Hidrasec (海兰赛); Mo Ni Ka (莫尼卡); *Fr.*: Diarfix; Tiorfan; Tiorfanor; Tiorfast; *Ger.*: Tiorfan†; *Gr.*: Hidrasec; *India*: Ad-DT; Ad-Sachet; Ad; Aquasec; Cadotril; Dirasec; Dotril; Enuff; Floradot; Hydral; Lomorest; Nodi; *Indon.*: Hidrasec†; *Ital.*: Tiorfix; *Mex.*: Hidrasec; *Neth.*: Hidrasec; *Philipp.*: Hidrasec; *Port.*: Tiorfan; *Spain*: Tiorfan; *Thai.*: Hidrasec; *UK*: Hidrasec; *Venez.*: Hidrasec.

Multi-ingredient Preparations. *India*: Aidia; Dotvil; Editor; Enuff Xtra.

Ramosetron Hydrochloride *(rINNM)*

Hidrocloruro de ramosetrón; Ibsetron Hydrochloride; Ramosétron, Chlorhydrate de; Ramosetrón, hidrocloruro de; Ramosetroni Hydrochloridum; YM-060; Рамосетрона Гидрохлорид.

(-)-(*R*)-1-Methylindol-3-yl 4,5,6,7-tetrahydro-5-benzimidazolyl ketone hydrochloride.

$C_{17}H_{17}N_3O.HCl$=315.8

CAS — 132036-88-5 (ramosetron); 132907-72-3 (ramosetron hydrochloride).

UNII — 9551LHD87E.

Profile

Ramosetron is a 5-HT_3 antagonist with general properties similar to those of ondansetron (p. 1872.1). Ramosetron hydrochloride is given for its antiemetic properties in the management of nausea and vomiting induced by cancer chemotherapy in a usual oral dose of 100 micrograms once daily. Alternatively, it may be given intravenously in a usual dose of 300 micrograms once daily; an additional dose of 300 micrograms may be given if needed, to a maximum daily dose of 600 micrograms. Ramosetron is also under

investigation in the management of diarrhoea-predominant irritable bowel syndrome.

Diarrhoea. Ramosetron has been tried with some success in a case of diabetic diarrhoea that had not responded to conventional antidiarrhoeals.[1]

1. Murao S, Hosokawa H. Serotonin 5-HT3 receptor antagonist for treatment of severe diabetic diarrhea. *Diabetes Care* 2010; 33: e38.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ai Ke An (艾可安); Lei Mai Xin (雷迈欣); Nasea (奈西雅); Shan Cheng (善成); Wei Yi Shu (维意舒); *Indon.*: Nasea; *Jpn*: Nasea; *Philipp.*: Nasea; *Thai.*: Irribow; Nasea.

Ranitidine *(BAN, USAN, rINN)*

AH-19065; Ranitidiini; Ranitidin; Ranitidina; Ranitidinum; Ранитидин.

NN-Dimethyl-5-[2-(1-methylamino-2-nitrovinylamino) ethylthiomethyl]furfurylamine.

$C_{13}H_{22}N_4O_3S$=314.4

CAS — 66357-35-5.

ATC — A02BA02.

ATC Vet — QA02BA02.

UNII — 884KT10YB7.

Ranitidine Hydrochloride *(BANM, rINNM)*

AH-19065; Hidrocloruro de ranitidina; Ranitidiinihydrokloridi; Ranitidin Hidroklorür; Ranitidina, hidrocloruro de; Ranitidine, chlorhydrate de; Ranitidin-hidroklorid; Ranitidinhydrochlorid; Ranitidin-hydrochlorid; Ranitidinhydroklorid; Ranitidini hydrochloridum; Ranitidino hidrochloridas; Ranitydyny chlorowodorek; Ранитидина Гидрохлорид.

$C_{13}H_{22}N_4O_3S,HCl$=350.9

CAS — 66357-59-3.

ATC — A02BA02.

ATC Vet — QA02BA02.

UNII — BK76465IHM.

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

Ph. Eur. 8: (Ranitidine Hydrochloride). A white or pale yellow, crystalline powder. It exhibits polymorphism. Freely soluble in water; sparingly soluble or slightly soluble in dehydrated alcohol; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 4.5 to 6.0. Store in airtight containers. Protect from light.

USP 36: (Ranitidine Hydrochloride). A white to pale yellow, practically odourless, crystalline powder. It is sensitive to light and to moisture. Very soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH of 4.5 to 6.0. Store in airtight containers. Protect from light.

Incompatibility and stability. References.

1. Chilvers MR, Lysne JM. Visual compatibility of ranitidine hydrochloride with commonly used critical-care medications. *Am J Hosp Pharm* 1989; 46: 2057–8.
2. Wohlford JG, *et al.* More information on the visual compatibility of hetastarch with injectable critical-care drugs. *Am J Hosp Pharm* 1990; 47: 297–8.
3. Williams MF, *et al.* In vitro evaluation of the stability of ranitidine hydrochloride in total parenteral nutrition mixtures. *Am J Hosp Pharm* 1990; 47: 1574–9.
4. Galante LJ, *et al.* Stability of ranitidine hydrochloride at dilute concentration in intravenous infusion fluids at room temperature. *Am J Hosp Pharm* 1990; 47: 1580–4.
5. Galante LJ, *et al.* Stability of ranitidine hydrochloride with eight medications in intravenous admixtures. *Am J Hosp Pharm* 1990; 47: 1606–10.
6. Stewart JT, *et al.* Stability of ranitidine in intravenous admixtures stored frozen, refrigerated, and at room temperature. *Am J Hosp Pharm* 1990; 47: 2043–6.
7. Montoro JB, Pou L. Comment on stability of ranitidine hydrochloride in total nutrient admixtures. *Am J Hosp Pharm* 1991; 48: 2384.
8. Stewart JT, *et al.* Stability of ranitidine hydrochloride and seven medications. *Am J Hosp Pharm* 1994; 51: 1802–7.
9. Crowther RS, *et al.* In vitro stability of ranitidine hydrochloride in enteral nutrient formulas. *Ann Pharmacother* 1995; 29: 859–62.
10. Allwood MC, Martin H. Factors influencing the stability of ranitidine in TPN mixtures. *Clin Nutr* 1995; 14: 171–6.

Uses and Administration

Ranitidine is a histamine H_2-antagonist with actions and uses similar to those of cimetidine (p. 1827.2).

Ranitidine may be given orally or parenterally by the intravenous or intramuscular routes. Although most preparations contain ranitidine hydrochloride, strengths and doses are expressed in terms of the base. Ranitidine hydrochloride 111.6 mg is equivalent to about 100 mg of ranitidine. Doses of ranitidine may need to be adjusted in patients with renal impairment, and in children. For discussion of dosage in children and renal impairment, see below.

In the management of benign **gastric and duodenal ulceration** (p. 1813.2) a single daily oral dose of 300 mg at bedtime or 150 mg twice daily (in the morning and at bedtime) is given initially for at least 4 weeks. Up to 300 mg twice daily may be used if necessary. Where appropriate a maintenance dose of 150 mg daily may be given at bedtime. To treat ulcers associated with NSAID therapy, ranitidine 150 mg twice daily or 300 mg at bedtime may be given for 8 to 12 weeks; for duodenal ulcers, a higher dose of 300 mg twice daily for 4 weeks has also been used. (To *prevent* NSAID-associated ulcers, UK licensed product information recommends an oral dose of 150 mg twice daily given with NSAID treatment; although unlicensed, the *BNF* suggests a higher dose of 300 mg twice daily may be used.)

For duodenal ulcer associated with *Helicobacter pylori* infection, ranitidine in a usual oral dose of 300 mg once daily at bedtime or 150 mg twice daily may be given as part of triple therapy with amoxicillin 750 mg and metronidazole 500 mg, both given orally, three times daily, for 2 weeks. Therapy with ranitidine should then be continued for a further 2 weeks.

In **gastro-oesophageal reflux disease** (p. 1807.2) the oral dose is 150 mg twice daily or 300 mg at bedtime for up to 8 weeks or, if required, 12 weeks. This may be increased to 150 mg four times daily for up to 12 weeks in severe cases. In the maintenance of healing erosive oesophagitis, a dose of 150 mg twice daily may be used. In pathological hypersecretory conditions, such as the **Zollinger-Ellison syndrome**, (p. 1814.3) the initial oral dose is usually 150 mg twice or three times daily and may be increased if necessary; doses of up to 6 g daily have been used. Alternatively, an intravenous infusion may be given, initially at a rate of 1 mg/kg per hour; the rate may be increased by increments of 500 micrograms/kg per hour, beginning after 4 hours, if required. Intravenous doses up to 2.5 mg/kg per hour and infusion rates up to 220 mg/hour have been used.

For the management of patients at risk from **stress ulceration** of the upper gastrointestinal tract, parenteral therapy may be given as a slow intravenous injection of a 50-mg priming dose followed by a continuous intravenous infusion of 125 to 250 micrograms/kg per hour. Oral doses of 150 mg twice daily may be given once oral feeding is resumed.

In patients at risk of developing the **acid aspiration syndrome** (p. 1804.2) during general anaesthesia, an oral dose of 150 mg may be given 2 hours before the induction of anaesthesia and preferably also 150 mg the previous evening. Alternatively, a dose of 50 mg may be given by intramuscular or slow intravenous injection 45 to 60 minutes before the induction of anaesthesia. In obstetric patients at the start of labour, an oral dose of 150 mg may be given and may be repeated at intervals of 6 hours if required.

In patients with chronic episodic **dyspepsia** (p. 1806.3), a dose of 150 mg twice daily orally for up to 6 weeks may be given. For the short-term symptomatic relief of dyspepsia a dose of 75 mg, repeated if necessary up to a maximum of 4 doses daily, may be taken. Treatment should be restricted to a maximum of 2 weeks of continuous use at one time.

PARENTERAL DOSAGE.

The usual dose of ranitidine by intramuscular or intravenous injection is 50 mg, which may be repeated every 6 to 8 hours; the intravenous injection should be given slowly over not less than 2 minutes and should be diluted to contain 50 mg in 20 mL. For an intermittent intravenous infusion the recommended dose in the UK is 25 mg/hour given for 2 hours which may be repeated every 6 to 8 hours. A rate of 6.25 mg/hour has been suggested for continuous intravenous infusion although higher rates may be used for conditions such as Zollinger-Ellison syndrome or in patients at risk from stress ulceration (see above).

Administration in children. Ranitidine is used in children to heal duodenal and gastric ulcers and to prevent stress ulceration in critically ill patients. It is licensed in children, although indications, age ranges, and doses may vary from country to country. When given orally, ranitidine is licensed from ages 3 to 11 years and over 30 kg bodyweight in the UK, and from 1 month to 16 years in the USA.

In the treatment of duodenal and gastric ulcers, a usual oral dose of 4 to 8 mg/kg daily in 2 divided doses is given, to a maximum of 300 mg ranitidine daily, for 4 to 8 weeks. For maintenance US licensed product information recommends a dose of 2 to 4 mg/kg daily, to a maximum of 150 mg ranitidine daily.

In the treatment of gastro-oesophageal reflux disease, a usual oral dose of 5 to 10 mg/kg daily in 2 divided doses is given, to a maximum of 600 mg daily.

The *BNFC* suggests the same oral doses for 3 to 12 year olds as those licensed in the UK, but includes doses for younger children, for any indication:

- neonates: 2 mg/kg three times daily, although absorption can be unreliable, and a maximum dose of 3 mg/kg three times daily
- 1 to 6 months: 1 mg/kg three times daily; maximum 3 mg/kg three times daily
- 6 months to 3 years: 2 to 4 mg/kg twice daily

It also suggests adult doses for children aged 12 to 18 years, see Uses and Administration above.

Ranitidine may also be given intravenously to children when oral treatment is not possible. UK licensed product information recommends the following doses in children aged 6 months to 11 years:

Treatment of peptic ulcer and gastro-oesophageal reflux disease:

- initially 2 or 2.5 mg/kg (maximum 50 mg) as a slow intravenous injection over 10 minutes followed by intermittent infusion of 1.5 mg/kg every 6 to 8 hours *or*
- a loading dose of 450 micrograms/kg as a slow intravenous injection over at least 2 minutes followed by a continuous infusion of 150 micrograms/kg per hour

Prophylaxis of stress ulceration:

- 1 mg/kg (maximum 50 mg) as a slow intravenous injection over at least 2 minutes, every 6 to 8 hours *or*
- 125 to 250 micrograms/kg per hour as a continuous infusion

The *BNFC* also suggests intravenous doses for children according to age, for all indications:

- neonate: 0.5 to 1 mg/kg by slow intravenous injection every 6 to 8 hours
- 1 month to 18 years: 1 mg/kg (to a maximum of 50 mg) every 6 to 8 hours, either by slow intravenous injection or by intermittent infusion at a rate of 25 mg/hour

In the USA, ranitidine is given intravenously to treat children from 1 month to 16 years of age with duodenal ulcer. A dose of 2 to 4 mg/kg daily in 3 or 4 divided doses at 6 to 8 hourly intervals (maximum of 50 mg per dose) is given either by slow intravenous injection over 5 minutes, or by intermittent infusion over 20 minutes.

Administration in renal impairment. A study in patients with varying degrees of renal impairment[1] found that the mean terminal half-life of ranitidine was increased from 2.09 hours in subjects with normal renal function to between 4.23 and 8.45 hours in patients with renal impairment, the degree of prolongation being proportional to the degree of impairment as measured by glomerular filtration rate. As a result of these findings it was recommended that the dose of ranitidine should be halved in patients with a glomerular filtration rate of 20 mL/minute or less. Licensed product information therefore recommends that dosage of ranitidine be reduced in patients with severe renal impairment.

For patients with a creatinine clearance of less than 50 mL/minute, an *oral* dose of 150 mg daily at bedtime is recommended. This may be cautiously increased to 150 mg every 12 hours if needed and reduced back to 150 mg daily if maintenance treatment is required.

For *parenteral* use, licensed recommendations vary between countries. In the UK, individual doses may be reduced to 25 mg, while the frequency is adjusted in the USA to give a recommended usual dose of 50 mg every 18 to 24 hours, which may be cautiously increased to every 12 hours or more often if necessary.

Ranitidine 150 mg daily provided adequate serum concentrations without excessive accumulation in 20 patients undergoing regular haemodialysis.[2] The serum-ranitidine concentrations fell by about 50% during a 4-hour haemodialysis session but less than 3% of the dose was removed and supplemental doses after dialysis were considered unnecessary. Licensed product information in the UK and USA recommends that the timing of doses is adjusted so that they are given at the end of dialysis.

1. Dixon JS, *et al.* The effect of renal function on the pharmacokinetics of ranitidine. *Eur J Clin Pharmacol* 1994; 46: 167–71.
2. Comstock TJ, *et al.* Ranitidine accumulation in patients undergoing chronic hemodialysis. *J Clin Pharmacol* 1988; 28: 1081–5.

Cystic fibrosis. A comparative study involving 29 patients with cystic fibrosis (p. 177.2) found that ranitidine was more effective than cisapride in improving dyspeptic symptoms and gastric emptying and distension.[1] Antisecretory drugs are also used in this condition to decrease the inactivation of oral pancreatic enzyme therapy.

1. Cucchiara S, *et al.* Ultrasound measurement of gastric emptying time in patients with cystic fibrosis and effect of ranitidine on delayed gastric emptying. *J Pediatr* 1996; 128: 485–8.

Immunomodulation. Like cimetidine (see p. 1827.3), ranitidine has been proposed to have immunoregulatory effects. However, ranitidine 300 mg twice daily had no effect on absolute CD4 cell counts or plasma HIV RNA in patients with HIV infection in a placebo-controlled study.[1] Similarly, ranitidine had no significant benefit in patients with gastric cancer (see Malignant Neoplasms, p. 1828.1).

1. Bartlett JA, *et al.* A placebo-controlled trial of ranitidine in patients with early human immunodeficiency virus infection. *J Infect Dis* 1998; 177: 231–4.

Skin disorders. As with cimetidine (p. 1828.2), ranitidine has been tried in various skin disorders. Oral ranitidine 300 mg twice daily for up to 16 weeks has been reported to be of benefit as an adjuvant to local treatment with corticosteroids and a moisturising ointment in patients with *atopic dermatitis*.[1] There are reports of improvements in *psoriasis* after use of ranitidine,[2-4] although this is a field that is notoriously difficult to evaluate because of the chronic relapsing and remitting nature of the disease, and others have failed to show benefit.[5]

1. Veien NK, *et al.* Ranitidine treatment of hand eczema in patients with atopic dermatitis: a double-blind placebo-controlled trial. *J Am Acad Dermatol* 1995; 32: 1056–7.
2. Witkamp L, *et al.* An open prospective clinical trial with systemic ranitidine in the treatment of psoriasis. *J Am Acad Dermatol* 1993; 28: 778–81.
3. Smith KC. Ranitidine useful in the management of psoriasis in a patient with acquired immunodeficiency syndrome. *Int J Dermatol* 1994; 33: 220–1.
4. Kristensen JK, *et al.* Systemic high-dose ranitidine in the treatment of psoriasis: an open prospective clinical trial. *Br J Dermatol* 1995; 133: 905–8.
5. Çetin L, *et al.* High-dose ranitidine is ineffective in the treatment of psoriasis. *Br J Dermatol* 1997; 137: 1021–2.

Adverse Effects

As for Cimetidine, p. 1828.3. Unlike cimetidine, ranitidine has little or no anti-androgenic effect, despite isolated reports of gynaecomastia and impotence.

General references.

1. Wormsley KG. Safety profile of ranitidine: a review. *Drugs* 1993; 46: 976–85.
2. Mills JG, *et al.* The safety of ranitidine in over a decade of use. *Aliment Pharmacol Ther* 1997; 11: 129–37.

Meningitis. A 30-year-old man developed aseptic meningitis on 3 occasions after use of ranitidine.[1] In each case symptoms resolved rapidly on withdrawal of the drug.

1. Durand JM, *et al.* Ranitidine and aseptic meningitis. *BMJ* 1996; 312: 886. Correction. *Ibid.*: 1392.

Precautions

As for Cimetidine, p. 1830.2.

Allergy testing. For mention of the effect of ranitidine on allergy testing, see Cimetidine, p. 1830.2.

Helicobacter pylori testing. For reference to the effect of ranitidine on the urea breath test for *Helicobacter pylori*, see p. 1830.2.

Hepatic impairment. For a report of increased resistance to H_2-antagonists in patients with liver cirrhosis, see Cimetidine, p. 1830.3.

Porphyria. Although licensed product information recommends that ranitidine should be avoided in patients with a history of acute porphyria, reports of porphyria associated with its use have been rare and inconclusive. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ranitidine 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 07/10/11)

Pregnancy. For information on the use of H_2-antagonists during pregnancy, see Cimetidine, p. 1830.3.

Renal impairment. For evidence of reduced clearance of ranitidine in patients with renal impairment see Administration in Renal Impairment, p. 1882.3.

Interactions

Unlike cimetidine (p. 1830.3), ranitidine does not seem to affect cytochrome P450 isoenzymes to any great extent, and therefore is considered to have little effect on drugs metabolised by this route. However, like other H_2-antagonists, its effects on gastric pH may alter the absorption of drugs whose absorption is dependent on an acid gastric pH.

A review comparing the drug interactions of ranitidine with those of cimetidine.[1]

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.

Alcohol. Any interaction between H_2-antagonists and alcohol is generally thought unlikely to be clinically significant (see p. 1735.2).

Antacids. For discussion of the effect of antacids on the bioavailability of H_2-antagonists, see Cimetidine, p. 1831.1.

Cisapride. For mention of the effect of cisapride on the bioavailability of ranitidine, see Cimetidine, p. 1831.1.

Sucralfate. For information on the effect of sucralfate on the bioavailability of H_2-antagonists, see Cimetidine, p. 1831.1.

Pharmacokinetics

Ranitidine is readily absorbed from the gastrointestinal tract with peak concentrations in plasma occurring about 2 to 3 hours after oral doses. Food does not significantly impair absorption. The bioavailability of ranitidine after oral doses is about 50%. Ranitidine is rapidly absorbed after intramuscular injection, with peak plasma concentrations occurring in about 15 minutes. It is weakly bound, about 15%, to plasma proteins.

The elimination half-life is about 2 to 3 hours and is increased in renal impairment. A small proportion of ranitidine is metabolised in the liver to the *N*-oxide, the *S*-oxide, and desmethylranitidine; the *N*-oxide is the major metabolite but accounts for only about 4 to 6% of a dose. About 30% of an oral dose and 70% of an intravenous dose is excreted unchanged in the urine in 24 hours, primarily by active tubular secretion; there is some excretion in the faeces. Ranitidine crosses the placental barrier and is distributed into breast milk.

Distribution into breast milk. A study in a mother given multiple doses of ranitidine showed higher concentrations in breast milk than in serum; the minimum milk concentration occurred between 1 and 2 hours after a dose and the highest concentration was towards the end of the 12-hour dosing interval.[1] The amount that would be ingested by the infant could not be reliably estimated because of the variable milk to serum ratio.

1. Kearns GL, *et al.* Appearance of ranitidine in breast milk following multiple dosing. *Clin Pharm* 1985; 4: 322–4.

Enterohepatic recycling. Some individuals have a second peak in the plasma concentration of ranitidine, which could be due to enterohepatic recirculation. However, only 0.7 to 2.6% and 0.3 to 1.0% of a dose of ranitidine was excreted into the bile of 3 patients in 24 hours after 50 mg given intravenously or 300 mg given orally respectively, indicating that significant recirculation did not occur.[1]

1. Klotz U, Walker S. Biliary excretion of H_2-receptor antagonists. *Eur J Clin Pharmacol* 1990; 39: 91–2.

Neonates. Renal function is limited in the first month of life, and reduced clearance of ranitidine would be expected. Blood samples taken from 27 full-term neonates given a single intravenous dose of ranitidine 2.4 mg/kg revealed the following pharmacokinetic data: elimination half-life, 3.45 hours; total volume of distribution, 1.52 litres/kg; total plasma clearance, 5.02 mL/kg per minute.[1] None of the infants had renal or hepatic impairment. In another study[2] in 13 full-term neonates undergoing extracorporeal membrane oxygenation, the elimination half-life was increased to 6.61 hours after an intravenous dose of 2 mg/kg ranitidine. A sustained increase in gastric pH was seen with this dose, and the authors suggested that a dosage interval of 12 hours or longer may be sufficient for intermittent intravenous use in this population. Alternatively, a continuous infusion of ranitidine 2 mg/kg daily was recommended to maintain the initial increase in pH. See also Administration in Children, p. 1882.2.

1. Fontana M, *et al.* Ranitidine pharmacokinetics in newborn infants. *Arch Dis Child* 1993; 68: 602–3.
2. Wells TG, *et al.* Pharmacokinetics and pharmacodynamics of ranitidine in neonates treated with extracorporeal membrane oxygenation. *J Clin Pharmacol* 1998; 38: 402–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acidex; Adesial†; Alivian; Dualid; Espaven; Faboacid R; Fendibina; Gastrial; Gastrolets; Gastrosedol; Gastrozac; Labsidex; Lorbitidina; Luvier; Notrab; Prednocris; Ranimed; Ranitic†; Ranitral; Ranitul; Raticina; Reco; Reflux; Sustac; Taural; Teogrand; Tomag; Ulcotenk; Urgis†; Vingional; Vizerul; Zantac; *Austral.*: Ausran; Mylanta 12 Hour Action; Rani 2; Ranihexal†; Ranitic†; Ranoxyl; Ulcaid; Zantac; *Austria*: Ranic; Raninorm; Ulsal; Zantac; *Belg.*: Docranit†; Gastran†; Ranitimed†; Zantac; *Braz.*: Antagon; Antak; Antidin; Aziliv; Label; Logat; Neosac; Randine; Raniblok; Raniclor†; Ranidin; Ranidina; Ranidine†; Raniflex; Ranitil; Ranitin†; Ranitinol; Ranition; Ranitrat; Tekadin; Ulceridina†; Ulcerocin; Ulcoren; Ulcidin; Zadine; Zylium; *Canad.*: Acid Reducer; Maximum Strength Acid Reducer; Novo-Ranidine†; Nu-Ranit; Zantac; *Chile*: Ranicel†; Ranitax†; Tipac; Zantac; *China*: Ai Ke Ting (艾克汀); Ai Ke Wei (艾可谓); De Te Li Er (德特利尔); Dong Yi (东易); FuWei (孚卫); Histac (西斯塔); Jing Lu (菁璐); JinWeiHe (津卫和); Jiu Ao (九奥); Ke Ao Si (可奥斯); Lanbaixing (兰百幸); Ou Hua Da (欧化达); Pu Er Tai (普而太); Qi Di (奇迪); Shan De Kang (善得康); Yi Zhen Kang (依真慷); Zantac (善卫得); *Cz.*: Histac†; Ranisan; Ranital; Ulcosan; Zantac†; *Denm.*: Acikure; Kuracid; Ranicodan; Syrex; Zantac; *Fin.*: Inside; Ranicur†; Ranimex†; Ranisan; Ranixal; Zantac; *Fr.*: Azantac; Raniplex; *Ger.*: Junizac†; Ran Lich†; Rani-nerton†; Rani-Puren†; Raniberl†; Ranibeta; Ranicux; Raniprotect; Ranitic†; Ranitidoct†; Sostril†; Zantic; *Gr.*: Alphadine; Aova; Baroxal; Bindazac; Blumol; Brixoral; Ceftrinal; Epadoren; Ezopta; Galebiron; Gaproxen; Gertocalm; Lomadryl; Lumaren; Narigen; Nipodur; Nitised; Odanet; Ptinolin; Ranicion; Ranizac; Restopon; Ribolin; Rothonal; Semuele; Smaril; Soredine; Specinor; Sveltanet; Synthomanet; Tupast; Ulcomet; Verlost; Yara; Zantac; Zoliden; Zurfix; *Hong Kong*: Hyzan; LAtac†; Lumeran; Novo-Ranidine†; Radin†; Randact†; Ranidine†; Raniplex†; Ranital; Ranolta; Simetac†; Synitidine†; Ulticer; Uni-Rantact†; Zantac; Zendhin; *Hung.*: Histac; Ranitic; Ulceran; Ulcosin†; *Umaren*; Zantac; *India*: Aciloc; Actiran; Aztec; Becotac; Consec; Din; Emtec; Entac; Giran; Healcer; Helkoss; Histac; Hytide; Intac; Kamtac; Lantac; Lydin; Manotac; Meditin; Nilcer; Nitin; R-Loc; Rantac; Ultac; Zinetac; *Indon.*: Acran; Aldin†; Anitid; Chopintac; Conranin; Fordin; Gastridin; Getidin; Hexer; Radin; Rancus; Ranicare; Ranilex; Ranin; Ranivell; Ranticid; Rantin; Ratan; Ratinal; Renatac; Scanarin; Titan; Tricker; Tyran; Ulceranin; Wiacid; Xeradin; Zantac; Zantadin; Zantifar; Zenti; Zumaran†; *Irl.*: Bellran†; Gertac; Ranitic; Ranopine; Xanomel†; Zantac; *Israel*: Zanidex†; Zantac; Zaridex; *Ital.*: Dolillux; Raniben; Ranibloc; Ranidex†; Ranidil; Sensigard; Ulcex; Zantac; *Jpn*: Zantac; *Malaysia*: Arnetin; Gastril; Histac; Hyzan†; Vesyca; X'tac; Zantac; Zendhin; *Mex.*: Acloral; Agrisen†; Aldivina; Anistal; Anticina†; Avintac; Azantac; Bio-Gast; Cauteridol†; Credaxol; Dinaxin; Driges; Flatmed; Galidrin; Gastrec; Gastridin; Histac†; Iqfadina; Katalem; Microtid; Midaven; Neugal†; Offentina†; Phartidine; Radyn; Ranepal; Ranifarn; Ranifur; Raniger; Ranisen; Ranulin; Raudil; Redacid; Sarcitec; Serranit; Serviradine; Sinhdoran; Syngasy; Terodul; Tianak; Ulcevit; Ulgastrin; Ulkodin; Ulmodhyl; Ulsaven; Ultran; Unitin; *Neth.*: Azantac†; Kruidvat maagzuurremmer ranitidine; Zantac; *Norw.*: Inside Brus†; Zantac; *NZ*: H_2RA; Peptisoothe; Zantac; *Philipp.*: Aceptin; Aciloc; Aciran; Alisazim; Ameket; Ceranid†; Clodine; Contracid; Dalycrid; Danitin; Diranite; Entac; Equaline; Eu-Ran†; Gastrone; Ildecep; Incid; Increph; Intac; Loracid; Microtec; Mordek; Normaxid; Pep-Bloc; Peptica; RA Bloc; Ramadine; Ranae; Randin; Ranisan; Ranitab; Ranitac; Ranitalis; Ranitein; Ranivint; Rantizec; Rapidin; Raxide; Renfort; Rentsan; Ulcedrug; Ulcemed; Ulcepac; Ulceragon; Ulceral†; Ulcergo; Ulcerix; Ulci-Cure; Ulcin; Ulran; Zantac; Zantol; Zeltac; Zeptag; Zerdin; Zidaxim; *Pol.*: Gastranin Zdrovit; Novo-Ranidine†; Raniberl; Ranic; Ranigast; Ranimax; Ranisan; Ranitin†; Riflux; Solvertyl; Zantac; *Port.*: Bloculcer; Efective†; Gastridina; Gastrolav; Gastrulcer; Pep-Rani; Peptab; Peptifar†; Ranitine; Stacer; *Tecradina*; Zantac; *Rus.*: Aciloc (Ацилок); Histac (Гистак); Ranigast (Ранигаст); Ranisan (Ранисан); Ranitine (Ранитин); Rantac (Рантак); Ulcodin (Улкодин); Ulran (Ульран); Zantac (Зантак); Zantin (Зантин); Zoran (Зоран); *S.Afr.*: Austac; GI-Tak; Histak; R-Loc; Ranihexal; Ranit; Ulcaid†; Ultak; Zantac; *Singapore*: Aciloc; Beatac; Gastril; Histac; Hyzan; Lumaren; Neoceptin-R; Ranidine; Ratic; SP-Gastril; Vesyca; Xanidine; Zantac; Zendhin; Zynol; *Spain*: Alquen; Aracidina†; Arcid†; Ardoral; Coralen; Denulcer†; Fagus†; Leiracid; Ranidin†; Ranubert†; Tanidina; Terposen; Zantac; *Swed.*: Artonil†; Inside; Rani-Q; Stomacid; Zantac; *Switz.*: Ranimed; Ulcidine†; Zantic; *Thai.*: Acicare; Aciloc; Histac; R-Loc; Ramag; Ranicid; Ranid; Ranidine; Ranin; Ranit-VC; Rantac; Rantodine; Ratic; Ratica; Utac†; Xanidine; Zanamet; Zantac; Zantidon; Zardil†; *Turk.*: Ranitab; Ranitine; Raniver; Ranobel; Rozon†; Santanol†; Ulcuran; Zandid; Zantac; *UAE*: Rantag; *UK*: Gavilast; Ranitic; Ranitil; Rantec; Ranzac; Zantac; *USA*: Zantac; *Venez.*: Aplom; Enteral; Gastac; Ranibloc; Retamin; Vizerul; Zantac.

Multi-ingredient Preparations. *Arg.*: Euciton Reflux; Gastrosedol Plus; Megalex; *China*: Ge Lai Shi (格来士); Yi Shuang Bi (易双必); Yilishu (宜立舒); *India*: Acidom-O; Acidom; Aciloc RD; Actiran-D; Actispas-R; Alcirid-O; Alotac; Avispas; Aztec-D; Doran-O; Gaspaz; Helkoss-D; Manotac Plus; Meditin Plus; Mefar-PD; Normaxin-RT; *Mex.*: Ergex; Pepti-Max.

Pharmacopoeial Preparations

BP 2014: Ranitidine Injection; Ranitidine Oral Solution; Ranitidine Tablets;
USP 36: Ranitidine in Sodium Chloride Injection; Ranitidine Injection; Ranitidine Oral Solution; Ranitidine Tablets.

Ranitidine Bismuth Citrate *(BAN, USAN)*

GR-122311X; Ranitidin Bizmut Sitrat; Ranitidin Bizmutreks; Ranitidina y bismuto, citrato de; Ranitidine Bismutrex; Ранитидин Висмут Цитрат.

N-[2-{[5-[(Dimethylamino)methyl]furfuryl]thio}-ethyl]-*N'*-methyl-2-nitro-1,1-ethenediamine, compound with bismuth (3+) citrate (1:1).

$C_{13}H_{22}N_4O_3S,C_6H_5BiO_7$=712.5

CAS — 128345-62-0.

ATC — A02BA07.

ATC Vet — QA02BA07.

UNII — 7AJ51I17KG.

Profile

Ranitidine bismuth citrate is a combination of ranitidine and a bismuth citrate complex, which dissociates in the stomach and releases ranitidine and bismuth; it therefore possesses both the actions of the bismuth compounds (p. 1822.2) and of ranitidine (p. 1882.1). It has been used in the management of peptic ulcer disease (p. 1813.2), and has

been given with antibacterials for the eradication of *Helicobacter pylori* infection and the prevention of relapse of peptic ulcer disease.

Blackening of the tongue and faeces is common with ranitidine bismuth citrate, and gastrointestinal disturbances, headache, mild anaemia, and altered liver enzyme values have been reported. Rarely, hypersensitivity reactions (including anaphylaxis), have occurred. It was not suitable for long-term or maintenance therapy because of the risk of bismuth accumulation.

Reviews.
1. Anonymous. Pylorid. H. pylori and peptic ulcer. *Drug Ther Bull* 1996; 34: 69–70.
2. Chiba N, *et al.* Ranitidine bismuth citrate. *Can J Gastroenterol* 2001; 15: 389–98.

Peptic ulcer disease. Although proton pump inhibitor-based *Helicobacter pylori* eradication regimens are more commonly used (see p. 1813.2), regimens containing ranitidine bismuth citrate have also been tried as alternatives with some success.[1]

1. Gisbert JP, *et al.* Systematic review and meta-analysis: proton pump inhibitor vs. ranitidine bismuth citrate plus two antibiotics in Helicobacter pylori eradication. *Helicobacter* 2005; 10: 157–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Pylorisin†; ***Braz.***: Pylorid; ***China***: Jindele (金得乐); Ruibei (瑞倍); Shu Wei (舒威); Si Fu Si (斯伏丝); ***Fin.***: Pylorid†; ***Gr.***: Pylorid; ***Mex.***: Azanplus†; ***Philipp.***: Pylorid; ***Singapore***: Pylorid; ***Thai.***: Pylorid†; ***Turk.***: Pylorid; ***Venez.***: Pylorid.

Multi-ingredient Preparations. ***Austral.***: Pylorid-KA†.

Rebamipide *(rINN)*

Rebamipida; Rébamipide; Rebamipidum; Ребамипид.
(±)-α-(*p*-Chlorobenzamido)-1,2-dihydro-2-oxo-4-quinolinepropionic acid.
$C_{19}H_{15}ClN_2O_4$=370.8
CAS — 90098-04-7; 111911-87-6.

Profile

Rebamipide is stated to possess cytoprotective properties and is used in the treatment of peptic ulcer disease (p. 1813.2) and gastritis in usual oral doses of 100 mg three times daily. It has also been used rectally for the treatment of intestinal inflammation. Rebamipide eye drops are under investigation in the treatment of dry eye.

References.
1. Makiyama K, *et al.* Efficacy of rebamipide enemas in active distal ulcerative colitis and proctitis: a prospective study report. *Dig Dis Sci* 2005; 50: 2323–9.
2. Miyata M, *et al.* Successful treatment of severe pouchitis with rebamipide refractory to antibiotics and corticosteroids: a case report. *World J Gastroenterol* 2006; 12: 656–8.
3. Miwa H, *et al.* Effect of a gastro-protective agent, rebamipide, on symptom improvement in patients with functional dyspepsia: a double-blind placebo-controlled study in Japan. *J Gastroenterol Hepatol* 2006; 21: 1826–31.
4. Terano A, *et al.* Rebamipide Clinical Study Group. Rebamipide, a gastroprotective and anti-inflammatory drug, promotes gastric ulcer healing following eradication therapy for Helicobacter pylori in a Japanese population: a randomized, double-blind, placebo-controlled trial. *J Gastroenterol* 2007; 42: 690–3.
5. Park SH, *et al.* Comparison of prevention of NSAID-induced gastrointestinal complications by rebamipide and misoprostol: a randomized, multicenter, controlled trial—STORM STUDY. *J Clin Biochem Nutr* 2007; 40: 148–55.
6. Du Y, *et al.* Anti-inflammatory effects of rebamipide according to Helicobacter pylori status in patients with chronic erosive gastritis: a randomized sucralfate-controlled multicenter trial in China—STARS study. *Dig Dis Sci* 2008; 53: 2886–95.
7. Sugai S, *et al.* Efficacy and safety of rebamipide for the treatment of dry mouth symptoms in patients with Sjögren's syndrome: a double-blind placebo-controlled multicenter trial. *Mod Rheumatol* 2009; 19: 114–24.
8. Naito Y, Yoshikawa T. Rebamipide: a gastrointestinal protective drug with pleiotropic activities. *Expert Rev Gastroenterol Hepatol* 2010; 4: 261–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Huining (惠宁); Mucosta (康固思达); ***Indon.***: Becantex; Mucosta; ***Jpn***: Mucosta; ***Malaysia***: Mucosta; ***Philipp.***: Gastrix; Mucosta; ***Thai.***: Mucosta.

Renzapride *(BAN, rINN)*

ATL-1251; AZM-112 (renzapride hydrochloride); BRL-24924A; Renzaprida; Renzapridum; Рензаприд.
(±)-*endo*-4-Amino-*N*-(1-azabicyclo[3.3.1]non-4-yl)-5-chloro-o-anisamide.
$C_{16}H_{22}ClN_3O_2$=323.8
CAS — 88721-77-1; 112727-80-7.
UNII — 9073C0W4E9.

Profile

Renzapride is a substituted benzamide with prokinetic actions on gastrointestinal motility. It also has 5-HT_4 agonist and 5-HT_3 antagonist activity. It has been investigated for the management of gastrointestinal disorders including irritable bowel syndrome.

References.
1. Tack J, *et al.* Pilot study of the efficacy of renzapride on gastrointestinal motility and symptoms in patients with constipation-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* 2006; 23: 1655–65.
2. George AM, *et al.* Clinical trial: renzapride therapy for constipation-predominant irritable bowel syndrome—multicentre, randomized, placebo-controlled, double-blind study in primary healthcare setting. *Aliment Pharmacol Ther* 2008; 27: 830–7.
3. Lembo AJ, *et al.* Clinical trial: renzapride treatment of women with irritable bowel syndrome and constipation - a double-blind, randomized, placebo-controlled, study. *Aliment Pharmacol Ther* 2010; 31: 979–90.

Reslizumab *(USAN, rINN)*

Reslizumabum; Sch-55700; Реслизумаб.
CAS — 241473-69-8.

NOTE. The name Cinquil has been used as a trade mark for reslizumab.

Profile

Reslizumab is a humanised monoclonal antibody that is under investigation for the treatment of paediatric eosinophilic oesophagitis, hypereosinophilic syndrome, and asthma.

References.
1. Walsh GM. Reslizumab, a humanized anti-IL-5 mAb for the treatment of eosinophil-mediated inflammatory conditions. *Curr Opin Mol Ther* 2009; 11: 329–36.
2. Walsh GM. Reslizumab for pediatric eosinophilic esophagitis. *Immunotherapy* 2010; 2: 461–5.

Revaprazan *(rINN)*

Revaprazán; Révaprazan; Revaprazanum; Ревапразан.
N-(4-Fluorophenyl)-4,5-dimethyl-6-[(1*RS*)-1-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]pyrimidin-2-amine.
$C_{22}H_{23}FN_4$=362.5
CAS — 199463-33-7.
UNII — 5P184180P5.

Revaprazan Hydrochloride *(USAN, rINNM)*

Hidrocloruro de revaprazán; Révaprazan, Chlorhydrate de; Revaprazani Hydrochloridum; SB-641257A; YH-1885; Ревапразана Гидрохлорид.
N-(4-Fluorophenyl)-5,6-dimethyl-4-[(1*RS*)-1-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]pyrimidin-2-amine hydrochloride.
$C_{22}H_{23}FN_4.HCl$=398.9
CAS — 178307-42-1.
UNII — 4DQ6T10R64.

Profile

Revaprazan is a proton pump inhibitor that is under investigation for the management of gastric and duodenal ulceration, functional dyspepsia, and gastro-oesophageal reflux disease.

References.
1. Sorbera LA, *et al.* Revaprazan hydrochloride. *Drugs Of The Future* 2004; 29: 455.
2. Yu K-S, *et al.* Pharmacokinetic and pharmacodynamic evaluation of a novel proton pump inhibitor, YH1885, in healthy volunteers. *J Clin Pharmacol* 2004; 44: 73–82.

Rhubarb

Chinese Rhubarb; Korzeń rzewienia; Rabarbarų šaknys; Rabarbaro; Rabarberrot; Raparperinjuuri; Ravent; Rebarbaragyökértörzs; Reveňový kořen; Rhabarber; Rhabarberwurzel; Rhei Radix; Rhei Rhizoma; Rheum; Rhubarb Rhizome; Rhubarbe; Ruibarbo; Ревень Аптечный.
ATC Herb — HA06AB5015 (Rheum palmatum: root).
UNII — A47JP5ZG9M (Rheum officinale root).

Description. Indian rhubarb (Himalayan rhubarb) consists of the dried rhizome and roots of *Rheum emodi, R. webbianum,* or some other related species of *Rheum.*

Rhapontic rhubarb (Chinese rhapontica) consists of the dried rhizomes of *R. rhaponticum.* It may occur as an adulterant of rhubarb, and pharmacopoeias specify a test to confirm its absence. Garden rhubarb, of which the leafstalks are used as food, is derived from *R. rhaponticum.*

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn. Chin.* and *Jpn* also permit *Rheum tanguticum,* and *Jpn* also permits *R. coreanum.*

Ph. Eur. 8: (Rhubarb). The whole or cut, dried underground parts of *Rheum palmatum* or of *R. officinale* or of hybrids of these two species or of a mixture. The underground parts are often divided; the stem and most of the bark with the rootlets are removed. It contains not less than 2.2% of hydroxyanthracene derivatives, expressed as rhein ($C_{15}H_8O_6$ = 284.2), calculated with reference to the dried drug. Protect from light.

Uses and Administration

Rhubarb is an anthraquinone stimulant laxative used similarly to senna (p. 1885.2). It also exerts an astringent action due to the presence of gallic acid derivatives and tannins.

Homoeopathy

Rhubarb has been used in homoeopathic medicines under the following names: Rheum; Rhei radix; Rheum palmatum; Rheum officinale.

Adverse Effects and Precautions

As for Senna, p. 1885.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Femi-loges; Phyto-Strol; ***Pol.***: Laxitab; Radirex; Rzewex†.

Multi-ingredient Preparations. ***Arg.***: LX-30†; Oralsone Topic; Parodium; Pyralvex; Wunderbalsam; ***Austral.***: Betaine Digestive Aid; Burdock Complex; Neo-Cleanse; ***Austria***: Eucarbon; Phytovir; Pyralvex; Silberne†; ***Belg.***: Pyralvex; ***Braz.***: Camomila Eparema; Gotas Preciosas; ***Canad.***: Herbal Laxative†; Herbolax†; Laxanat; Laxatil; Laxolax Phyto†; Melange de Plantes Formula L1 Laxatif†; Stomach Ease; Ultra-Lax†; ***Chile***: Parodium Cz.: Dr Theiss Schweden Krauter†; Dr Theiss Schwedenbitter†; Eucarbon; Pyralvex†; Species Cholagogae Planta†; Zlucnikova Cajova Smes; ***Fr.***: Depuratum; Parodium; Pyralvex; Resource Rhubagil†; Tisane D'Ars†; ***Ger.***: Pyralvex†; ***Gr.***: Pyralvex; ***Hong Kong***: Hepatofalk†; Pyralvex†; ***Hung.***: Bano Svedkeseru; Bolus Laxans; Eucarbon; ***India***: Agloliv; ***Indon.***: Pyralvex†; ***Israel***: Eucarbon; Novicarbon†; ***Ital.***: Alosen†; Amaro Medicinale; Caramelle alle Erbe Digestive; Colax†; Dis-Cinil Complex; Eparema-Levul; Eparema; Eucarbon; Eupatol; Lactolas; Lassativi Vetegali†; Pyralvex; ***Jpn***: Bofutsushosan; Choijokito; Daijokito; Dalobotampito; Daiokanzoto; Daisaikoto; Inchinkoto; Jidabokuippo; Jizusoippo; Junchoto; Keishikashakuyakudaioto; Mashiningan; Otsujito; San'oshashinto; Tokakujokito; Tsudosan; ***Malaysia***: Eucarbon Herbal; Eucarbon; ***Neth.***: Pyralvex; ***Philipp.***: Boie Carminative (Carminasen); Pyralvex; ***Pol.***: Betasol; Diges-Tonic; Laxantol†; Rhelax; ***Port.***: Pyralvex; ***Rus.***: Parodium (Пародиум); ***S.Afr.***: Eucarbon†; Helmontskruie†; Lewensessens; Moultons Herbal Extract†; Pyralvex; Wonderkroonessens; ***Singapore***: Pyralvex; Sankaijo; ***Spain***: Crislaxo; Laxante Bescansa Aloico†; Pyralvex; Solucion Schoum; ***Switz.***: Padma-Lax; Padmed Laxan; Parsenn Creme pour herpes; Phytovir; Pyralvex; Schweden-Mixtur H; ***Thai.***: Pyralvex; Rheum; Sahakarn Mist Stomachic; ***Turk.***: Eucarbon; Karboseptin; Piraldyne; Pyralvex; ***UK***: Acidosis; Digestive; Fam-Lax Senna; Fam-Lax; HRI Golden Seal Digestive; Indian Brandee; Jacksons Herbal Laxative; Pegina; Pyralvex; Rhuaka; Stomach Mixture; Wind & Dyspepsia Relief; ***Ukr.***: Eucarbon (Эукарбон); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; ***USA***: Black-Draught; ***Venez.***: Cynascool; Natrossil; Pinvex; Rheu-Tarx 1.

Homoeopathic Preparations. ***Austral.***: Snore Eze; ***Canad.***: Essigent†; Vegetal Tonic; ***Fr.***: Camilia; Momordica Complexe No 109†; Tonique Vegetal; ***Switz.***: Camilia.

Pharmacopoeial Preparations
BP 2014: Compound Rhubarb Tincture.

Roxatidine Acetate Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de acetato de roxatidina; Hoe-062 (roxatidine); Hoe-760; Pifatidine Hydrochloride; Roxatidina, hidrocloruro de acetato de; Roxatidine, Acétate Chlorhydrique de; Roxatidini Acetati Hydrochloridum; TZU-0460; Роксатидина Ацетат Гидрохлорид.
N-[3-[(α-Piperidino-*m*-tolyl)oxy]propyl]glycolamide acetate monohydrochloride.
$C_{17}H_{26}N_2O_3.C_2H_2O_2.HCl$=384.9
CAS — 78273-80-0 (roxatidine); 97900-88-4 (roxatidine hydrochloride); 78628-28-1 (roxatidine acetate); 93793-83-0 (roxatidine acetate hydrochloride).
ATC — A02BA06.
ATC Vet — QA02BA06.
UNII — 60426GOR1E.

Pharmacopoeias. In *Jpn.*

Stability. The stability of roxatidine acetate hydrochloride in parenteral nutrition solutions was influenced by storage temperature and amino acid content and composition.[1]

1. Oh J, *et al.* Stability of roxatidine acetate in parenteral nutrient solutions containing different amino acid formulations. *Am J Health-Syst Pharm* 2005; 62: 289–91.

Uses and Administration

Roxatidine acetate hydrochloride is an H_2-antagonist with actions and uses similar to those of cimetidine (p. 1827.2).

In the management of **peptic ulcer disease** the oral dose is 150 mg at bedtime or 75 mg twice daily for 4 to 6 weeks. Where appropriate a maintenance dose of 75 mg at bedtime may be given to prevent the recurrence of ulcers. In **gastro-oesophageal reflux disease** the recommended dose is 150 mg at bedtime or 75 mg twice daily for 6 to 8 weeks. Gastritis has been managed with 75 mg once daily in the evening, and a dose of 75 mg twice daily has been used for **Zollinger-Ellison** syndrome.

When used as a **pre-anaesthetic** medication, a dose of roxatidine acetate hydrochloride 75 mg is given 1 hour before anaesthesia by slow intravenous injection. Alternatively, an oral dose of 75 mg is given in the evening on the day before surgery and repeated 2 hours before the induction of anaesthesia; alternatively a single dose of 150 mg may be given the night before surgery.

Roxatidine acetate hydrochloride may also be given intravenously for the treatment of **upper gastrointestinal tract haemorrhage** in a dose of 75 mg twice daily by slow intravenous injection or by intravenous infusion.

For dosage in renal impairment, see below.

Reviews.

1. Murdoch D: Roxatidine acetate: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic potential in peptic ulcer disease and related disorders. *Drugs* 1991; 42: 240–60.

Administration in renal impairment. The dosage of roxatidine acetate hydrochloride should be reduced in patients with renal impairment. Suggested oral doses for peptic ulcer disease or gastro-oesophageal reflux disease are based on creatinine clearance (CC):

- CC 20 to 50 mL/minute: 75 mg once daily
- CC less than 20 mL/minute: 75 mg every 2 days

However, results in 6 patients with chronic renal failure and CC less than 20 mL/minute indicated that giving the recommended dose of roxatidine acetate hydrochloride, 75 mg every other day, was inadequate to maintain gastric pH above 4 for more than 6 hours. Subsequent study in 8 patients showed that a dose of 75 mg daily was well tolerated and effective.[1]

For prophylaxis of peptic ulcers, the following oral doses have been suggested based on CC:

- CC 20 to 50 mL/minute: 75 mg every 2 days
- CC less than 20 mL/minute: 75 mg twice weekly

1. Gladziwa U, *et al.* Pharmacokinetics and pharmacodynamics of roxatidine in patients with renal insufficiency. *Br J Clin Pharmacol* 1995; 39: 161–7.

Adverse Effects and Precautions

As for Cimetidine, p. 1828.3. Unlike cimetidine, roxatidine has little or no anti-androgenic effect, despite isolated reports of reductions in libido.

Interactions

Unlike cimetidine (p. 1830.3) roxatidine does not appear to affect cytochrome P450 isoenzymes, and therefore is considered to have little effect on drugs metabolised by this route. However, like other H_2-antagonists its effects on gastric pH may alter the absorption of drugs whose absorption is dependent on an acid gastric pH.

Pharmacokinetics

Roxatidine acetate hydrochloride is rapidly and almost completely absorbed from the gastrointestinal tract with peak concentrations in plasma occurring about 1 to 4 hours after oral doses. It is rapidly hydrolysed to the active desacetyl metabolite, roxatidine, by esterases in the liver, small intestine, and serum.

Over 90% of a dose is excreted in the urine as roxatidine and other metabolites. The elimination half-life of roxatidine is about 4 to 6 hours and is prolonged in renal impairment.

Roxatidine crosses the placenta and small amounts have been reported to be distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Roxane; *India*: Rotane; *Ital.*: Gastralgin; Neo H2: Roxit; *Jpn*: Altat; *Spain*: Zarocs†.

Senna

Alexandrian senna (senna pods, Alexandrian); Alexandrian senna (senna leaf); Alexandrian senna pods; Alexandrian senna, senna leaf; Alexandrian senna, senna pods; Alexandrian senna leaf;

inflammatory bowel disease. Prolonged use should generally be avoided.

Although anthraquinone derivatives may be distributed into breast milk the concentration achieved after usual maternal dosage is thought to be insufficient to affect the nursing infant (see also below).

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving senna, 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 21/11/06)

Colonic perforation. There were early reports of colonic perforation with faecal peritonitis,[1,2] in one case fatal,[1] after use of a senna preparation containing total sennosides 142 mg for bowel preparation before barium enema. In 1985, the strength of the UK preparation was halved to contain 72 mg of total sennosides; it was subsequently withdrawn, although a similar preparation, at the higher strength, remains available in some countries. To reduce the risk of colonic perforation, patients with suspected stricture, inflammatory bowel disease, or impending obstruction should not receive a bowel stimulant.[2]

1. Galloway D, *et al.* Faecal peritonitis after laxative preparation for barium enema. *BMJ* 1982; 284: 472.
2. Cave-Bigley D. Faecal peritonitis after laxative preparation for barium enema. *BMJ* 1982; 284: 740.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies senna 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 07/10/11)

Pregnancy. A retrospective case-control study involving 22 843 infants with congenital abnormalities and 38 151 healthy matched controls (of whom 506 and 937 respectively had mothers who had taken senna for constipation during pregnancy) found no association between abnormality and maternal use of senna.[1]

1. Ács N, *et al.* Senna treatment in pregnant women and congenital abnormalities in their offspring—a population-based case-control study. *Reprod Toxicol* 2009; 28: 100–4.

Pharmacokinetics

There is some absorption of anthraquinone laxatives after oral doses. Absorbed anthraquinones are metabolised in the liver. Unabsorbed senna is hydrolysed in the colon by bacteria to release the active free anthraquinones. Anthraquinones are excreted in urine and faeces and distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ciruela Fibra†; Laxiruela Ciruela Fibra; Laxiruela: Laxuave Sen; *Austral.*: Bekunis Tea†; Laxettes; Sennetabs; Senokot; *Austria*: Bekunis; Colonorm; Darmol; Pursennid; X-Prep; *Belg.*: Darlin†; Puca; Grains de Vals Senna; Midro; Prunasine; Senokot; *Braz.*: Senan; Senet†; Sennalax; *Canad.*: Agarol Extra†; Agarol with Sennosides†; Bekunis; Ex-Lax; Experience; Formula T1 Tea†; Herbal Laxative†; Laxative Pills; Senokot; Swiss Kriss†; *Chile*: Cholax; Naturlax; *Cz.*: Caj z Listu Senny; List Senny; Senalax; Sennove Lusky; *Denm.*: Thea Bona; *Fin.*: Exprep†; Pursennid; *Fr.*: Grains de Vals; Pursennide; Senokot; Tisane des Familles†; Tisane Franklin†; X-Prep; *Ger.*: Bekunis Instant; Bekunis-Krautertee N; Depuran†; Midro Abfuhr; Midro Tee; Neda Fruchtewurfel†; Ramend; *Gr.*: Bekunis; Pursennid: X-Prep; *Hong Kong*: Senokot; Senoside; *Hung.*: Darmol: Regulax; Tisasen; X-Prep; *India*: Glaxenna; Senade; Senalax; *Irl.*: Ex-Lax†; Senokot; *Israel*: Bekunis; Ex-Lax†; Florilax†; Jungborn; Laxikal Forte; *Ital.*: Falquilax; Pursennid; Tisana Kelemata; X-Prep; *Malaysia*: Senokot; *Mex.*: Arsen†; Bekunis; C-Motil; Ciruelax Comp; Ciruelax TE†; Lagenbach; Senokot; X-Prep; *Neth.*: Bekunis Plantaardig†; Bekunis Senna†; Puca excellent; Sennocol; X-Praep; *Norw.*: Pursennid; Senokot†; X-Prep†; *NZ*: Senokot; *Philipp.*: Laxen; Senalax; Senokot; *Pol.*: Bekunis; Figura 1; Regulax; Senalax; Senefol; X-Prep†; Xenna; *Port.*: Bekunis Laxante Natural; Bekunis; Pursennide; Senolax; X-Prep; *Rus.*: Glaxenna (Глаксенна); Herbion Laksana (Гербион Лаксана); Regulax (Регулакс); Senade (Сенаде); Senadexin (Сенадексин); Senalex (Сеналекс); Tisasen (Тисасен); *S.Afr.*: Black Forest†; Depuran; Gal†; Hamburg Tea; Laxador Senna; Sennalax†; Senokot; Soflax; X-Prep; *Singapore*: Bekunis; Senokot; *Spain*: Arkocapsulas Sen; Bekunis; Justelax†; Laxante Bescansa Normal†; Laxante Olan; Laxante Salud; Neholis; X-Prep; *Swed.*: Linella; Pursennid; *Switz.*: Bekunis; Darmol; Fuca N†; Grains de Vals Nouvelle formule; Knobel Comprimes N†; Midro; Pursennide; X-Prep; *Thai.*: Emulax Senna; Senokot; *Turk.*: Pursennid; Roha-Lax; Sennalax; Senokot; X-M; *UAE*: Laxal; *UK*: Ex-Lax; Nylax with Senna; Senokot; Sure-Lax; *Ukr.*: Regulax (Регулакс); Senadex (Сенадекс)†; *USA*: Black-Draught†; Dosaflex; Dr Edwards Olive; Evac-U-Gen; Ex-Lax; Fletchers Castoria; Lax Pills; Little Tummys Laxative; Maximum Relief Ex-Lax; Pedia-Lax; Senexon; Senna Smooth; Senna-Gen; Senokot; Senokotxtra; X-Prep†; *Venez.*: Laxovar; Senlax; Senokot.

Multi-ingredient Preparations. *Arg.*: Agiolax; Candilax†; Cirulaxia; Delgacin; Gelax; Laxiruela; LX-30†; Medilaxan; Rapilax Fibras; Yuyo; *Austral.*: Agiolax; Chemists Own Natural Laxative with Softener; Colon Care; Coloxyl with Senna; Combilax†; Detox Program; Neo-Cleanse; Sennesoft; Soflax; *Austria*: Abfuhrtee St Severin; Agiolax; Carilax; Entschlackender Abfuhrtee EF-EM-ES; Eucarbon; Frugelletten; Laxalpin†; Mag Kottas Krauterexpress Abfuhrtee; Midro Tee; Neda Fruchtewurfel; Planta Lax; The Chambard-Tee; *Belg.*: Agiolax; Herbesan; *Braz.*: Agiolax; Fitolax†; Florlax; Fontolax; Laxtam; Naturetti; Tamaril; Tamarine; Tamarine; *Canad.*: Bekunis†; Control†; Doulax; Elliminex; Fiber Plus; Formula B-1†; Herba Tone†; Herbal Laxative plus Yogurt†; Herbal Laxative†; Herbal Tabs†; Herbolax†; Laxanat; Laxolax; Linoforce; Melange de Plantes Formula L1 Laxatif†; Metab Herbs No 1†; Metab Herbs†; Senna-S; Senokot-S; Stomach Ease; Traditional Herbal Laxative†; Ultra-Lax†; *Chile*: Bilaxil; Instalax; Mielax†; Naturlax†; Tamarine; Te Laxante†; *China*: Agiolax (艾者思); *Cz.*: Agiolax†; Dr Theiss Schweden Krauter†; Dr Theiss Schwedenbitter†; Eucarbon; Projimava; Reduktan; *Denm.*: Dix†; *Fin.*: Agiolax; *Fr.*: Afra†; Agiolax; Boldoflorine; Boldoflorine; Boribel Tisane No 13†; Herbesan; Ideolaxyl; Laxilo†; Mediflor Contre la Constipation Passagere No 7; Modane; Mucinum a l'Extrait de Cascara; Olivalax; Santane C_6†; Tamarine†; Tisane D'Ars†; Tisane Garfield†; Tisane Provencale no 1; Tisane Saint-Urbain†; Ultratransit; Yerbalaxa; *Ger.*: Agiolax; Alasenn; *Gr.*: Agiolax; Tamarine; *Hong Kong*: Agiolax; Mucinum†; *Hung.*: Agiolax; Bano Svedkeseru; Bolus Laxans; Eucarbon; Herbalax; Super Colon Cleanse; *India*: Bolax; Constiсare; Evacuol; *Irl.*: Agiolax; *Israel*: Agiolax; Eucarbon; Jungborn†; Lido Tea†; Midro-Tea; Novicarbon†; *Ital.*: Agiolax; Alosen†; Colax†; Combilax; Confetti Lassativi CM; Cuscutinet; Eucarbon; Fibrolax Complex; Lactolas; Midro; Miracolon; Ortisan; Tamarine; Tisana Kelemata; *Jpn*: Circanetten; *Malaysia*: Agiolax; Eucarbon Herbal; Eucarbon; *Mex.*: Agiolax; Ciruelax Jalea; Fruticoline; Jarabe de Manzanas; Laxacaps; MD Lax; Naturetti; *Neth.*: Agiolax; Herbesan†; Prunacolon; Prunasine; *Norw.*: Agiolax†; *NZ*: Coloxyl with Senna; Laxsol; *Philipp.*: Boie Carminative (Carminasen); Castoria; *Pol.*: Agiolax; Laxamix†; Melisana Klosterfrau; Normosan†; Senalax K; *Port.*: Agiolax; Bekunis; Mucinum; Xarope de Macas Reinetas; *Rus.*: Proctophytol (Проктофитол); *S.Afr.*: Agiolax; Clairo†; Eucarbon†; *Singapore*: Sankaijo; *Spain*: Agiolax; Bekunis Complex; Crislaxo; Docuxen†; Farmasul; Jarabe Manceau; Laxante Sanatorium†; LinoMed; Modane; Pruina; Puntual; Puntualex; Pursenid; *Swed.*: Agiolax†; *Switz.*: Agiolax; Dragees aux figues avec du sene; Fruttasan†; Lapidar 10; Linoforce; LinoMed; Midro Tee; Phyto-Laxia†; Schweden-Mixtur H; Tisane laxative; Tisane Provencale no 1; Valverde Constipation dragees; Valverde Constipation sirop; *Thai.*: Agiolax; Circanetten; Hemorrhoid Relief; *Turk.*: Bekunis; Eucarbon; Karboseptin; *UK*: Athera; Califig; Califig; Cassilax; Cleansing Herbs; Dual-Lax Extra Strong; Dual-Lax Normal Strength; Fam-Lax Senna; Fibre Plus; Jacksons Herbal Laxative; Kas-Bah; Laxative Tablets; Linoforce; Lion Cleansing Herbs; Lustys Herbalene; Manevac; Modern Herbals Laxative; Modern Herbals Menopause; Natural Herb Tablets; Out-of-Sorts; Pripsen†; Rhuaka; Senokot Dual Relief; Skin Cleansing; Tabritis; *Ukr.*: Eucarbon (Эукарбон); Picosen (Пикосен); Softovak (Софтовак); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; *USA*: Black-Draught; Dok Plus; Ex-Lax Gentle Strength†; Laxacin; Perdiem†; Peri-Colace; Senna Plus; Senna Prompt; Senna-S; Senokot-S; X-Prep Bowel Evacuant Kit-1†; *Venez.*: Agiolax; Rheu-Tarx 1; Senokot con Docusato.

Homoeopathic Preparations. *UK*: Laxadoron.

Pharmacopoeial Preparations

BP 2014: Senna Liquid Extract; Senna Tablets; Standardised Senna Granules;

Ph. Eur.: Senna Leaf Dry Extract, Standardised;

USP 36: Senna Fluidextract; Senna Syrup; Sennosides Tablets.

Simeticone *(BAN, rINN)*

Activated Dimethicone; Activated Dimethylpolysiloxane; Activated Dimeticone; Antifoam A; Antifoam AF; Simethicone (USAN); Simeticon; Simeticona; Siméticone; Simeticonum; Simetikon; Simetikonas; Simetikoni; Szimetikon; Симетикон.

CAS — 8050-81-5.

NOTE. Do not confuse with Dimeticone (p. 2209.3).

Compounded preparations of simeticone may be represented by the following names:

- Co-simalcite *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of simeticone and hydrotalcite respectively.

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

Ph. Eur. 8: (Simeticone). It is prepared by incorporation of 4 to 7% silica into poly(dimethylsiloxane) with a degree of polymerisation between 20 and 400. It contains 90.5 to 99.0% of poly(dimethylsiloxane). It is a greyish-white, opalescent, viscous liquid. Practically insoluble in water and in methyl alcohol; very slightly soluble to practically insoluble in dehydrated alcohol; partly miscible with dichloromethane, with ethyl acetate, with methyl ethyl ketone, and with toluene.

USP 36: (Simeticone). A mixture of fully methylated linear siloxane polymers containing repeating units of the formula $[-(CH_3)_2SiO-]_n$ stabilised with trimethylsiloxy end-blocking units of the formula $[(CH_3)_3SiO-]$, and silicon dioxide. It contains not less than 90.5% and not more than 99% of polydimethylsiloxane and not less than 4% and not more than 7% of silicon dioxide. A translucent, grey, viscous fluid. Insoluble in water, in alcohol, and in dehydrated alcohol; the liquid phase is soluble 1 in 10 of chloroform, of ether, and of benzene, leaving a residue of silicon dioxide. Store in airtight containers.

Profile

Simeticone is a mixture of liquid dimeticones containing finely divided silicon dioxide to enhance the defoaming properties of the silicone. It lowers surface tension and when given orally causes bubbles of gas in the gastrointestinal tract to coalesce, thus aiding their dispersion.

Simeticone is used for the relief of flatulence and abdominal discomfort due to excess gastrointestinal gas in disorders such as dyspepsia (p. 1806.3) and gastro-oesophageal reflux disease (p. 1807.2). Doses of 100 to 250 mg three or four times daily have been given. For many gastrointestinal disorders, it is given with an antacid.

For doses in children, see below

Simeticone is also used as a defoaming agent in radiography or endoscopy of the gastrointestinal tract.

Administration in children. Simeticone can be given orally to infants to relieve symptoms of colic (see Gastrointestinal Spasm, p. 1807.1); 20 to 40 mg is given before feeds.

Gastrointestinal disorders. A brief review of the use of simeticone for gastrointestinal symptoms concluded that although it was commonly prescribed with an antacid, there was no good evidence that this provided additional benefit. When used alone simeticone probably helped to relieve minor postoperative and postprandial symptoms and was a useful aid in upper gastrointestinal endoscopy.[1] However, some considered there was no convincing evidence that simeticone, alone or with antacids, was effective for the treatment of eructation, flatulence, or other signs or symptoms of excess gastrointestinal gas.[2]

1. Anonymous. Dimethicone for gastrointestinal symptoms? *Drug Ther Bull* 1986; 24: 21–2.
2. Anonymous. Simethicone for gastrointestinal gas. *Med Lett Drugs Ther* 1996; 38: 57–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies silicones when used for gastrointestinal disorders 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 02/11/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aesim; Aflat; Carbogasol Forte; Carbogasol; Espaven Antigas; Factor AG; Metiorisan; Minicidez; Mylanta Gas; Simecon; *Austral.*: De-Gas; Gasbusters; Infacol; *Austria*: Antiflat; Disflatyl†; Lefaxin; SAB Simplex; *Belg.*: Imonogas; *Braz.*: Dimetiliv; Dimezin; Espasmo Flatol; Finigas; Flagass; Flatex; Flaticona; Flatol; Flucolic; For Gas; Gastroflat; Gazyme; Lufisan; Luftal; Meticone†; Mylanta Plus; Mylicon; Sanagas; Silidron; *Canad.*: Gas Relief; Gas-X; Infacol; Little Tummys Gas Relief; Ovol; Pediacol; Phazyme; Siligaz; Ultra Strength Gas Relief; Ultra Strength Ovol; Ultra Strength Phazyme; *Chile*: Flapex; Gasoff; *China*: Espumisan (柏西); Gascon (咖新康); *Cz.*: AeroOM; Espumisan; Lefax; SAB Simplex; *Denm.*: Aeropax; Imogas; Mylicon; *Fin.*: Cuplaton; Disflatyl; Minifom; *Fr.*: Imonogas; Polysilane; Siligaz; *Ger.*: Additiva†; Ceolat; Elugan; Endo-Paractol; Espumisan; Ilio-Funkton; Imogas; Lefax; SAB Simplex; *Gr.*: Ceolat; Infacol; Infacolic; *Hong Kong*: Air-X; Dentinox Colic Drops†; Disflatyl†; Gascon; Gasteel; Infacol; Ovol†; *Hung.*: Espumisan; Infacol; SAB Simplex; *India*: Dicon-I; Dimol; Tricaine-MPS; *Indon.*: Aeroson†; Disflatyl; Flatunict; Neolanta; *Irl.*: Dentinox Colic; Imogas; Infacol; *Israel*: Gazim X; Simicol; *Ital.*: Imogas; Meteosim; Mylicon; Mylicongas; Simecrin; Simetic; *Malaysia*: Cuplaton; Dentinox Colic Drops; Disflatyl; Gascoal; Gastyl; *Mex.*: Espaven Pediatrico; Liberan; *Neth.*: Aero-Om; Aeropax; *Norw.*: Imogas; Minifom; Siloxan; *NZ*: De-Gas; Infacol; *Philipp.*: Disflatyl; Restime; *Pol.*: Bobotic; Espumisan; Esputicon; Gastrosil; Infacol; Manti Gastop; Simet†; Ulgix; *Port.*: Aero-Om; Disflat; Imogas; *Rus.*: Bobotik (Боботик); Disflatyl (Дисфлатил); Espumisan (Эспумизан); SAB Simplex (САБ Симплекс); Simicol (Симикол); *S.Afr.*: Telament; *Singapore*: Cuplaton†; Gascoal; Infacol†; Rid-Wind; Simcone; *Spain*: Aero Red; Disolgas; Enterosilicona; Imonogas; *Swed.*: Imogaze; Minifom; *Switz.*: Aero-Om; Disflatyl; Flatulex; Meteor†; Polysilane†; *Thai.*: Air-X; Airrox†; Blow-X; Bubble Drops; Degas; Dioxzye; Disflatyl; Fa-x; Gas-

mad†; Gas-Med; Gas-MM; Gas-X; Gassi; Gastyl; Logastin; Mylom; Ovol†; Semeth; Sigas; Simcone; Simecon; Simetyl; Sitiicon†; V cap; Vin; *Turk.*: Antiflat; Ceolat; Flatsil; Metsil; *UAE*: Salinal; *UK*: Dentinox Colic Drops; Infacol; Wind-Eze; *Ukr.*: Боботик (Bobotik); Cuplaton (Куплатон); Disflatyl (Дисфлатил); Espumisan (Эспумизан); Infacol (Инфакол); SAB Simplex (Саб Симплекс); *USA*: Baby Gas-X; Bicarsim; Colicon; Extra Strength Mintox Plus; Flatulex; Gas Relief; Gas-X; Major-Con; Mylanta Gas; Mylicon; Phazyme; SonoRx†; *Venez.*: Antiflom; Flatoril.

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

Used as an adjunct in:. *Austria*: Prontobario; *Canad.*: Polibar Liquid†; Polibar Plus†; *Spain*: Bario Dif†.

Pharmacopoeial Preparations
BP 2014: Simeticone for Oral Use; Simeticone Suspension for Infants;
USP 36: Alumina, Magnesia, and Simethicone Oral Suspension; Alumina, Magnesia, and Simethicone Tablets; Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets; Calcium Carbonate, Magnesia, and Simethicone Tablets; Magaldrate and Simethicone Oral Suspension; Magaldrate and Simethicone Tablets; Simethicone Capsules; Simethicone Emulsion; Simethicone Oral Suspension; Simethicone Tablets.

Smectites

Смектиты.
ATC — A07BC05 (diosmectite).
ATC Vet — QA07BC05 (diosmectite).

Profile

Smectites are natural mineral clays composed mainly of aluminium silicates and include aluminium magnesium silicate (p. 2168.2), bentonite (p. 2170.3), and Fuller's earth (p. 1553.2). They have adsorbent properties and some, such as dioctahedral smectite (diosmectite), have been used in the management of diarrhoea. They are also used as pharmaceutical excipients and in industry.

References.
1. Szajewska H, *et al.* Meta-analysis: smectite in the treatment of acute infectious diarrhoea in children. *Aliment Pharmacol Ther* 2006; 23: 217–27.
2. Yen ZS, Lai MS. Smectite for acute diarrhoea in children. *Emerg Med J* 2006; 23: 65–6.
3. Guarino A, *et al.* Clinical role of diosmectite in the management of diarrhea. *Expert Opin Drug Metab Toxicol* 2009; 5: 433–40.
4. Dupont C, Vernisse B. Anti-diarrheal effects of diosmectite in the treatment of acute diarrhea in children: a review. *Paediatr Drugs* 2009; 11: 89–99.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Bi Qi (必奇); Ken Te Ling (肯特令); Li Xie (立福); Sai Li Mai (赛立迈); Si Ke Te (思克特); Si Mai Te (司迈特); Cz.: Smecta; *Fr.*: Smecta; *Ger.*: Colina; *Gr.*: Smecta; *Hong Kong*: Smecta; *Hung.*: Smecta; *Ital.*: Diosmectal; Nodia; *Malaysia*: Smecta; *Pol.*: Smecta; *Rus.*: Neosmektine (Неосмектин); Smecta (Смекта); *Singapore*: Smecta; *Thai.*: Smecta; *Ukr.*: Smecta (Смекта).

Multi-ingredient Preparations. *Belg.*: Barexal; *Fr.*: Diozinac KS; Diozinac; *Ger.*: Colina Spezial; *Irl.*: Smecta; *Ukr.*: Sorbex Baby (Сорбекс Малыш).

Sodium Gualenate *(rINN)*

Azulene Sodium Sulfonate; Azulene Soluble; Guaiazulene Sodium Sulphonate; Guaiazulene Soluble; Gualénate de Sodium; Gualenate Sodium; Gualenato de sodio; Natrii Gualenas; Натрия гуаленат.
Sodium 5-isopropyl-3,8-dimethyl-1-azulene sulfonate.
$C_{15}H_{17}NaO_3S$=300.3
CAS — 6223-35-4.
UNII — 19WSH095WP.

Profile

Sodium gualenate is the 3-sodium sulfonate salt of guaiazulene, a substance isolated from chamomile oil. Sodium gualenate has anti-inflammatory effects and is used orally, usually with glutamine, to treat peptic ulcer disease and gastritis. Sodium gualenate hydrate is used as an oral rinse or gargle to treat mouth and throat disorders including pharyngitis, tonsillitis, stomatitis, gingivitis, and glossitis. Sodium gualenate hydrate eye drops are used to treat eye disorders including conjunctivitis, keratitis, blepharitis, and scleritis.

References.
1. Ogata J, *et al.* Gargling with sodium azulene sulfonate reduces the postoperative sore throat after intubation of the trachea. *Anesth Analg* 2005; 101: 290–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Abodars; Azotesin; Azugaguru; Azulavine; Azulemic; Azulene; Azulene; Azuleone; Azunol; Azurinse†; *Emagen; Nozlen; Vowlo.*

Multi-ingredient Preparations. *Jpn*: AZ Combination; Azulemin; Azulene.Glutamine; Hachiazule; Manamin GA; Mesadorin S; Podonin-S; Ruefrien; Sedagaston; Towazuren; Youzuren S.

Sodium Picosulfate *(BAN, USAN, rINN)*

DA-1773; LA-391; Natrii Picosulfas; Natrii Picosulfas Monohydricus; Natrio pikosulfatas; Natriumpicosulfat; Natriumpikosulfaatti; Natriumpikosulfat; Nátrium-pikoszulfát; Picosulfate de Sodium; Picosulfato de sodio; Picosulphol; Pikosiran sodný monohydrát; Sodium picosulfate de; Sodium Picosulphate; Натрия Пикосульфат.
Disodium 4,4'-(2-pyridylmethylene)di(phenyl sulphate).
$C_{18}H_{13}NNa_2O_8S_2.H_2O$=499.4
CAS — 10040-45-6 (anhydrous sodium picosulfate); 1307301-38-7 (sodium picosulfate monohydrate).
ATC — A06AB08.
ATC Vet — QA06AB08.
UNII — LR57574HN8.

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

Ph. Eur. 8: (Sodium Picosulfate). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol.

Uses and Administration

Sodium picosulfate is a stimulant laxative related to bisacodyl (p. 1821.1) used for the treatment of constipation (p. 1804.3) and for evacuation of the colon before investigational procedures or surgery. When taken orally it is metabolised by colonic bacteria to an active form that stimulates bowel movements. It is usually effective within 6 to 12 hours although when used with magnesium citrate for bowel evacuation an effect may be seen within 3 hours.

For constipation it is given as a single oral dose of 5 to 10 mg, usually at bedtime. (For doses in children see below.)

For bowel evacuation, a dose of sodium picosulfate 10 mg with magnesium citrate (p. 1857.1) is given in the morning and again in the afternoon of the day before examination.

References.
1. Hoy SM, *et al.* Sodium picosulfate/magnesium citrate: a review of its use as a colorectal cleanser. *Drugs* 2009; 69: 123–36.

Administration in children. In the UK, the following oral doses of sodium picosulfate have been recommended for children in the treatment of constipation; the dose is usually given at night:

- 1 month to 4 years: 250 micrograms/kg (maximum 5 mg)
- 4 to 10 years: 2.5 to 5 mg
- over 10 years: 5 to 10 mg

Most UK licensed product information gives similar doses to those above for bowel cleansing. Alternatively, some recommend that children may be given the following doses of a sachet containing sodium picosulfate 10 mg (with magnesium citrate):

- 1 to 2 years: ¼ sachet in the morning and ¼ sachet in the afternoon
- 2 to 4 years: ½ sachet in the morning and ½ sachet in the afternoon
- 4 to 9 years: 1 sachet in the morning and ½ sachet in the afternoon
- over 9 years: 1 sachet in the morning and 1 sachet in the afternoon

Adverse Effects and Precautions

As for Bisacodyl, p. 1821.2.

Bowel evacuation. The National Patient Safety Agency in the UK released a warning[1] about oral bowel cleansing preparations after reports of fatalities and harm from the improper use of these products. Particularly highlighted were electrolyte imbalance or dehydration due to inappropriate fluid intake or use of these products despite a clinical contra-indication. In Australia, the Adverse Drug Reactions Advisory Committee has also warned that low volume sodium picosulfate solutions may cause marked dehydration, hyponatraemia, other electrolyte abnormalities, and associated complications. Patients at particular risk include infants, the elderly, the frail, and those with congestive heart failure or with renal impairment.[2] It may be appropriate to carry out bowel preparation in hospital for those at risk.[1,3,4] Accumulation of magnesium may occur in patients with severe renal impairment given some magnesium-containing preparations, and an alternative should be used. Bowel cleansing preparations may affect the absorption of oral medicines given at the same time. Caution is also advised when these preparations are given with other medicines that affect fluid and electrolyte balance.[1]

A grand mal seizure in a 64-year-old female given sodium picosulfate with magnesium citrate was assumed to have been caused by hyponatraemia; the patient had normal electrolyte concentrations in the period before taking the bowel preparation. Care is needed when sodium picosulfate solutions are used in those with a low seizure threshold or potential sodium depletion.[5]

Although caution is advised with the use of bowel cleansing preparations in patients with inflammatory bowel disease, sodium picosulfate with magnesium citrate was considered a safe and effective bowel cleansing agent in adults[6] and children[7] with these problems. They tolerated the preparation as well as patients with other colonic disorders with no adverse effect on their disease symptoms. Patients should be kept well hydrated and this treatment should not be used in suspected toxic dilatation of the colon.

1. National Patient Safety Agency. Rapid Response Report: reducing risk of harm from oral bowel cleansing solutions (issued 19th February, 2009). Available at: http://www.npsa.nhs.uk/nrls/alerts-and-directives/rapidrr/reducing-risk-of-harm-from-oral-bowel-cleansing-solutions/ (accessed 08/06/09)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Electrolyte disturbances with sodium picosulphate bowel cleansing products. *Aust Adverse Drug React Bull* 2002; 21: 2. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0202.pdf (accessed 03/07/08)
3. Lewis M, *et al.* Bowel preparation at home in elderly people. *BMJ* 1997; 314: 74.
4. Hanning CD. Bowel preparation at home in elderly people. *BMJ* 1997; 314: 74.
5. Prizelle FA, *et al.* Hyponatremia and seizures after bowel preparation: report of three cases. *Dis Colon Rectum* 2005; 48: 393–6.
6. McDonagh AJG, *et al.* Safety of Picolax (sodium picosulphate-magnesium citrate) in inflammatory bowel disease. *BMJ* 1989; 299: 776–7.
7. Evans M, *et al.* Safety of Picolax in inflammatory bowel disease. *BMJ* 1989; 299: 1101–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sodium picosulfate 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 07/10/11)

Pharmacokinetics

Like bisacodyl (p. 1821.2), sodium picosulfate is metabolised by colonic bacteria to the active compound bis(*p*-hydroxyphenyl)pyridyl-2-methane. Only a small amount of sodium picosulfate is absorbed after an oral dose; this is subsequently excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Agarol; Chicle; Cirulaxia; Dagol; Dulcolax; Factor Laxante; Feen-A-Mint; Gotalax; Granulax; Kritel; Laxamin; Modaton; Opalino; Rapilax; Trali; Verilax; Yodolin; *Austral.*: Dulcolax SP; *Austria*: Agaffin; Agiopic†; Guttalax; Laxasan; *Belg.*: Dulcolax Picosulphate; Fructines; Laxoberon; Picolaxine; *Braz.*: Cronoplex; Diltin; Forlax†; Guttalax; Rapilax; *Chile*: Aguala; Cronolax; Dulcolax; Guttalax; Laxantil; Laxoberal†; *Cz.*: Agiolax Pico†; Guttalax; Laxygal; Progut†; Regulax Pikosulfat; *Denm.*: Actilax; Laxoberal; Picolon; *Fin.*: Laxoberon; *Fr.*: Fructines; *Ger.*: Agiolax Pico; Darmol Pico; Dulcolax NP; Laxans-ratiopharm Pico; Laxoberal; Liquidepur mit Natriumpicosulfat†; Regulax Picosulfat; *Gr.*: Guttalax; Laxatol; *Hong Kong*: Sur-Lax; *Hung.*: Guttalax; Laxygal; *India*: Asilax Plus; Colax; Coso; Cremalax; Dyrset-Eze; Laxatab; Laxicare; Laxkair; Laxopic; Laxsure; Novalax Plus; Oslax; *Indon.*: Laxoberon; *Irl.*: Agiolax Pico†; Dulcolax; Laxoberal†; *Ital.*: Buchessina GM; Falquigut; Gocce Lassative Aicardi; Guttalax; *Jpn*: Laxoberon; *Mex.*: Anara; Laxoberon; Motilaxil; *Neth.*: Dulcodruppels; Dulcopearls; Pico-Salax; *Norw.*: Laxoberal; *Philipp.*: Dulcolax SP; Laxoberal†; *Port.*: Dulcogotas; Fructines; Guttalax; Laxodal; Picolax; *Rus.*: Guttalax (Гутталакс); Laxigal (Лакигал); Regulax Picosulphate (Регулакс Пикосульфат); Slabicap (Слабикап); Slabilen (Слабилен); *Spain*: Contumax; Evacuol; Ezor; Gutalax†; Lubrilax; Skilax†; *Swed.*: Cilaxoral; Laxoberal; *Switz.*: Dulcolax Picosulfat; Fructines; Laxoberon; *Turk.*: Dulcolax; *UK*: Dulcolax; *Ukr.*: Agiolax Pico (Агиолакс Пико)†; Guttalax (Гутталакс); Picolax (Пиколакс); *Venez.*: Lasoberon.

Multi-ingredient Preparations. *Arg.*: Agarol; Cascara Sagrada Oligoplex; Natulax Plus; *Austral.*: Colonprep; PicoPrep; Prep Kit-C; *Belg.*: Pilules de Vichy†; *Braz.*: Agarol; *Canad.*: Pico-Salax; Picodan; Purg-Odan; *Chile*: Agarol; *Cz.*: Picoprep; *Denm.*: CitraFleet; Picoprep; *Fin.*: CitraFleet; Picoprep; *Fr.*: CitraFleet; Picoprep; *Ger.*: CitraFleet; Picoprep; *Hong Kong*: Picolax; *Hung.*: Picoprep; *India*: Cremaffin Plus; Daffolac-P; Gudlax-Plus; Laxicare; Laxit Plus; Momplus; *Irl.*: CitraFleet; Picolax; *Israel*: Pico-Salax; *Malaysia*: Picoprep†; *Neth.*: Picoprep; *Norw.*: CitraFleet; Picoprep; *NZ*: Picoprep; Prepkit-C; *Port.*: CitraFleet; *S.Afr.*: Picoprep†; *Spain*: CitraFleet; Emuliquen Laxante; *Swed.*: CitraFleet; Picoprep; *Switz.*: Laxasan; Picoprep; *UK*: CitraFleet; Picolax; *Ukr.*: Picosen (Пикосен); *USA*: Prepopik.

Pharmacopoeial Preparations
BP 2014: Compound Sodium Picosulfate Powder for Oral Solution; Sodium Picosulfate Oral Solution.

Anhydrous Sodium Sulfate

Anhydrous Sodium Sulphate; Dried Sodium Sulphate; Exsiccated Sodium Sulphate; Natrii Sulfas; Natrii sulfas anhydricus; Natrio sulfatas; Bevandenis; Natrium Sulfuricum Siccatum; Natriumsulfaatti, vedetön; Natriumsulfat, vattenfritt; Síran sodný; Sodium (sulfate de) anhydre; Sodu siarczan bezwodny; Sulfato de sodio anhidro; Vízmentes nátrium-szulfát; Безводный Сульфат Натрия.

Na_2SO_4=142.0

CAS — 7757-82-6.

ATC — A06AD13; A12CA02.

ATC Vet — QA06AD13; QA12CA02.

UNII — 36KCS0R750.

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

US includes a single monograph for both the anhydrous form and the decahydrate.

Ph. Eur. 8: (Sodium Sulfate, Anhydrous). A white or almost white, hygroscopic powder. Freely soluble in water. Store in airtight containers.

USP 36: (Sodium Sulfate). It contains 10 molecules of water of hydration or is anhydrous. The decahydrate loses between 51 and 57% of its weight on drying and the anhydrous form loses not more than 0.5% of its weight. Large, colourless, odourless, transparent crystals or a granular powder. It effloresces rapidly in air, liquefies in its water of hydration at about 33 degrees, and loses all of its water of hydration at about 100 degrees. Freely soluble in water; insoluble in alcohol; soluble in glycerol. Store in airtight containers, preferably at a temperature not exceeding 30 degrees.

Sodium Sulfate

E514; Glauber's Salt; Natrii Sulfas Decahydricus; Natrii Sulphas; Natrio sulfatas dekahidratas; Natrium Sulfuricum Crystallisatum; Natriumsulfaattidekahydraatti; Natriumsulfat-Decahydrat; Natriumsulfatdekahydrat; Nátrium-szulfát-dekahidrát; Síran sodný dekahydrát; Sodium (sulfate de) décahydraté; Sodium Sulphate; Sodium Sulphate Decahydrate; Sodu siarczan dziesięciowodny; Sulfato de sodio; Глауберова Соль; Сульфат Натрия.

$Na_2SO_4.10H_2O$=322.2

CAS — 7727-73-3 (sodium sulfate decahydrate).

ATC — A06AD13; A12CA02.

ATC Vet — QA06AD13; QA12CA02.

UNII — 0YPR65R21J.

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

US includes a single monograph for both the anhydrous form and the decahydrate.

Ph. Eur. 8: (Sodium Sulfate Decahydrate; Sodium Sulfate BP 2014). A white or almost white, crystalline powder or colourless, transparent crystals. Freely soluble in water; practically insoluble in alcohol. It partly dissolves in its own water of crystallisation at about 33 degrees. It loses between 52.0 and 57.0% of its weight on drying.

USP 36: (Sodium Sulfate). It contains 10 molecules of water of hydration or is anhydrous. The decahydrate loses between 51 and 57% of its weight on drying and the anhydrous form loses not more than 0.5% of its weight. Large, colourless, odourless, transparent crystals or a granular powder. It effloresces rapidly in air, liquefies in its water of hydration at about 33 degrees, and loses all of its water of hydration at about 100 degrees. Freely soluble in water; insoluble in alcohol; soluble in glycerol. Store in airtight containers, preferably at a temperature not exceeding 30 degrees.

Profile

Sodium sulfate has been used as an osmotic laxative (p. 1804.1). It is also given in dilute solution (about 0.5%) with a high molecular weight macrogol for prompt bowel evacuation before investigational procedures or surgery (see Macrogols, p. 2548.1).

Sodium sulfate is also used as an additive in foods.

For the general properties of sodium salts, see p. 1795.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Celloids SS 69†; *China*: Chang Le (畅乐); *Israel*: Moviprep.

Multi-ingredient Preparations. *Arg.*: Magnesia Phosphorica I Oligoplex; Tractoclin; *Austral.*: Duo Celloids SPSS†; Duo Celloids SSMP†; Duo Celloids SSPC†; Duo Celloids SSS†; Magnesium Compound; *Austria*: Moviprep; *Belg.*: Moviprep; *Canad.*: Lithines du Dr Gustin†; Moviprep; Normo Gastryl†; *China*: ZhengQing (正清); *Cz.*: Fortrans; *Denm.*: Moviprep; *Fin.*: Moviprep; *Fr.*: Actisoufre; Digedryl; Fortrans; Hepargitol; Maalox Digestion Difficile; Moviprep; Oxyboldine; Sel D; Tisane D'Arsi†; *Gr.*: Izetafin; *Hong Kong*: Fortrans; *Irl.*: Moviprep; *Ital.*: Moviprep; *Malaysia*: Fortrans; *Mex.*: Cholal Modificado; *Neth.*: Moviprep; *Norw.*: Moviprep; *NZ*: Moviprep; Prepkit-C; *Philipp.*: Neutrazid; *Pol.*: Fortrans; Sal Carolinum Factitium; Sal Ems Artificiale; Sal Ems Factitium; Sal Vichy Factitium; *Port.*: Fortrans; *Rus.*: Fortrans (Фортранс); *Singapore*: Fortrans; *Spain*: Darmen Salt; Leberetic†; Lebersal; Moviprep; Salcedol; *Switz.*: Moviprep; Padma-Lax; Padmed Laxan; *Thai.*: Ulgastrin; *UK*: Moviprep; *Ukr.*: Fortrans (Фортранс); *USA*: Suclear; Suprep Bowel Prep; Triv.

Homoeopathic Preparations. *Austral.*: IBS Eze; *Austria*: Galstena; Lobelia Med Complex; Lymphomyosot; Tartephedreel; *Canad.*: Bioactiv N†; Combinaison†; Cynara Complex†; Diamite; Homeo-Form P†; Homeoknop Ikoplex 13†; Hylands Bioplasma; Ikoplex 14†; Lympatox; Melange†; Minerals+; Nuage Bioplasma†; Osteel†; Rexorubia†; Sore Throat L39†; *Chile*: Bioactiv N; Ikoplex No 10; Ikoplex No 13; Ikoplex No 14; Ikoplex No 17; Ikoplex No 2; Ikoplex No 7; Ikoplex No 8; Similibus; *Cz.*: Lymphomyosot; *Fr.*: Berberis Complexe No 83; Hepatocynesine†; Mercurius Solubilis Complexe No 39; Rexorubia; Sulfur Complexe No 12; *Ger.*: A-Bomin; Anovin; Drufusan N†; Drufusan; Flenin; Galloselect; Hepar-Hevert; Infihepan; Lymphomyosot N; Lymphomyosot; *Hung.*: Lymphomyosot; Osteoheel; *Neth.*: Lymfelite; Rhodolith-Gastreu R46; *Rus.*: Atma (Атма); Galstena (Галстена); *S.Afr.*: Lymphomyosot; *Switz.*: Osteoheel; *Ukr.*: Atma (Атма); Galstena (Галстена); Lymphomyosot (Лімфоміозот); Lymphomyosot N (Лімфоміозот Н).

Pharmacopoeial Preparations
USP 36: PEG 3350 and Electrolytes for Oral Solution; Sodium Sulfate Injection.

Sodium Tartrate

Dinátrium-tartarát; Disodium L-Tartrate; E335 (sodium tartrate or monosodium tartrate); Natriumtartrat; Sodu winian; Tartrato de sodio; Tartrato di sodio; Виннокислый Натрий.

Disodium 2,3-dihydroxybutanedioate.

$C_4H_4O_2(CO_2Na)_2.2H_2O$=230.1

CAS — 868-18-8 (anhydrous sodium tartrate); 6106-24-7 (sodium tartrate dihydrate).

ATC — A06AD21.

ATC Vet — QA06AD21.

UNII — QTO9J84MDD.

Pharmacopoeias. In *USNF.*

USNF 31: (Sodium Tartrate). Transparent, colourless, odourless crystals. Freely soluble in water; insoluble in alcohol. pH of a 10% solution in water is between 7 and 9. Store in airtight containers.

Sodium Bitartrate

E335 (sodium tartrate or monosodium tartrate); Monosodium Tartrate; Sodium Acid Tartrate; Sodium Hydrogen Tartrate.

Sodium 2,3-dihydroxybutanedioate.

$C_4H_5NaO_6$=172.1

CAS — 526-94-3.

UNII — 75E631I9H07.

Profile

Sodium tartrate has been used as an osmotic laxative. It is used as a food additive. Sodium bitartrate is used as an acidity regulator.

For the general properties of sodium salts, see p. 1795.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Limonade Asepta; *Gr.*: Alka-Coup.

Multi-ingredient Preparations. *Austral.*: Amosan†.

Sofalcone *(pINN)*

Sofalcona; Sofalconum; SU-88; Софалькон.

[5-[(3-Methyl-2-butenyl)oxy]-2-[*p*-[(3-methyl-2-butenyl)oxy]cinnamoyl]phenoxy]acetic acid.

$C_{27}H_{30}O_6$=450.5

CAS — 64506-49-6.

UNII — 2B668TJX8E.

Profile

Sofalcone is reported to possess cytoprotective properties and is used in the treatment of gastritis and peptic ulcer disease (p. 1813.2). An oral dose of 100 mg is given 3 times daily.

References.
1. Isomoto H, *et al.* Sofalcone, a mucoprotective agent, increases the cure rate of Helicobacter pylori infection when combined with rabeprazole, amoxicillin and clarithromycin. *World J Gastroenterol* 2005; 11: 1629–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Solon.

Sterculia

E416; Goma esterculia; Goma Karaya; Indian Tragacanth; Karaya; Karaya Gum; Sterculia Gum; Sterkúlia; Tragacante Indio; Камедь Карайи; Стеркулия Жгучая (*Sterculia urens*).

CAS — 9000-36-6.

ATC — A06AC03.

ATC Vet — QA06AC03.

ATC Herb — HA06AC5011 (Sterculia urens: *gum*).

UNII — 73W9IQY50Q.

Pharmacopoeias. In *Br.* and *Fr.*

BP 2014: (Sterculia). The gum obtained from *Sterculia uren.* and other species of *Sterculia*. Irregular or vermiform pieces greyish-white with a brown or pink tinge, with an odour resembling that of acetic acid. It contains not less than 14.0% of volatile acid (or not less than 10.0% if supplied in powdered form), calculated as acetic acid. Sparingly soluble in water, but swells into a homogeneous, adhesive, gelatinous mass; practically insoluble in alcohol. Store at a temperature not exceeding 25 degrees.

Uses and Administration

Sterculia is used similarly to ispaghula (p. 1849.2) as a bulk laxative and for adjusting faecal consistency. It has also been used as an aid to appetite control in the management of obesity (p. 2315.1) but there is little evidence of efficacy. It is usually taken in the form of granules containing sterculia 62%; the dose is 1 to 2 sachets or 1 to 2 heaped 5 mL spoonfuls orally once or twice daily after meals. (For a dose in children see below.) The granules are washed down without chewing with plenty of water. They may also be taken sprinkled onto soft foods such as yogurt.

Sterculia is used topically, as a paste or powder, for skin protection and sealing in the fitting of ileostomy and colostomy appliances. It has also been used in dental fixative powders, and as an emulsifier and stabiliser in foods.

Administration in children. In the UK, the recommended oral dose of granules, containing sterculia 62%, for constipation in children aged 6 to 12 years is ½ to 1 sachet, or ½ to one 5 mL spoonful, once or twice daily after meals. Children over 12 years may be dosed as for adults, see Uses and Administration, above. The granules are washed down without chewing with plenty of water. They may also be taken sprinkled onto soft foods such as yogurt.

Adverse Effects and Precautions

As for Ispaghula, p. 1849.2. There is a risk of intestinal or oesophageal obstruction and faecal impaction, especially if such compounds are swallowed dry. Therefore they should always be taken with sufficient fluid and should not be taken immediately before going to bed. They should be avoided by patients who have difficulty swallowing.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sterculia 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 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Normafibe; *Belg.*: Normacol; *Braz.*: Corega; *Canad.*: Normacol; *Fr.*: Normacol; *Hong Kong*: Normacol†; *Irl.*: Normacol; *Ital.*: Normacol; *Neth.*: Normacol; *NZ*: Normacol; *S.Afr.*: Normacol; *Singapore*: Normacol; *Swed.*: Inolaxol; *Switz.*: Colosan mite; Colosan travel; Inolaxine†; Normacol; *UK*: Normacol.

Multi-ingredient Preparations. *Austral.*: Normacol Plus; *Fr.*: Kaologeais†; Karayal; Laxilo†; Poly-Karaya; *Gr.*: Normacol Plus; *Hong Kong*: Normacol Plus†; *India*: Evacuol; Kanormal†; *Irl.*: Normacol Plus; *NZ*: Granocol†; Normacol Plus; *Port.*: Normacol Plus; *S.Afr.*: Normacol Plus; *Singapore*: Normacol Plus; *Switz.*: Colosan plus; *UK*: Normacol Plus.

Homoeopathic Preparations. *Austral.*: Elimitona Slim & Detox.

Pharmacopoeial Preparations
BP 2014: Sterculia Granules.

Sucralfate (BAN, USAN, rINN)

Sucralfato; Sucralfatum; Sukralfaatti; Sükralfat; Sukralfat; Сукральфат.

Sucrose hydrogen sulphate basic aluminium salt; Sucrose octakis(hydrogen sulphate), aluminium complex; β-D-Fructofuranosyl-α-D-glucopyranoside octakis (hydrogen sulphate) aluminium complex.

$C_{12}H_mAl_{16}O_nS_8$.

CAS — 54182-58-0.

ATC — A02BX02.

ATC Vet — QA02BX02.

UNII — XX73205DH5.

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

Ph. Eur. 8: (Sucralfate). A white or almost white, amorphous powder. Practically insoluble in water, in alcohol, and in dichloromethane. It dissolves in dilute solutions of mineral acids and alkali hydroxides.

USP 36: (Sucralfate). The hydrous basic aluminium salt of sucrose octasulfate. Store in airtight containers.

Uses and Administration

Sucralfate is a cytoprotective drug that, under acid gastrointestinal conditions, forms an adherent complex with proteins that coats the gastric mucosa and is reported to have a special affinity for ulcer sites. It also inhibits the action of pepsin and adsorbs bile salts.

Sucralfate has been used in the treatment of peptic ulcer disease (p. 1813.2) and chronic gastritis. It is given orally and should be taken on an empty stomach before meals and at bedtime. The usual dose is 1 g four times daily or 2 g twice daily for 4 to 8 weeks; if necessary the dose may be increased to a maximum of 8 g daily. If longer-term therapy is required sucralfate may be given for up to 12 weeks. Where appropriate a maintenance dose of 1 g twice daily may be given to prevent the recurrence of duodenal ulcers.

For prophylaxis of gastrointestinal haemorrhage from stress ulceration the usual dose of sucralfate is 1 g six times daily; a dose of 8 g daily should not be exceeded. For children's doses see below.

Administration in children. Although sucralfate is not licensed in the UK for use in children under 15 years, the *BNFC* recommends the following oral doses for the treatment of peptic ulcer disease, or the prophylaxis of stress ulceration in children in intensive care (but see also under Bezoar Formation, below):

- 1 month to 2 years: 250 mg four to six times daily
- 2 to 12 years: 500 mg four to six times daily
- 12 to 15 years: 1 g four to six times daily
- 15 to 18 years: adult doses may be given, see above

The oral suspension blocks fine-bore feeding tubes and tablets should be crushed and dispersed in water instead.

Gastrointestinal bleeding. Sucralfate is an effective drug for the prophylaxis and management of stress-induced gastrointestinal bleeding in severely ill patients but whether it should be chosen over an H_2-antagonist has been subject to debate. One study suggested it might reduce the risk of late-onset pneumonia compared with ranitidine.[1] Another study[2] found ranitidine to be more effective than sucralfate in reducing the risk of gastrointestinal bleeding; while there was a trend towards a lower rate of pneumonia among patients receiving sucralfate, the difference was not significant. However, meta-analyses[3] found an increased risk of pneumonia with ranitidine compared with sucralfate, but no difference in the rate of pneumonia with sucralfate and placebo; insufficient data were available to conduct a meta-analysis of sucralfate's efficacy in terms of rates of bleeding, and a reassessment of recommendations for the prophylaxis of stress ulcers was called for. Later guidelines[4] concluded that the use of sucralfate did not influence the incidence of ventilator-associated pneumonia compared with placebo. For further discussion of stress ulceration and bleeding, including the use of sucralfate, see under Peptic Ulcer Disease, p. 1813.2. There is also some evidence from a study[5] that sucralfate reduces gastrointestinal bleeding associated with NSAID use, although it does not prevent drug-induced gastric erosion.

In a study to assess whether oral prophylactic sucralfate could ameliorate the symptoms of acute radiation proctitis, sucralfate was found to increase the incidence of rectal bleeding compared with placebo; the cause of this increased bleeding was unclear.[6]

1. Prod'hom G, *et al.* Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine, or sucralfate as prophylaxis for stress ulcer: a randomized controlled trial. *Ann Intern Med* 1994; 120: 653–62.
2. Cook D, *et al.* A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. *N Engl J Med* 1998; 338: 791–7.
3. Messori A, *et al.* Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: meta-analysis of randomised controlled trials. *BMJ* 2000; 321: 1103–6.
4. Dodek P, *et al.* Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. *Ann Intern Med* 2004; 141: 305–13.
5. Hudson N, *et al.* Effect of sucralfate on aspirin induced mucosal injury and impaired haemostasis in humans. *Gut* 1997; 41: 19–23.
6. Kneebone A, *et al.* The effect of oral sucralfate on the acute proctitis associated with prostate radiotherapy: a double-blind, randomized trial. *Int J Radiat Oncol Biol Phys* 2001; 51: 628–35.

Gastro-oesophageal reflux disease. Although sucralfate has been tried for gastro-oesophageal reflux disease (p. 1807.2) the results of studies have been inconsistent.[1-3] However, if lifestyle or dietary measures prove insufficient for the management of heartburn in pregnancy, sucralfate may be considered for first-line therapy.

1. Orlando RC. Sucralfate therapy and reflux esophagitis: an overview. *Am J Med* 1991; 91 (suppl 2A): 123S–124S.
2. Klinkenberg-Knol EC, *et al.* Pharmacological management of gastro-oesophageal reflux disease. *Drugs* 1995; 49: 695–710.
3. Simon B, *et al.* Sucralfate gel versus placebo in patients with non-erosive gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1996; 10: 441–6.

Mouth ulceration. Sucralfate has been investigated as a mouth rinse in the treatment and prophylaxis of stomatitis induced by cancer chemotherapy[1-3] although evidence of benefit for any drug is ambiguous (see Mucositis, p. 732.1). One study[2] in 40 patients found a significant reduction in symptoms among 23 evaluable patients given sucralfate prophylactically. Seven patients withdrew due to aggravation of chemotherapy-induced nausea. It was suggested that to overcome this problem, the suspension should have a neutral taste, should not be swallowed after rinsing, and that rinsing should not be started until nausea had stopped. However, another study[4] involving 80 patients treated with fluorouracil for colorectal cancer found no significant difference in self-reported mucositis symptoms between patients given sucralfate suspension and those given placebo.

Sucralfate has also been reported to be of benefit in patients with recurrent aphthous stomatitis (mouth ulceration—p. 1811.2). A study involving 21 such patients over 2 years found that topical application of sucralfate suspension 4 times daily was superior to treatment with an antacid (aluminium hydroxide with magnesium hydroxide) or placebo.[5]

In patients with Behçet's syndrome (p. 1601.1), topical sucralfate suspension significantly decreased the frequency, healing time, and pain of oral ulceration, as well as the healing time and pain of genital ulceration,[6] when compared with placebo.

1. Pfeiffer P, *et al.* A prospective pilot study on the effect of sucralfate mouth-swishing in reducing stomatitis during radiotherapy of the oral cavity. *Acta Oncol* 1990; 29: 471–3.
2. Pfeiffer P, *et al.* Effect of prophylactic sucralfate suspension on stomatitis induced by cancer chemotherapy: a randomized, double-blind cross-over study. *Acta Oncol* 1990; 29: 171–3.
3. Allison RR, *et al.* Symptomatic acute mucositis can be minimized or prophylaxed [sic] by the combination of sucralfate and fluconazole. *Cancer Invest* 1995; 13: 16–22.
4. Nottage M, *et al.* Sucralfate mouthwash for prevention and treatment of 5-fluorouracil-induced mucositis: a randomized, placebo-controlled trial. *Support Care Cancer* 2003; 11: 41–7.
5. Rattan J, *et al.* Sucralfate suspension as a treatment of recurrent aphthous stomatitis. *J Intern Med* 1994; 236: 341–3.
6. Alpsoy E, *et al.* The use of sucralfate suspension in the treatment of oral and genital ulceration of Behçet disease: a randomized, placebo-controlled, double-blind study. *Arch Dermatol* 1999; 135: 529–32.

Skin ulceration. Sucralfate is of interest for its actions on epithelial wound healing,[1] and has reportedly been applied topically with some success to treat bleeding skin ulcers (p. 1690.1) associated with malignancy,[2] and to promote the healing of chronic venous ulcers.[3,4] It has been suggested that sucralfate promotes angiogenesis by binding to, and preventing degradation of, basic fibroblast growth factor (bFGF).[3] Topical sucralfate 7% cream was also reported to decrease pain and speed healing of the wound after open surgical removal of haemorrhoids.[5]

1. Masuelli L, *et al.* Topical use of sucralfate in epithelial wound healing: clinical evidences and molecular mechanisms of action. *Recent Pat Inflamm Allergy Drug Discov* 2010; 4: 25–36.
2. Regnard CFB. Control of bleeding in advanced cancer. *Lancet* 1991; 337: 974.
3. Tsakayannis D, *et al.* Sucralfate and chronic venous stasis ulcers. *Lancet* 1994; 343: 424–5.
4. Tumino G, *et al.* Topical treatment of chronic venous ulcers with sucralfate: a placebo controlled randomized study. *Int J Mol Med* 2008; 22: 17–23.
5. Gupta PJ, *et al.* Topical sucralfate decreases pain after hemorrhoidectomy and improves healing: a randomized, blinded, controlled study. *Dis Colon Rectum* 2008; 51: 231–4.

Adverse Effects and Precautions

Constipation is the most frequently reported adverse effect of sucralfate although diarrhoea, nausea, vomiting, flatulence, or gastric discomfort may also occur. Other adverse effects include dry mouth, dizziness, drowsiness, headache, vertigo, back pain, and skin rashes. Hypersensitivity reactions such as pruritus, oedema, urticaria, respiratory difficulty, rhinitis, laryngospasm, and facial swelling have been reported.

Great caution is needed in patients with renal impairment (below) as absorption and accumulation of aluminium may cause adverse effects.

Bezoar formation. As of March 1999, the UK CSM was aware of 7 reports worldwide of bezoar formation associated with sucralfate use in intensive care patients.[1] It advised caution in the use of sucralfate in seriously ill patients because of the risks of bezoar formation and intestinal obstruction.[1] Patients with delayed gastric emptying or receiving concomitant enteral feeds may be at increased risk. A report by the French Pharmacovigilance System at about the same time made similar recommendations but also contra-indicated the use of sucralfate in premature and immature neonates.[2]

1. CSM/MCA. Bezoar formation with sulcralfate [sic] (Antepsin). *Current Problems* 1999; 25: 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 07/11/06)
2. Guy C, Ollagnier M. Sucralfate et bézoard: bilan de l'enquête officielle de pharmacovigilance et revue de la littérature. *Therapie* 1999; 54: 55–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sucralfate 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 06/10/11)

Renal impairment. Sucralfate under acid conditions can release aluminium ions that may be absorbed systemically. Significant increases in the urinary excretion of aluminium have been seen in healthy subjects given sucralfate 4 g daily,[1,2] reflecting gastrointestinal absorption of aluminium; aluminium concentrations in serum and urine were significantly higher in patients with chronic renal impairment than in subjects with normal renal function,[3] and similar serum increases have been seen in children with acute renal failure.[4] Aluminium toxicity in patients with normal renal function receiving sucralfate would not be expected, but seizures, muscle weakness, bone pain,[1] and severe aluminium encephalopathy[5] have been reported in patients with end-stage renal disease requiring dialysis. Sucralfate should be used with caution in patients with renal impairment, especially if other aluminium-containing agents are also taken, and such patients should be monitored for signs of aluminium toxicity.[4,6]

1. Robertson JA, *et al.* Sucralfate, intestinal aluminium absorption, and aluminium toxicity in a patient on dialysis. *Ann Intern Med* 1989; 111: 179–81.
2. Allain P, *et al.* Plasma and urine aluminium concentrations in healthy subjects after administration of sucralfate. *Br J Clin Pharmacol* 1990; 29: 391–5.
3. Burgess E, *et al.* Aluminum absorption and excretion following sucralfate therapy in chronic renal insufficiency. *Am J Med* 1992; 92: 471–5.
4. Thorburn K, *et al.* Aluminum accumulation in critically ill children on sucralfate therapy. *Pediatr Crit Care Med* 2001; 2: 247–9.
5. Withers DJ, *et al.* Encephalopathy in patient taking aluminium-containing agents, including sucralfate. *Lancet* 1989; ii: 674.
6. Hemstreet BA. Use of sucralfate in renal failure. *Ann Pharmacother* 2001; 35: 360–4.

Interactions

Sucralfate may interfere with the absorption of other drugs and it has been suggested that there should be an interval of 2 hours between giving sucralfate and other non-antacid medication. Some of the drugs reported to be affected by sucralfate include cimetidine, ranitidine, digoxin, fluoroquinolone antibacterials, ketoconazole, levothyroxine, phenytoin, tetracycline, quinidine, theophylline, and possibly warfarin. The recommended interval between sucralfate and antacids is 30 minutes. An interval of 1 hour should elapse between giving sucralfate and enteral feeding.

Pharmacokinetics

Sucralfate is only slightly absorbed from the gastrointestinal tract after oral doses. However, there can be some release of aluminium ions and of sucrose sulfate; small quantities of sucrose sulfate may then be absorbed and excreted, primarily in the urine; some absorption of aluminium may also occur (see Renal Impairment, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Antepsin; Gastromed; Netunal; Sucralmax; *Austral.*: Carafate; Ulcyte; *Austria*: Sucralan; Sucralbene†; Sucramed; Ulcogant; *Belg.*: Ulcogant†; *Braz.*: Sucrafilm; *Canad.*: Novo-Sucralate†; Sulcrate; *Chile*: Mulcatel; Sulcran; *China*: Disuo (迪索); Dixian (迪先); Hua Di (华迪); Shu Ke Jie (舒可捷); Shukefei (舒克菲); Sucrate (素可立); SuShun (速顺); Weidi (卫迪); WeiYi (渭依); *Cz.*: Sucralan†; Ulcogant; Venter; *Denm.*: Antepsin; *Fin.*: Alsucral; Antepsin; *Fr.*: Keal; Ulcar; *Ger.*: Sucrabest; Ulcogant; *Gr.*: Dolisec; Melicide;

The symbol † denotes a preparation no longer actively marketed

Peptonorm; Sucrate; Ufarene; *Hong Kong*: Sucari; Sucrate; Ulsanic; *Hung.*: Alusulin; Ulcogant; Venter; *India*: Adcot; Acral; Alfatet†; Alifate; Bluegel-SF; Crasia; Cural; Daffocid; Erocot; Gard Plus; Lacrate; Magalcid-S; Sucrase; *Indon.*: Inpepsa; Musin; Neciblok; Protat; Propepsa; Ulcumaag; Ulsafate; Ulsicral; Ulsidex; *Irl.*: Antepsin; *Israel*: Ulsanic; *Ital.*: Antepsin; Citogel; Crafilm; Escudo; Gastrogel; Sucralfin; Sucramal; Sucrate; Sucroril; Sugar; Sugast; Suril; Ulcrast; *Jpn*: Ulcerlmin; *Malaysia*: Alsucral†; Ulcertec†; *Mex.*: Apo-Lato; Discral; Duodenel; Metixane; Ulsicral; Unival; *Neth.*: Ulcogant; *Norw.*: Antepsin; *NZ*: Carafate; *Philipp.*: Iselpin; *Pol.*: Ulgastran; Venter; *Port.*: Calfate†; Cinebil; Ulcermate; Ulcermin; Ulcimer; *Rus.*: Sucrat (Сукрат); Venter (Вентер); *S.Afr.*: Ulcetab†; Ulsanic; *Singapore*: Alsucral†; Ulcertec†; *Spain*: Urbal; *Swed.*: Andapsin; *Switz.*: Ulcogant; *Thai.*: Sucral; Sucrate; Ulcefate; Ulcrafate; Ulsanic; *Turk.*: Antepsin†; *UAE*: Sucralose; *UK*: Antepsin; *Ukr.*: Venter (Вентер); *USA*: Carafate; Orafate; ProThelial; *Venez.*: Cicalfate; Dip; Exinol; Ulcram; Ulcon.

Multi-ingredient Preparations. *Arg.*: Cicalfate; *Chile*: Cicalfate; *Fr.*: Cicalfate; *Gr.*: Profenil Complex; *India*: Acicot-O; Adcral-O; Acral-O; Alcocid; Crasia-O; Daffocid-O; Erocot-O; Esfate-O; Focri-O; Greycid; Kulent-O; Kulfi; Lacrate-O; Lorcus-O; Oxefate-O.

Used as an adjunct in:. *Gr.*: Vofen; *Ital.*: Ketodol.

Pharmacopoeial Preparations
USP 36: Sucralfate Tablets.

Sulfasalazine *(BAN, USAN, rINN)*

Salatsosulfapyridiini; Salazosulfapyridin; Salazosulfapyridine; Salazosulfapyridinum; Salicylazosulfapyridine; SI-88; Sulfasalatsiini; Sülfasalazin; Sulfasalazin; Sulfasalazina; Sulfasalazinas; Sulfasalazinum; Sulfasalazyna; Sulphasalazine; Szulfaszalazin; Сульфасалазин.

4-Hydroxy-4′-(2-pyridylsulphamoyl)azobenzene-3-carboxylic acid.

$C_{18}H_{14}N_4O_5S$=398.4

CAS — 599-79-1.

ATC — A07EC01.

ATC Vet — QA07EC01.

UNII — 3XC8GUZ6CB.

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

Ph. Eur. 8: (Sulfasalazine). A bright yellow or brownish-yellow, fine powder. Practically insoluble in water and in dichloromethane; very slightly soluble in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Sulfasalazine). A fine odourless bright yellow or brownish-yellow powder. Practically insoluble in water, in chloroform, in ether, and in benzene; soluble 1 in 2900 of alcohol, and 1 in 1500 of methyl alcohol; soluble in aqueous solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Uses and Administration

Sulfasalazine is a compound of a sulfonamide, sulfapyridine, with 5-aminosalicylic acid (mesalazine). Its activity is generally considered to lie in the 5-aminosalicylic acid moiety, which is released in the colon by bacterial metabolism, although intact sulfasalazine has some anti-inflammatory properties in its own right.

In inflammatory bowel disease (p. 1808.3) it is used alone or as an adjunct to corticosteroids in the treatment of active ulcerative colitis and is effective in maintaining remission. Sulfasalazine may also be effective in the treatment of active Crohn's disease, particularly of the colon, but it does not appear to be of value in maintaining remissions. Sulfasalazine is also used as a disease modifying drug in the treatment of severe or progressive rheumatoid arthritis (below).

In **inflammatory bowel disease** the usual initial dose of sulfasalazine is 1 to 2 g orally 4 times daily in the UK. However, doses over 4 g daily are associated with an increased risk of toxicity, and in the USA, therefore, the usual dose is 1 g given 3 or 4 times daily, and an initial dose of 500 mg every 6 to 12 hours may be recommended to lessen gastrointestinal adverse effects. Enteric-coated tablets are also claimed to reduce the incidence of adverse gastrointestinal effects. The overnight interval between doses should not exceed 8 hours. On remission the dose in patients with ulcerative colitis is gradually reduced to 2 g daily and then generally continued indefinitely.

Sulfasalazine is also given rectally, as suppositories, initially at a dose of 1 g at night and in the morning. After three weeks the dosage is gradually reduced according to response. Rectal sulfasalazine can be given as 0.5 to 1 g night and morning as an adjunct to treatment by mouth.

In **rheumatoid arthritis** treatment is usually started with an oral dose of 500 mg daily, as enteric-coated tablets, for the first week; dosage is then increased by 500 mg daily each week to a maximum of 3 g daily given in 2 to 4 divided doses according to tolerance and response.

For doses in children, see below.

Administration in children. In children with inflammatory bowel disease, sulfasalazine can be used alone or as an adjunct to corticosteroids to treat active ulcerative colitis and to maintain remission. Sulfasalazine may also be used to treat active Crohn's disease, particularly of the colon, but it does not appear to be of value in maintaining remissions. Sulfasalazine is also used as a disease modifying drug in the treatment of juvenile rheumatoid arthritis.

To treat active **inflammatory bowel disease**, children 2 years of age or older may be given oral sulfasalazine 40 to 60 mg/kg daily in divided doses. This can be reduced to 20 to 30 mg/kg daily to maintain remission in ulcerative colitis.

Sulfasalazine can also be given rectally as suppositories; the *BNFC* suggests the following doses for children according to age:

- 5 to 8 years: 500 mg twice daily
- 8 to 12 years: 500 mg in the morning and 1 g at night
- 12 to 18 years: 0.5 to 1 g twice daily

Sulfasalazine has also been used for polyarticular **juvenile rheumatoid arthritis** (see also below). US licensed product information recommends that children aged 6 years and older who have not responded adequately to salicylates or other NSAIDs may be given an oral dose of 30 to 50 mg/kg daily in two divided doses, to a maximum of 2 g daily. To reduce adverse gastrointestinal effects, an enteric-coated tablet is used and the initial dose should be a quarter to a third of the planned maintenance; it is then increased weekly to reach the maintenance dose after one month.

Although sulfasalazine is not licensed for juvenile rheumatoid arthritis in the UK, the *BNFC* suggests that children aged 2 to 18 years may be given an initial oral dose of 5 mg/kg twice daily for 1 week. The dose is then increased to 10 mg/kg twice daily for 1 week, then 20 mg/kg twice daily for 1 week, and maintained on a dose of 20 to 25 mg/kg twice daily. For children aged 2 to 12 years the maximum dose suggested is 2 g daily, and 3 g daily for children aged 12 to 18 years.

Psoriasis. In a double-blind placebo-controlled study involving 50 patients with moderate to severe plaque-type psoriasis (p. 1688.1), sulfasalazine 3 to 4 g daily produced a significantly greater clinical improvement than placebo after 4 weeks of treatment with a further improvement at 8 weeks.[1]

See also Psoriatic Arthritis, below.

1. Gupta AK, *et al.* Sulfasalazine improves psoriasis: a double-blind analysis. *Arch Dermatol* 1990; **126**: 487–93.

Pyoderma gangrenosum. Sulfasalazine is licensed in some countries for the treatment of pyoderma gangrenosum (p. 1688.3), a condition that may be associated with inflammatory bowel disease, although published evidence of benefit is scanty.

References.

1. Shenefelt PD. Pyoderma gangrenosum associated with cystic acne and hidradenitis suppurativa controlled by adding minocycline and sulfasalazine to the treatment regimen. *Cutis* 1996; **57**: 315–9.

Rheumatoid arthritis. Sulfasalazine is considered to be a useful disease-modifying antirheumatic drug (DMARD) in the treatment of rheumatoid arthritis (p. 13.2). Studies have found a beneficial clinical effect of sulfasalazine, compared with placebo, on tender and swollen joints, pain, and erythrocyte sedimentation rate.[1,2] Meta-analyses[3,4] of generally short-term comparative studies suggest that sulfasalazine is roughly comparable in efficacy to methotrexate, intramuscular gold (sodium aurothiomalate), and penicillamine. Other reviews[2,5] have also suggested that it may have similar efficacy to hydroxychloroquine and leflunomide. Although there are regional differences in the prescription of DMARDs, sulfasalazine has been widely used for initial therapy, especially of less severe disease.[5] In an open study[6] of 200 patients with rheumatoid arthritis who were randomly allocated to treatment with sulfasalazine or auranofin, 31% of the sulfasalazine recipients were still taking the drug after 5 years compared with 15% of auranofin recipients. Improvement over baseline was still significant at 5 years for those patients receiving sulfasalazine but not in those treated with auranofin. Although one study[7] failed to find convincing evidence that using sulfasalazine with methotrexate was more effective than either drug alone, other studies have shown that combination treatment with sulfasalazine plus methotrexate and hydroxychloroquine was more effective than methotrexate alone or with sulfasalazine or hydroxychloroquine or the combination of sulfasalazine with hydroxychloroquine.[8–10] A review of sulfasalazine use in the management of rheumatoid arthritis concluded that combination therapy may be of benefit in patients with early or advanced rheumatoid arthritis but that there is still a need for studies to determine the efficacy and tolerability of various combinations.[5]

1. Suarez-Almazor ME, *et al.* Sulfasalazine for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 28/02/06).
2. Weinblatt ME, *et al.* Sulfasalazine treatment for rheumatoid arthritis: a metaanalysis of 15 randomized trials. *J Rheumatol* 1999; **26**: 2123–30.
3. Felson DT, *et al.* The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. *Arthritis Rheum* 1990; **33**: 1449–61.
4. Capell HA, *et al.* Second line (disease modifying) treatment in rheumatoid arthritis: which drug for which patient? *Ann Rheum Dis* 1993; **52**: 425–8.
5. Plosker GL, Croom KF. Sulfasalazine: a review of its use in the management of rheumatoid arthritis. *Drugs* 2005; **65**: 1825–49.
6. McEntegart A, *et al.* Sulfasalazine has a better efficacy/toxicity profile than auranofin—evidence from a 5 year prospective, randomized trial. *J Rheumatol* 1996; **23**: 1887–90.
7. Dougados M, *et al.* Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. *Ann Rheum Dis* 1999; **58**: 220–5.
8. O'Dell JR, *et al.* Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996; **334**: 1287–91.
9. O'Dell JR, *et al.* Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or combination of the three medications: results of a two-year randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; **46**: 1164–70.
10. Dale J, *et al.* Combination therapy for rheumatoid arthritis methotrexate and sulfasalazine together or with other DMARDs. *Nat Clin Pract Rheumatol* 2007; **3**: 450–8.

JUVENILE IDIOPATHIC ARTHRITIS. Juvenile idiopathic arthritis (p. 12.1) is generally managed similarly to rheumatoid arthritis, but there is limited experience with the use of some antirheumatic drugs in children. Sulfasalazine has produced significant improvement in studies of patients with juvenile chronic arthritis; a literature review found that it was consistently reported to be of benefit.[1] Adverse effects were reported to be similar to those in adults, with the exception of a serum-sickness-like reaction which was mostly seen in systemic onset patients and may be unique to juvenile rheumatoid arthritis.[1] For doses see Administration in Children, above.

1. Brooks CD. Sulfasalazine for the management of juvenile rheumatoid arthritis. *J Rheumatol* 2001; **28**: 845–53.

Spondyloarthropathies. *ANKYLOSING SPONDYLITIS.* Sulfasalazine has been found to be effective[1] in the treatment of active ankylosing spondylitis (p. 14.3), but there is evidence that it is more useful in the treatment of active disease and peripheral articular manifestations than in the management of chronic long-standing disease.[2–4] The active moiety appears to be sulfapyridine rather than mesalazine.[5] Sulfasalazine was no better than placebo for the treatment of inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis, but it was more effective than placebo in a subgroup of patients with no peripheral arthritis.[6]

1. Perraz MB, *et al.* Meta-analysis of sulfasalazine in ankylosing spondylitis. *J Rheumatol* 1990; **17**: 1482–6.
2. Clegg DO, *et al.* Comparison of sulfasalazine and placebo in the treatment of ankylosing spondylitis: a Department of Veterans Affairs Cooperative study. *Arthritis Rheum* 1996; **39**: 2004–12.
3. Clegg DO, *et al.* Comparison of sulfasalazine and placebo for the treatment of axial and peripheral articular manifestations of the seronegative spondyloarthropathies: a Department of Veterans Affairs cooperative study. *Arthritis Rheum* 1999; **42**: 2325–9.
4. Chen J, Liu C. Sulfasalazine for ankylosing spondylitis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 28/02/06).
5. Taggart A, *et al.* Which is the active moiety of sulfasalazine in ankylosing spondylitis? A randomized, controlled study. *Arthritis Rheum* 1996; **39**: 1400–5.
6. Braun J, *et al.* Efficacy of sulfasalazine in patients with inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis: a multicentre randomised controlled trial. *Ann Rheum Dis* 2006; **65**: 1147–53.

PSORIATIC ARTHRITIS. A systematic review[1] of interventions for psoriatic arthritis (see Spondyloarthropathies, p. 14.3) concluded that sulfasalazine was one of only two drugs with published evidence of well proven efficacy in psoriatic arthritis (the other being high-dose parenteral methotrexate).

See also under Psoriasis, above.

1. Jones G, *et al.* Interventions for treating psoriatic arthritis. Available in The Cochrane Database of Systematic Reviews, Issue 3. Chichester: John Wiley; 2000 (accessed 29/04/05).

Adverse Effects and Precautions

Since sulfasalazine is metabolised to sulfapyridine and 5-aminosalicylic acid (mesalazine), its adverse effects and precautions are similar to those of sulfonamides (see Sulfamethoxazole, p. 365.3) and of mesalazine (p. 1860.1). Many adverse effects have been attributed to the sulfapyridine moiety and appear to be more common if serum-sulfapyridine concentrations are greater than 50 micrograms/mL, if the daily dose of sulfasalazine is 4 g or more, or in slow acetylators of sulfapyridine.

The most commonly reported adverse effects include nausea and vomiting, abdominal discomfort, anorexia, headache, fever, and skin rash.

Adverse effects can be broadly divided into 2 groups:

- dose-related effects are dependent on acetylator phenotype, and largely predictable; this group includes nausea and vomiting, headache, haemolytic anaemia, and methaemoglobinaemia

- hypersensitivity reactions are essentially unpredictable and usually occur at the start of treatment; this group includes aplastic anaemia, hepatic and pulmonary dysfunction, vasculitis, auto-immune haemolysis, and rash such as toxic epidermal necrolysis, Stevens-Johnson syndrome, and drug rash with eosinophilia and systemic symptoms (DRESS).

Oligospermia, reversible on withdrawal of sulfasalazine, has also been reported. Sulfasalazine treatment may result in yellow-orange discoloration of skin, urine, and other body fluids. Some soft contact lenses may be stained. Adverse effects on the CNS include insomnia, depression, hallucinations, vertigo, convulsions, aseptic meningitis, ataxia, encephalopathy, peripheral neuropathy, and tinnitus.

Sulfasalazine should not be given to patients with a history of sensitivity to *sulfonamides or salicylates. Use in* children under 2 years of age is contra-indicated because of the risk of kernicterus. Use in children with juvenile rheumatoid arthritis may result in a serum sickness-like reaction. Caution is required when used in patients with severe allergy or asthma.

Blood counts should be performed at the start of therapy and frequently thereafter, particularly during the first 3 months of treatment. If a blood dyscrasia is suspected treatment should be stopped immediately and a blood count performed. Patients or their carers should be told how to recognise signs of blood toxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, jaundice, bruising or bleeding develop. Care is advisable in patients with G6PD deficiency because of the risk of haemolytic anaemia.

Sulfasalazine should be used with caution in hepatic or renal impairment. Liver function tests should be carried out at monthly intervals for the first 3 months of treatment. Periodic monitoring of kidney function has also been recommended.

The adverse effects associated with the use of *sulfasalazine in patients with inflammatory bowel disease*[1] or rheumatoid arthritis have been reviewed.[2,3] The type and incidence of adverse effects appear to be similar in both groups of patients.[2] Although most reactions are minor and patients may continue therapy at the same or reduced dosage, some patients stop treatment because of adverse effects and in these cases a hyposensitisation regimen may be considered.[1,4,5] **Hyposensitisation** should not be attempted in patients with a history of a serious adverse effect such as agranulocytosis, toxic epidermal necrolysis, erythema multiforme, frank haemolysis, or a severe hypersensitivity reaction.[1,4,5] An alternative to hyposensitisation in patients with inflammatory bowel disease who cannot tolerate sulfasalazine is to try a drug that supplies the active 5-aminosalicylic acid component without sulfapyridine, as the latter is thought to be responsible for many of the adverse effects. Examples include balsalazide, mesalazine, and olsalazine; however, some patients still experience hypersensitivity, see under Mesalazine, p. 1860.1.

1. Taffet SL, Das KM. Sulfasalazine: adverse effects and desensitization. *Dig Dis Sci* 1983; **28**: 833–42.
2. Amos RS, *et al.* Sulphasalazine for rheumatoid arthritis: toxicity in 774 patients monitored for one to 11 years. *BMJ* 1986; **293**: 420–3.
3. Farr M, *et al.* Side effect profile of 200 patients with inflammatory arthritides treated with sulphasalazine. *Drugs* 1986; **32** (suppl 1): 49–53.
4. Purdy BH, *et al.* Desensitization for sulfasalazine skin rash. *Ann Intern Med* 1984; **100**: 512–14.
5. Bax DE, Amos RS. Sulphasalazine in rheumatoid arthritis: desensitising the patient with a skin rash. *Ann Rheum Dis* 1986; **45**: 139–40.

Breast feeding. Small amounts of sulfasalazine and its sulfapyridine metabolites are excreted in breast milk; the concentrations of sulfasalazine and total sulfapyridine may be up to 30% and 50% of maternal serum concentrations respectively.[1] Bloody diarrhoea in a breast-fed infant whose mother was taking sulfasalazine 3 g daily has been reported.[2] The mother was a slow acetylator with a relatively high blood concentration of sulfapyridine, which contributed to the appearance of the drug in the infant's blood. Based on this report, the American Academy of Pediatrics[3] considers that sulfasalazine should be given with caution to breast-feeding mothers. However, others consider that continued treatment with sulfasalazine can generally be recommended to breast-feeding mothers of healthy infants.[4] A small study initially involving 17 mother-child pairs concluded sulfasalazine treatment could continue throughout pregnancy and lactation. The study found negligible amounts of sulfasalazine, and its main metabolite sulfapyridine, were transferred to the child via breast feeding. The authors did however warn that this conclusion could not be applied to a prematurely born child or a child with haemolytic disease.[5]

1. Khan AKA, Truelove SC. Placental and mammary transfer of sulphasalazine. *BMJ* 1979; **2**: 1553.
2. Branski D, *et al.* Bloody diarrhea—a possible complication of sulfasalazine transferred through human breast milk. *J Pediatr Gastroenterol Nutr* 1986; **5**: 316–17.
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 28/02/06)
4. Peppercorn MA. Sulfasalazine and related new drugs. *J Clin Pharmacol* 1987; **27**: 260–5.
5. Esbjörner E, *et al.* Sulphasalazine and sulphapyridine serum levels in children to mothers treated with sulphasalazine during pregnancy and lactation. *Acta Paediatr Scand* 1987; **76**: 137–42.

Effects on the blood. Blood disorders constitute 19% of all reactions reported with sulfasalazine.[1] As of June 1993 the UK CSM was aware of 191 reports of neutropenia, leucopenia, or agranulocytosis (22 fatal), 44 reports of bone marrow depression or aplastic anaemia (13 fatal) and 30 reports of thrombocytopenia (1 fatal).[1]

Although blood dyscrasias were initially thought to be caused by the sulfapyridine moiety, subsequent experience has shown that the aminosalicylates can also cause haematological reactions (see Mesalazine, p. 1860.2). The risk of blood dyscrasias with sulfasalazine has been estimated at 0.6 per 1000 in those given the drug for inflammatory bowel disease, but about 10 times greater in patients receiving sulfasalazine for rheumatoid arthritis.[2]

Sulfasalazine inhibits folic acid absorption, interferes with its metabolism, and can increase folic acid requirements through haemolysis of red blood cells.[3,4] These effects are not usually significant in patients with inflammatory bowel disease unless there are additional factors causing folate deficiency, such as intercurrent illness or an exacerbation of bowel disease.[3,4] However, clinical folate deficiency with macrocytosis, megaloblastic anaemia, or pancytopenia has been reported rarely.[3,4] Macrocytic anaemia associated with sulfasalazine may occur more commonly in patients with rheumatoid arthritis; it was found in 7 of 50 patients within 3 to 4 months of starting treatment with sulfasalazine.[5] The effects of sulfasalazine on folic acid metabolism appear to be dose-related and respond to withdrawal or dosage reduction, and folic acid supplements;[3-5] intravenous folinic acid may sometimes be needed.[4] Although the effects may be potentially serious, they are not a contra-indication to continuing sulfasalazine treatment.[4,5]

Patients with a history of leucopenia associated with gold therapy for rheumatoid arthritis should not be given sulfasalazine since a similar reaction may occur.[6]

1. CSM/MCA. Sulphasalazine and fatal blood dyscrasias. *Current Problems* 1993; **19**: 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024455&RevisionSelectionMethod=LatestReleased (accessed 02/07/08)
2. CSM/MCA. Blood dyscrasias and mesalazine. *Current Problems* 1995; **21**: 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)
3. Swinson CM, *et al.* Role of sulphasalazine in the aetiology of folate deficiency in ulcerative colitis. *Gut* 1981; **22**: 456–61.
4. Logan ECM, *et al.* Sulphasalazine associated pancytopenia may be caused by acute folate deficiency. *Gut* 1986; **27**: 868–72.
5. Prouse PJ, *et al.* Macrocytic anaemia in patients treated with sulphasalazine for rheumatoid arthritis. *BMJ* 1986; **293**: 1407.
6. Blíddal H, *et al.* Gold-induced leucopenia may predict a similar adverse reaction to sulphasalazine. *Lancet* 1987; **i**: 390.

Effects on the cardiovascular system. Reports include Raynaud's syndrome with sulfasalazine[1] and myocarditis with sulfasalazine and with mesalazine.[2] Myocarditis leading to fatal cardiogenic shock has been reported in a patient receiving mesalazine and it has been recommended that sulfasalazine or mesalazine should be replaced by glucocorticoids if cardiac symptoms arise.[3] See also under Mesalazine, p. 1860.2, and under Balsalazide, p. 1820.3.

1. Reid J, *et al.* Raynaud's phenomenon induced by sulphasalazine. *Postgrad Med J* 1980; **56**: 106–7.
2. Agnholt J, *et al.* Cardiac hypersensitivity to 5-aminosalicylic acid. *Lancet* 1989; **i**: 1135.
3. Kristensen KS, *et al.* Fatal myocarditis associated with mesalazine. *Lancet* 1990; **335**: 605.

Effects on fertility. Although successful pregnancies have been reported in the partners of men taking sulfasalazine,[1,2] male infertility is a well recognised complication of sulfasalazine treatment. Untreated inflammatory bowel disease is not associated with abnormal seminal quality or infertility, but oligospermia, reduced sperm motility, and an increase in morphological abnormalities are seen after treatment with sulfasalazine which may lead to infertility.[1-4] Oligospermia has been reported in 86% of men with inflammatory bowel disease treated with sulfasalazine.[1] Seminal characteristics and fertility return to normal within 2 to 3 months of withdrawing sulfasalazine and successful pregnancies have been reported after withdrawal.[1-3] The mechanism involved is thought to be a direct toxic effect on immature and developing spermatozoa, possibly due to the sulfapyridine moiety.[2-4] Improvement in seminal characteristics and successful pregnancies have been reported following substitution of mesalazine[4,5] or balsalazide[6] for sulfasalazine in patients with ulcerative colitis. However, reversible infertility, similar to that caused by sulfasalazine, has also been reported with mesalazine.[7]

1. Birnie GG, *et al.* Incidence of sulphasalazine-induced male infertility. *Gut* 1981; **22**: 452–5.
2. Riley SA, *et al.* Sulphasalazine induced seminal abnormalities in ulcerative colitis: results of mesalazine substitution. *Gut* 1987; **28**: 1008–12.
3. Toovey S, *et al.* Sulphasalazine and male infertility: reversibility and possible mechanism. *Gut* 1981; **22**: 445–51.
4. Ó'Moráin C, *et al.* Reversible male infertility due to sulphasalazine: studies in man and rat. *Gut* 1984; **25**: 1078–84.
5. Cann PA, Holdsworth CD. Reversal of male infertility on changing treatment from sulphasalazine to 5-aminosalicylic acid. *Lancet* 1984; **i**: 1119.
6. McIntyre PB, Lennard-Jones JE. Reversal with balsalazide of infertility caused by sulphasalazine. *BMJ* 1984; **288**: 1652–3.
7. Chermesh I, Eliakim R. Mesalazine-induced reversible infertility in a young male. *Dig Liver Dis* 2004; **36**: 551–2.

Effects on the gastrointestinal tract. Sulfasalazine-induced exacerbations of ulcerative colitis have been reported[1,2] and are probably caused by the salicylate moiety rather than sulfapyridine.[3] Other reported effects include intestinal villous atrophy.[4]

1. Schwartz AG, *et al.* Sulfasalazine-induced exacerbation of ulcerative colitis. *N Engl J Med* 1982; **306**: 409–12.
2. Ring PA, *et al.* Sulfasalazine-induced colitis complicating idiopathic ulcerative colitis. *Can Med Assoc J* 1984; **131**: 43–5.
3. Shanahan F, Targan S. Sulfasalazine and salicylate-induced exacerbation of ulcerative colitis. *N Engl J Med* 1987; **317**: 455.
4. Smith MA, *et al.* Angioimmunoblastic lymphadenopathy, sulphasalazine exposure and villous atrophy. *Postgrad Med J* 1985; **61**: 337–8.

Effects on the hair. Alopecia occurred on 2 occasions[1] after starting sulfasalazine 2 or 3 g daily in a patient with ulcerative colitis. On both occasions normal hair growth returned after treatment was stopped, and the patient was later successfully desensitised. However, alopecia that developed in another patient during sulfasalazine treatment did not recur on rechallenge.[2] In this case postpartum alopecia was considered to be the cause and these authors doubted whether sulfasalazine causes alopecia at all. Hair loss has been reported in 2 patients receiving mesalazine enemas.[3] However, remission of alopecia universalis has been reported during sulfasalazine treatment of rheumatoid arthritis.[4]

1. Breen EG, Donnelly S. Alopecia associated with sulphasalazine (Salazopyrin). *BMJ* 1986; **292**: 802.
2. Pich A, Eliakim R. Does sulfasalazine induce alopecia? *J Clin Gastroenterol* 1988; **10**: 466.
3. Kutty PK, *et al.* Hair loss and 5-aminosalicylic acid enemas. *Ann Intern Med* 1982; **97**: 785–6.
4. Jawad ASM, Scott DGI. Remission of alopecia universalis during sulphasalazine treatment for rheumatoid arthritis. *BMJ* 1989; **298**: 675.

Effects on the kidneys. UK licensed product information advises that adequate fluid intake and avoidance of urinary acidifiers may reduce the incidence of crystalluria and stone formation. For reports of nephrotic syndrome and of interstitial nephritis associated with sulfasalazine treatment, see under Mesalazine, p. 1860.3.

Effects on the pancreas. The UK CSM had received 6 reports of pancreatitis associated with sulfasalazine as of February 1994.[1] There had been further reports associated with mesalazine (see p. 1860.3). However, a large Danish population-based case-control study concluded neither sulfasalazine nor mesalazine was associated with an increased risk of pancreatitis, and that any increased risk might be associated with inflammatory bowel disease itself.[2]

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 02/07/08)
2. Munk EM, *et al.* Inflammatory bowel diseases, 5-aminosalicylic acid and sulfasalazine treatment and risk of acute pancreatitis: a population-based case-control study. *Am J Gastroenterol* 2004; **99**: 884–8.

Effects on the respiratory system. Although one study reviewed 50 cases of sulfasalazine-induced pulmonary complications, pulmonary toxicity remains a rare adverse effect.[1] Most reports include dyspnoea, cough, pulmonary infiltrates, fever, and eosinophilia, usually developing in the first few months of treatment although they may occur after several years.[1-3] Symptoms are generally readily reversible on withdrawal of sulfasalazine, although death due to fibrosing alveolitis has been reported,[2] and the need for corticosteroid therapy remains debatable.[1] These effects have also occurred with mesalazine, p. 1861.1; they have been reported in patients with a history of sensitivity to salicylates, sulfonamides, or with no known sensitivity to these drugs.[2,3] Bronchiolitis obliterans organising pneumonia has been reported in a patient with rheumatoid arthritis receiving sulfasalazine;[4] clinical improvement occurred after sulfasalazine was stopped and corticosteroid therapy started.

1. Parry SD, *et al.* Sulphasalazine and lung toxicity. *Eur Respir J* 2002; **19**: 756–64.
2. Wang KK, *et al.* Pulmonary infiltrates and eosinophilia associated with sulfasalazine. *Mayo Clin Proc* 1984; **59**: 343–6.
3. Jordan A, Cowan RE. Reversible pulmonary disease and eosinophilia associated with sulphasalazine. *J R Soc Med* 1988; **81**: 233–5.
4. Ulubaş B, *et al.* Bronchiolitis obliterans organizing pneumonia associated with sulfasalazine in a patient with rheumatoid arthritis. *Clin Rheumatol* 2004; **23**: 249–51.

Effects on taste. Metallic taste has occurred in patients taking sulfasalazine for ulcerative colitis,[1] although diseases causing changes in gastrointestinal absorption may lead to zinc deficiency, which has itself been associated with a metallic taste. There has also been a report of two patients developing a reversible taste dysfunction, while taking sulfasalazine for rheumatoid arthritis.[2]

1. Ogburn RM. Sulfamethazine-related dysgeusia. *JAMA* 1979; 241: 837.
2. Marcus RW. Sulfasalazine induced taste disturbances. *J Rheumatol* 1991; 18: 634–5.

Lupus. A study in 11 patients with sulfasalazine-induced lupus found that induction of disease was more likely in patients who were slow acetylators of sulfapyridine, and who had HLA haplotypes associated with idiopathic SLE.[1] Furthermore, the risk of developing persistent SLE and lupus nephritis increased with duration of treatment and cumulative dose of sulfasalazine. Lupus-like syndrome has also occurred with mesalazine (p. 1861.1).

1. Gunnarsson L *et al.* Predisposing factors in sulphasalazine-induced systemic lupus erythematosus. *Br J Rheumatol* 1997; 36: 1089–94.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sulfasalazine 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 03/10/11)

Pregnancy. Sulfasalazine and its sulfapyridine metabolites readily cross the placenta resulting in similar concentrations in the cord serum and maternal serum at delivery.[1,2] The concentration of the 5-aminosalicylic acid component of sulfasalazine in both cord serum and maternal serum is negligible.[1] There have been isolated reports of congenital abnormalities associated with use of sulfasalazine during pregnancy including coarctation of the aorta with a ventricular septal defect,[3,4] and genito-urinary disorders.[4] There is also a theoretical risk of kernicterus in the neonate if sulfasalazine is given close to delivery (see p. 366.2). However, given the concentrations of sulfasalazine and its metabolites found in cord blood, the risk of kernicterus from maternal use is considered minimal.[2] There have been many successful and uncomplicated pregnancies during sulfasalazine therapy and the general consensus favours continuing sulfasalazine throughout pregnancy when indicated.[1,3–6] (See also Mesalazine, p. 1861.1.) The minimum effective dose should be used and since sulfasalazine may precipitate folate deficiency (see Effects on the Blood, p. 1891.2), folic acid supplements are recommended.[7]

1. Khan AKA, Truelove SC. Placental and mammary transfer of sulphasalazine. *BMJ* 1979; 2: 1553.
2. Järnerot G *et al.* Placental transfer of sulphasalazine and sulphapyridine and some of its metabolites. *Scand J Gastroenterol* 1981; 16: 693–7.
3. Hoo JJ *et al.* Possible teratogenicity of sulfasalazine. *N Engl J Med* 1988; 318: 1128.
4. Newman NM, Correy JF. Possible teratogenicity of sulphasalazine. *Med J Aust* 1983; 1: 528–9.
5. Peppercorn MA. Sulfasalazine and related new drugs. *J Clin Pharmacol* 1987; 27: 260–5.
6. Korelitz BI. Commentary: observations on sulfasalazine in Crohn's disease and ulcerative colitis. *J Clin Pharmacol* 1987; 27: 265–6.
7. Byron MA. Treatment of rheumatic diseases. *BMJ* 1987; 294: 236–8.

Interactions

Giving sulfasalazine with antibacterial therapy may reduce conversion of sulfasalazine to its active metabolite (see below).

Sulfasalazine has been reported to interfere with the absorption of digoxin (p. 1357.3) or folic acid (see Effects on the Blood, p. 1891.2) from the gastrointestinal tract.

Antibacterials. Since the effects of sulfasalazine depend on release of 5-aminosalicylic acid by bacterial metabolism in the gut, any drug that reduces the intestinal microflora may rednce the production of active metabolite. Evidence for this has been seen in patients also given *rifampicin* and *ethambutol*,[1] or in subjects also given *ampicillin*.[2] However, a decrease in clinical effect does not seem to have been seen.

1. Shaffer JL, Houston JB. The effect of rifampicin on sulphapyridine plasma concentrations following sulphasalazine administration. *Br J Clin Pharmacol* 1985; 19: 526–8.
2. Houston JB *et al.* Azo reduction of sulphasalazine in healthy volunteers. *Br J Clin Pharmacol* 1982; 14: 395–8.

Antineoplastics. For mention of 5-aminosalicylates such as sulfasalazine inhibiting the metabolism of thiopurine antineoplastics, and increasing their toxicity, see Gastrointestinal Drugs, p. 822.1.

Pharmacokinetics

About 15% of an oral dose of sulfasalazine is absorbed from the small intestine, although some of this is subsequently returned to the intestine in bile via enterohepatic circulation. The great majority of the dose reaches the colon where the azo bond is cleaved by the action of the intestinal flora, producing sulfapyridine and 5-aminosalicylic acid (mesalazine). Results in patients who have undergone colectomy suggest that between 60 and 90% of the total dose is metabolised in this way, but the degree of metabolism depends both on the activity of the intestinal flora and the speed of intestinal transit; colonic metabolism is reduced in patients with diarrhoea (for example, in active inflammatory bowel disease).

The small amount of intact sulfasalazine that is absorbed is extensively protein bound and subsequently excreted unchanged in urine. It crosses the placenta and is found in breast milk.

After cleavage of the sulfasalazine molecule about 60 to 80% of available sulfapyridine is absorbed, and undergoes extensive metabolism by acetylation, hydroxylation, and glucuronidation. Peak steady-state concentrations of sulfapyridine are higher in slow acetylators than fast acetylators after similar doses and the former are 2 to 3 times more likely to have adverse effects. Some 60% of the original dose of sulfasalazine is excreted in urine as sulfapyridine and its metabolites. As with sulfasalazine, absorbed sulfapyridine crosses the placenta and is found in breast milk.

The 5-aminosalicylic acid (5-ASA) moiety is much less well absorbed. About one-third of liberated 5-ASA is absorbed and almost all of this is acetylated and excreted in urine. For further details of the pharmacokinetics of 5-aminosalicylic acid see under Mesalazine, p. 1861.2.

Reviews.

1. Klotz U. Clinical pharmacokinetics of sulphasalazine, its metabolites and other prodrugs of 5-aminosalicylic acid. *Clin Pharmacokinet* 1985; 10: 285–302.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Azulfidine; Flogostop; *Austral.*: Pyralin; Salazopyrin; *Austria*: Salazopyrin; *Belg.*: Salazopyrine; *Braz.*: Azulfin; Salazoprin; *Canad.*: Salazopyrin; *Chile*: Azulfidine; *China*: Chang Jian Ning (长建宁); Salazopyrin; Weilufen (维柳芬); *Cz.*: Salazopyrin; *Denm.*: Salazopyrin; *Fin.*: Salazopyrin; *Fr.*: Salazopyrine; *Ger.*: Azulfidine; Colo-Pleon; Pleon RA; *Gr.*: Salopyrine; *Hong Kong*: Salazopyrin; *Hung.*: Salazopyrin; *India*: Iwata; Saaz; Salazar; Sazo; *Indon.*: Lazafin; Sulcolon; *Irl.*: Salazopyrin; *Israel*: Salazopyrin; *Ital.*: Salazopyrin; *Jpn*: Azulfidine; *Malaysia*: Salazopyrin; *Mex.*: Azulfidina; *Neth.*: Salazopyrine; *Norw.*: Salazopyrin; *NZ*: Salazopyrin; *Pol.*: Salazopyrin; *Port.*: Salazopirina; *S.Afr.*: Salazopyrin; *Singapore*: Salazopyrin; *Spain*: Salazopyrina; *Swed.*: Salazopyrin; *Switz.*: Salazopyrin; *Thai.*: Salazine; Salazopyrin; Saridine; *Turk.*: Salazopyrin; *UK*: Salazopyrin; Sulazine; *Ukr.*: Salazopyrin (Салазопирин); *USA*: Azulfidine; *Venez.*: Azulfidine.

Pharmacopoeial Preparations

BP 2014: Gastro-resistant Sulfasalazine Tablets; Sulfasalazine Tablets;

USP 36: Sulfasalazine Delayed-release Tablets; Sulfasalazine Tablets.

Sulglicotide *(BAN, rINN)*

Sulglicotida; Sulglicotidum; Sulglycotide; Сульгликотид.

CAS — 54182-59-1.

ATC — A02BX08.

ATC Vet — QA02BX08.

Profile

Sulglicotide is a sulfated glycopeptide with cytoprotective properties extracted from pig duodenum. It has been used in the treatment of peptic ulcer disease and other gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Gliptide†.

Tamarind

Tamarindo; West Indian Tamarind; Плоды Тамаринда; Индийский Финик; Тамаринд.

ATC Herb — HA06AC5012 (Tamarindus indica: fruit).

UNII — 2U9H66X7VX.

Pharmacopoeias. In *Fr.*

Profile

Tamarind is the fruits of *Tamarindus indica* (Leguminosae) freed from the brittle outer part of the pericarp and preserved with sugar or syrup. It contains tartaric, citric, and malic acid and their salts. Tamarind is used as a laxative with senna.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Delabarre.

Multi-ingredient Preparations. *Arg.*: Laxiruela; *Austria*: Prugelletten; *Braz.*: Pitolax†; Florlax; Fontolax; Laxtam; Naturetti Tamarli; Tamarine; Tamarine; *Chile*: Bebe Dep; Tamarine; *Fr.*: Tamarine†; Transifine; Ultratransit; *Gr.*: Tamarine; *Hung.*: Tamarinlax; *Ital.*: Ortisan; Tamarine; *Mex.*: MD Lax; Naturetti; *Spain*: Dentomicin†; Pruina; *UK*: Pure Plan.

Homoeopathic Preparations. *Fr.*: Tamarindus Complexe No 95†.

Teduglutide *(BAN, USAN, rINN)*

ALX-0600; [2-Glycine]-1-33-glucagon-like Peptide II; Teduglutida; Téduglutide; Teduglutidum; Тедуглутид.

$C_{164}H_{252}N_{44}O_{55}S$=3752.1.

CAS — 287714-30-1.

UNII — 7M19191IKG.

Uses and Administration

Teduglutide is an analogue of endogenous human glucagon-like peptide 2 (GLP-2) that acts as an agonist at GLP-2 receptors in the distal intestine. It increases intestinal and portal blood flow, inhibits gastric acid secretion, decreases intestinal motility, and promotes repair of the intestinal mucosa. Teduglutide is used in the management of patients with short bowel syndrome. A dose of 50 micrograms/kg is given by subcutaneous injection once daily. This initial dose may be titrated to a lower dose if necessary to improve tolerability. Doses should be reduced in moderate to severe renal impairment, see Administration in Renal Impairment, below.

Teduglutide is under investigation in Crohn's disease.

References.

1. Jeppesen PB. Teduglutide, a novel glucagon-like peptide 2 analog, in the treatment of patients with short bowel syndrome. *Therap Adv Gastroenterol* 2012; 5: 159–71.
2. Norholt LM, *et al.* Treatment of adult short bowel syndrome patients with teduglutide. *Expert Opin Pharmacother* 2012; 13: 235–43.
3. Burness CB, McCormack PL. Teduglutide: a review of its use in the treatment of patients with short bowel syndrome. *Drugs* 2013; 73: 935–47.

Administration in renal impairment. Exposure to teduglutide is increased in renal impairment and the usual dose (see Uses and Administration, above) should be reduced by 50% in patients with moderate to severe impairment (creatinine clearance < 50 mL/minute) or end-stage renal disease.

Adverse Effects and Precautions

The most common adverse effects associated with teduglutide include injection site reactions, abdominal pain and distension, nausea and vomiting, headaches, peripheral oedema, and upper respiratory-tract infections. Other adverse effects include flatulence, hypersensitivity reactions, changes to appetite, sleep disturbances, cough, skin haemorrhage, arthralgia, renal colic, chest pain, and night sweats. Patients with a stoma reported a higher incidence of stoma complications. Teduglutide enhances fluid absorption, and fluid overload and congestive heart failure have been seen during treatment. Intestinal obstruction has been reported; teduglutide should be withheld until it has resolved.

Teduglutide has the potential to cause hyperplastic changes including neoplasia and should not be used in patients with active gastrointestinal malignancy. In those at increased risk of malignancy or with an active non-gastrointestinal malignancy, the benefits and risks of treatment should be considered. Patients should be monitored for small bowel neoplasia. Colorectal polyps may develop during teduglutide therapy; before starting treatment a colonoscopy should be carried out and any polyps removed. Subsequently, a colonoscopy should be carried out at least every 5 years.

Cholecystitis, cholangitis, and cholelithiasis have been reported, and there have been adverse effects on the pancreas such as pancreatitis. Monitoring of the function of the gallbladder and pancreas should be carried out before and during treatment.

Antibodies to teduglutide have developed in some patients, and may cross-react with endogenous glucagon-like peptide-2. Concentrations of C-reactive protein increased when teduglutide therapy was started and then gradually declined with ongoing treatment. The long term impact of these changes is unknown.

Interactions

Teduglutide can increase the absorption of other drugs such as benzodiazepines; increased concentrations of prazepam were noted when teduglutide was started, which led to

deterioration of mental status. Caution is required when teduglutide is used with drugs that require titration or have a narrow therapeutic index.

Pharmacokinetics

Subcutaneous injection of teduglutide has an absolute bioavailability of 88% in healthy subjects, with peak plasma concentrations reached between 3 to 5 hours after a dose. No accumulation is seen after repeated doses. The metabolic pathway of teduglutide is unknown, but it is expected to be degraded into small peptides and amino acids via catabolic pathways, in a similar manner to endogenous glucagon-like peptide-2. Teduglutide is mainly cleared by the kidneys; plasma clearance has a similar value to the glomerular filtration rate. The mean terminal half-life is about 2 hours in healthy subjects and 1.3 hours in patients with short bowel syndrome. Exposure to teduglutide is reduced in patients with moderate hepatic impairment. In those with moderate to severe renal impairment or end-stage renal disease, exposure to teduglutide increases with the degree of impairment. Exposure is increased by a factor of 2.6 in patients with end-stage renal disease compared with healthy subjects.

References.

1. Marier J-F, *et al.* Pharmacokinetics, safety, and tolerability of teduglutide, a glucagon-like peptide-2 (GLP-2) analog, following multiple ascending subcutaneous administrations in healthy subjects. *J Clin Pharmacol* 2008; **48**: 1289–99.
2. Marier J-F, *et al.* Population pharmacokinetics of teduglutide following repeated subcutaneous [sic] administrations in healthy participants and in patients with short bowel syndrome and Crohn's disease. *J Clin Pharmacol* 2010; **50**: 36–49.
3. Nave R, *et al.* Pharmacokinetics of teduglutide in subjects with renal impairment. *Eur J Clin Pharmacol* 2013; **69**: 1149–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA:* Gattex.

Tegaserod Maleate *(BANM, USAN, rINNM)*

HTF-919; Maleato de tegaserod; SDZ-HTF-919; Tégasérod, Maléate de; Tegaserod, maleato de; Tegaserodi Maleas; Teracepoda Maneat.

1-[[(5-Methoxyindol-3-yl)methylene]amino]-3-pentylguanidine maleate.

$C_{16}H_{23}N_5O.C_4H_4O_4$=417.5

CAS — 145158-71-0 (tegaserod); 189188-57-6 (tegaserod maleate).

ATC — A06AX06.

ATC Vet — QA06AX06.

UNII — E5XNT3RF5A.

Stability and compatibility. Crushed tablets of tegaserod were found to be stable in water, and apple juice; the latter may mask the taste of the drug. Orange juice, milk, or yogurt were not recommended as vehicles because of incomplete dissolution or uncertainty about stability.[1]

1. Carrier M-N, *et al.* Stability and compatibility of tegaserod from crushed tablets mixed in beverages and foods. *Am J Health-Syst Pharm* 2004; **61**: 1135–42.

Uses and Administration

Tegaserod is a partial agonist at 5-HT_4 receptors and has prokinetic properties. Although it has been withdrawn in most countries because of an apparent high incidence of cardiovascular ischaemic events (see Effects on the Heart, below), it is still licensed in some for use in women below the age of 55 for the short-term treatment of irritable bowel syndrome (p. 1810.3), particularly the constipation-predominant form. It is also used for the treatment of chronic idiopathic constipation (p. 1804.3) in women less than 55 years of age. Efficacy in men and the elderly has not been established.

Tegaserod is given orally as the maleate but doses are expressed in terms of the base; 8.31 mg of tegaserod maleate is equivalent to about 6 mg of tegaserod. It is given in a dose of 6 mg twice daily before food. For irritable bowel syndrome, it is given for a maximum of 12 weeks; treatment should be stopped if no response is seen after 4 weeks.

References.

1. Evans BW, *et al.* Tegaserod for the treatment of irritable bowel syndrome and chronic constipation. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 17/03/08).

Adverse Effects and Precautions

The most common adverse effects of tegaserod have been gastrointestinal disturbances including abdominal pain, diarrhoea, nausea, vomiting, and flatulence. Diarrhoea generally occurs within the first week of treatment and is usually transient but may be severe. Ischaemic colitis has been reported. Headache, dizziness, migraine, insomnia, fatigue, leg or back pain, and arthropathy have also been commonly reported.

Serious and sometimes fatal cardiovascular ischaemic events such as myocardial infarction, unstable angina pectoris, and stroke have occurred with tegaserod, and have led to its withdrawal from the market in most of the world. Cardiovascular adverse effects may also include hypotension and arrhythmias. Other adverse effects have included effects on the nervous system such as depression, and other gastrointestinal effects including cholelithiasis and dyspepsia.

Treatment has been contra-indicated in patients with a history of cardiovascular disease, bowel obstruction or biliary disease, abdominal adhesions, or diarrhoea, as well as in those with severe renal or moderate to severe hepatic impairment.

References.

1. Basler WL, Schoenfeld P. Safety profile of tegaserod, a 5-HT_4 receptor agonist, for the treatment of irritable bowel syndrome. *Drug Safety* 2004; **27**: 619–31.
2. Quigley EM, *et al.* Safety and tolerability of tegaserod in patients with chronic constipation: pooled data from two phase III studies. *Clin Gastroenterol Hepatol* 2006; **4**: 605–13.

Effects on the gastrointestinal tract. Severe diarrhoea, leading to hypovolaemia, hypotension, and syncope has been seen occasionally in patients receiving tegaserod. Some patients required hospitalisation for rehydration, and patients should be advised to stop taking the drug and seek medical attention if severe diarrhoea or associated dizziness or lightheadedness develop. In addition, ischaemic colitis has been reported rarely, and the drug should be stopped immediately in patients who develop symptoms such as rectal bleeding, bloody diarrhoea, or new and worsening abdominal pain.[1] The FDA noted that it had received 20 reports of ischaemic colitis in patients taking tegaserod between August 2002 and March 2004; in 3 cases, the effect only developed after several months (7 to 13) of therapy.[2] However, in reply the manufacturer (*Novartis*) suggested that there was no evidence from post-marketing surveillance to support an increased rate of ischaemic colitis over that normally seen in patients with irritable bowel syndrome, who are at increased risk of this diagnosis, nor any obvious pharmacological mechanism for such an adverse effect.[3]

1. Novartis, Canada. Important safety update: diarrhea and ischemic colitis in patients using Zelnorm (tegaserod hydrogen maleate) (issued 28/04/04). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/zelnorm_hpc-cps_e.pdf (accessed 07/07/06)
2. Brinker AD, *et al.* Tegaserod and ischemic colitis. *N Engl J Med* 2004; **351**: 1361–3.
3. Joelsson BE, *et al.* Tegaserod and ischemic colitis. *N Engl J Med* 2004; **351**: 1363–4.

Effects on the heart. In an analysis of pooled data from 29 studies, 13 out of 11 614 patients taking tegaserod had serious cardiovascular ischaemic events, compared with 1 out of 7031 patients taking placebo. Events included unstable angina pectoris, stroke, and myocardial infarction, one of which was fatal.[1-3] Most of these patients had at least one cardiovascular risk factor, but for some, no cardiovascular disease or risk had been diagnosed at the onset of treatment with tegaserod.[2] Patients taking tegaserod should seek medical attention if they have severe chest pain, dyspnoea, dizziness, sudden onset of weakness, difficulty walking or talking, or any other symptoms suggestive of myocardial infarction or stroke.[1] However, a large observational cohort study[4] involving over 55 000 patients in US general practice could not find any increased risk of cardiovascular event or stroke in users of tegaserod compared with matched controls.

1. FDA Public Health Advisory. Tegaserod maleate (marketed as Zelnorm) (issued 30th March 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm051284.htm (accessed 15/07/10)
2. Novartis, Canada. Health Canada endorsed important safety information on Zelnorm (tegaserod hydrogen maleate) (issued 30th March 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/zelnorm_hpc-cps_2_e.pdf (accessed 31/05/07)
3. Novartis, USA. Urgent: marketing and sales suspension notice for Zelnorm tablets, 2-mg and 6-mg all lots within expiry (issued 30th March 2007). Available at: http://www.zelnorm.com/Dr_Doctor_Letter.pdf (accessed 31/05/07)
4. Loughlin J, *et al.* Tegaserod and the risk of cardiovascular ischemic events: an observational cohort study. *J Cardiovasc Pharmacol Ther* 2010; **15**: 151–7.

Pharmacokinetics

Tegaserod is rapidly absorbed from the gastrointestinal tract and peak plasma levels occur after about 1 hour. The absolute bioavailability of an oral dose is 10%; this is reduced by the presence of food. Tegaserod is widely distributed into the tissues and is about 98% bound to plasma proteins. Presystemic acid-catalysed hydrolysis in the stomach, and then oxidation and glucuronidation, produces the main metabolite, which is inactive; direct systemic glucuronidation also occurs. Two-thirds of an oral dose is excreted unchanged in the faeces and one-third excreted in the urine primarily as the main metabolite. The terminal half-life of tegaserod is about 11 hours.

Reviews.

1. Appel-Dingemanse S. Clinical pharmacokinetics of tegaserod, a serotonin 5-HT_4 receptor partial agonist with promotile activity. *Clin Pharmacokinet* 2002; **41**: 1021–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Altezerod; Coloserod; Prociner; Tegarod; Zelmac; *Braz.*: Zelmac; *Chile*: Colonaid; Distimax†; Tegasir†; Ther†; Zelmac†; *China*: Chang Luo Ning (常罗宁); Kai Le Ning (开乐宁); Zelmac (泽马可); *Hong Kong*: Zelmac†; *India*: Ibsinorm; Irbez; Tegibs; Tegod; *Indon.*: Zelmac†; *Mex.*: Zelmac; *NZ*: Zelmac; *Philipp.*: Zelnorm†; *Rus.*: Zelmac (Зелмак); *S.Afr.*: Zelnorm†; *Singapore*: Zelmac; *Thai.*: Zelmac†; *Turk.*: Zelmac; *Venez.*: Zelmac.

Tenatoprazole *(rINN)*

Benatoprazole; Enatoprazole; Tenatoprazol; Ténatoprazole; Tenatoprazolum; TU-199; Тенатопразол.

(±)-5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1*H*-imidazo[4,5-*b*]pyridine.

$C_{16}H_{18}N_4O_3S$=346.4

CAS — 113712-98-4.

UNII — RE0689TX2K.

Profile

Tenatoprazole is a proton pump inhibitor that is under investigation for the treatment of gastro-oesophageal reflux disease.

Teprenone *(rINN)*

E-671; Geranylgeranylacetone (5*E*,9*E*,13*E* isomer); Teprenona; Téprénone; Teprenonum; Тепренон.

6,10,14,18-Tetramethyl-5,9,13,17-nonadecatetraen-2-one, mixture of (5*E*,9*E*,13*E*) and (5*Z*,9*E*,13*E*) isomers.

$C_{23}H_{38}O$=330.6

CAS — 6809-52-5 (teprenone); 3796-63-2 (5E,9E,13E isomer); 3796-64-3 (5Z,9E,13E isomer).

UNII — S8S8451A4O.

Profile

Teprenone is a cytoprotective drug that is used in the treatment of gastritis and peptic ulcer disease (p. 1813.2) in a usual oral dose of 50 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Selbex (施维舒); *Indon.*: Purubex; *Jpn*: Selbex; *Philipp.*: Selbex; *Thai.*: Selbex.

Tiemonium Iodide *(BAN, rINN)*

Ioduro de tiemonio; TE-114; Tiemonii Iodidum; Tiemonio, ioduro de; Tiémonium, Iodure de; Тиемония Йодид.

4-[3-Hydroxy-3-phenyl-3-(2-thienyl)propyl]-4-methylmorpholinium iodide.

$C_{18}H_{24}INO_2S$=445.4

CAS — 6252-92-2 (tiemonium); 144-12-7 (tiemonium iodide).

ATC — A03AB17.

ATC Vet — QA03AB17.

UNII — FZ2LZ7U304.

Tiemonium Metilsulfate

Tiemonio, metilsulfato de; Tiemonium Methylsulphate; Тиемония Метилсульфат.

4-[3-Hydroxy-3-phenyl-3-(2-thienyl)propyl]-4-methylmorpholinium methylsulphate.

$C_{19}H_{27}NO_6S_2$=429.5

CAS — 6504-57-0.

Profile

Tiemonium iodide and tiemonium metilsulfate are quaternary ammonium antimuscarinics with peripheral effects similar to those of atropine (p. 1312.1) and are used in the relief of visceral spasms.

Tiemonium metilsulfate is given in an oral dose of 100 to 300 mg daily in divided doses. It has also been given by intramuscular or slow intravenous injection or rectally as a suppository.

Tiemonium iodide has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Visceralgine; *Indon.*: Visceralgine.

Multi-ingredient Preparations. *Belg.*: Asodal†; *Fr.*: Colchimax.

Timepidium Bromide *(rINN)*

Bromuro de timepidio; SA-504; Timepidii Bromidum; Timepidio, bromuro de; Timépidium, Bromure de; Тимепидия бромид.

3-[Di-(2-thienyl)methylene]-5-methoxy-1,1-dimethylpiperidinium bromide monohydrate.

$C_{17}H_{22}BrNOS_2,H_2O$=418.4

CAS — 35035-05-3.

ATC — A03AB19.

ATC Vet — QA03AB19.

UNII — 8R9E4766V4.

Pharmacopoeias. In *Jpn.*

Profile

Timepidium bromide is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p. 1312.1). It has been given for the symptomatic treatment of visceral spasms in usual oral doses of 30 mg three times daily. It has also been given by subcutaneous, intramuscular, and intravenous injection in a dose of 7.5 mg.

Urinary metabolites of timepidium may cause a reddish coloration of the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Sesden; *Jpn*: Sesden; *Singapore*: Sesden†.

Tiquizium Bromide *(pINN)*

Bromuro de tiquizio; HSR-902; Tiquizii Bromidum; Tiquizio, bromuro de; Tiquizium, Bromure de; Тихизия бромид.

trans-3-(Di-2-thienylmethylene)octahydro-5-methyl-2*H*-quinolizinium bromide.

$C_{19}H_{24}BrNS_2$=410.4

CAS — 71731-58-3.

UNII — 659K6049SF.

Profile

Tiquizium bromide is an antimuscarinic with actions similar to those of atropine (p. 1312.1). It is used as an antispasmodic (p. 1803.3) in the treatment of gastrointestinal spasm, biliary tract disease, and urolithiasis; a suggested oral dose is 5 to 10 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Thiaton.

Tropisetron *(BAN, rINN)*

Tropisetrón; Tropisétron; Tropisetroni; Tropisetronum; Трописетрон.

1α*H*,5α*H*-Tropan-3α-yl indole-3-carboxylate.

$C_{17}H_{20}N_2O_2$=284.4

CAS — 89565-68-4.

ATC — A04AA03.

ATC Vet — QA04AA03.

UNII — 6I81SNIK1W.

Tropisetron Hydrochloride *(BANM, rINNM)*

Hidroclorur de tropisetrón; ICS-205-930; Tropisétron, Chlorhydrate de; Tropisetrón, hidrocloruro de; Tropisetron-hydrochlorid; Tropisetroni hydrochloridum; Трописетрона гидрохлорид.

$C_{17}H_{20}N_2O_2$,HCl=320.8

CAS — 105826-92-4.

ATC — A04AA03.

ATC Vet — QA04AA03.

UNII — A19338Q2YO.

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

Ph. Eur. 8: (Tropisetron Hydrochloride). A white or almost white powder. Freely soluble or soluble in water; sparingly soluble in alcohol; very slightly soluble in dichloromethane.

Uses and Administration

Tropisetron is a 5-HT_3 antagonist with an antiemetic action similar to that of ondansetron (p. 1872.2). It is used in the prevention of nausea and vomiting induced by cytotoxic therapy and in the treatment and prevention of postoperative nausea and vomiting (p. 1811.3).

Tropisetron is given as the hydrochloride by slow intravenous injection or infusion, or orally. Doses are expressed in terms of tropisetron base; 5.64 mg of tropisetron hydrochloride is equivalent to about 5 mg of tropisetron base.

For the *prophylaxis* of acute **nausea and vomiting** associated with cytotoxic **chemotherapy** a single dose of 5 mg may be given by slow intravenous injection or infusion on the day of treatment, shortly before chemotherapy. The injection is given over not less than 1 minute; it may be given into a running infusion. For infusion, it is diluted into 100 mL of a suitable infusion fluid (such as sodium chloride 0.9% or glucose 5%), and given over 15 minutes. Subsequent doses of 5 mg daily are given orally, in the morning at least one hour before food, for a further 5 days.

For the *treatment* of **postoperative** nausea and vomiting 2 mg may be given by slow intravenous injection (over not less than 30 seconds), or by infusion (over 15 minutes), within 2 hours of the end of anaesthesia. For *prophylaxis*, the same dose may be given shortly before induction of anaesthesia.

For doses in children, see below.

References.

1. Lee CR, *et al.* Tropisetron: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential as an antiemetic. *Drugs* 1993; 46: 925–43.
2. Simpson K, *et al.* Tropisetron: an update of its use in the prevention of chemotherapy-induced nausea and vomiting. *Drugs* 2000; 59: 1297–1315.
3. Kranke P, *et al.* Tropisetron zur Prophylaxe von Übelkeit und Erbrechen in der postoperativen Phase: eine quantitative systematische Übersicht. *Anaesthesist* 2002; 51: 805–14.

Administration in children. Tropisetron hydrochloride is used in children to prevent nausea and vomiting induced by cytotoxic chemotherapy; doses are expressed in terms of tropisetron base. Children over 2 years of age have been given tropisetron 200 micrograms/kg (maximum dose 5 mg) before chemotherapy, by intravenous injection over at least 1 minute, or by infusion (at a concentration of 50 micrograms/mL in a suitable infusion fluid, over about 15 minutes). In children weighing less than 25 kg the same dose may be given intravenously once daily for up to a further 4 days as required. In those weighing more than 25 kg, a dose of 5 mg may be given orally once daily for up to a further 5 days; if oral dosage is not possible, 5 mg may be given intravenously.

Fatigue. Tropisetron has been reported to be of benefit in patients with chronic fatigue, see under Uses and Administration of Ondansetron, p. 1873.1.

Pain. For reference to the use of tropisetron in various painful syndromes, see under Uses and Administration of Ondansetron, p. 1873.1.

Pruritus. Tropisetron and other 5-HT_3 antagonists have been investigated for the management of pruritus (see under Ondansetron, p. 1873.1).

Adverse Effects and Precautions

As for Ondansetron, p. 1873.2. Fatigue, abdominal pain, and diarrhoea may also occur. Visual hallucinations, and an increase in blood pressure in patients with pre-existing hypertension, have been noted at high repeated doses. ECG changes such as prolongation of QT interval have been noted with high-dose intravenous tropisetron. The drug should therefore be used with caution in patients with cardiac rhythm or conduction disturbances. Care should be taken when driving or operating machinery. No dosage reduction is considered necessary in renal or hepatic impairment despite possible reductions in clearance.

Carcinogenicity. The manufacturer (*Novartis, UK*) has reported an increased incidence of hepatic neoplasms in male *mice* given high doses of tropisetron but it is suggested that these effects are both species and sex specific.

Effects on the cardiovascular system. For a discussion of the effects of 5-HT_3 antagonists on the cardiovascular system, see under Ondansetron, p. 1873.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tropisetron 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 07/10/11)

Interactions

Drugs that induce or inhibit hepatic enzymes may affect plasma concentrations of tropisetron. Licensed product information considers that any changes are usually unlikely to be clinically relevant with the recommended doses.

Tropisetron should be used with caution with antiarrhythmics, beta blockers, or drugs likely to prolong the QT interval, including those likely to cause electrolyte disturbances (see Ondansetron, p. 1874.2).

Pharmacokinetics

Tropisetron is well absorbed after oral doses. Peak plasma concentrations occur within 3 hours. Absolute bioavailability depends on the dose since first-pass metabolism is saturable. It is 71% bound to plasma proteins. Tropisetron is metabolised by hydroxylation and conjugation, and metabolites are excreted mainly in the urine with a small amount in the faeces. The cytochrome P450 isoenzyme CYP2D6 is involved in tropisetron metabolism, and shows genetic polymorphism. The elimination half-life is about 8 hours in extensive metabolisers and up to 45 hours in poor metabolisers. Clearance is also reduced in patients with renal impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Navoban; *Austral.*: Navoban; *Austria*: Navoban; *Belg.*: Novaban; *Chile*: Navoban†; *China*: Di Ou Ping (迪欧平); Gai Ge En (盖格恩); Guang Di (广迪); He Tai (和太); Luo Ting (罗亭); Navoban (歌必享); NiTai-Mei (尼泰美); Pu Luo Lin (普洛林); Qi Qiong (齐琼); Que Zhi Du (确芝杜); Rui Qi Tai (瑞齐泰); Sai Ge En (赛格恩); Shu Ji (纾吉); Tuo Li Shi Ning (妥立士宁); Wei Rui Te (维瑞特); Xin Bei (欣贝); Xin Shun Er (欣顺尔); YanDi (岩迪); *Denm.*: Navoban; *Fr.*: Navoban†; *Ger.*: Navoban†; *Gr.*: Navoban; *Hong Kong*: Navoban; *Hung.*: Navoban; *Indon.*: Navoban; Setrovel; *Ital.*: Navoban; *Jpn*: Navoban; *Malaysia*: Navoban; *Mex.*: Navoban; *Neth.*: Novaban; *Norw.*: Navoban; *NZ*: Navoban; *Philipp.*: Hensetron; Navoban; *Pol.*: Navoban†; *Port.*: Navoban; *Rus.*: Navoban (Навобан); Tropindol (Тропиндол); *S.Afr.*: Navoban†; *Spain*: Navoban†; Saronil†; *Swed.*: Navoban; *Switz.*: Navoban; *Thai.*: Navoban†; *Turk.*: Navoban; *Ukr.*: Navoban (Навобан); *Venez.*: Navoban.

Troxipide *(rINN)*

Troxipida; Troxipidum; Троксипид.

(±)-3,4,5-Trimethoxy-*N*-3-piperidylbenzamide.

$C_{15}H_{22}N_2O_4$=294.4

CAS — 30751-05-4.

ATC — A02BX11.

ATC Vet — QA02BX11.

UNII — W6QJX1Q00Z.

Profile

Troxipide is used for its cytoprotective properties in the treatment of gastritis and peptic ulcer disease (p. 1813.2) in a usual oral dose of 100 mg three times daily, after food.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ke Fen Qi (科芬奇); Shuqi (殊奇); *Jpn*: Aplace.

Urogastrone

Anthelone; EGF-URO; Epidermal Growth Factor; Murodermina; Uroanthelone; Uroenterone; Urogastrona; Уроластрон.

CAS — 9010-53-1.

UNII — TZK30RF92W.

Pharmacopoeias. *Chin.* includes monographs for recombinant human epidermal growth factor suitable for external use.

Profile

Urogastrone is a polypeptide first isolated from human urine. Two forms have been identified, β and γ urogastrone. The β form consists of 53 amino acids and is distinguishable from the γ form by an additional terminal arginine residue. The β form is reported to be identical to human epidermal growth factor and this term is widely used in the literature.

Urogastrone inhibits gastric acid secretion and has been tried in the treatment of peptic ulcer disease and other gastrointestinal disorders but its rapid destruction in the stomach has limited its clinical use.

It is a potent stimulator of cellular proliferation and has also been used as an aid to wound healing.

Reviews.
1. Granul-Bilska AT, *et al.* Wound healing: the role of growth factors. *Drugs Today* 2003; 39: 787–800.
2. Klenkler B, Sheardown H. Growth factors in the anterior segment: role in tissue maintenance, wound healing and ocular pathology. *Exp Eye Res* 2004; 79: 677–88.

Gastrointestinal disorders. Intravenous infusion of urogastrone 250 nanograms/kg over 1 hour has been reported[1,2] to reduce the secretion of gastric acid in patients with duodenal ulcer (p. 1813.2) or the Zollinger-Ellison syndrome (p. 1814.3). Ulcer pain was relieved 30 to 60 minutes after the start of the infusion.[2] A dose of 100 nanograms/kg per hour by intravenous infusion has been used with partial success in an infant with microvillous atrophy[3] and was apparently beneficial in an infant with necrotising enteritis.[4]

Human epidermal growth factor has also shown some promise in the treatment of active ulcerative colitis. In a small study,[5] patients received daily enemas containing either recombinant human epidermal growth factor (5 micrograms in 100 mL) or placebo; all patients also received oral mesalazine. Ten of the 12 patients in the urogastrone group were in remission after 2 weeks treatment compared with 1 of the 12 patients in the placebo group, and this benefit was maintained for up to 12 weeks.

1. Koffman CG, *et al.* Effect of urogastrone on gastric secretion and serum gastrin concentration in patients with duodenal ulceration. *Gut* 1982; 23: 951–6.
2. Elder JB, *et al.* Effect of urogastrone in the Zollinger-Ellison syndrome. *Lancet* 1975; ii: 424–7.
3. Walker-Smith JA, *et al.* Intravenous epidermal growth factor/urogastrone increases small-intestinal cell proliferation in congenital microvillous atrophy. *Lancet* 1985; ii: 1239–40.
4. Sullivan PB, *et al.* Epidermal growth factor in necrotising enteritis. *Lancet* 1991; 338: 53–4.
5. Sinha A, *et al.* Epidermal growth factor enemas with oral mesalamine for mild-to-moderate left-sided ulcerative colitis or proctitis. *N Engl J Med* 2003; 349: 350–7.

Wound healing. For a general discussion of the management of wounds and ulcers, see p. 1690.1.

In a randomised double-blind study in 61 patients with diabetic foot ulcers, adding human epidermal growth factor 0.04% to an ulcer cream containing protein-free bovine blood extract was shown to significantly enhance wound healing and reduce healing time compared with either the cream alone or the cream plus human epidermal growth factor 0.02%.[1] Topical application of recombinant human epidermal growth factor 0.02% has also been reported to reduce pain and promote healing of exfoliated skin lesions in a patient with drug-induced Stevens-Johnson syndrome.[2]

The effect on the rate of wound healing of a cream containing sulfadiazine silver plus recombinant human epidermal growth factor (10 micrograms/mL) was compared with sulfadiazine silver alone in 12 patients each requiring skin grafts at 2 donor sites.[3] The cream containing epidermal growth factor accelerated the rate of epidermal regeneration in all patients and reduced the average time to 100% healing by about 1.5 days. Patients were followed up for a maximum of 1 year after cessation of therapy and no complications or clinical evidence of neoplasia at the healed donor sites occurred.

In contrast, recombinant human epidermal growth factor as an ophthalmic solution containing 30 or 100 micrograms/mL was investigated in patients who had undergone keratoplasty, but the weaker solution had no effect on the rate of re-epithelialisation, and the more concentrated one was actually associated with slower healing.[4]

1. Tsang MW, *et al.* Human epidermal growth factor enhances healing of diabetic foot ulcers. *Diabetes Care* 2003; 26: 1856–61.
2. Tsang MW, *et al.* The use of recombinant human epidermal growth factor (rhEGF) in a gentleman with drug-induced Steven Johnson syndrome. *Dermatol Online J* 2004; 10: 25.
3. Brown GL, *et al.* Enhancement of wound healing by topical treatment with epidermal growth factor. *N Engl J Med* 1989; 321: 76–9.
4. Dellaert MMMJ, *et al.* Influence of topical human epidermal growth factor on postkeratoplasty re-epithelialisation. *Br J Ophthalmol* 1997; 81: 391–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Thai.*: Regen-D.

Multi-ingredient Preparations. *Chile*: FCE; *Ukr.*: Ebermin (Эбермин).

Valethamate Bromide

Valetamat Bromür; Valetamato, bromuro de; Валетамата бромид.

Diethylmethyl[2-(3-methyl-2-phenylvaleryloxy)ethyl] ammonium bromide.

$C_{19}H_{32}BrNO_2$=386.4

CAS — 16376-74-2 (valethamate); 90-22-2 (valethamate bromide).

UNII — 6XFR940M2A.

Profile

Valethamate bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been given orally, by injection or rectally in the symptomatic treatment of visceral spasms.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Epidosin; Osdil; Valosin; *Indon.*: Epidosin; *Turk.*: Epidosin.

Multi-ingredient Preparations. *Turk.*: Epidosin Compozitum.

Vedolizumab *(USAN, rINN)*

LDP-02; MLN-0002; MLN-02; Védolizumab; Vedolizumabum; Ведолизумаб.

Immunoglobulin G1, anti-(human integrin LPAM-1 (lymphocyte Peyer's patch adhesion molecule 1))(human-*Mus musculus* heavy chain); disulfide with human-*Mus musculus*κ-chain, dimer.

CAS — 943609-66-3.

UNII — 9RV78Q2002.

Profile

Vedolizumab is a humanised monoclonal antibody under investigation for the treatment of inflammatory bowel disease.

References.
1. Feagan BG, *et al.* Treatment of active Crohn's disease with MLN0002, a humanized antibody to the α4β7 integrin. *Clin Gastroenterol Hepatol* 2008; 6: 1370–7.
2. Soler D, *et al.* The binding specificity and selective antagonism of vedolizumab, an anti-α4β7 integrin therapeutic antibody in development for inflammatory bowel diseases. *J Pharmacol Exp Ther* 2009; 330: 864–75.

Zaldaride *(rINN)*

CGS-9343B (zaldaride maleate); Zaldarida; Zaldaridum; Зальдарид.

(±)-1-[1-[(4-Methyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl)methyl]-4-piperidyl]-2-benzimidazolinone.

$C_{26}H_{28}N_4O_2$=428.5

CAS — 109826-26-8 (zaldaride); 109826-27-9 (zaldaride maleate).

UNII — GH66PET6S3.

Profile

Zaldaride is a calmodulin antagonist that has been investigated as the maleate for the treatment of diarrhoea.

Diarrhoea. Studies in patients with travellers' diarrhoea (p. 1805.2) have indicated that zaldaride in oral doses of 20 mg as the maleate four times daily is an effective antidiarrhoeal.[1,2] It was somewhat less effective than loperamide when given without a loading dose,[2] but a regimen of 40 mg initially, followed by 20 mg, about every 6 hours was as effective as loperamide 4 mg initially followed by 2 mg after each unformed stool.[3]

1. DuPont HL, *et al.* Zaldaride maleate, an intestinal calmodulin inhibitor, in the therapy of travelers' diarrhea. *Gastroenterology* 1993; 104: 709–15.
2. Okhuysen PC, *et al.* Zaldaride maleate (a new calmodulin antagonist) versus loperamide in the treatment of traveler's diarrhea: randomized, placebo-controlled trial. *Clin Infect Dis* 1995; 21: 341–4.
3. Silberschmidt G, *et al.* Treatment of travellers' diarrhoea: zaldaride compared with loperamide and placebo. *Eur J Gastroenterol Hepatol* 1995; 7: 871–5.

General Anaesthetics

This chapter includes drugs used for the induction and maintenance of general anaesthesia. General anaesthetics are given either by inhalation or by intravenous or occasionally intramuscular injection (see Table 1, below).

Table 1. Classification of general anaesthetics.

Injectable	Inhalational
Barbiturate	*Halogenated*
Methohexital	Chloroform
Thiamylal	Desflurane
Thiopental	Enflurane
	Halothane
Miscellaneous	Isoflurane
Alfadolone	Methoxyflurane
Alfaxolone	Sevoflurane
Etomidate	Trichloroethylene
Ketamine	*Miscellaneous*
Propanidid	Cyclopropane
Propofol	Anaesthetic Ether
Sodium Oxybate	Nitrous Oxide
Tiletamine	Xenon

Uses of General Anaesthetics

General anaesthetics depress the CNS and cause loss of consciousness associated with an inability to perceive pain. An ideal anaesthetic would produce unconsciousness, analgesia, and muscle relaxation suitable for all surgical procedures and would be metabolically inert and rapidly eliminated. No anaesthetic fulfils all these requirements in safe concentrations and it is customary to use several drugs to achieve the required conditions while minimising the risk of toxicity.

The activity of any anaesthetic is dependent on its ability to reach the brain. With inhalational anaesthetics there has to be a transfer from the alveolar space to the blood, then to the brain; recovery is a function of the removal of the anaesthetic from the brain. With injectable anaesthetics their activity is similarly dependent on their ability to penetrate the blood-brain barrier and recovery in turn is governed by their redistribution and excretion. The potency of inhalational anaesthetics is often expressed in terms of *minimum alveolar concentrations*, known as MAC values. The MAC of an anaesthetic is the concentration at 1 atmosphere that will produce immobility in 50% of subjects exposed to a noxious stimulus. Values given under the individual monographs are based on use without nitrous oxide as the latter can reduce the MAC. Other factors including age, body temperature, and concurrent medication such as premedicants and opioid analgesics can also affect MAC values.

General references.
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2. García-Miguel FJ, *et al.* Preoperative assessment. *Lancet* 2003; 362: 1749–57.
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4. Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* 2003; 362: 1921–8.
5. Sakai EM, *et al.* Inhalation anesthesiology and volatile liquid anesthetics: focus on isoflurane, desflurane, and sevoflurane. *Pharmacotherapy* 2005; 25: 1773–88.
6. Stachnik J. Inhaled anesthetic agents. *Am J Health-Syst Pharm* 2006; 63: 623–34. Correction. *ibid.*: 2436.
7. Nathan N, Odin I. Induction of anaesthesia: a guide to drug choice. *Drugs* 2007; 67: 701–23.
8. Lerman J. Inhalation agents in pediatric anaesthesia—an update. *Curr Opin Anaesthesiol* 2007; 20: 221–6.
9. Bovill JG. Inhalation anaesthesia: from diethyl ether to xenon. In: Schüttler J, Schwilden H, eds. *Handb Exp Pharmacol: Modern Anesthetics*. Berlin: Springer-Verlag, 2008; 182 (II): 121–42.
10. Ekstein M, *et al.* Monitored anaesthesia care in the elderly: guidelines and recommendations. *Drugs Aging* 2008; 25: 477–500.
11. Pietrini D, *et al.* New trends in pediatric anesthesia. *Minerva Anestesiol* 2009; 75: 191–9.
12. Landoni G, *et al.* Halogenated anaesthetics and cardiac protection in cardiac and non-cardiac anaesthesia. *Ann Card Anaesth* 2009; 12: 4–9.
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14. Sneyd JR, Rigby-Jones AE. New drugs and technologies, intravenous anaesthesia is on the move (again). *Br J Anaesth* 2010; 105: 246–54.

Anaesthesia. Many drugs are involved in achieving and maintaining conditions suitable for surgery. Conventional general anaesthesia may be divided into several stages including:

- premedication
- induction
- muscle relaxation and intubation
- maintenance
- analgesia
- reversal

A brief outline of the drugs typically used in each stage follows.

For **premedication**, benzodiazepines such as diazepam, lorazepam, midazolam, or temazepam, and some phenothiazines such as promethazine or alimemazine, may be given to sedate and relieve *anxiety* in apprehensive patients. Butyrophenones such as droperidol have also been used. The benzodiazepines have useful amnestic and muscle-relaxant properties and short-acting oral forms are common in current regimens. The phenothiazines and butyrophenones are rarely used now although their antiemetic actions may be useful to control *postoperative nausea and vomiting* (p. 1811.3). Cloral hydrate is still used in some countries for pre-operative sedation, particularly in children. The use of barbiturates has largely ceased. For sedation of children the oral route is often preferred to injections, or the rectal route may be used in exceptional circumstances.

Antimuscarinics such as atropine, glycopyrronium, and hyoscine may be given to inhibit excessive *bronchial* and *salivary secretions* induced by intubation, upper airway surgery, and some anaesthetics, although such use is less common nowadays. Antimuscarinics are also given as premedicants to reduce the intra-operative bradycardia and hypotension induced by drugs such as suxamethonium, halothane, or propofol or by vagal stimulation. Hyoscine also provides some degree of amnesia.

Opioids, including morphine and its derivatives, papaveretum and pethidine, have been widely used before surgery to reduce anxiety, smooth induction of anaesthesia, reduce overall anaesthetic requirements, and provide pain relief during and after surgery. The routine use of opioids as premedicants is now rare and generally restricted to patients already in pain. However, they continue to find a role at induction (below).

Patients may also be given drugs that reduce the danger from regurgitation and *aspiration* of gastric contents (see Aspiration Syndromes, p. 1804.2), such as the histamine H_2-antagonists, cimetidine and ranitidine, and the proton pump inhibitor, omeprazole. Other drugs used include sodium citrate to neutralise gastric acidity and metoclopramide to stimulate gastric emptying. Cardiovascular drugs may be needed during surgery to control *blood pressure* and counteract *arrhythmias*.

The aim of **induction** is to produce anaesthesia rapidly and smoothly. Induction may be achieved with intravenous or inhalational anaesthetics but intravenous induction may be more pleasant for the patient. Intravenous drugs used include the barbiturate thiopental, the benzodiazepine midazolam, and other anaesthetics such as etomidate, propofol, or ketamine. Small doses of short-acting opioids, for example alfentanil, fentanyl, or remifentanil, given before or at induction allow the use of smaller induction doses of some drugs used for anaesthesia, and this technique is particularly suitable for poor-risk patients.

After induction, **muscle relaxation** with a rapidly acting depolarising neuromuscular blocker such as suxamethonium aids **intubation** of the patient. Longer acting, competitive neuromuscular blockers may then be given to allow procedures such as abdominal surgery to be carried out under lighter anaesthesia. For more detail, see Anaesthesia, p. 2028.1.

Maintenance of anaesthesia may be achieved with an inhalational anaesthetic, an intravenous anaesthetic, or an intravenous opioid, either alone or in combination.

Opioid analgesics may also be given for **analgesia** as supplements during general anaesthesia (see also Balanced Anaesthesia, under Anaesthetic Techniques, below). Long-acting opioids such as morphine or papaveretum may cause postoperative respiratory depression. The short-acting opioid fentanyl, and its congeners alfentanil and sufentanil, appear to produce fewer circulatory changes and may be preferred to other opioids, especially in cardiovascular surgery; remifentanil may be valuable for its very short duration of action. Various combinations of analgesic techniques, including the use of pre-emptive analgesia, are used or are being investigated for the management of surgical pain (see Postoperative Analgesia, p. 6.1).

At the end of surgery drugs are sometimes given to accelerate recovery by **reversal** of the effects of the various agents used during anaesthesia. The *neuromuscular block* produced by competitive neuromuscular blockers may be reversed with anticholinesterases such as neostigmine and edrophonium but atropine or glycopyrronium are also needed to prevent bradycardia and other muscarinic actions developing. The selective relaxant binding agent, sugammadex, is also used for the reversal of neuromuscular blockade induced by rocuronium or vecuronium. The opioid antagonist naloxone has been given to reverse opioid-induced *respiratory depression*. However, it may antagonise the analgesic effects of the opioids in the control of postoperative pain and the increasing use of short-acting intravenous opioid analgesics should reduce the need for its use. Flumazenil is a benzodiazepine antagonist that is used to reverse the *central sedative effects* of benzodiazepines in anaesthetic procedures.

ANAESTHETIC TECHNIQUES. A balanced combination of drugs with different actions is often used to provide the various components of general anaesthesia including unconsciousness, muscle relaxation, and analgesia. This technique, termed **balanced anaesthesia**, has been reported to minimise intra-operative cardiovascular depression, to facilitate a rapid return of consciousness, and to have a low incidence of postoperative adverse effects such as nausea and vomiting, and excitation. Typically an opioid is given before or with induction and anaesthesia is induced using nitrous oxide and an intravenous barbiturate such as thiopental. The opioid is then given in small incremental doses to achieve and maintain adequate analgesia during surgery. Opioid analgesics commonly used in this technique include morphine, fentanyl, sufentanil, and alfentanil; buprenorphine and nalbuphine have also been used.

In **total intravenous anaesthesia** (TIVA), induction and maintenance of anaesthesia is achieved with one or more anaesthetics given intravenously. This allows high inspired oxygen concentrations in situations where hypoxaemia may otherwise occur, and is advantageous in surgery where delivery of inhaled anaesthetic may be difficult (for example in bronchoscopy). Combinations used in TIVA include propofol with alfentanil or fentanyl, and midazolam with alfentanil. Neuromuscular blockers are given to produce muscle relaxation but there can be difficulty in assessing the depth of anaesthesia in patients who are paralysed for mechanical ventilation, and there have been reports of awareness during procedures under TIVA (see also Intraoperative Awareness, under Precautions, p. 1897.3). Target-controlled infusion (TCI) systems are used in some countries to control the speed of induction and depth of anaesthesia by specifying target blood concentrations.

Although now largely obsolete, use of a neuroleptic with an opioid analgesic produces an altered state of consciousness known as **neuroleptanalgesia** in which the patient is calm and indifferent to the surroundings yet is responsive to commands. The technique was used for diagnostic or therapeutic procedures such as minor surgery, endoscopy, and changing dressings. Neuroleptanalgesia can be converted to **neuroleptanaesthesia** by the concurrent administration of nitrous oxide in oxygen; a muscle relaxant may also be included. Neuroleptanaesthesia is particularly useful if the patient's cooperation is required, as consciousness soon returns once the nitrous oxide is stopped. The neuroleptic most commonly used was droperidol and it was usually given with fentanyl although other opioids have also been used. These procedures have since evolved into **conscious sedation** and **monitored anaesthesia care** techniques using newer drugs such as propofol or remifentanil, with or without midazolam.

Ketamine used alone can produce a state of **dissociative anaesthesia** similar to that of neuroleptanalgesia in which the patient may appear to be awake but is unconscious. Marked analgesia and amnesia are produced, but there may be an increase in muscle tone and emergence reactions. Dissociative anaesthesia is considered suitable for use in various diagnostic procedures, dressing changes, and in minor surgery not requiring muscle relaxation.

Techniques using **local anaesthetics** are discussed on p. 1977.2.

Adverse Effects of General Anaesthetics and their Treatment

The complex regimens used in general anaesthesia may produce complications both during and after the procedure. Adverse effects that may occur with general anaesthesia include involuntary muscle movements, hiccup, coughing, bronchospasm, laryngospasm, apnoea, respiratory depression, hypotension, cardiac arrhythmias, and mild hypothermia. Regurgitation and aspiration of gastric contents (Mendelson's syndrome) is a potential cause of morbidity

and mortality associated with general anaesthesia, especially in obstetrics and in emergency surgery (see Aspiration Syndromes, p. 1804.2).

After general anaesthesia many patients will be drowsy and mental performance may be impaired for at least 24 hours. Postoperative nausea with or without vomiting is common in the absence of antiemetic prophylaxis; nausea may last for 2 days but vomiting seldom persists beyond the first day (for details of postoperative vomiting and its management, see p. 1811.3). Other relatively common postanaesthetic effects include anorexia, malaise, fatigue, dizziness, and headache. Delirium has been noted in at least 10% of elderly general surgical patients and in up to 50% of elderly patients undergoing hip fracture repair.

Sore throat is frequent in patients who have been intubated or have had a throat pack inserted. Dry mouth as a result of premedication can add to the patient's discomfort. Manipulations for the maintenance of a clear airway may result in postoperative jaw pain.

Muscle pain, typically involving the neck, shoulders, and upper abdomen, may occur if the neuromuscular blocker suxamethonium has been given. It is usually worse on the second postoperative day and may last up to 6 days. Shoulder ache after laparoscopy resolves after 24 hours; it is due to accumulation of carbon dioxide under the diaphragm. Backache may occur after epidural or spinal anaesthesia. Urinary retention may follow regional block, cystoscopic or gynaecological surgery, or when there is prostatism.

Malignant hyperthermia (malignant hyperpyrexia—see under Dantrolene, p. 2024.1) is a rare but potentially fatal complication of general anaesthesia that may be induced by inhalational anaesthetics (mainly halogenated hydrocarbons).

Hepatotoxicity may occur in patients who are sensitised to halogenated anaesthetics; halothane has been associated with severe hepatotoxicity and is largely superseded by newer agents.

Sensitisation of the myocardium to beta-adrenergic stimulation occurs with some anaesthetics.

There has been concern over the possible danger to anaesthetists, dentists, and other personnel from exposure to volatile anaesthetics.

References.

1. Anonymous. Following up day case anaesthesia in general practice. *Drug Ther Bull* 1990; 28: 81–2.
2. O'Keeffe ST, NíChonchubhair Á. Postoperative delirium in the elderly. *Br J Anaesth* 1994; 73: 673–87.
3. Marcantonio ER, *et al.* A clinical prediction rule for delirium after elective noncardiac surgery. *JAMA* 1994; 271: 134–9.
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6. Fee JPH, Thompson GH. Comparative tolerability profiles of the inhaled anaesthetics. *Drug Safety* 1997; 16: 157–70.
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8. Mandal PK, *et al.* Inhaled anesthesia and cognitive performance. *Drugs Today* 2009; 45: 47–54.
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Effects on neurodevelopment. There has been some concern[1,2] that exposure to anaesthetics might have adverse effects on neurological and cognitive development of neonates and young children. Results of studies have been conflicting, and further research is needed; however, it has been suggested that elective procedures using general anaesthesia should be avoided below the age of 3 years.[2]

1. Loepke AW, Soriano SG. An assessment of the effects of general anesthetics on developing brain structure and neurocognitive function. *Anesth Analg* 2008; 106: 1681–1707.
2. Rappaport B, *et al.* Defining safe use of anesthesia in children. *N Engl J Med* 2011; 364: 1387–90.

Hypersensitivity. Type I hypersensitivity reactions related to various aspects of the procedure have occurred during general anaesthesia.[1–4] In most patients the release of histamine and other mediators such as prostaglandins and leukotrienes is of no clinical importance but in a few susceptible individuals anaphylaxis may result; the mortality rate is estimated to range from 3 to 9%. Anaphylaxis may occur at any time, with 90% of reactions appearing at induction of anaesthesia.[4]

Neuromuscular blockers are associated with the highest (50 to 70%) incidence of anaphylaxis, followed by latex (12 to 20%) and antibacterials (15%).[4,5] (For details of hypersensitivity reactions associated with neuromuscular blockers, see under Adverse Effects of Suxamethonium, p. 2038.2.) Anaphylactic reactions to the general anaesthetics thiopental and propofol are uncommon, with an estimated incidence of 1 in 30 000 and 1 in 60 000, respectively; reactions to etomidate and ketamine are very rare and there appear to be no published reports associated with halogenated volatile anaesthetics.[3–6] Other agents used during general anaesthesia that are rarely associated with anaphylaxis include local anaesthetics, opioid analgesics, NSAIDs, colloids, contrast media, and disinfectants.[3–6]

Many factors to identify those at risk have been proposed over the years along with suggested modifications for anaesthetic management. Routine prophylaxis with histamine H_1- and histamine H_2-antagonists has been advocated by some as part of anaesthetic management but others recommend such use only in susceptible patients with known risk factors;[7] however, there is no evidence that prophylactic treatment with H_1-and H_2-antagonists and corticosteroids actually decreases the severity of anaphylaxis.[5,7,8] Preventing re-exposure to implicated agents and avoiding other known causes of histamine release are the mainstay of prophylaxis in susceptible patients.[5,8]

1. McKinnon RP, Wildsmith JAW. Histaminoid reactions in anaesthesia. *Br J Anaesth* 1995; 74: 217–28.
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8. Fisher MM, Doig GS. Prevention of anaphylactic reactions to anaesthetic drugs. *Drug Safety* 2004; 27: 393–410.

Nausea and vomiting. For a discussion on postoperative nausea and vomiting and its management, see p. 1811.3.

Shivering and its treatment. Postoperative shivering, also referred to as spontaneous postanaesthetic tremor, can occur in up to 65% of patients recovering from general anaesthesia;[1,2] its aetiology and relationship to thermoregulation is unclear.[1,3,4] Postoperative shivering may be part of a more generalised neurological disturbance associated with anaesthesia.[1] It also occurs after regional anaesthesia, especially when given epidurally, but this is probably produced by different mechanisms.[3] Muscular activity during shivering greatly increases metabolic rate, oxygen consumption, and cardiac output and may cause complications in patients with cardiac or respiratory disorders. It can also strain surgical sutures, raise intra-ocular pressure, and impede haemodynamic monitoring.

Although the relationship between postoperative shivering, body temperature, and heat loss is unclear, patients may respond to **warming** their environment and the use of blankets.[1,3,5] Postoperative shivering may sometimes be an appropriate thermoregulatory response to a low body temperature,[3] and it is important before starting therapy to check the patient's temperature and take suitable steps to avoid hypothermia.[1]

Many **drugs** have been tried for the management of postoperative shivering including the central and respiratory stimulant doxapram, the α_2-agonist clonidine, and the opioid analgesic pethidine.[2,4,6,7] Reviews have discussed[1–4,7] other opioids that have been tried including morphine, alfentanil, butorphanol, fentanyl, and sufentanil but studies suggest that not all opioids are effective or that some may only be effective when given epidurally. However, this may be due to the use of insufficient doses rather than a true difference between opioids.[8] Tramadol and nefopam have also been tried.[2,6,7] Neuromuscular blockers have been used after cardiac surgery in order to reduce cardiovascular stress.[9] Vecuronium might be preferable to pancuronium as it does not increase myocardial work and may be associated with fewer complications.[10] However, as profound neuromuscular block is required to inhibit shivering, repeated or higher doses of vecuronium might be required to prevent recurrence. Other drugs that have been investigated include ketanserin,[2] ketamine,[11,12] and magnesium sulfate.[2]

1. Crossley AWA. Postoperative shivering. *Br J Hosp Med* 1993; 49: 204–8.
2. Alfonsi P. Postanaesthetic shivering: epidemiology, pathophysiology, and approaches to prevention and management. *Drugs* 2001; 61: 2193–2205.
3. Anonymous. Perioperative shivering. *Lancet* 1991; 338: 547–8.
4. Kranke P, *et al.* Pharmacological treatment of postoperative shivering: a quantitative systematic review of randomized controlled trials. *Anesth Analg* 2002; 94: 453–60.
5. Sajid MS, *et al.* The role of perioperative warming in surgery: a systematic review. *Sao Paulo Med J* 2009; 127: 231–7.
6. Kranke P, *et al.* Single-dose parenteral pharmacological interventions for the prevention of postoperative shivering: a quantitative systematic review of randomized controlled trials. *Anesth Analg* 2004; 99: 718–27.
7. Kranke P, *et al.* Postoperative shivering in children: a review on pharmacologic prevention and treatment. *Pediatr Drugs* 2003; 5: 373–83.
8. Alfonsi P, *et al.* Fentanyl, as pethidine, inhibits post anaesthesia shivering. *Br J Anaesth* 1993; 70 (suppl 1): 38.
9. Cruise C, *et al.* Comparison of meperidine and pancuronium for the treatment of shivering after cardiac surgery. *Can J Anaesth* 1992; 39: 563–8.
10. Dupuis J-Y, *et al.* Pancuronium or vecuronium for treatment of shivering after cardiac surgery. *Anesth Analg* 1994; 79: 472–81.
11. Dal D, *et al.* Efficacy of prophylactic ketamine in preventing postoperative shivering. *Br J Anaesth* 2005; 95: 189–92.
12. Kose EA, *et al.* The efficacy of ketamine for the treatment of postoperative shivering. *Anesth Analg* 2008; 106: 120–2.

Precautions for General Anaesthetics

Patients with impaired function of the adrenal cortex, for example, those who are being treated, or have recently been treated, with corticosteroids, may develop hypotension with the stress of anaesthesia. Treatment with corticosteroids, pre-operatively and postoperatively, may be necessary. Patients taking other long-term medication such as antiplatelet drugs, oral anticoagulants, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, oestrogens, MAOIs, or lithium may need to change their dosage or therapy, or stop altogether, before major elective surgery.

Patients with chronic diseases such as diabetes or hypertension, or who are taking antivirals for HIV infection, may need adjustment to their therapy before anaesthesia. Anaesthetics should be used with caution in patients with cardiac, respiratory, renal, or hepatic impairment and care may be needed in elderly or obese patients.

Patients should not undertake hazardous tasks such as driving for at least 24 hours after a general anaesthetic; alcohol should also be avoided.

Children. For concerns about the potential effects of general anaesthesia on neurodevelopment in young children, see under Adverse Effects and Treatment, above.

Intraoperative awareness. Intraoperative awareness during general anaesthesia, defined as consciousness and explicit memory of surgical events, has a reported incidence of 0.1 to 0.2% in adults[1,2] and 0.8% in children.[3,4] Risk factors include light anaesthesia and a history of awareness.[1] Neuromuscular blockade-induced paralysis may also contribute by preventing the patient giving signs of awareness.[2] Recommended preventive measures include premedication with sedative or amnestic drugs, induction with sufficient doses of intravenous anaesthetic, the use of effective analgesic techniques during surgery, avoiding or minimising the use of neuromuscular blockers, the use of potent inhalational anaesthetics instead of total intravenous anaesthesia, and ensuring adequate concentrations of inspired anaesthetic gas.[2] The use of brain function monitors to determine depth of anaesthesia is controversial, since none has been proven to be uniformly reliable;[2] some authorities[5,6] advocate against their routine use, and instead recommend the use of clinical techniques (such as checking purposeful or reflex movement) and conventional monitoring systems (such as ECG, blood pressure, heart rate, end-tidal anaesthetic concentration, and capnography).

1. Ghoneim MM, *et al.* Awareness during anesthesia: risk factors, causes and sequelae—a review of reported cases in the literature. *Anesth Analg* 2009; 108: 527–35.
2. Mashour GA, *et al.* Intraoperative awareness: from neurobiology to clinical practice. *Anesthesiology* 2011; 114: 1218–1233.
3. Davidson AJ, *et al.* Awareness during anesthesia in children: a prospective cohort study. *Anesth Analg* 2005; 100: 653–61.
4. Malviya S, *et al.* The incidence of intraoperative awareness in children: childhood awareness and recall evaluation. *Anesth Analg* 2009; 109: 1421–7.
5. American Society of Anesthesiologists Task Force on Intraoperative Awareness. Practice advisory for intraoperative awareness and brain function monitoring: a report by the American Society of Anesthesiologists Task Force on Intraoperative Awareness. *Anesthesiology* 2006; 104: 847–64.
6. Association of Anaesthetists of Great Britain and Ireland. Recommendations for standards of monitoring during anaesthesia and recovery. 4th ed. (issued March 2007). Available at: http://www.aagbi.org/sites/default/files/standardsofmonitoring07.pdf (accessed 27/05/11)

Interactions of General Anaesthetics

Sensitisation of the myocardium to beta-adrenergic stimulation occurs with some anaesthetics and ventricular fibrillation may occur if *sympathomimetics* such as adrenaline and isoprenaline are also used. Enhanced hypotensive effects may result when anaesthetics are given with *ACE inhibitors*, *tricyclic antidepressants* (which may also increase the risk of arrhythmias), *MAOIs* (see also Anaesthesia, under Precautions for Phenelzine, p. 444.1), *antihypertensives*, *antipsychotics*, or *beta blockers*. The effects of *competitive neuromuscular blockers* may be increased by inhalational anaesthetics. The use of anaesthetics with other *CNS depressant drugs* such as those used for premedication may produce synergistic effects on the CNS and, in some cases, a smaller dose of general anaesthetic should be given.

Reviews.

1. Wood M. Pharmacokinetic drug interactions in anaesthetic practice. *Clin Pharmacokinet* 1991; 21: 285–307.
2. Ransom ES, Mueller RA. Safety considerations in the use of drug combinations during general anaesthesia. *Drug Safety* 1997; 16: 88–103.
3. Eilers H, Niemann CU. Clinically important drug interactions with intravenous anaesthetics in older patients. *Drugs Aging* 2003; 20: 969–80.
4. Zaniboni A, *et al.* Chemotherapy and anaesthetic drugs: too little is known. *Lancet Oncol* 2005; 6: 176–81.
5. Ingelmo PM, *et al.* Interactions between general and regional anesthesia. *Minerva Anestesiol* 2006; 72: 437–45.

6. Hendrickx JFA, *et al.* Is synergy the rule? A review of anesthetic interactions producing hypnosis and immobility. *Anesth Analg* 2008; 107: 494–506.
7. Wong A, Townley SA. Herbal medicines and anaesthesia. *Cont Edu Anaesth Crit Care Pain* 2011; 11: 14–17.

Alfadolone Acetate *(BANM, rINNM)*

Acetato de alfadolona; Alfadolona, acetato de; Alfadolone, Acétate d'; Alfadoloni Acetas; Alphadolone Acetate; GR-2/1574; Альфадолона Ацетат.

3α,21-Dihydroxy-5α-pregnane-11,20-dione 21-acetate.

$C_{23}H_{34}O_5$=390.5.

CAS — 14107-37-0 (alfadolone); 23930-37-2 (alfadolone acetate).

UNII — 00TN4GS00S.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Alfadolone Acetate). A white to creamy white powder. Practically insoluble in water and in petroleum spirit; soluble in alcohol; freely soluble in chloroform.

Profile

Alfadolone acetate has been used to enhance the solubility of alfaxalone (below). It possesses some anaesthetic properties and is considered to be about half as potent as alfaxalone.

Alfaxalone *(BAN, rINN)*

Alfaksaloni; Alfaxalon; Alfaxalona; Alfaxalonum; Alphaxalone; GR-2/234; Альфаксалон.

3α-Hydroxy-5α-pregnane-11,20-dione.

$C_{21}H_{32}O_3$=332.5.

CAS — 23930-19-0.

ATC — N01AX05.

ATC Vet — QN01AX05.

UNII — BD07M97B2A.

NOTE. The name Saffan has been used as a trade mark for mixtures of alfadolone acetate with alfaxalone.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Alfaxalone). A white to creamy white powder. Practically insoluble in water and in petroleum spirit; soluble in alcohol; freely soluble in chloroform.

Profile

Alfaxalone was formerly used with alfadolone acetate (above) 'Althesin', as an intravenous anaesthetic for induction and maintenance of general anaesthesia.

Adverse reactions associated with polyoxyl castor oil (present as a vehicle) led to the general withdrawal of alfaxalone with alfadolone acetate from human use. It is still used in veterinary medicine.

Chloroform

Chloroforme; Chloroformio; Chloroformium Anesthesicum; Chloroformum; Chloroformum pro Narcosi; Cloroform; Cloroformio; Cloroformo; Formil tricloruro; Hloroforms; Kloroform; Kloroformi; Trichlorometano; Trichlorométhane; Tricloruro de metano; Tricloruro de metilo; Трихлорметан; Хлороформ.

Trichloromethane.

$CHCl_3$=119.4.

CAS — 67-66-3.

ATC — N01AB02.

ATC Vet — QN01AB02.

UNII — 7V31YC746X.

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

BP 2014: (Chloroform). A colourless volatile liquid with a characteristic odour. Not more than 5.0% v/v distils below 60 degrees and the remainder distils at 60 degrees to 62 degrees. It contains 1.0 to 2.0% v/v of ethyl alcohol; amylene 50 micrograms/mL is permitted as an alternative to ethyl alcohol.

Slightly soluble in water; miscible with dehydrated alcohol, with ether, with fixed and volatile oils, and with most other organic solvents. Store in containers with glass stoppers or other suitable closures. Protect from light. The label should state whether it contains ethyl alcohol or amylene.

Stability. The addition of a small percentage of alcohol greatly retards the gradual oxidation that occurs when chloroform is exposed to air and light, and which results in its becoming contaminated with the very poisonous carbonyl chloride (phosgene) and with chlorine; the alcohol also serves to decompose any carbonyl chloride that may have been formed.

From a study[1] of chloroform losses from chloroform water and from 6 typical BPC mixtures under various conditions of storage the following shelf-lives were recommended:

- chloroform solutions and non-sedimented mixtures could be stored in well-closed well-filled containers for 2 months at ambient temperatures
- when stored in partially-filled containers and periodically opened the shelf-life should not exceed 2 weeks
- sedimented mixtures could be stored for 2 months in well-closed well-filled containers, but because loss of chloroform could be expected in containers periodically opened such mixtures should be prepared as required or packed in their final containers
- for chloroform-containing mixtures in the home a shelf-life of 2 weeks was suggested

1. Lynch M, *et al.* Chloroform as a preservative in aqueous systems: losses under "in-use" conditions and antimicrobial effectiveness. *Pharm J* 1977; 219: 507–10.

Storage. It has been recommended[1] that if the period of use would exceed 6 weeks, PVC bottles should not be used for storing or dispensing: Chloroform and Morphine Tincture, or aqueous mixtures containing more than 5% thereof; mixtures or dispersions in which chloroform is present in excess of its aqueous solubility; aqueous mixtures containing chloroform and high concentrations of electrolytes; or of mixtures containing chloroform water.

1. Anonymous. Plastics medicine bottles of rigid PVC. *Pharm J* 1973; 210: 100.

Uses and Administration

Chloroform is a volatile halogenated anaesthetic that was used by inhalation, but safer drugs are now preferred in general anaesthesia.

Chloroform is used as a carminative and as a flavouring agent and preservative. For these purposes it is usually employed as Chloroform Spirit (BP 2014) or Double-strength Chloroform Water (BP 2014) but doubts have been cast on the safety of the long-term use of chloroform in mixtures.

Externally, chloroform has a rubefacient action.

Chloroform is also used as a solvent.

Anaesthesia. An historical review of the use of chloroform in clinical anaesthesia.[1]

1. Payne JP. Chloroform in clinical anaesthesia. *Br J Anaesth* 1981; 53: 115–155.

Adverse Effects and Precautions

Chloroform depresses respiration and produces hypotension. Cardiac output is reduced and arrhythmias may develop. Poisoning can lead to respiratory depression and cardiac arrest. Delayed hepatotoxic and nephrotoxic reactions have occurred 6 to 24 hours after a dose; symptoms may include abdominal pain, vomiting, and, at a later stage, jaundice.

Liquid chloroform is irritant to the skin and mucous membranes and may cause burns if spilt on them. Suitable precautions should be taken to avoid skin contact with chloroform as it can penetrate skin and produce systemic toxicity. Chloroform is not flammable. Care should be taken not to vaporise chloroform in the presence of a flame because of the production of toxic gases.

In the UK medicinal products are limited to a chloroform content of not more than 0.5% (w/w or v/v as appropriate) of chloroform. Exceptions include supply by a doctor or dentist, or in accordance with his prescription, to a particular patient, and supply for anaesthetic purposes.

In the USA the FDA has banned the use of chloroform in medicines and cosmetics, because of reported carcinogenicity in *animals*. It has also been withdrawn from systemic use in other countries.

The sale within or import into England and Wales and Scotland of food containing any added chloroform is prohibited.

See also Adverse Effects and Precautions for General Anaesthetics, p. 1896.3.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving chloroform, 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 25/05/04)

Poisoning. There has been a report[1] of a 19 year-old man who drank about 75 mL of chloroform in an attempted suicide; he recovered after supportive care and intravenous acetylcysteine therapy. Another report[2] described a 46 year-old woman with chronic alcoholism who developed acute liver failure and rhabdomyolysis after chloroform inhalation and binge drinking; she died despite supportive care.

1. Dell'Agio DM, *et al.* Acute chloroform ingestion successfully treated with intravenously administered N-acetylcysteine. *J Med Toxicol* 2010; 6: 143–6.
2. Lionte C, Lethal complications after poisoning with chloroform – case report and literature review. *Hum Exp Toxicol* 2010; 29: 615–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Belg.*: Dentophar†; *India*: Eltuss; *Ital.*: Sekumatic†; *Rus.*: Eludril (Элюдрил); Espol (Эспол); *S. Afr.*: Diphenhydramine Expectorant Syrup†; Mrs Johnsons American Soothing Syrup†; SB Toothache Drops†; Tandpyndruppels†; Vicks Acta Plus†.

Pharmacopoeial Preparations

BP 2014: Chloroform and Morphine Tincture; Chloroform Spirit; Double-strength Chloroform Water.

Cyclopropane *(rINN)*

Ciclopropano; Ciklopropán; Ciklopropāns; Cyclopropaan; Cyclopropan; Cyclopropanum; Cyklopropan; Sikloprópan; Syklopropaani; Trimethylene; Trimetileno; Циклопропан.

C_3H_6=42.08

CAS — 75-19-4.

UNII — 99TB643425.

Pharmacopoeias. In *US*.

USP 36: (Cyclopropane). A colourless highly flammable gas with a characteristic odour and pungent taste. Freely soluble in alcohol; soluble in fixed oils. One volume dissolves in about 2.7 volumes of water at 15 degrees.

Stability. CAUTION. Mixtures of cyclopropane with oxygen or air at certain concentrations are explosive. Cyclopropane should not be used in the presence of an open flame or of any electrical apparatus liable to produce a spark. Precautions should be taken against the production of static electrical discharge.

Storage and supply. Cyclopropane is supplied compressed in metal cylinders. National standards are usually in operation for the labelling and marking of such cylinders.

Uses and Administration

Cyclopropane is an anaesthetic that has been given by inhalation for analgesia and induction and maintenance of general anaesthesia. It produces skeletal muscle relaxation, is non-irritant, and induction and recovery are rapid, but it is difficult to use and handle and other anaesthetics are generally preferred. Because of the risk of explosion, it has usually been given by means of a closed circuit. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) of 9.2%.

Adverse Effects and Precautions

Cyclopropane depresses respiration to a greater extent than many other anaesthetics. Laryngospasm, cardiac arrhythmias, or hepatic injury may occur. Cyclopropane increases the sensitivity of the heart to sympathomimetic amines. Malignant hyperthermia has also been reported. Postoperative nausea, vomiting, and headache are frequent.

Cyclopropane should be used with caution in patients with bronchial asthma and cardiovascular disorders. Premedication with atropine may be advisable to reduce vagal tone.

See also Adverse Effects and Precautions for General Anaesthetics, p. 1896.3.

Abuse. Two of 4 deaths from abuse of volatile anaesthetics in operating rooms were attributed to cyclopropane.[1]

1. Bass M. Abuse of inhalation anesthetics. *JAMA* 1984; 251: 604.

Malignant hyperthermia. Malignant hyperthermia has been associated with cyclopropane.[1]

1. Lipe PJ, *et al.* Malignant hyperthermia triggered by cyclopropane during cesarean section. *Anesthesiology* 1982; 56: 144–6.

Interactions

Care is advised if adrenaline or other sympathomimetics are given during cyclopropane anaesthesia. Potentiation of competitive neuromuscular blockers occurs after use of cyclopropane.

See also Interactions for General Anaesthetics, p. 1897.3.

Desflurane *(BAN, USAN, rINN)*

Desfluraan; Desfluraani; Desfluran; Desflurano; Desfluranum; Dezflurán; I-653; Десфлуран.

(±)-2-Difluoromethyl 1,2,2,2-tetrafluoroethyl ether.
$C_3H_2F_6O$=168.0
CAS — 57041-67-5.
ATC — N01AB07.
ATC Vet — QN01AB07.
UNII — CRS35BZ94Q.

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

Ph. Eur. 8: (Desflurane). A clear, colourless, mobile, heavy liquid. B.p. about 22 degrees. Practically insoluble in water; miscible with anhydrous alcohol. Store in a glass bottle fitted with a polyethylene-lined cap. Before opening the bottle, cool the contents to below 10 degrees.

USP 36: (Desflurane). Store in airtight containers at a temperature of 20 to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Replace cap securely after each use. Protect from light.

Uses and Administration

Desflurane is a volatile halogenated anaesthetic given by inhalation. It is structurally similar to isoflurane and has anaesthetic actions similar to those of halothane (p. 1902.2). The minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) ranges from about 6% in the elderly to about 11% in infants. It is non-flammable and non-explosive in clinical concentrations but, because of its low boiling-point, it must be delivered by a special vaporiser, preferably within a closed circuit system.

Desflurane is used for induction and maintenance of general anaesthesia (p. 1896.1), but because of its pungency is not recommended for induction in children. Concentrations of 4 to 11% v/v have been used for induction and usually produce surgical anaesthesia in 2 to 4 minutes. Concentrations of 2 to 6% v/v with nitrous oxide or 2.5 to 8.5% v/v in oxygen or oxygen-enriched air may be used to maintain anaesthesia. Higher concentrations of desflurane have been used but it is important to ensure adequate oxygenation; concentrations in excess of 17% v/v are not recommended. For concentrations used in patients with hepatic or renal impairment, see below.

As with other volatile halogenated anaesthetics supplemental neuromuscular blockers may be required. Recovery from anaesthesia is reported to be more rapid than with other halogenated anaesthetics.

Administration in children. Although desflurane is not recommended for induction of anaesthesia in children, it is used for the maintenance of anaesthesia in this group; concentrations given are as for adults (see Uses and Administration, above).

Administration in hepatic or renal impairment. Desflurane concentrations of 1 to 4% v/v in oxygen and nitrous oxide have been used in patients with chronic renal or hepatic impairment and during renal transplantation surgery.

Anaesthesia. The characteristics of desflurane have been reviewed.[1-6] Its advantages are considered to include rapid induction and emergence from anaesthesia, and minimal metabolism makes end-organ toxicity unlikely. Emergence from anaesthesia and recovery of psychomotor and cognitive skills with desflurane is more rapid than after anaesthesia with other halogenated volatile anaesthetics such as isoflurane and possibly than after the intravenous anaesthetic propofol. This is considered to be of particular advantage for outpatient treatment, but studies so far have found no difference in time to discharge with desflurane or other general anaesthetics. Furthermore, the incidence of nausea and vomiting with desflurane is significantly greater than after the use of propofol. Desflurane's pungency may also limit its use for induction especially in children, although it is suitable for maintenance in this group and may be particularly suitable for neonates.[4]

1. Caldwell JE. Desflurane clinical pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 1994; 27: 6–18.
2. Patel SS, Goa KL. Desflurane: a review of its pharmacodynamic and pharmacokinetic properties and its efficacy in general anaesthesia. *Drugs* 1995; 50: 742–67.
3. Young CJ, Apfelbaum JL. Inhalational anesthetics: desflurane and sevoflurane. *J Clin Anesth* 1995; 7: 564–77.
4. Hatch DJ. New inhalation agents in paediatric anaesthesia. *Br J Anaesth* 1999; 83: 42–9.
5. Umbrain V, *et al.* Desflurane: a reappraisal. *Acta Anaesthesiol Belg* 2002; 53: 187–91.
6. Sakai RM, *et al.* Inhalation anesthesiology and volatile liquid anesthetics: focus on isoflurane, desflurane, and sevoflurane. *Pharmacotherapy* 2005; 25: 1773–88.

Status epilepticus. For mention of the use of desflurane in the management of refractory status epilepticus, see p. 510.2.

Adverse Effects and Precautions

As with other halogenated anaesthetics, respiratory depression, hypotension, and arrhythmias may occur. Desflurane may rarely precipitate malignant hyperthermia in susceptible individuals; patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with desflurane. It appears to sensitise the myocardium to sympathomimetics to a lesser extent than halothane or enflurane. Nausea and vomiting have been reported in the postoperative period.

Desflurane is irritant to the airways and may provoke breath holding, apnoea, coughing, increased salivation, and laryngospasm. It is therefore not recommended for induction of anaesthesia in paediatric patients.

Desflurane may increase CSF pressure and should therefore be used with caution in patients with, or at risk of, raised intracranial pressure. In children with neuromuscular disease, particularly Duchenne muscular dystrophy, halogenated anaesthetics have been associated with very rare cases of hyperkalaemia resulting in cardiac arrhythmias and death during the postoperative period.

In order to minimise the risk of developing elevated carboxyhaemoglobin levels carbon dioxide absorbents in anaesthetic apparatus should not be allowed to dry out when delivering volatile anaesthetics such as desflurane (see below).

See also Adverse Effects and Precautions of General Anaesthetics, p. 1896.3 and p. 1897.3.

Carbon dioxide absorbents. Significant carboxyhaemoglobinaemia may develop rarely during anaesthesia with volatile anaesthetics given by circle breathing systems containing carbon dioxide absorbents.[1] The effect is only seen when the absorbent has become excessively dried out. The use of barium hydroxide lime (which is not available in the UK) as an absorbent produces more carbon monoxide than soda lime, particularly at low water content. No cases of this complication had been reported to date in the UK.

1. CSM/MCA. Safety issues in anaesthesia: volatile anaesthetic agents and carboxyhaemoglobinaemia. *Current Problems* 1997; 23: 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)

Effects on the cardiovascular system. A review[1] of *animal* and human studies concluded that the cardiorespiratory effects of desflurane were similar to those of isoflurane but that there might be better control of arterial pressure with desflurane during stressful stimuli. A study[2] in patients undergoing coronary artery bypass surgery showed that a state of haemodynamic stability suitable for patients at risk of myocardial ischaemia could be maintained when desflurane was used with the opioid analgesic fentanyl.

1. Warltier DC, Pagel PS. Cardiovascular and respiratory actions of desflurane: is desflurane different from isoflurane? *Anesth Analg* 1992; 75: S17–S31.
2. Parsons RS, *et al.* Comparison of desflurane and fentanyl-based anaesthetic techniques for coronary artery bypass surgery. *Br J Anaesth* 1994; 72: 430–8.

Effects on the liver. Although considered to be less hepatotoxic than some other halogenated anaesthetics (see under Adverse Effects of Halothane, p. 1902.3), delayed hepatotoxicity occurred in a 65-year-old woman after maintenance anaesthesia involving desflurane.[1] She had received halothane on two previous occasions which may have caused sensitisation. A fatal case[2] of acute liver failure associated with desflurane anaesthesia has been reported in a 53-year-old woman. She had significantly raised serum-alanine aminotransferase concentrations on first exposure but this was attributed to antibacterial toxicity; however, on second exposure 10 days later, she developed acute liver failure 96 hours after surgery and died despite supportive treatment. Hepatotoxicity has also been reported[3] after desflurane anaesthesia in a 15-month-old boy who had previously received isoflurane on two occasions, although it has been suggested[4] that this was more likely due to concomitant paracetamol therapy. Investigation of hepatocellular integrity (by measuring glutathione transferase alpha) in 30 women given desflurane indicated a mild subclinical disturbance.[5]

1. Martin JL, *et al.* Hepatotoxicity after desflurane anesthesia. *Anesthesiology* 1995; 83: 1125–9.
2. Chin MW, *et al.* Desflurane-induced acute liver failure. *Med J Aust* 2008; 189: 293–4.
3. Côté G, Bouchard S. Hepatotoxicity after desflurane anesthesia in a 15-month-old child with Mobius syndrome after previous exposure to isoflurane. *Anesthesiology* 2007; 107: 843–5.
4. Her C. Acetaminophen-induced, not desflurane-induced, hepatotoxicity. *Anesthesiology* 2008; 109: 570–1.
5. Tiainen P, *et al.* Changes in hepatocellular integrity during and after desflurane or isoflurane anaesthesia in patients undergoing breast surgery. *Br J Anaesth* 1998; 80: 87–9.

Effects on the respiratory tract. The irritant effect of desflurane on the lungs limits its role in the induction of anaesthesia, especially in children. Pre-operative use of nebulised lidocaine 4% failed to alleviate the response[1] although pretreatment with intravenous opioids may reduce the irritation.[2]

1. Bunting HB, *et al.* Effect of nebulized lignocaine on airway irritation and haemodynamic changes during induction of anaesthesia with desflurane. *Br J Anaesth* 1995; 75: 631–3.
2. Kong CF, *et al.* Intravenous opioids reduce airway irritation during induction of anaesthesia with desflurane in adults. *Br J Anaesth* 2000; 85: 364–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies desflurane 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 04/10/11)

Interactions

The effects of competitive neuromuscular blockers such as atracurium are enhanced by desflurane (see p. 2032.3). Lower doses of desflurane are required in those receiving opioids, benzodiazepines or other sedatives. Care is advised if adrenaline or other sympathomimetics are given to patients during desflurane anaesthesia.

See also Interactions of General Anaesthetics, p. 1897.3.

References.

1. Dale O. Drug interactions in anaesthesia: focus on desflurane and sevoflurane. *Baillieres Clin Anaesthesiol* 1995; 9: 105–17.

Pharmacokinetics

Desflurane has a low blood/gas partition coefficient and on inhalation its absorption, distribution, and elimination are reported to be more rapid than for other halogenated anaesthetics such as isoflurane or halothane. It is excreted mainly unchanged through the lungs. A small amount diffuses through the skin. About 0.02% of inhaled desflurane is metabolised in the liver and trichloroacetic acid has been detected in the serum and urine of patients given desflurane.

References.

1. Caldwell JE. Desflurane clinical pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 1994; 27: 6–18.
2. Eger EI. Physicochemical properties and pharmacodynamics of desflurane. *Anaesthesia* 1995; 50 (suppl): 3–8.
3. Wissing H, *et al.* Pharmacokinetics of inhaled anaesthetics in a clinical setting: comparison of desflurane, isoflurane and sevoflurane. *Br J Anaesth* 2000; 84: 443–9.
4. Lu CC, *et al.* Pharmacokinetics of desflurane uptake into the brain and body. *Anaesthesia* 2004; 59: 216–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Suprane; *Austral.*: Suprane; *Austria*: Suprane; *Belg.*: Suprane; *Canad.*: Suprane; *Chile*: Suprane; *China*: Suprane (优宁); *Cz.*: Suprane; *Denm.*: Suprane; *Fin.*: Suprane; *Fr.*: Suprane; *Ger.*: Suprane; *Gr.*: Suprane; *Hong Kong*: Suprane; *Hung.*: Suprane; *Indon.*: Suprane; *Irl.*: Suprane; *Israel*: Sulorane; *Ital.*: Suprane; *Jpn*: Supranet; *Malaysia*: Suprane; *Neth.*: Suprane; *Norw.*: Suprane; *NZ*: Suprane; *Philipp.*: Suprane; *Pol.*: Suprane; *Port.*: Suprane; *S.Afr.*: Suprane; *Singapore*: Suprane; *Spain*: Suprane; *Swed.*: Suprane; *Switz.*: Suprane; *Thai.*: Suprane; *Turk.*: Suprane; *UK*: Suprane; *USA*: Suprane.

Enflurane *(BAN, USAN, rINN)*

Anaesthetic Compound No. 347; Compound 347; Enfluraan; Enfluraani; Enfluran; Enflurano; Enfluranum; Methylflurether; NSC-115944; Энфлуран.
2-Chloro-1,1,2-trifluoroethyl difluoromethyl ether; 2-Chloro-1-(difluoromethoxy)-1,1,2-trifluoroethane.
$C_3H_2ClF_5O$=184.5
CAS — 13838-16-9.
ATC — N01AB04.
ATC Vet — QN01AB04.
UNII — 91I69L5AYS.

Pharmacopoeias. In *Jpn* and *US.*

USP 36: (Enflurane). A clear colourless volatile liquid having a mild sweet odour. Non-flammable. Distilling range 55.5 degrees to 57.5 degrees. Slightly soluble in water; miscible with organic solvents, with fats, and with oils. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Uses and Administration

Enflurane is a volatile halogenated anaesthetic given by inhalation. It is an isomer of isoflurane. It has anaesthetic actions similar to those of halothane (p. 1902.2). Enflurane has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) ranging from 1.7% in middle age to 2.5% in children. Enflurane is given using a calibrated vaporiser for induction and maintenance of general anaesthesia (p. 1896.1); it is also used in

subanaesthetic doses to provide analgesia in obstetrics and other painful procedures (below).

To avoid CNS excitement a short-acting barbiturate or other intravenous induction agent is recommended before the inhalation of enflurane. Anaesthesia may be induced using enflurane alone with oxygen or in nitrous oxide-oxygen mixtures. In general, enflurane concentrations of 2 to 4.5% v/v produce surgical anaesthesia in 7 to 10 minutes. Anaesthesia may be maintained with a concentration of 0.5 to 3% v/v of enflurane; a concentration of 3% v/v should not be exceeded. Although enflurane is reported to possess muscle relaxant properties, neuromuscular blockers may nevertheless be required. Postoperative analgesia may be necessary.

Concentrations of 0.25 to 1% v/v of enflurane are used to provide analgesia for vaginal delivery during childbirth and of 0.5 to 1% v/v to supplement other general anaesthetics during caesarean section.

Pain. Enflurane is used in subanaesthetic doses to provide analgesia in obstetrics and other painful procedures although a study[1] was unable to confirm that it had an analgesic effect at subanaesthetic concentrations.

1. Tomi K, *et al.* Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans. *Br J Anaesth* 1993; 70: 684–6.

Adverse Effects

As with other halogenated anaesthetics, respiratory depression, hypotension, and arrhythmias have been reported although the incidence of arrhythmias is lower with enflurane than with halothane. It sensitises the myocardium to sympathomimetics to a lesser extent than halothane. Compared with halothane, enflurane has a stimulant effect on the CNS and convulsions may occur when concentrations of enflurane are high or hypocapnia is present. Malignant hyperthermia has also been reported. Asthma and bronchospasm may occur. There have been reports of elevated serum-fluoride concentrations although resulting renal damage appears to be rare. There have been changes in measurements of hepatic enzymes and several reports of liver damage. Shivering, nausea, and vomiting have been reported in the postoperative period.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Effects on the blood. The development of carboxyhaemoglobinaemia in patients anaesthetised with volatile anaesthetics is discussed under Precautions, below.

Effects on the kidneys. The nephrotoxicity of volatile anaesthetics has been reviewed.[1] Although enflurane released inorganic fluoride it appeared to be safe in patients with normal renal function. It had also been given to patients with mild to moderate renal impairment without any further deterioration. There was an increase in serum-fluoride concentrations when enflurane was given to a group of patients who had been receiving isoniazid, but there was no change in kidney function. Pretreatment of patients with a single dose of disulfiram before anaesthesia was found to produce a consistent and almost complete inhibition of enflurane metabolism as shown by substantial reductions in plasma-fluoride concentrations and urinary excretion of fluoride.[2]

1. Mazze RI. Nephrotoxicity of fluorinated anaesthetic agents. *Clin Anaesthesiol* 1983; 1: 469–83.
2. Kharasch ED, *et al.* Clinical enflurane metabolism by cytochrome P450 2E1. *Clin Pharmacol Ther* 1994; 55: 434–40.

Effects on the liver. A review[1] of 58 cases of suspected enflurane hepatitis considered enflurane to be the likely cause of the liver damage in 24. There was biochemical evidence of liver damage in 23 of these cases. Histology reports were available for 15 patients and all showed some degree of hepatocellular necrosis and degeneration.

While the incidence of liver damage from enflurane seemed to be lower than from halothane, the character of the injury was similar.

Another review[2] of the same cases plus an additional 30 (88 in all) came to different conclusions; the main author was a consultant to the manufacturer of enflurane. Of the 88 patients with suspected enflurane hepatitis, 30 were rejected because of insufficient evidence and 43 were considered to have other factors known to produce liver injury. This left 15 possible cases of enflurane hepatitis compared with the 24 identified by the first review. While agreeing that in the rare patient unexplained liver damage follows enflurane anaesthesia, it was considered that the incidence was too small to suggest an association. No consistent histological pattern was identified in this study.

See also under Adverse Effects in Halothane, p. 1902.3.

1. Lewis JH, *et al.* Enflurane hepatotoxicity: a clinicopathologic study of 24 cases. *Ann Intern Med* 1983; 98: 984–92.
2. Eger EI, *et al.* Is enflurane hepatotoxic? *Anesth Analg* 1986; 65: 21–30.

Effects on respiration. Overall, enflurane is considered to produce more respiratory depression than halothane or isoflurane.[1,2]

1. Quail AW. Modern inhalation anaesthetic agents: a review of halothane, isoflurane and enflurane. *Med J Aust* 1989; 150: 95–102.
2. Merrett KL, Jones RM. Inhalational anaesthetic agents. *Br J Hosp Med* 1994; 52: 260–3.

Precautions

Enflurane should be used with caution in patients with convulsive disorders. High concentrations of enflurane may cause uterine relaxation. In order to minimise the risk of developing elevated carboxyhaemoglobin levels, carbon dioxide absorbents in anaesthetic apparatus should not be allowed to dry out when delivering volatile anaesthetics such as enflurane (see below).

As with other halogenated anaesthetics, patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with enflurane. In children with neuromuscular disease, particularly Duchenne muscular dystrophy, halogenated anaesthetics have been associated with very rare cases of hyperkalaemia resulting in cardiac arrhythmias and death during the postoperative period.

See also Precautions for General Anaesthetics, p. 1897.3.

Abuse. Report[1] of a fatality in a 29-year-old student nurse anaesthetist who had applied enflurane to the herpes simplex lesions of her lower lip. She was found with an empty 250 mL bottle of enflurane.

1. Lingenfelter RW. Fatal misuse of enflurane. *Anesthesiology* 1981; 55: 603.

Carbon dioxide absorbents. Significant carboxyhaemoglobinaemia may develop rarely during anaesthesia with volatile anaesthetics given by circle breathing systems containing carbon dioxide absorbents.[1] The effect is only seen when the absorbent has become excessively dried out. The use of barium hydroxide lime (which is not available in the UK) as an absorbent produces more carbon monoxide than soda lime, particularly at low water content. No cases of this complication had been reported to date in the UK.

1. CSM/MCA. Safety issues in anaesthesia: volatile anaesthetic agents and carboxyhaemoglobinaemia. *Current Problems* 1997; 23: 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies enflurane 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 04/10/11)

Interactions

Care is advised if adrenaline or other sympathomimetics are given to patients during enflurane anaesthesia. The effects of competitive neuromuscular blockers such as atracurium are enhanced by enflurane (see p. 2032.3).

See also Interactions of General Anaesthetics, p. 1897.3.

Antibacterials. For the effects of *isoniazid* on enflurane defluorination, see Effects on the Kidneys under Adverse Effects, above.

Antidepressants. It appeared likely that the enflurane-induced seizure activity seen in 2 patients could have been enhanced by *amitriptyline*.[1] It may be advisable to avoid the use of enflurane in patients requiring tricyclic antidepressants, especially when the patient has a history of seizures or when hyperventilation or high enflurane concentrations are a desired part of the anaesthetic technique.

1. Sprague DH, Wolf S. Enflurane seizures in patients taking amitriptyline. *Anesth Analg* 1982; 61: 67–8.

Disulfiram. For the effect of disulfiram on the metabolism of enflurane, see Effects on the Kidneys under Adverse Effects, above.

Pharmacokinetics

Enflurane is absorbed on inhalation. The blood/gas partition coefficient is low. It is mostly excreted unchanged through the lungs. Up to 10% of inhaled administered enflurane is metabolised in the liver, mainly to inorganic fluoride.

References.

1. Bengtson JP, *et al.* Uptake of enflurane and isoflurane during spontaneous and controlled ventilation. *Anaesth Intensive Care* 1992; 20: 191–5.
2. Devchand D, *et al.* The uptake of enflurane during anaesthesia. *Anaesthesia* 1995; 50: 491–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Enforan; *Austria* Ethrane†; *Braz.*: Enfluthane; Enuran; Etrane; *China*: Alyran (应力曼); Ethrane (易使宁); *Indon.*: Ethrane†; *Irl.*: Ethrane†; *Israel*: Alyrane†; *Ital.*: Ethrane; *Mex.*: Enfran†; Ethrane†; *Phil Ipp.*: Alyrane†; Endurane; Ethrane; *S.Afr.*: Ethrane; *Turk.* Ethrane; *USA*: Ethrane; *Venez.*: Ethrane.

Anaesthetic Ether

Aether ad Narcosin; Aether Anaestheticus; Aether pro Narcosi; Aether Purissimus; Altatáshoz való éter; Anestesiaeetteri; Anestesiaeetteri, Narkoosieetteri; Anestetinis eteris; Diethyl Ether; Dietil-éter; Dietilèter; Dietiletere; Dietileteris; Dietilēteris; Dietüüleeter; Dietyleter; Eeter; Éter; Éter anestésico; Eter dietylowy; Eter do narkozy; Éter etílico; Eter etylowy; Éter Purissimo; Etere Dietilico; Etere Etilico; Ether; Ether Anesthesicus; Éther anesthésique; Ether Anestheticus; Éther diéthylique; Ether Ethylicus; Ether Ethylicus pro Narcosi; Ether k narkóze; Ethyl Ether; Etoksüetaan; Etossietano; Etoxietano; Etüüleeter; Narkoosieetteri; Narkoseter.

$(C_2H_5)_2O$=74.12

CAS — 60-29-7.

ATC — N01AA01.

ATC Vet — QN01AA01.

NOTE. Some synonyms applied to anaesthetic ether may also be used for solvent ether (p. 2212.3). Care should be taken to differentiate between the two grades of ether.

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

Sweet Vitriol.

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

Ph. Eur. 8: (Ether, Anaesthetic). Diethyl ether to which an appropriate quantity of a non-volatile antoxidant may have been added. It contains not more than 2 g/litre of water. A clear, colourless, volatile, highly flammable, and very mobile liquid. Distillation range 34 degrees to 35 degrees.

Soluble 1 in 15 of water; miscible with alcohol and with fatty oils. Store at a temperature of 8 degrees to 15 degrees in airtight containers. Protect from light. Ether remaining in a partly used container may deteriorate rapidly. The label should state the name and concentration of any added non-volatile antoxidant.

USP 36: (Ether). It consists of 96 to 98% of $C_4H_{10}O$, the remainder consisting of alcohol and water. Ether for anaesthetic use contains not more than 0.2% of water. It is a colourless, mobile, highly flammable, highly volatile liquid, having a characteristic sweet, pungent odour. It is slowly oxidised by the action of air and light, with the formation of peroxides. Its vapour, when mixed with air and ignited, may explode. B.p. about 35 degrees.

Soluble 1 in 12 of water; miscible with alcohol, with chloroform, with dichloromethane, with petroleum spirit, with benzene, and with fixed and volatile oils; soluble in hydrochloric acid. Store in partly-filled, airtight containers, remote from fire and at a temperature not exceeding 40 degrees. Protect from light. Ether to be used for anaesthesia must be preserved in airtight containers of not more than 3 kg capacity and is not to be used for anaesthesia if it has been removed from the original container longer than 24 hours.

Labelling. The label should state that it is suitable for use as an anaesthetic.

Stability. Ether is very volatile and flammable and mixtures of its vapour with oxygen, nitrous oxide, or air at certain concentrations are explosive. It should not be used in the presence of an open flame or any electrical apparatus liable to produce a spark. Precautions should be taken against the production of static electrical discharge.

Storage. The Pharmaceutical Society of Great Britain's Department of Pharmaceutical Sciences found that free ether, even in low concentrations, caused softening of PVC bottles and was associated with loss by permeation.[1]

1. Anonymous. Plastics medicine bottles of rigid PVC. *Pharm J* 1973; 210: 100.

Uses and Administration

Ether is an anaesthetic given by inhalation. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) of 1.92%. Ether is still used in some countries for the induction and maintenance of general anaesthesia although it has been replaced in many other countries by the halogenated anaesthetics. It possesses a respiratory stimulant effect in all but the deepest planes of

anaesthesia. Ether also possesses analgesic and muscle relaxant properties. Premedication with an antimuscarinic such as atropine is necessary to reduce salivary and bronchial secretions.

Solvent ether is described on p. 2212.3.

Adverse Effects

Ether has an irritant action on the mucous membrane of the respiratory tract; it stimulates salivation and increases bronchial secretion. Laryngeal spasm may occur. Ether causes vasodilatation which may lead to a severe fall in blood pressure and it reduces blood flow to the kidneys; it also increases capillary bleeding. The bleeding time is unchanged but the prothrombin time may be prolonged. Ether may cause malignant hyperthermia in certain individuals. Alterations in kidney and liver function have been reported. Convulsions occasionally occur. Hyperglycaemia due to gluconeogenesis has been noted.

Recovery is slow from prolonged ether anaesthesia and postoperative vomiting is common. Acute overdosage of ether is characterised by respiratory failure and cardiac arrest.

Dependence on ether or ether vapour has been reported. Prolonged contact with ether spilt on any tissue produces necrosis.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Precautions

Ether anaesthesia is contra-indicated in patients with diabetes mellitus, impaired kidney function, raised CSF pressure, and severe liver disease. Its use is not advisable in hot and humid conditions in patients with fever, as convulsions are liable to occur, particularly in children and in patients who have been given atropine.

See also Precautions for General Anaesthetics, p. 1897.3.

Interactions

Ether enhances the action of competitive neuromuscular blockers to a greater degree than most other anaesthetics. However, it does not potentiate the arrhythmogenic effect of sympathomimetics, including adrenaline, as much as other inhalational anaesthetics.

See also Interactions of General Anaesthetics, p. 1897.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *S.Afr.*: Hoffmans Druppels.

Homoeopathic Preparations. *Fr.*: Strophantus Compose; *Ger.*: Angioton H; Angioton S†; Corselect N; Crataegus comp; Diacard.

Etomidate *(BAN, USAN, rINN)*

Etomidaat; Etomidaatti; Etomidat; Etomidát; Etomidatas; Étomidate; Etomidato; Etomidatum; R-16659; R-26490 (etomidate sulfate); Этомидат.

R-(+)-Ethyl 1-(α-methylbenzyl)imidazole-5-carboxylate.

$C_{14}H_{16}N_2O_2$=244.3

CAS — 33125-97-2.

ATC — N01AX07.

ATC Vet — QN01AX07.

UNII — Z226288598.

NOTE. Do not confuse with edetate; see Inappropriate Administration under Sodium Edetate, p. 1551.2.

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

Ph. Eur. 8: (Etomidate). A white or almost white powder. M.p. about 68 degrees. Very slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Etomidate). A white or almost white powder. Very slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

Uses and Administration

Etomidate is an intravenous anaesthetic used for the induction of general anaesthesia (p. 1896.1). Anaesthesia is rapidly induced and may last for 6 to 10 minutes with a single usual dose. Recovery is usually rapid without hangover effect. Etomidate has no analgesic activity.

For the induction of anaesthesia, etomidate is available as a conventional or an emulsion injection formulation. The usual dose is 300 micrograms/kg of etomidate given slowly, preferably into a large vein in the arm, although a lower dose of 150 micrograms/kg of the emulsion formulation may be sufficient. An initial dose of 150 to 200 micrograms/kg is recommended in the elderly, subsequently adjusted according to effects (see also below). Dosage should also be reduced in hepatic cirrhosis. Children may require up to 30% more than the usual adult dose (i.e. up to 400 micrograms/kg). Opioid analgesics or benzodiazepines as premedication reduce myoclonic muscle movements; opioids also reduce injection site pain. A neuromuscular blocker is necessary if intubation is required.

Administration in children. Etomidate is used in children for the induction of anaesthesia; for details of doses, which may be proportionately larger than in adults, see Uses and Administration, above. US licensed product information does not recommend the use of etomidate below 10 years of age. In the UK, etomidate emulsion is licensed for use in those aged over 6 months, although it may be given to younger patients in emergencies, and other formulations do not specify a minimum age; the *BNFC* suggests all etomidate products may be used for induction from 1 month of age.

Administration in the elderly. A study[1] in elderly patients has shown that although reducing the rate of intravenous injection of etomidate reduces the speed of induction, the dosage required is also reduced. Giving etomidate 0.2% solution at a rate of 10 mg/minute induced anaesthesia in a mean of 89.6 seconds and required a mean dose of 110 micrograms/kg. Corresponding values for a rate of 40 mg/minute were 47.7 seconds and 260 micrograms/kg, respectively.

1. Berthoud MC, *et al.* Comparison of infusion rates of three I.v. anaesthetic agents for induction in elderly patients. *Br J Anaesth* 1993; 70: 423–7.

Anaesthesia. Etomidate might be useful for induction if rapid tracheal intubation is required with a competitive neuromuscular blocker as it has been shown to reduce the time to onset of block with vecuronium.[1,2] Indeed, etomidate has been suggested[2,3] by some to be the agent of choice for rapid sequence induction of anaesthesia in emergency settings; advantages include rapid onset and short duration of action, predictable clinical effect, and haemodynamic stability. However, there is considerable controversy about its use in critically-ill patients, see Effects on the Endocrine System, below.

1. Gill RS, Scott RPF. Etomidate shortens the onset time of neuromuscular block. *Br J Anaesth* 1992; 69: 444–6.
2. Bergen JM, Smith DC. A review of etomidate for rapid sequence intubation in the emergency department. *J Emerg Med* 1997; 15: 221–30.
3. Nestor NB, Burton JH. ED use of etomidate for rapid sequence induction. *Am J Emerg Med* 2008; 26: 946–50.

Cushing's syndrome. There have been reports[1–4] of benefit with the use of etomidate for acute control of hypercortisolaemia associated with Cushing's syndrome (p. 2559.1), particularly if the oral route is not available.

1. Greening JE, *et al.* Efficient short-term control of hypercortisolaemia by low-dose etomidate in severe paediatric Cushing's disease. *Horm Res* 2005; 64: 140–3.
2. Johnson TN, Canada TW. Etomidate use for Cushing's syndrome caused by an ectopic adrenocorticotropic hormone-producing tumor. *Ann Pharmacother* 2007; 41: 350–3.
3. Dabbagh A, *et al.* Etomidate infusion in the critical care setting for suppressing the acute phase of Cushing's syndrome. *Anesth Analg* 2009; 108: 238–9.
4. Mettauer N, Brierley J. A novel use of etomidate for intentional adrenal suppression to control severe hypercortisolemia in childhood. *Pediatr Crit Care Med* 2009; 10: e37–e40.

Status epilepticus. General anaesthesia may be used to control refractory tonic-clonic status epilepticus (p. 510.2). A short-acting barbiturate such as thiopental is usually used, but other anaesthetics including etomidate have also been tried[1] for intractable convulsive status epilepticus. However, like several other anaesthetics there have been reports of seizures associated with its use in anaesthesia,[2,3] especially in patients with epilepsy.

1. Yeoman P, *et al.* Etomidate infusions for the control of refractory status epilepticus. *Intensive Care Med* 1989; 15: 255–9.
2. Nicoll K, Callender J. Etomidate-induced convulsion prior to electroconvulsive therapy. *Br J Psychiatry* 2000; 177: 373.
3. Sen H, *et al.* Epileptic seizure during anaesthesia induction with etomidate. *Middle East J Anesthesiol* 2010; 20: 723–5.

Adverse Effects and Precautions

Excitatory phenomena (especially involuntary myoclonic muscle movements, which are sometimes severe) are common after injection of etomidate, but may be reduced by giving an opioid analgesic or a short-acting benzodiazepine beforehand. Pain on injection may be reduced by giving etomidate into a large vein in the arm rather than into the hand, or, again, by premedication with an opioid analgesic. Convulsions may occur rarely, as may laryngospasm and cardiac arrhythmias. Hypersensitivity reactions including anaphylaxis have been reported. Etomidate is associated with less hypotension than other drugs commonly used for induction.

Because etomidate inhibits adrenocortical function during maintenance anaesthesia (see below) its use is limited to induction of anaesthesia. Supplementary corticosteroid therapy should be considered in at-risk patients, particularly those with adrenocortical dysfunction.

Etomidate should be used with care in the elderly, who may be more prone to cardiac depression; lower doses may be required. The dose of etomidate should also be reduced in patients with hepatic cirrhosis. Caution may be appropriate in patients with pre-existing epilepsy.

See also Adverse Effects and Precautions for General Anaesthetics, p. 1896.3.

Effects on the endocrine system. Etomidate used for sedation in an intensive care unit was implicated in an increase in mortality.[1] However, there is considerable controversy about the effects of etomidate on mortality in critically-ill patients (such as those with severe trauma or sepsis) when given as a single bolus dose for induction.[2] One systematic review[3] concluded that the use of etomidate for rapid tracheal intubation in critically-ill patients was associated with an increased risk of mortality; however, another review[4] that included patients receiving routine surgical anaesthesia found this effect to be statistically insignificant.

The UK CSM agreed that etomidate could cause a significant fall in circulating plasma-cortisol concentrations, unresponsive to corticotropin stimulation.[5] Other regulators have taken similar views in restricting the use of etomidate, which is now not given by prolonged infusion, essentially limiting its licensed use to induction of anaesthesia. Licensed product information advises that the postoperative rise in serum-cortisol concentration, which has been noted after thiopental induction, is delayed for about 3 to 6 hours when etomidate is used for induction.

A study comparing the effects of etomidate with those of methohexital on the adrenocortical function of neonates borne by mothers who received these agents for induction of anaesthesia before caesarean section indicated that there was no evidence to preclude the use of etomidate in such patients. However, regardless of which anaesthetic agent was used, early feeding was recommended to avoid neonatal hypoglycaemia.[6]

The inhibitory effect of etomidate on adrenocortical function has been used to control episodes of hypercortisolaemia; for details, see Cushing's Syndrome, above.

1. Ledingham IM, Watt I. Influence of sedation on mortality in critically ill multiple trauma patients. *Lancet* 1983; i: 1270.
2. Kulstad EB, *et al.* Etomidate as an induction agent in septic patients: red flags or false alarms? *West J Emerg Med* 2010; 11: 161–72.
3. Albert SG, *et al.* The effect of etomidate on adrenal function in critical illness: a systematic review. *Intensive Care Med* 2011; 37: 901–10.
4. Hohl CM, *et al.* The effect of a bolus dose of etomidate on cortisol levels, mortality, and health services utilization: a systematic review. *Ann Emerg Med* 2010; 56: 105–13.e5.
5. Goldberg A. Etomidate. *Lancet* 1983; ii: 60.
6. Crozier TA, *et al.* Effects of etomidate on the adrenocortical and metabolic adaptation of the neonate. *Br J Anaesth* 1993; 70: 47–53.

Hypersensitivity. Reactions involving immediate widespread cutaneous flushing or urticaria attributed to etomidate have been described.[1] There have also been reports[2,3] of anaphylactic reactions after injection of etomidate.

1. Watkins J. Etomidate: an 'immunologically safe' anaesthetic agent. *Anaesthesia* 1983; 38 (suppl): 34–8.
2. Krumholz W, *et al.* Ein fall von anaphylaktoider reaktion nach gabe von etomidat. *Anaesthesist* 1984; 33: 161–2.
3. Sold M, Rothhammer A. Lebensbedrohliche anaphylaktoide reaktion nach etomidat. *Anaesthesist* 1985; 34: 208–10.

Interactions

A reduced dose of etomidate may be necessary in patients who have received antipsychotics, sedatives, or opioids. The hypnotic effect of etomidate has been potentiated by other sedative drugs.

See also Interactions of General Anaesthetics, p. 1897.3.

Calcium-channel blockers. Prolonged anaesthesia and Cheyne-Stokes respiration after etomidate injection has been reported in 2 patients also given *verapamil*.[1]

1. Moore CA, *et al.* Potentiation of etomidate anesthesia by verapamil: a report of two cases. *Hosp Pharm* 1989; 24: 24–5.

General anaesthetics. For a report of synergy between *propofol* and etomidate, see p. 1912.2.

Pharmacokinetics

After injection, etomidate is rapidly redistributed from the CNS to other body tissues, and undergoes rapid metabolism in the liver and plasma. Pharmacokinetics are complex and have been described by both 2- and 3-compartment models. Etomidate is about 76% bound to plasma proteins. It is mainly excreted in the urine, but some is excreted in the bile. It may cross the placenta and is distributed into breast milk.

References.

1. Levron JC, Assoune P. Pharmacocinétique de l'étomidate. *Ann Fr Anesth Reanim* 1990; 9: 123–6.
2. Sfez M, *et al.* Comparaison de la pharmacocinétique de l'étomidate chez l'enfant et chez l'adulte. *Ann Fr Anesth Reanim* 1990; 9: 127–31.
3. Esener Z, *et al.* Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum. *Br J Anaesth* 1992; 69: 586–8.
4. Kaneda K, *et al.* Population pharmacokinetics and pharmacodynamics of brief etomidate infusion in healthy volunteers. *J Clin Pharmacol* 2011; 51: 482–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Hypnomidate; *Belg.*: Hypnomidate; *Braz.*: Hypnomidate; *China*: Fu Er Li (福尔利); *Cz.*: Hypnomidate; *Fr.*: Hypnomidate; *Ger.*: Hypnomidate; *Gr.*: Hypnomidate; *Mex.*: Hypnomidate; *Neth.*: Hypnomidate; *Pol.*: Hypnomidate; *Port.*: Hypnomidato; *S.Afr.*: Hypnomidate; *Spain*: Hypnomidate; *Turk.*: Hypnomidate; *UK*: Hypnomidate; *USA*: Amidate.

Pharmacopoeial Preparations
USP 36: Etomidate Injection.

Fospropofol Sodium *(rINNM)*

Fospropofol Disodium (USAN); Fospropofol sódico; Fospropofol Sodique; GPI-15715; Natrii Fospropofolum; PQ-1002; Натрий Фоспропофол.

[2,6-Bis(1-methylethyl)phenoxy]methyl disodium phosphate.

$C_{13}H_{19}Na_2O_5P$=332.2

CAS — 258516-89-1 (fospropofol); 258516-87-9 (fospropofol sodium).

UNII — 30868AY0IF.

Profile

Fospropofol is a prodrug of propofol (p. 1909.3) that is given intravenously as the sodium salt for sedation (p. 1032.2) in adult patients undergoing diagnostic or therapeutic procedures. In those aged under 65 years, and who are healthy or have mild systemic disease, an initial bolus injection of 6.5 mg/kg (minimum: 385 mg, maximum: 577.5 mg) may be followed by supplemental doses of 1.6 mg/kg (minimum: 105 mg, maximum: 140 mg) given no more frequently than every 4 minutes. Patients aged 65 years and older, or those with severe systemic disease, should be given 75% of the usual initial (minimum: 297.5 mg, maximum: 437.5 mg) and supplemental (minimum: 70 mg, maximum: 105 mg) doses.

References.

1. Fechner J, *et al.* Pharmacokinetics and pharmacodynamics of GPI 15715 or fospropofol (Aquavan injection): a water-soluble propofol prodrug. In: Schüttler J, Schwilden H, eds. *Handb Exp Pharmacol: Modern Anesthetics.* Berlin: Springer-Verlag, 2008; 182 (III): 253–66.
2. Levitzky BE, Vargo JJ. Fospropofol disodium injection for the sedation of patients undergoing colonoscopy. *Ther Clin Risk Manag* 2008; 4: 733–8.
3. Silvestri GA, *et al.* A phase 3, randomized, double-blind study to assess the efficacy and safety of fospropofol disodium injection for moderate sedation in patients undergoing flexible bronchoscopy. *Chest* 2009; 135: 41–7.
4. Garnock-Jones KP, Scott LJ. Fospropofol. *Drugs* 2010; 70: 469–77.
5. Gan TJ, *et al.* Safety evaluation of fospropofol for sedation during minor surgical procedures. *J Clin Anesth* 2010; 22: 260–7.
6. Pergolizzi JV, *et al.* Perspectives on the role of fospropofol in the monitored anesthesia care setting. *Anesthesiol Res Pract* 2011; 2011: 458920.
7. Bengalorkar GM, *et al.* Fospropofol: clinical pharmacology. *J Anaesthesiol Clin Pharmacol* 2011; 27: 79–83.

Preparations

Proprietary Preparations (details are given in Volume B)

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

Halothane *(BAN, rINN)*

Alotano; Halotaani; Halotan; Halotán; Halotanas; Halotano; Halothan; Halothanum; Phthorothanum; Галотан.

(RS)-2-Bromo-2-chloro-1,1,1-trifluoroethane.

$CHBrClCF_3$=197.4

CAS — 151-67-7.

ATC — N01AB01.

ATC Vet — QN01AB01.

UNII — UQT9G45D1P.

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

Ph. Eur. 8: (Halothane). A clear, colourless, mobile, dense, non-flammable liquid. Distillation range 49 degrees to 51 degrees. Slightly soluble in water; miscible with dehydrated alcohol and with trichloroethylene. Halothane contains 0.01% w/w of thymol. Store at a temperature not greater than 25 degrees in airtight containers. Protect from light.

USP 36: (Halothane). A colourless, mobile, non-flammable, heavy liquid having a characteristic odour resembling that of chloroform. It contains not less than 0.008% and not more than 0.012% of thymol, by weight, as a stabiliser. It should contain not more than 0.03% of water. Distillation range 49 degrees to 51 degrees.

Slightly soluble in water; miscible with alcohol, with chloroform, with ether, and with fixed oils. Store in airtight containers at a temperature not greater than 40 degrees. Protect from light. Dispense only in the original container.

Incompatibility. In the presence of moisture, halothane reacts with many metals. Rubber and some plastics deteriorate when in contact with halothane vapour or liquid.

Stability. Halothane contains 0.01% w/w of thymol as a stabiliser; some commercial preparations may also contain up to 0.00025% w/w of ammonia. Thymol does not volatilise with halothane and therefore accumulates in the vaporiser. It may give a yellow colour to any remaining liquid; halothane that has discoloured should be discarded.

Uses and Administration

Halothane is a volatile halogenated anaesthetic given by inhalation. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) ranging from 0.64% in the elderly to 1.08% in infants. It is non-flammable and is not explosive when mixed with oxygen at normal atmospheric pressure. It is not irritant to the skin and mucous membranes and does not produce necrosis when spilt on tissues. It suppresses salivary, bronchial, and gastric secretions and dilates the bronchioles. However, its use has diminished due to the risk of hepatotoxicity; in the UK, it is only available on a named-patient basis and in other countries, such as the USA, it has been withdrawn from the market.

Halothane is used for the induction and maintenance of general anaesthesia (p. 1896.1) and is given using a calibrated vaporiser to provide close control over the concentration of inhaled vapour.

Anaesthesia may be induced initially with 0.5% v/v of halothane in oxygen or mixtures of nitrous oxide and oxygen, and increased gradually, according to response, to a concentration of 2 to 4% v/v. It takes up to about 5 minutes to attain surgical anaesthesia and halothane produces little or no excitement in the induction period. The more usual practice is to induce anaesthesia with an intravenous agent. Anaesthesia is maintained with concentrations of 0.5 to 2% v/v depending on the flow rate used; the lower concentration is usually suitable for the elderly.

Adequate muscle relaxation is only achieved with deep anaesthesia so a neuromuscular blocker is given to increase muscular relaxation if necessary.

Administration in children. Halothane has been used for the induction and maintenance of general anaesthesia in children; however, in the UK, it is now mainly used by specialist anaesthetists to manage difficult airways. Doses are as for adults (see Uses and Administration, above).

Status asthmaticus. Inhalational anaesthetics such as halothane; isoflurane, and sevoflurane, have occasionally been used in the management of life-threatening acute severe asthma (p. 1195.2) unresponsive to standard measures.

References.

1. Restrepo RD, *et al.* Halothane, an effective infrequently used drug, in the treatment of pediatric status asthmaticus: a case report. *J Asthma* 2005; 42: 649–51.
2. Shankar V, *et al.* Isoflurane therapy for severe refractory status asthmaticus in children. *Intensive Care Med* 2006; 32: 927–33.
3. Thomson H, *et al.* Use of the AnaConDa® anaesthetic delivery system to treat life-threatening asthma. *Anaesthesia* 2007; 62: 295–6.
4. Burburan SM, *et al.* Anaesthetic management in asthma. *Minerva Anestesiol* 2007; 73: 357–65.
5. Watanabe K, *et al.* Prolonged sevoflurane inhalation therapy for status asthmaticus in an infant. *Pediatr Anesth* 2008; 18: 543–5.
6. Vaschetto R, *et al.* Inhalational anesthetics in acute severe asthma. *Curr Drug Targets* 2009; 10: 826–32.
7. Tobias JD. Inhalational anesthesia: basic pharmacology, end organ effects, and applications in the treatment of status asthmaticus. *J Intensive Care Med* 2009; 24: 361–71.

Adverse Effects

As with other halogenated anaesthetics, halothane has a depressant action on the cardiovascular system and reduces blood pressure; signs of overdosage are bradycardia and profound hypotension. It is also a respiratory depressant and can cause cardiac arrhythmias; there have been instances of cardiac arrest. The sensitivity of the heart to sympathomimetic amines is increased.

Adverse effects on the liver have limited its use in recent years (see below); these effects range from liver dysfunction to fatal hepatitis and necrosis and are more frequent following repeated use.

Halothane can produce nausea, vomiting, and shivering. Malignant hyperthermia has been reported.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Review.

1. Kharasch ED. Adverse drug reactions with halogenated anesthetics. *Clin Pharmacol Ther* 2008; 84: 158–62.

Effects on the cardiovascular system. The incidence of cardiac arrhythmias is higher with halothane than with enflurane or isoflurane; also the arrhythmogenic threshold with injected adrenaline is lower with halothane than isoflurane or enflurane.

Arrhythmias are considered to be very common in children anaesthetised with halothane and in the UK it is recommended that it should not be used for dental procedures outside hospital in those under 18 years old.

A review[1] of the mechanisms involved suggested that at physiologically relevant concentrations, halogenated anaesthetics interact mainly with the repolarising potassium channels hERG and I_{Ks}, as well as with calcium and sodium channels at slightly higher concentrations. Inhibition of these produces proarrhythmic changes such as slowing of repolarisation and conduction. Other mechanisms, including alteration of catecholamine-induced signal transduction and possibly effects on neuronal pathways may also contribute to arrhythmogenesis.

1. Himmel HM. Mechanisms involved in cardiac sensitization by volatile anesthetics: general applicability to halogenated hydrocarbons? *Crit Rev Toxicol* 2008; 38: 773–803.

Effects on the kidneys. Renal failure has been reported after halothane anaesthesia,[1,2] sometimes with concurrent liver failure.[2]

1. Cotton JR, *et al.* Acute renal failure following halothane anesthesia. *Arch Pathol Lab Med* 1976; 100: 628–9.
2. Gelman ML, Lichtenstein NS. Halothane-induced nephrotoxicity. *Urology* 1981; 17: 323–7.

Effects on the liver. Liver damage has been recognised as an adverse effect of halothane for many years[1-3] and continues to be reported.[4] It may be severe, and associated with a high mortality.

Two types of hepatotoxicity are recognised: in **type I** there is a minor disturbance in liver function shown by increases in liver enzyme values; this may occur in up to 30% of patients given halothane,[5] or more if activity is measured by glutathione-S-transferase rather than serum aminotransferase.[6] Subsequent re-exposure to halothane is not necessarily associated with liver damage.[2,7]

Type II hepatotoxicity, which is rarer, involves massive liver cell necrosis; reported incidences[2] range from 1 in 2500 to 1 in 36 000. Type II liver toxicity is characterised by several clinical features: non-specific gastrointestinal upset, delayed pyrexia, jaundice, eosinophilia, serum autoantibodies, rash, and arthralgia.[1,3] Biochemical tests of liver function show changes typical of hepatocellular damage; histological features are typified by centrilobular necrosis.[3] Several **risk factors** for development of serious toxicity have become apparent;[1-3] they include repeated exposure, previous adverse reactions to halothane (jaundice, pyrexia), female gender, obesity, middle age, genetic predisposition, enzyme induction, and a history of drug allergy.

The **causes** of halothane hepatotoxicity have been debated. Type I reactions may result from toxic products of halothane metabolism, possibly influenced by genetic factors or from an imbalance between hepatic oxygen supply and demand. Changes in cellular calcium homoeostasis may also be involved. Type II reactions are most likely immune-mediated.[2,3] It has been suggested[3] that metabolism of halothane produces a reactive metabolite which binds covalently to proteins in the endoplasmic reticulum of hepatocytes. In susceptible patients it is believed that these metabolite-modified proteins provoke an immune response which is responsible for the liver damage. Findings[8,9] have implicated the cytochrome P450 isoenzyme CYP2E1 as having a major role in the metabolism of halothane and patients with high levels of this isoenzyme may be predisposed to developing immune-medicated liver damage after halothane exposure.

The UK CSM,[10] after receiving 84 further reports of hepatotoxicity between 1978 and 1985, issued the following **guidelines** on **precautions** to be taken before using halothane:

- a careful anaesthetic history should be taken to determine previous exposure and previous reactions to halothane
- repeated exposure to halothane within a period of at least 3 months should be avoided unless there are overriding clinical circumstances. An opinion has been expressed that the 3-month interval between exposures would be unlikely to prevent hepatotoxicity[2]
- a history of unexplained jaundice or pyrexia in a patient following exposure to halothane is an absolute contra-indication to its future use in that patient

These guidelines were reiterated in 1997 after the CSM was notified of a further 15 cases of acute liver failure all requiring transplantation.[11]

The problem of patients sensitised to halothane who require **subsequent anaesthesia** with a volatile anaesthetic has been discussed.[5] Although the incidence of hepatotoxicity produced by *enflurane* appears to be less than with halothane, it is of a similar nature and there have been reports of several patients who apparently had cross-sensitivity to both. Hepatotoxicity with *isoflurane* appears to be rare and it was suggested that for the majority of patients sensitised to halothane, isoflurane would be likely to be free

from hepatotoxic effects. However, there has been a report[12] of a patient who had had two previous exposures to isoflurane and subsequently developed liver function abnormalities after receiving halothane. Hepatotoxicity with *desflurane* (see p. 1899.2) might also be associated with sensitisation to halothane or isoflurane.

1. Rosenak D, *et al.* Halothane and liver damage. *Postgrad Med J* 1989; 65: 129–35.
2. Neuberger JM. Halothane and hepatitis: incidence, predisposing factors and exposure guidelines. *Drug Safety* 1990; 5: 28–38.
3. Ray DC, Drummond GB. Halothane hepatitis. *Br J Anaesth* 1991; 67: 84–99.
4. Eghtesadi-Araghi P, *et al.* Halothane hepatitis in Iran: a review of 59 cases. *World J Gastroenterol* 2008; 14: 5322–6.
5. Kenna JG, Neuberger JM. Immunopathogenesis and treatment of halothane hepatitis. *Clin Immunother* 1995; 3: 108–24.
6. Allan LG, *et al.* Hepatic glutathione S-transferase release after halothane anaesthesia: open randomised comparison with isoflurane. *Lancet* 1987; i: 771–4.
7. Neuberger J, Williams R. Halothane anaesthesia and liver damage. *BMJ* 1984; 289: 1136–9.
8. Kharasch ED, *et al.* Identification of the enzyme responsible for oxidative halothane metabolism: implications for prevention of halothane hepatitis. *Lancet* 1996; 347: 1367–71.
9. Kenna JC, *et al.* Formation of the C[F]$_2$CO-protein antigens implicated in the pathogenesis of halothane hepatitis is catalyzed in human liver microsomes in vitro by CYP 2E1. *Br J Clin Pharmacol* 1997; 43: 209.
10. CSM. Halothane hepatotoxicity. *Current Problems 18* 1986. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20244256&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)
11. CSM/MCA. Safety issues in anaesthesia: reminder: hepatotoxicity with halothane. *Current Problems* 1997; 23: 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2032306&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)
12. Slayter KL, *et al.* Halothane hepatitis in a renal transplant patient previously exposed to isoflurane. *Ann Pharmacother* 1993; 27: 101.

Precautions

The risk of halothane hepatitis led the UK CSM to issue guidelines on its use (see Effects on the Liver, under Adverse Effects, p. 1902.3). It is also recommended that patients be informed of any reactions and that this be done in addition to the updating of the patients' medical records.

It is recommended in the UK that halothane should not be used for dental procedures outside hospital in patients under 18 years old.

Halothane reduces uterine muscle tone during pregnancy and generally its use is not recommended in obstetrics because of the increased risk of postpartum haemorrhage.

Premedication with atropine has been recommended to reduce vagal tone and to prevent bradycardia and severe hypotension.

Measures may need to be taken to counteract any increase in CSF pressure or in cerebral blood flow. Halothane should be used with caution in patients with phaeochromocytoma.

As with other halogenated anaesthetics, patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with halothane. In children with neuromuscular disease, particularly Duchenne muscular dystrophy, halogenated anaesthetics have been associated with very rare cases of hyperkalaemia resulting in cardiac arrhythmias and death during the postoperative period.

See also Precautions for General Anaesthetics, p. 1897.3.

Abuse. A brief review[1] of abuse of volatile anaesthetics found that of 14 patients who had ingested or sniffed halothane 10 had died. Another patient who had injected halothane intravenously also died. There has also been another report[2] of fatalities resulting from acute pulmonary oedema after intravenous injection of halothane.

1. Yamashita M, *et al.* Illicit use of modern volatile anaesthetics. *Can Anaesth Soc J* 1984; 31: 76–9.
2. Berman P, Tattersall M. Self-poisoning with intravenous halothane. *Lancet* 1982; ii: 340.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving halothane, and the last available guidance from the American Academy of Pediatrics[1] considered that it was therefore usually compatible with breast feeding.

Trace amounts of halothane have been detected in the breast milk of an anaesthetist exposed to environmental halothane in the operating theatre.[2]

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 25/05/04)
2. Coté CJ, *et al.* Trace concentrations of halothane in human breast milk. *Br J Anaesth* 1976; 48: 541–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies halothane 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 04/10/11)

Interactions

Adrenaline and most other sympathomimetics, and theophylline should be avoided during halothane anaesthesia since they can produce cardiac arrhythmias; the risk of arrhythmias is also increased if halothane is used in patients receiving dopaminergics. The effects of competitive neuromuscular blockers such as atracurium, and of ganglion blockers such as trimetaphan are enhanced by halothane and if required they should be given in reduced dosage. Morphine increases the depressant effects of halothane on respiration. Chlorpromazine also enhances the respiratory depressant effect of halothane. The effects of both ergometrine and oxytocin on the parturient uterus are diminished by halothane.

See also Interactions of General Anaesthetics, p. 1897.3.

Antiepileptics. For a case of *phenytoin* intoxication associated with halothane anaesthesia, see p. 542.2.

Benzodiazepines. *Midazolam* has been reported to potentiate the anaesthetic action of halothane.[1]

1. Inagaki Y, *et al.* Anesthetic interaction between midazolam and halothane in humans. *Anesth Analg* 1993; 76: 613–17.

General anaesthetics. For a report that halothane increases serum concentrations of *propofol*, see p. 1912.2.

Neuromuscular blockers. For the potentiation of the neuromuscular blockade of neuromuscular blockers such as *atracurium* by halothane, see p. 2032.3. For increased toxicity during halothane anaesthesia, see *suxamethonium* p. 2039.3.

Trichloroethane. Evidence of chronic cardiotoxicity was seen in 2 patients after repeated exposure to trichloroethane.[1] In both cases there was circumstantial evidence of a deterioration after routine anaesthetic use of halothane.

1. McLeod AA, *et al.* Chronic cardiac toxicity after inhalation of 1,1,1-trichloroethane. *BMJ* 1987; 294: 727–9.

Xanthines. For references to increased cardiotoxicity when patients taking *theophylline* were anaesthetised with halothane, see p. 1236.2.

Pharmacokinetics

Halothane is absorbed on inhalation. It has a relatively low solubility in blood and is more soluble in the neutral fats of adipose tissue than in the phospholipids of brain cells. Up to 80% of inhaled halothane is excreted unchanged through the lungs. Up to 20% is metabolised by the liver by oxidative and, under hypoxic conditions, reductive pathways. Urinary metabolites include trifluoroacetic acid and bromide and chloride salts (oxidative pathway) and fluoride salts (reductive pathway). Halothane diffuses across the placenta and has been detected in breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ineltano; *Austral.*: Fluothane†; *Braz.*: Fluothane; *Cz.*: Narcotan†; *Gr.*: Fluothane; *Hung.*: Narcotan†; *India*: Fluothane; Hypnothane; *Indon.*: Fluothane†; *NZ*: Fluothane; *Pol.*: Narcotan†; *Rus.*: Narcotan (Наркотан); *Turk.*: Fluothane.

Multi-ingredient Preparations. *Braz.*: Tanohalo.

Isoflurane *(BAN, USAN, rINN)*

Compound 469; Isofluraani; Isofluran; Isoflurano; Isoflurum; Izofluran; Izoflurán; Izofluranas; Изофлуран.

1-Chloro-2,2,2-trifluoroethyl difluoromethyl ether; 2-Chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane.

$C_3H_2ClF_5O$=184.5

CAS — 26675-46-7.

ATC — N01AB06.

ATC Vet — QN01AB06.

UNII — CS9AKD70P.

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

Ph. Eur. 8: (Isoflurane). A clear, colourless, mobile, heavy liquid. B.p. about 48 degrees. It is non-flammable. Practically insoluble in water; miscible with dehydrated alcohol and with trichloroethylene. Store in airtight containers. Protect from light.

USP 36: (Isoflurane). A clear, colourless, volatile liquid having a slight odour. B.p. about 49 degrees. Insoluble in water; miscible with common organic solvents and with fats and oils. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Isoflurane is a volatile halogenated anaesthetic given by inhalation. It is an isomer of enflurane and has anaesthetic actions similar to those of halothane (p. 1902.2). Isoflurane has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) ranging from 1.05% in the elderly to 1.87% in infants. It is used in the induction and maintenance of general anaesthesia (p. 1896.1) although induction is more often carried out using an intravenous anaesthetic. Isoflurane is also used in subanaesthetic doses to provide analgesia in obstetrics and other painful procedures.

Isoflurane is given using a calibrated vaporiser. If it is used for induction then it is given with oxygen or oxygen and nitrous oxide mixtures and induction should start with an isoflurane concentration of 0.5% v/v increased to 1.5 to 3% v/v which generally produces surgical anaesthesia within 10 minutes. Its pungency may limit the rate of induction. Anaesthesia may be maintained with a concentration of 1 to 2.5% v/v with oxygen and nitrous oxide mixtures; 1.5 to 3.5% v/v may be required if used only with oxygen. Isoflurane 0.5 to 0.75% v/v with oxygen and nitrous oxide mixtures is suitable to maintain anaesthesia for caesarean section. Although isoflurane is reported to possess muscle relaxant properties, neuromuscular blockers may nevertheless be required. Recovery is rapid.

Administration in children. Isoflurane is used for the induction and maintenance of general anaesthesia in children; doses are as for adults (see Uses and Administration, above).

Anaesthesia. *CAESAREAN SECTION.* Isoflurane 0.8% v/v has been found to be a suitable supplement to nitrous oxide-oxygen anaesthesia for patients undergoing caesarean section.[1] It has been suggested[2] that an overpressure technique might be of use to further reduce awareness in such patients. Giving isoflurane at a concentration of 2% v/v for 5 minutes followed by concentrations of 1.5% v/v for the next 5 minutes and 0.8% v/v thereafter produced higher arterial concentrations of isoflurane in patients undergoing caesarean section than when it was given at a concentration of 1% v/v throughout.[2]

1. Dwyer R, *et al.* Uptake of halothane and isoflurane by mother and baby during Caesarean section. *Br J Anaesth* 1995; 74: 379–83.
2. McCrirrick A, *et al.* Overpressure isoflurane at Caesarean section: a study of arterial isoflurane concentrations. *Br J Anaesth* 1994; 72: 122–4.

Pain. Isoflurane is used in subanaesthetic doses to provide analgesia in obstetrics and other painful procedures but studies[1,2] have been unable to confirm that it had an analgesic effect at subanaesthetic concentrations. The use of isoflurane 0.2 or 0.25% v/v in a mixture of nitrous oxide 50% v/v and oxygen 50% v/v has been studied.[3,4]

1. Tomi K, *et al.* Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans. *Br J Anaesth* 1993; 70: 684–6.
2. Roth D, *et al.* Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by evoked potentials. *Br J Anaesth* 1996; 76: 38–42.
3. Wee MYK, *et al.* Isoflurane in labour. *Anaesthesia* 1993; 48: 369–72.
4. Bryden FM, *et al.* Isoflurane for removal of chest drains after cardiac surgery. *Br J Anaesth* 1994; 73: 712P–713P.

Sedation. *INTENSIVE CARE.* The various drugs used to provide sedation in intensive care are discussed on p. 1033.1. Isoflurane is not usually considered for such a purpose but in a comparative 24-hour study[1] in 60 patients requiring mechanical ventilation, isoflurane 0.1 to 0.6% v/v in an air-oxygen mixture produced satisfactory sedation for a greater proportion of time than did the continuous infusion of midazolam 10 to 200 micrograms/kg per hour. Patients given isoflurane also recovered more rapidly. Isoflurane has also been used successfully for sedation over 5 days in a 3-year-old infant who required ventilation for pneumonia, a complication of the child's myasthenia gravis.[2] However, there has been some concern over high plasma fluoride concentrations after prolonged use of isoflurane (see under Metabolism in Pharmacokinetics, p. 1904.3).

1. Kong KL, *et al.* Isoflurane compared with midazolam for sedation in the intensive care unit. *BMJ* 1989; 298: 1277–80.
2. McBeth C, Watkins TGL. Isoflurane for sedation in a case of congenital myasthenia gravis. *Br J Anaesth* 1996; 77: 672–4.

Status epilepticus. General anaesthesia may be used to control refractory tonic-clonic status epilepticus (p. 510.2). A short-acting barbiturate such as thiopental is usually used. Despite rare reports of seizures associated with the use of isoflurane in anaesthetic procedures (see Effects on the Nervous System, under Adverse Effects and Precautions, p. 1904.2) it has been used successfully,[1-3] typically

in concentrations of 0.5 to 1% v/v, to control refractory convulsive status epilepticus. Although some[4] consider that isoflurane-induced coma may be more easy to control than barbiturate-induced coma, the use of isoflurane may be limited by the need for special anaesthetic equipment and continuous EEG monitoring. Magnetic resonance imaging (MRI) signal abnormalities have been reported[5] with prolonged (up to 85 days) use of isoflurane in high concentrations (up to 2.5% v/v) for refractory status epilepticus; the authors suggested that these MRI findings may be indicative of neurotoxicity.

1. Mecke RI, *et al.* Isoflurane for the management of status epilepticus. *DICP Ann Pharmacother* 1989; 23: 579–81.
2. Hilz MJ, *et al.* Isoflurane anaesthesia in the treatment of convulsive status epilepticus. *J Neurol* 1992; 239: 135–7.
3. Mirsattari SM, *et al.* Treatment of refractory status epilepticus with inhalational anesthetic agents isoflurane and desflurane. *Arch Neurol* 2004; 61: 1254–9.
4. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; 1: 26–44.
5. Pugsse JB, *et al.* Prolonged high-dose isoflurane for refractory status epilepticus: is it safe? *Anesth Analg* 2010; 111: 1520–4.

Adverse Effects and Precautions

As with other halogenated anaesthetics, respiratory depression, hypotension, arrhythmias, and malignant hyperthermia have been reported; patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with isoflurane. Isoflurane differs from halothane and enflurane in that it produces less cardiac depression than either drug and heart rate may be increased. Also isoflurane sensitises the myocardium to sympathomimetics to a lesser extent than halothane and enflurane. The incidence of cardiac arrhythmias is lower with isoflurane than with halothane. Shivering, nausea, and vomiting have been reported in the postoperative period.

Induction with isoflurane is not as smooth as with halothane and this may be connected with its pungency; breath holding, coughing, and laryngospasm may occur. It has been reported to increase the cerebrospinal pressure and should be used with caution in patients with raised intracranial pressure. In children with neuromuscular disease, particularly Duchenne muscular dystrophy, halogenated anaesthetics have been associated with very rare cases of hyperkalaemia resulting in cardiac arrhythmias and death during the postoperative period. Isoflurane relaxes the uterine muscle; increased blood loss may occur after curettage or termination of pregnancy.

In order to minimise the risk of developing elevated carboxyhaemoglobin levels, carbon dioxide absorbents in anaesthetic apparatus should not be allowed to dry out when delivering volatile anaesthetics such as isoflurane (see below).

See also Adverse Effects and Precautions of General Anaesthetics, p. 1896.3 and p. 1897.3.

A comparison[1] of isoflurane and halothane for outpatient dental anaesthesia in children considered that isoflurane would produce fewer arrhythmias than halothane, but that the ease of induction and the quality of anaesthesia was inferior to that with halothane. Others[2] also found a higher incidence of coughing, salivation, and laryngospasm with isoflurane than halothane, but felt that it could be used as an alternative.

Further information on the adverse effects profile of isoflurane can be obtained from the report of and commentaries on an extensive multicentre study of patients undergoing anaesthesia with this agent.[3,4]

1. Cattermole RW, *et al.* Isoflurane and halothane for outpatient dental anaesthesia in children. *Br J Anaesth* 1986; 58: 385–9.
2. McAteer PM, *et al.* Comparison of isoflurane and halothane in outpatient paediatric dental anaesthesia. *Br J Anaesth* 1986; 58: 390–3.
3. Forrest JB, *et al.* A multi-centre clinical evaluation of isoflurane. *Can Anaesth Soc J* 1982; 29 (suppl): S1–S69.
4. Levy WJ. Clinical anaesthesia with isoflurane: a review of the multicentre study. *Br J Anaesth* 1984; 56: 101S–112S.

Carbon dioxide absorbents. Significant carboxyhaemoglobinaemia may develop rarely during anaesthesia with volatile anaesthetics given by circle breathing systems containing carbon dioxide absorbents.[1] The effect is only seen when the absorbent has become excessively dried out. The use of barium hydroxide lime (which is not available in the UK) as an absorbent produces more carbon monoxide than soda lime, particularly at low water content. No cases of this complication had been reported to date in the UK.

1. CSM/MCA. Safety issues in anaesthesia: volatile anesthetic agents and carboxyhaemoglobinaemia. *Current Problems* 1997; 23: 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2032306&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)

Effects on the cardiovascular system. Isoflurane is considered to produce less cardiovascular depression than halothane. However, the results of a study[1] suggest that while this may be true for young patients, in elderly patients isoflurane appears to have a cardiac depressant effect similar to that of halothane.

1. McKinney MS, *et al.* Cardiovascular effects of isoflurane and halothane in young and elderly adult patients. *Br J Anaesth* 1993; 71: 696–701.

CEREBRAL BLOOD FLOW. Autoregulation of cerebral blood flow appears to be impaired at higher concentrations of isoflurane. A study[1] in healthy subjects found that increasing isoflurane anaesthesia from a concentration of 1 to 2 minimum alveolar concentration (MAC) increased cerebral blood flow and reduced cerebral oxygen metabolism.

1. Olsen KS, *et al.* Effect of 1 or 2 MAC isoflurane with or without ketanserin on cerebral blood flow autoregulation in man. *Br J Anaesth* 1994; 72: 66–71.

CORONARY CIRCULATION. Halothane, enflurane, and isoflurane decrease coronary perfusion pressure, coronary blood flow, ventricular function, and myocardial oxygen demand. Halothane and enflurane have a variable effect on coronary vascular resistance, but isoflurane dilates coronary vessels.[1] There has been concern over the potential of isoflurane to produce coronary steal and whether this effect is detrimental in patients with ischaemic heart disease.[2] However, despite conflicting results of individual studies[3-6] an early review[7] concluded that isoflurane could be used safely even in high-risk patients with coronary artery disease provided that blood pressure and heart rate were maintained close to baseline concentrations. A subsequent review[8] considered that more recent evidence supported the use of isoflurane as the anaesthetic agent of choice in patients with coronary heart disease.

1. Quail AW. Modern inhalational anaesthetic agents: a review of halothane, isoflurane and enflurane. *Med J Aust* 1989; 150: 95–102.
2. Stoelting RK. Anesthesiology. *JAMA* 1991; 265: 3103–5.
3. Buffington CW, *et al.* The prevalence of steal-prone coronary anatomy in patients with coronary artery disease: an analysis of the coronary artery surgery study registry. *Anesthesiology* 1988; 69: 721–7.
4. Inoue K, *et al.* Does isoflurane lead to a higher incidence of myocardial infarction and perioperative death than enflurane in coronary artery surgery? A clinical study of 1178 patients. *Anesth Analg* 1990; 71: 469–74.
5. Slogoff S, *et al.* Steal-prone coronary anatomy and myocardial ischemia associated with four primary anesthetic agents in humans. *Anesth Analg* 1991; 72: 22–7.
6. Stühmeier KD, *et al.* Isoflurane does not increase the incidence of intraoperative myocardial ischaemia compared with halothane during vascular surgery. *Br J Anaesth* 1992; 69: 602–6.
7. Hogue CW, *et al.* Anesthetic-induced myocardial ischemia: the isoflurane-coronary steal controversy. *Coron Artery Dis* 1993; 4: 413–19.
8. Agnew NM, *et al.* Isoflurane and coronary heart disease. *Anaesthesia* 2002; 57: 338–47.

Effects on the kidneys. See under Metabolism in Pharmacokinetics, below.

Effects on the liver. Of 45 cases of isoflurane-associated hepatotoxicity reported to the FDA between 1981 and 1984 there was some other cause for the liver damage in 29. While isoflurane might have been one of the causes of the damage in the other 16 cases, there was not a reasonable likelihood of an association between isoflurane and postoperative liver impairment.[1] Subsequent rare cases of hepatotoxicity,[2-8] sometimes fatal,[2,5,7,8] have suggested that isoflurane may induce hepatitis, though much less frequently than halothane, and that there may be cross-sensitisation with other halogenated anaesthetics.

See also under the Adverse Effects of Halothane, p. 1902.3.

1. Stoelting RK, *et al.* Hepatic dysfunction after isoflurane anesthesia. *Anesth Analg* 1987; 66: 147–53.
2. Carrigan TW, Straughen WJ. A report of hepatic necrosis and death following isoflurane anesthesia. *Anesthesiology* 1987; 67: 581–3.
3. Sinha A, *et al.* Isoflurane hepatotoxicity: a case report and review of the literature. *Am J Gastroenterol* 1996; 91: 2406–9.
4. Hasan F. Isoflurane hepatotoxicity in a patient with a previous history of halothane-induced hepatitis. *Hepatogastroenterology* 1998; 45: 518–22.
5. Turner GB, *et al.* Fatal hepatotoxicity after re-exposure to isoflurane: a case report and review of the literature. *Eur J Gastroenterol Hepatol* 2000; 12: 955–9.
6. Malnick SDH, *et al.* Acute cholestatic hepatitis after exposure to isoflurane. *Ann Pharmacother* 2002; 36: 261–3.
7. Ihtiyar E, *et al.* Fatal isoflurane hepatotoxicity without re-exposure. *Indian J Gastroenterol* 2006; 25: 41–2.
8. Kusuma HR, *et al.* Pulminant hepatic failure after repeated exposure to isoflurane. *Indian J Anaesth* 2011; 55: 290–2.

Effects on the nervous system. Seizures associated with induction of anaesthesia with isoflurane have been reported in patients without known neurological abnormalities and not undergoing neurosurgery.[1,2] However, data from a retrospective analysis of patients undergoing intracranial surgery indicated that when convulsions occurred postoperatively in these conditions, it was the neurosurgical procedures rather than the anaesthetics that were responsible.[3]

See also Status Epilepticus, under Uses and Administration, p. 1903.3.

1. Poulton TJ, Ellingson RJ. Seizure associated with induction of anesthesia with isoflurane. *Anesthesiology* 1984; 61: 471–6.
2. Hymes JA. Seizure activity during isoflurane anesthesia. *Anesth Analg* 1985; 64: 367–8.
3. Christys AR, *et al.* Retrospective study of early postoperative convulsions after intracranial surgery with isoflurane or enflurane anaesthesia. *Br J Anaesth* 1989; 62: 624–7.

Effects on the respiratory tract. A study[1] conducted mainly in adults found that humidification of anaesthetic mixtures containing isoflurane could reduce respiratory complications such as coughing, laryngospasm, and breath holding that were usually associated with the use of isoflurane for induction. However, a similar study[2] in children failed to confirm these findings.

For a report of occupational asthma associated with exposure to isoflurane and sevoflurane, see Occupational Exposure, under Precautions of Sevoflurane, p. 1913.3.

1. van Heerden PV, *et al.* Effect of humidification on inhalation induction with isoflurane. *Br J Anaesth* 1990; 64: 235–7.
2. McAuliffe GL, *et al.* Effect of humidification on inhalation induction with isoflurane in children. *Br J Anaesth* 1994; 73: 587–9.

Effects on the skin. There have been rare reports of contact dermatitis to isoflurane in anaesthetists.[1,2]

1. Caraffini S, *et al.* Isoflurane: an uncommon cause of occupational airborne contact dermatitis. *Contact Dermatitis* 1998; 38: 286.
2. Muncaster A, *et al.* Allergic contact dermatitis to isoflurane. *Br J Dermatol* 1999; 141: (suppl 55): 96–7.

Hypersensitivity. For a report of hypersensitivity reactions, including asthma, angioedema, and dermatitis, associated with occupational exposure to isoflurane and sevoflurane, see Occupational Exposure, under Precautions of Sevoflurane, p. 1913.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies isoflurane 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 04/10/11)

Interactions

The effects of competitive neuromuscular blockers such as atracurium are enhanced by isoflurane (see p. 2032.3). Care is advised if adrenaline and other sympathomimetics are given during isoflurane anaesthesia.

See also Interactions of General Anaesthetics, p. 1897.3.

Antineoplastics. Prolongation of the QT_c interval to above 440 milliseconds has been seen during anaesthesia with isoflurane 0.5% v/v in women who had received *anthracycline*-based (doxorubicin or epirubicin) chemotherapy for breast cancer.[1]

1. Owczuk R, *et al.* Is prolongation of the QTc interval during isoflurane anaesthesia more prominent in women pretreated with anthracyclines for breast cancer? *Br J Anaesth* 2004; 92: 658–61.

General anaesthetics. For a report that isoflurane increases serum concentrations of *propofol*, see p. 1912.2.

Pharmacokinetics

Isoflurane is absorbed on inhalation. The blood/gas partition coefficient is lower than that of enflurane or halothane. It is mostly excreted unchanged through the lungs. About 0.2% of inhaled isoflurane is metabolised, mainly to inorganic fluoride.

Metabolism. In 26 patients sedated with isoflurane for 24 hours, plasma fluoride ion concentration increased from a mean of 4.03 nanomol/mL to 13.57 nanomol/mL in 12 hours after stopping sedation.[1] These fluoride concentrations were considered to be too low to cause clinical renal dysfunction. In 30 patients sedated with isoflurane for up to 127 hours (mean duration was 36 hours), mean plasma fluoride ion concentration increased[2] to 20.01 nanomol/mL during sedation and continued rising for 16 hours after stopping isoflurane to a maximum mean concentration of 25.34 nanomol/mL; thereafter, levels gradually declined to normal values by the fifth day. Despite the increased plasma fluoride ion concentrations, no biochemical or clinical evidence of deterioration in renal function was found. Giving isoflurane for 34 days to a patient with tetanus who required sedation to facilitate mechanical ventilation resulted[3] in sustained fluoride ion concentrations of 50 nanomol/mL and a peak concentration of 87 nanomol/mL. Although such concentrations are considered to be potentially nephrotoxic no clinical effect on renal function was found.

1. Kong KL, *et al.* Isoflurane sedation for patients undergoing mechanical ventilation: metabolism to inorganic fluoride and renal effects. *Br J Anaesth* 1990; 64: 159–62.
2. Spencer EM, *et al.* Plasma inorganic fluoride concentrations during and after prolonged (>24h) isoflurane sedation: effect on renal function. *Anesth Analg* 1991; 73: 731–7.
3. Stevens JJWM, *et al.* Prolonged use of isoflurane in a patient with tetanus. *Br J Anaesth* 1993; 70: 107–109.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Forane; Zuflax; *Austral.*: AErrane; Forthane†; *Austria*: Forane; *Belg.*: Forene; *Braz.*: For-

ane; Isoforine; Isoran; *Canad.*: AErrane; Forane; *Chile*: Forene; *China*: AErrane (艾恩美); Forane (活宁); Ning Fen (宁芬); Terrell (宝龄托利儿); Yi Mei Ning (怡美宁); *Cz.*: AErrane; Forane; *Denm.*: Forene†; *Fin.*: Forene†; *Fr.*: AErrane; Forene; *Ger.*: Forene; *Gr.*: Forenium; *Hong Kong*: AErrane†; Forane†; *Hung.*: AErrane; Forane; *India*: AErrane; Forane; Isorane; *Indon.*: AErrane; Forane†; Terrell; *Irl.*: AErrane; Forane; *Israel*: AErrane; Forane; *Ital.*: AErrane; Forane; *Malaysia*: Forane; *Mex.*: Forane; Sofloran†; *Neth.*: AErrane†; Forene†; *Norw.*: Forene; *NZ*: AErrane; Forane†; Forthane; *Philipp.*: AErrane; Florane; Forane; *Pol.*: AErrane; Forane; *Port.*: Forene; *Rus.*: AErran (Аэрран); Forane (Форан); *S.Afr.*: AErrane†; Forane; Isofor; *Singapore*: AErrane; Forane; *Spain*: AErrane; Forane; *Swed.*: Forene; *Switz.*: Forene; *Thai.*: AErrane; Forane; *Turk.*: AErrane; Forane; Isofludem; *UK*: AErrane; Forane; *USA*: Forane; Terrell; *Venez.*: Forene.

Ketamine Hydrochloride

(BANM, USAN, rINNM)

CI-581; CL-369; CN-52372-2; Hidrocloruro de ketamina; Ketamiinihydrokloridi; Ketamin Hidroklorür; Ketamina, hidrocloruro de; Kétamine, chlorhydrate de; Ketaminhidroklorid; Ketaminhydrochlorid; Ketamin-hydrochlorid; Ketaminhydroklorid; Ketamini Hydrochloridum; Ketamino hidrochloridas; Ketaminy chlorowodorek; Кетамина Гидрохлорид; Кетамин Хидрохлорид.

(±)-2-(2-Chlorophenyl)-2-methylaminocyclohexanone hydrochloride.

$C_{13}H_{16}ClNO,HCl=274.2$

CAS — 6740-88-1 (ketamine); 1867-66-9 (ketamine hydrochloride).

ATC — N01AX03.

ATC Vet — QN01AX03.

UNII — O18YUO0I83.

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

Animal trank; Animal tranquilizer; Bump; Cat tranquilizer; Cat valium; Elephant tranquilizer; Green; Honey oil; Horse tranquilizer; Jet; Jet fuel; K; "K"; K wire; Kay Jay; K-blast; Keets; Keezy; Keller; Kellys day; Kenny; Ket; Keta; Ketaset; KFC; Kit kat; Kit-Kat; Kitty; KKK; Klarko K Kat; Klarky Kat; Kustard; Lady K; Naughty horsey; Old Man; Property of Sir John; Purple; Regretamine; Special K; Special "K"; Special la coke; Super acid; Super C; Super K; Tranquilizer; Triple K; Vetamine; Vitamin K; Wonky.

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

Ph. Eur. 8: (Ketamine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 10% solution in water has a pH of 3.5 to 4.1. Protect from light.

USP 36: (Ketamine Hydrochloride). A white crystalline powder having a slight characteristic odour. Soluble 1 in 4 of water, 1 in 14 of alcohol, 1 in 60 of dehydrated alcohol and of chloroform, and 1 in 6 of methyl alcohol; practically insoluble in ether. pH of a 10% solution in water is between 3.5 and 4.1. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Incompatibility. Ketamine hydrochloride is incompatible with soluble barbiturates. US licensed product information recommends that when use of diazepam and ketamine is required they should be given separately and not mixed in the same giving equipment.

Esketamine Hydrochloride *(BANM, rINNM)*

Esketamiinihydrokloridi; Esketamina, hidrocloruro de; Eskétamine, Chlorhydrate d'; Esketamine, chlorhydrate de; Esketaminhydrochlorid; Esketamin-hydrochlorid; Esketaminhydroklorid; Esketamini hydrochloridum; Esketamino hidrochloridas; Hidrocloruro de esketamina; *S*-Ketamine Hydrochloride; Эскетамина Гидрохлорид.

CAS — 33643-46-8 (esketamine).

ATC — N01AX14.

ATC Vet — QN01AX14.

UNII — LBP1H3SP2Z.

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

Ph. Eur. 8: (Esketamine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 10% solution in water has a pH of 3.5 to 4.5. Protect from light.

Uses and Administration

Ketamine is an anaesthetic given by intravenous injection, intravenous infusion, or intramuscular injection. It produces dissociative anaesthesia characterised by a trance-like state, amnesia, and marked analgesia which may persist into the recovery period. There is often an increase in muscle tone and the patient's eyes may remain open for all or part of the period of anaesthesia. Ketamine is used in general anaesthesia for diagnostic or short surgical operations that do not require skeletal muscle relaxation, for the induction of anaesthesia to be maintained with other drugs, and as a supplementary anaesthetic (see p. 1896.1). It also has good analgesic properties in subanaesthetic doses. It is considered to be of particular value in children requiring frequent repeated anaesthesia. Recovery is relatively slow.

Ketamine is given as the hydrochloride but doses are expressed in terms of the equivalent amount of base; ketamine hydrochloride 1.15 mg is equivalent to about 1 mg of ketamine. The following doses have been used in adults and children:

- For induction, the dose given by *intravenous injection* may range from the equivalent of 1 to 4.5 mg/kg of ketamine; a dose of 2 mg/kg given intravenously over 60 seconds usually produces surgical anaesthesia within 30 seconds of the end of the injection and lasting for 5 to 10 minutes.
- The initial *intramuscular* dose may range from 6.5 to 13 mg/kg; an intramuscular dose of 10 mg/kg usually produces surgical anaesthesia within 3 to 4 minutes lasting for 12 to 25 minutes. For diagnostic or other procedures not involving intense pain an initial intramuscular dose of 4 mg/kg has been used.
- Additional intravenous or intramuscular doses, ranging from half to the full induction dose, may be given for maintenance.
- For induction by *intravenous infusion* a total dose of 0.5 to 2 mg/kg is usually given at an appropriate infusion rate. Maintenance is achieved with 10 to 45 micrograms/kg per minute, the infusion rate being adjusted according to response.

Use should be preceded by atropine or another suitable antimuscarinic. Diazepam or another benzodiazepine may be given before surgery or as an adjunct to ketamine to reduce the incidence of emergence reactions.

The *S*-isomer, esketamine, is also given for similar uses in anaesthesia.

Reviews.

1. Hirota K, Lambert DG. Ketamine: its mechanism(s) of action and unusual clinical uses. *Br J Anaesth* 1996; 77: 441–4.
2. Wolff K, Winstock AR. Ketamine: from medicine to misuse. *CNS Drugs* 2006; 20: 199–218.
3. Sinner B, Graf BM. Ketamine. In: Schüttler J, Schwilden H, eds. *Handb Exp Pharmacol: Modern Anesthetics*. Berlin: Springer-Verlag, 2008; 182 (II): 313–33.
4. Aroni F, *et al.* Pharmacological aspects and potential new clinical applications of ketamine: reevaluation of an old drug. *J Clin Pharmacol* 2009; 49: 957–64.
5. Persson J. Wherefore ketamine? *Curr Opin Anaesthesiol* 2010; 23: 455–60.

Administration. Although ketamine hydrochloride is usually given intravenously or intramuscularly, oral[1,2] and rectal[3] dosage has been used successfully in children. Intranasal use of ketamine with midazolam in a neonate requiring anaesthesia has also been reported.[4] Unfortunately the onset of sedation with these three routes is too slow for emergency procedures and therefore a jet-injector of ketamine was developed[5] to provide non-traumatic, painless, and rapid anaesthesia in children. Intranasal and transdermal use may be useful in the management of pain (below); oral, rectal, and subcutaneous routes have also been tried.[6]

1. Tobias JD, *et al.* Oral ketamine premedication to alleviate the distress of invasive procedures in pediatric oncology patients. *Pediatrics* 1992; 90: 537–41.
2. Gutstein HB, *et al.* Oral ketamine preanesthetic medication in children. *Anesthesiology* 1992; 76: 28–33.
3. Lökken P, *et al.* Conscious sedation by rectal administration of midazolam or midazolam plus ketamine as alternatives to general anesthesia for dental treatment of uncooperative children. *Scand J Dent Res* 1994; 102: 274–80.
4. Louon A, *et al.* Sedation with nasal ketamine and midazolam for cryotherapy in retinopathy of prematurity. *Br J Ophthalmol* 1993; 77: 529–30.
5. Zsigmond EK, *et al.* A new route, jet-injection for anesthetic induction in children–ketamine dose-range finding studies. *Int J Clin Pharmacol Ther* 1996; 34: 84–8.
6. Kronenberg RH. Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. *J Pain Palliat Care Pharmacother* 2002; 16: 27–35.

Administration in children. Ketamine is used in general anaesthesia in children; for details of doses, see Uses and Administration, above.

Nonketotic hyperglycinaemia. Ketamine was tried with strychnine in a neonate with severe nonketotic hyperglycinaemia (p. 2623.2) and resulted in neurological improvement, although motor development remained unsatisfactory.[1] It was thought that ketamine might act by blocking NMDA receptors, which are activated in the CNS by glycine.

1. Tegtmeyer-Metadorf H, *et al.* Ketamine and strychnine treatment of an infant with nonketotic hyperglycinaemia. *Eur J Pediatr* 1995; 154: 649–53.

Pain. For a discussion of pain and its management, see p. 4.1. Ketamine is used for its analgesic action in neuropathic or other pain unresponsive to conventional analgesics. (For mention of its use for outpatient procedures in children, see p. 5.2.) Reviews have found the evidence for such use to be limited,[1–4] and have also differed on its value for postoperative pain.[5–7] Some have suggested[1,3,4] that ketamine is a reasonable third-line option for pain where standard analgesics have failed; however, such use may be limited by its adverse effects. Subcutaneous, intramuscular, intravenous, epidural, intrathecal, intranasal, transdermal, rectal, and oral routes have all been tried.[1,8] Ketamine has also been used topically.[9]

1. Hocking G, Cousins MJ. Ketamine in chronic pain management: an evidence-based review. *Anesth Analg* 2003; 97: 1730–9.
2. Bell RF, *et al.* Ketamine as an adjuvant to opioids for cancer pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/06/05).
3. Ben-Ari A, *et al.* Chronic administration of ketamine for analgesia. *J Pain Palliat Care Pharmacother* 2007; 21: 7–14.
4. Blonk ML *et al.* Use of oral ketamine in chronic pain management: a review. *Eur J Pain* 2010; 14: 466–72.
5. Subramaniam K, *et al.* Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. *Anesth Analg* 2004; 99: 482–95.
6. Ella N, Tramèr MR. Ketamine and postoperative pain—a quantitative systematic review of randomised trials. *Pain* 2005; 113: 61–70.
7. Bell RF, *et al.* Perioperative ketamine for acute postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 16/05/06).
8. Kronenberg RH. Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. *J Pain Palliat Care Pharmacother* 2002; 16: 27–35.
9. Finch PM, *et al.* Reduction of allodynia in patients with complex regional pain syndrome: a double-blind placebo-controlled trial of topical ketamine. *Pain* 2009; 146: 18–25.

Psychiatric disorders. A small preliminary randomised placebo-controlled study reported[1] rapid reductions in severity of depression after an intravenous infusion of ketamine hydrochloride 500 micrograms/kg was given to patients with treatment-resistant depression (see Depression, p. 398.1); the effect began within 2 hours, and was sustained for up to 1 week after infusion. Single infusions of the same dose have also improved suicidal ideation in those with treatment-resistant depression[2] and reduced severity of depression as an adjunct in those with treatment-resistant bipolar depression (see Bipolar Disorder, p. 397.2).[3] The role of ketamine, an NMDA antagonist, and the glutamatergic system in the treatment of mood disorders has been reviewed.[4,5]

1. Zarate CA, *et al.* A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 2006; 63: 856–64.
2. DiazGranados N, *et al.* Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry* 2010; 71: 1605–11.
3. Diazgranados N, *et al.* A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry* 2010; 67: 793–802.
4. Machado-Vieira R, *et al.* Ketamine and the next generation of antidepressants with a rapid onset of action. *Pharmacol Ther* 2009; 123: 143–50.
5. Zarate C, *et al.* Glutamatergic modulators: the future of treating mood disorders? *Harv Rev Psychiatry* 2010; 18: 293–303.

Status epilepticus. There have been isolated reports[1–3] of the successful use of ketamine in the control of refractory status epilepticus (p. 510.2).

1. Prüss H, Holtkamp M. Ketamine successfully terminates malignant status epilepticus. *Epilepsy Res* 2008; 82: 219–22.
2. Hsieh CY, *et al.* Terminating prolonged refractory status epilepticus using ketamine. *Clin Neuropharmacol* 2010; 33: 165–7.
3. Yeh PS, *et al.* Oral ketamine controlled refractory nonconvulsive status epilepticus in an elderly patient. *Seizure* 2011. Available at: http://dx.doi.org/10.1016/j.seizure.2011.06.001 (accessed 28/09/11)

Adverse Effects

Emergence reactions are common during recovery from ketamine anaesthesia and include vivid often unpleasant dreams, confusion, hallucinations, and irrational behaviour. Children and elderly patients appear to be less sensitive. Patients may also develop increased muscle tone, sometimes resembling seizures. Blood pressure and heart rate may be temporarily increased by ketamine; hypotension, arrhythmias, and bradycardia have occurred rarely.

Respiration may be depressed after rapid intravenous injection or with high doses. Apnoea and laryngospasm have occurred. Diplopia and nystagmus may occur. Nausea and vomiting, lachrymation, hypersalivation, and raised intra-ocular and CSF pressure have also been reported. Transient rashes and pain at the site of injection may occur.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Effects on the cardiovascular system. Ketamine has been advocated by some for maintaining or increasing cardiovascular performance in selected patients during induction of anaesthesia as it may increase blood pressure and heart rate.[1] However, there have been reports of reduced cardiac and pulmonary performance in severely ill patients[1] and of arrhythmias.[2]

Some of the cardiovascular effects of ketamine may be attenuated by premedication with diazepam[2] or clonidine.[3]

1. Waxman K, *et al.* Cardiovascular effects of anesthetic induction with ketamine. *Anesth Analg* 1980; 59: 355–8.

2. Cabbabe EB, Behbahani PM. Cardiovascular reactions associated with the use of ketamine and epinephrine in plastic surgery. *Ann Plast Surg* 1985; 15: 50–2.
3. Tanaka M, Nishikawa T. Oral clonidine premedication attenuates the hypertensive response to ketamine. *Br J Anaesth* 1994; 73: 758–62.

Effects on the liver. Changes in liver enzyme values have occurred after ketamine in an initial dose of 1 mg/kg followed by continuous infusion as a 0.1% solution.[1]

1. Dundee JW, *et al.* Changes in serum enzyme levels following ketamine infusions. *Anaesthesia* 1980; 35: 12–16.

Effects on mental state. Mental disturbances after ketamine anaesthesia may vary in incidence from less than 5% to greater than 30%,[1] but a subsequent review[2] assessed the general frequency at 10 to 20%; sedating drugs are effective at preventing and terminating such emergence reactions. Episodes of vomiting are generally associated with emergence from dissociative states. See also Abuse, below.

1. White PF, *et al.* Ketamine—its pharmacology and therapeutic uses. *Anesthesiology* 1982; 56: 119–36.
2. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. *Am J Emerg Med* 2008; 26: 985–1028.

Effects on the skin. Harlequin-like colour skin changes were reported[1] in a 9-month-old boy during anaesthesia with ketamine 15 mg. A transient patchy erythematous rash is seen on the upper torso in about 5 to 20% of adult patients given ketamine;[2] it disappears without treatment within about 20 minutes, and does not recur with further doses of the drug.

1. Wagner DL, Sewell AD. Harlequin color change in an infant during anesthesia. *Anesthesiology* 1985; 62: 695.
2. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. *Am J Emerg Med* 2008; 26: 985–1028.

Malignant hyperthermia. Malignant hyperthermia has been reported in a patient given ketamine.[1]

1. Rasore-Quartino A, *et al.* Forma atipica di ipertermia maligna: osservazione di un caso da ketamina. *Pathologica* 1985; 77: 609–17.

Precautions

Ketamine is contra-indicated in patients in whom elevation of blood pressure would be a serious hazard including those with hypertension, eclampsia or pre-eclampsia, severe coronary or myocardial disease, cerebrovascular accident, or cerebral trauma. Cardiac function should be monitored in patients found to have hypertension or cardiac decompensation. Ketamine should be used with caution in patients with elevated CSF pressure. It can raise intra-ocular pressure and should not be used in the presence of eye injury or increased intra-ocular pressure.

Ketamine does not reliably suppress pharyngeal and laryngeal reflexes and mechanical stimulation of the pharynx should be avoided unless a muscle relaxant is used.

Ketamine should be used with caution in patients with neurotic traits or psychiatric disorders. Verbal, tactile, and visual stimuli should be kept to a minimum during recovery in an attempt to reduce the risk of emergence reactions.

See also Precautions for General Anaesthetics, p. 1897.3.

Abuse. Healthcare workers in the USA were alerted to the dangers associated with the abuse of ketamine as long ago as 1979.[1] Similar concern had also been voiced in the UK[2] over the abuse of ketamine at social gatherings where it has been taken intranasally or orally; it has also been injected intramuscularly.[3] A WHO expert committee[4] considered in 2006 that the available information on ketamine was not sufficient to warrant international control. Studies in *animals* have shown that ketamine can produce dependence, however, reports of dependence in humans are limited (see below). Although tolerance may occur there is no evidence of a withdrawal syndrome (but see below). Ketamine abuse has been reported in several countries.

Ketamine produces a state of psychological dissociation resulting in hallucinations and out of body or near death experiences. It can induce a state of helplessness in which the user loses awareness of the environment and this with severe loss of coordination and pronounced analgesia can put the user at great risk. Furthermore, some users experience a state in which they are unconcerned about whether they live or die. Ketamine has the potential for compulsive repeated use and there have been reports of users self-injecting ketamine several times daily for prolonged periods. Dependency may develop[5,6] and withdrawal symptoms requiring detoxification can occur.[6] Frequent use may produce long-lasting memory impairment.[7,8] Other adverse effects include a report[9] of an acute dystonic reaction in a 20-year old man following self-administration of ketamine intravenously.

In one case series[10] of 20 patients presenting to hospital after ketamine abuse the most common symptoms included anxiety, chest pain, and palpitations. Frequent complications included agitation and rhabdomyolysis. Symptoms were generally short lived with most patients discharged within 5 hours. A more recent retrospective case-note review[11] of 233 patients, also presenting to hospital after ketamine abuse, found the most common presenting symptoms to be impaired consciousness, increased blood pressure, tachycardia, abdominal pain or tenderness, hyperthermia, and dizziness. Symptoms resolved with supportive treatment in most of these patients and none had developed major complications.

Some[2] suggest that patients seeking medical attention are best placed in a quiet darkened room to recover with diazepam being given for unresponsive panic attacks while others advocate that such patients should be admitted to an intensive care unit for close monitoring.[12] The use of intravenous fluids to prevent rhabdomyolysis has also been recommended.[10]

Long-term and frequent abuse of ketamine has been associated with adverse effects on the urinary tract;[13-16] time to onset was reported[17] to range from 1 month to several years. Patients may present with symptoms of dysuria, frequency, urgency, urinary incontinence, suprapubic pain, and haematuria. Examination has shown in some cases a contracted shrunken bladder and ulcerative cystitis. Complications have included hydronephrosis and renal impairment. Dilated common bile duct, presenting as epigastric pain, and abnormal liver function tests have also been reported[18,19] with long-term abuse.

Ketamine is tasteless, odourless, and colourless and has been misused to incapacitate the victim and produce amnesia in sexual assaults and drug-facilitated rape ('date rape').[6]

1. Anonymous. Ketamine abuse. *FDA Drug Bull* 1979; 9: 24.
2. Jansen KLR. Non-medical use of ketamine. *BMJ* 1993; 306: 601–2.
3. National Institute on Drug Abuse. Club drugs (GHB, Ketamine, and Rohypnol) (updated July 2010). Available at: http://www.drugabuse.gov/pdf/infofacts/ClubDrugs10.pdf (accessed 28/03/11)
4. WHO. WHO expert committee on drug dependence: thirty-fourth report. *WHO Tech Rep Ser* 942 2006. Also available at: http://libdoc.who.int/trs/WHO_TRS_942_eng.pdf (accessed 06/08/08)
5. Jansen KLR, Darracot-Cankovic R. The nonmedical use of ketamine, part two: a review of problem use and dependence. *J Psychoactive Drugs* 2001; 33: 151–8.
6. Smith KM, *et al.* Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and γ-hydroxybutyrate. *Am J Health-Syst Pharm* 2002; 59: 1067–76.
7. Curran HV, Monaghan L. In and out of the K-hole: a comparison of the acute and residual effects of ketamine in frequent and infrequent ketamine users. *Addiction* 2001; 96: 749–60.
8. Morgan CJA, *et al.* Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. *Addiction* 2010; 105: 121–33. Correction. *ibid.*: 766.
9. Pelser JM, Orban DJ. Dystonic reaction after ketamine abuse. *Ann Emerg Med* 1982; 11: 673–5.
10. Weiner AL, *et al.* Ketamine abusers presenting to the emergency department: a case series. *J Emerg Med* 2000; 18: 447–51.
11. Ng SH, *et al.* Emergency department presentation of ketamine abusers in Hong Kong: a review of 233 cases. *Hong Kong Med J* 2010; 16: 6–11.
12. Gill PA. Non-medical use of ketamine. *BMJ* 1993; 306: 1340.
13. Chu PSK, *et al.* 'Street ketamine'-associated bladder dysfunction: a report of ten cases. *Hong Kong Med J* 2007; 13: 311–13.
14. Shahani R, *et al.* Ketamine-associated ulcerative cystitis: a new clinical entity. *Urology* 2007; 69: 810–12.
15. Cottrell AM, *et al.* Urinary tract disease associated with chronic ketamine use. *BMJ* 2008; 336: 973.
16. Chu PS-K, *et al.* The destruction of the lower urinary tract by ketamine abuse: a new syndrome? *BJU Int* 2008; 102: 1616–22.
17. Tsai T-H, *et al.* Ketamine-associated bladder dysfunction. *Int J Urol* 2009; 16: 826–9.
18. Wong SW, *et al.* Dilated common bile ducts mimicking choledochal cysts in ketamine abusers. *Hong Kong Med J* 2009; 15: 53–6.
19. Ng SH, *et al.* Dilated common bile ducts in ketamine abusers. *Hong Kong Med J* 2009; 15: 157.

Neurosurgery. Although the idea that ketamine should not be used in patients at risk from rises in intracranial pressure has limited its use in neurosurgical patients, a review[1] considered that if used with controlled ventilation and a GABA receptor agonist, and without nitrous oxide, it did not appear to have adverse effects in this group; there is evidence suggesting that it may have neuroprotective properties in some circumstances.[1,2]

1. Himmelseher S, Durieux ME. Revising a dogma: ketamine for patients with neurological injury? *Anesth Analg* 2005; 101: 524–34.
2. Hudetz JA, Pagel PS. Neuroprotection by ketamine: a review of the experimental and clinical evidence. *J Cardiothorac Vasc Anesth* 2010; 24: 131–42.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ketamine 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 04/10/11)

Interactions

Inhalational anaesthetics, such as ether and halothane, and other cerebral depressants may prolong the effect of ketamine and delay recovery. Prolonged recovery has also occurred when barbiturates and/or opioids have been given with ketamine. It has been recommended that ketamine should not be used with ergometrine.

See also Interactions of General Anaesthetics, p. 1897.3.

Neuromuscular blockers. For the enhancement of the effect of *tubocurarine* or *atracurium* by ketamine, see p. 2032.3.

Thyroid drugs. For a reference to increased cardiovascular adverse effects with *levothyroxine*, see p. 2342.1.

Xanthines. For a reference to seizures and tachycardia attributed to an interaction between ketamine and *theophylline*, see p. 1236.2.

Pharmacokinetics

After intravenous boluses, ketamine shows a bi- or triexponential pattern of elimination. The alpha phase lasts about 45 minutes with a half-life of 10 to 15 minutes. This first phase, which represents ketamine's anaesthetic action, is terminated by redistribution from the CNS to peripheral tissues and hepatic biotransformation to an active metabolite norketamine. Other metabolic pathways include hydroxylation of the cyclohexone ring and conjugation with glucuronic acid. The beta phase half-life is about 2.5 hours. Ketamine is excreted mainly in the urine as metabolites. It crosses the placenta.

References.

1. Clements JA, Nimmo WS. Pharmacokinetics and analgesic effect of ketamine in man. *Br J Anaesth* 1981; 53: 27–30.
2. Grant IS, *et al.* Pharmacokinetics and analgesic effects of IM and oral ketamine. *Br J Anaesth* 1981; 53: 805–9.
3. Grant IS, *et al.* Ketamine disposition in children and adults. *Br J Anaesth* 1983; 55: 1107–11.14c: 144P.
4. Geisslinger G, *et al.* Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method. *Br J Anaesth* 1993; 70: 666–71.
5. Malinovsky J-M, *et al.* Ketamine and norketamine plasma concentrations after iv, nasal and rectal administration in children. *Br J Anaesth* 1996; 77: 203–7.
6. Hijazi Y, *et al.* Pharmacokinetics and haemodynamics of ketamine in intensive care patients with brain or spinal cord injury. *Br J Anaesth* 2003; 90: 155–60.
7. Weber F, *et al.* S-ketamine and s-norketamine plasma concentrations after nasal and i.v. administration in anesthetized children. *Pediatr Anesth* 2004; 14: 983–8.
8. Sigtermans M, *et al.* S(+)-ketamine effect on experimental pain and cardiac output: a population pharmacokinetic-pharmacodynamic modeling study in healthy volunteers. *Anesthesiology* 2009; 111: 892–903.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cost; Inducmina; Ketalar†; Ketanest; *Austral.*: Ketalar; *Austria*: Ketanest; *Belg.*: Ketalar; *Braz.*: Clortamina; Ketalar; *Canad.*: Ketalar; *Cz.*: Calypsol; Narkamon; *Fin.*: Ketalar; Ketanest; *Ger.*: Ketanest; *Gr.*: Ketalar; Ketanest; *Hong Kong*: Ketalar; *Hung.*: Calypsol; *India*: Aneket; Hypnoket; Keta; Ketafast; Ketajex; Ketalar; Ketam; Ketamax; Ketmin; Ketsia; Kmin; *Indon.*: Anesject; Ivanes; Ketalar; KTM; *Irl.*: Ketalar; *Israel*: Ketalar; *Malaysia*: Kanox; Ketava; *Mex.*: Ketalin; *Neth.*: Ketanest; *Norw.*: Ketalar; *NZ*: Ketalar; *Philipp.*: Ketacor; Ketaject†; Ketamax; Ketazol; Quetanex†; *Pol.*: Calypsol†; Ketanest; *Port.*: Ketalar; *Rus.*: Calypsol (Калипсол); *S.Afr.*: Brevinaze†; *Spain*: Ketolar; *Swed.*: Ketalar; *Switz.*: Ketalar; *Thai.*: Calypsol; Ketalar; *Turk.*: Ketalar; *UK*: Ketalar; *Ukr.*: Calypsol (Калипсол)†; *USA*: Ketalar; *Venez.*: Keiran.

Pharmacopoeial Preparations
BP 2014: Ketamine Injection;
USP 36: Ketamine Hydrochloride Injection.

Methohexital *(BAN, rINN)*

Méthohexital; Methohexitalum; Methohexitone; Metoheksitaali; Metohexital; Метогекситал.

(±)-5-Allyl-1-methyl-5-(1-methylpent-2-ynyl)barbituric acid; 1-Methyl-5-(1-methyl-2-pentynyl)-5-(2-propenyl)-2,4,6 (1*H*,3*H*,5*H*)-pyrimidinetrione.

$C_{14}H_{18}N_2O_3$=262.3

CAS — 151-83-7; 18652-93-2.

ATC — N01AF01; N05CA15.

ATC Vet — QN01AF01; QN05CA15.

UNII — E5B8ND5IPE.

Pharmacopoeias. In *US.*

USP 36: (Methohexital). A white to faintly yellowish-white crystalline odourless powder. M.p. 92 degrees to 96 degrees but the range between beginning and end of melting does not exceed 3 degrees. Very slightly soluble in water; slightly soluble in alcohol, in chloroform, and in dilute alkalis.

Methohexital Sodium *(BANM, rINNM)*

Compound 25398; Enallynymalnatrium; Méthohexital Sodique; Methohexitone Sodium; Metohexital sódico; Natrii Methohexitalum; Натрий Метогекситал.

$C_{14}H_{17}N_2NaO_3$=284.3

CAS — 309-36-4; 22151-68-4; 60634-69-7.

ATC — N01AF01; N05CA15.

ATC Vet — QN01AF01; QN05CA15.

UNII — 60200PNZ7Q.

Pharmacopoeias. *US* includes Methohexital Sodium for Injection.

USP 36: (Methohexital Sodium for Injection). A freeze-dried sterile mixture of methohexital sodium and anhydrous sodium carbonate as a buffer, prepared from an aqueous solution of methohexital, sodium hydroxide, and sodium carbonate. It is a white to off-white, essentially odourless, hygroscopic powder. pH of a 5% solution in water is between 10.6 to 11.6.

Incompatibility. Solutions of methohexital sodium are incompatible with acidic substances including some antibacterials, antipsychotics, neuromuscular blockers, antimuscarinics, and analgesics. Compounds commonly listed as incompatible include atropine sulfate, pethidine hydrochloride, metocurine iodide, fentanyl citrate, morphine sulfate, pentazocine lactate, silicones, suxamethonium chloride, tubocurarine chloride, and compound sodium lactate injection. Only preservative-free diluents should be used to reconstitute methohexital sodium; precipitation may occur if a diluent containing a bacteriostatic agent is used.

Stability. Solutions of methohexital sodium in Water for Injections are stable for at least 6 weeks at room temperature; however reconstituted solutions should be stored no longer than 24 hours as they contain no bacteriostatic agent. Solutions in glucose or sodium chloride injections are stable only for about 24 hours.

Uses and Administration

Methohexital is a short-acting barbiturate anaesthetic that has actions similar to those of thiopental (p. 1915.2) but it is about 2 to 3 times more potent. It is given as the sodium salt and has similar uses to thiopental in anaesthesia. Induction of anaesthesia is less smooth than with thiopental and there may be excitatory phenomena. It has a shorter duration of action than thiopental and recovery after an induction dose occurs within 5 to 7 minutes although drowsiness may persist for some time.

As with other barbiturate anaesthetics the dose of methohexital required varies greatly according to the state of the patient and the nature of other drugs also being used (see under Precautions of Thiopental, p. 1916.2, and Interactions of Thiopental, p. 1916.2, for further details). Methohexital sodium is usually given intravenously as a 1% solution. Higher concentrations may markedly increase the incidence of adverse effects. A typical dose for induction of anaesthesia is 50 to 120 mg (usual range 1 to 1.5 mg/kg) given at a rate of about 10 mg (1 mL of a 1% solution) every 5 seconds. For the maintenance of general anaesthesia methohexital sodium may be given by intravenous injection in doses of 20 to 40 mg every 4 to 7 minutes as required or it may be given as a 0.2% solution by continuous intravenous infusion at a rate of 3 mL/minute.

For dosage in children, see below.

Administration in children. Although intravenous use is considered preferable in adults, in the USA methohexital sodium has been licensed for use in children aged over 1 month only by the intramuscular and rectal routes: usual doses for the induction of anaesthesia are 6.6 to 10 mg/kg intramuscularly, as a 5% solution, or 25 mg/kg rectally, as a 1% solution. In some countries methohexital sodium has also been given intravenously to children.

Administration in the elderly. It is usually recommended that the dosage of barbiturate anaesthetics is reduced in the elderly. A study[1] in elderly patients has shown that although reducing the rate of intravenous dosage reduces the speed of induction, the dosage required is also reduced. Giving methohexital sodium 0.5% at a rate of 25 mg/minute induced anaesthesia in a mean of 83.8 seconds and required a mean dose of 560 micrograms/kg. Corresponding values for a rate of 100 mg/minute were 43.6 seconds and 1 mg/kg, respectively.

1. Berthoud MC, *et al.* Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients. *Br J Anaesth* 1993; 70: 423–7.

Dental sedation. Some anaesthetics are used as sedatives in dental procedures (see p. 1032.2). Methohexital has been tried for patient-controlled sedation in oral surgery under local anaesthesia.[1] In a group of 42 patients, results with 2.5 mg of methohexital compared favourably with those obtained in patients receiving 5 mg of propofol on demand, although patients in the methohexital group had a greater degree of postoperative drowsiness.

1. Hamid SK, *et al.* Comparison of patient-controlled sedation with either methohexitone or propofol. *Br J Anaesth* 1996; 77: 727–30.

Adverse Effects and Precautions

As for Thiopental Sodium, p. 1916.1.

Excitatory phenomena are more common and induction less smooth with methohexital than with thiopental. Methohexital should be used with caution, if at all, in patients with a history of epilepsy.

See also Adverse Effects and Precautions for General Anaesthetics, p. 1896.3.

Incidence of adverse effects. In a study of 4379 uses of methohexital in 2722 dental patients the total intravenous dose ranged from 20 mg to 560 mg (with a mean of 151 mg), and the duration of treatment was 8 to 32 minutes.[1] Complications included: restlessness not controlled by diazepam (292 cases), respiratory complications (214), uncontrollable crying during recovery (73), pain along vein (45) with thrombophlebitis (5), jactitations (22), and allergic reactions (10).

1. McDonald D. Methohexitone in dentistry. *Aust Dent J* 1980; 25: 335–42.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving methohexital, and the last available guidance from the American Academy of Pediatrics[1] considered that it was therefore usually compatible with breast feeding.

In a study[2] of 9 breast-feeding women undergoing general anaesthesia, it was estimated that the exposure of a breast-fed infant to methohexital would be less than 1% of the maternal dose after induction with methohexital. Breast feeding was not interrupted during the study and none of the infants appeared drowsy or sedated.

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 26/05/04)
2. Borgatta L, *et al.* Clinical significance of methohexital, meperidine, and diazepam in breast milk. *J Clin Pharmacol* 1997; 37: 186–92.

Effects on the nervous system. Two case reports of seizures induced by methohexital in children with seizure disorders.[1] Seizures are considered a rare adverse effect of methohexital. In 48 000 patients given methohexital, only 3 developed clonic-type seizures.[2]

A case of a tonic-clonic seizure possibly due to an interaction between paroxetine and methohexital is discussed below.

1. Rockoff MA, Goudsouzian NG. Seizures induced by methohexital. *Anesthesiology* 1981; 54: 333–5.
2. Metriyakool K. Seizures induced by methohexital. *Anesthesiology* 1981; 55: 718.

Pain on injection. Methohexital is associated with severe pain particularly if veins on the back of the hands are used. The incidence of pain on injection may be reduced by using a forearm vein or by pre-injection with lidocaine.

Porphyria. Licensed product information contra-indicates the use of methohexital in patients with latent or manifest porphyria.

Rebound anaesthesia. Rebound of anaesthesia with abolition of reflexes and depression of respiration occurred in a 6-year-old boy[1] 100 minutes after anorectal induction with 27.6 mg/kg methohexital.

1. Kaiser H, Al-Rafai S. Wie sicher ist die rektale Narkoseeinleitung mit Methohexital in der Kinderanaesthesie? *Anaesthesist* 1985; 34: 359–60.

Interactions

As for Thiopental Sodium, p. 1916.2.

Antidepressants. A 42-year-old woman[1] had a generalised tonic-clonic seizure immediately after being anaesthetised with methohexital for the last in a series of 6 electroconvulsive therapies. She had been receiving *paroxetine* throughout the series. A previous course, without concurrent paroxetine, had been uneventful.

1. Folkerts H. Spontaneous seizure after concurrent use of methohexital anesthesia for electroconvulsive therapy and paroxetine: a case report. *J Nerv Ment Dis* 1995; 183: 115–16.

Pharmacokinetics

Methohexital is less lipid soluble than thiopental but concentrations sufficient to produce anaesthesia are attained in the brain within 30 seconds of an intravenous dose. Methohexital is also absorbed when given rectally, producing an effect within about 5 to 15 minutes. Recovery from anaesthesia occurs quickly as a result of rapid metabolism and redistribution into other body tissues. Methohexital does not appear to concentrate in fatty tissues to the same extent as other barbiturate anaesthetics. Protein binding has been reported to be about 73%. Methohexital is rapidly metabolised in the liver through demethylation and oxidation. The terminal half-life ranges from 1.5 to 6 hours. Methohexital diffuses across the placenta and has been detected in breast milk.

References.

1. Swerdlow BN, Holley FO. Intravenous anaesthetic agents: pharmacokinetic-pharmacodynamic relationships. *Clin Pharmacokinet* 1987; 12: 79–110.
2. Le Normand Y, *et al.* Pharmacokinetics and haemodynamic effects of prolonged methohexitone infusion. *Br J Clin Pharmacol* 1988; 26: 589–94.
3. Redke F, *et al.* Pharmacokinetics and clinical experience of 20-h infusions of methohexitone in intensive care patients with postoperative pyrexia. *Br J Anaesth* 1991; 66: 53–9.
4. van Hoogdalem EJ, *et al.* Pharmacokinetics of rectal drug administration, part I: general considerations and clinical applications of centrally acting drugs. *Clin Pharmacokinet* 1991; 21: 11–26.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Brietal†; *Austria*: Brietal; *Neth.*: Brietal; *Pol.*: Brietal†; *Rus.*: Brietal (Бриетал); *USA*: Brevital.

Pharmacopoeial Preparations

USP 36: Methohexital Sodium for Injection.

Methoxyflurane (BAN, USAN, rINN)

Methoxyfluran; Méthoxyflurane; Methoxyfluranum; Metoksifluraani; Metoxifluran; Metoxiflurano; NSC-110432; Метоксифлуран.

2,2-Dichloro-1,1-difluoro-1-methoxyethane; 2,2-Dichloro-1,1-difluoroethyl methyl ether.

$C_3H_4Cl_2F_2O$=165.0

CAS — 76-38-0.

ATC — N02BG09.

ATC Vet — QN02BG09.

UNII — 30905R8O7B.

Pharmacopoeias. In *US.*

USP 36: (Methoxyflurane). A clear, practically colourless, mobile liquid having a characteristic odour. It may contain a suitable stabiliser. B.p. about 105 degrees. Soluble 1 in 500 of water; miscible with alcohol, with acetone, with chloroform, with ether, and with fixed oils. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Uses and Administration

Methoxyflurane is a volatile halogenated anaesthetic given by inhalation. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) of 0.16%, but because of its low vapour pressure, induction of general anaesthesia with methoxyflurane is slow. In recommended concentrations it is non-flammable and not explosive when mixed with oxygen. Methoxyflurane possesses good analgesic properties. It does not produce appreciable skeletal muscle relaxation at the concentrations used. Methoxyflurane does not relax the uterus and has little effect on uterine contractions during labour. It is used in subanaesthetic doses to provide analgesia for painful procedures and trauma. In anaesthetic doses, it has been used mainly for maintenance of general anaesthesia (p. 1896.1), but safer anaesthetics are preferred because of its nephrotoxicity.

Concentrations of about 0.2 to 0.7% v/v are used to provide analgesia to conscious patients. The recommended maximum total dose for intermittent self-administration is 6 mL of liquid daily or 15 mL weekly; use on consecutive days is not recommended.

References.

1. Babl FE, *et al.* Inhaled methoxyflurane as a prehospital analgesic in children. *Emerg Med Australas* 2006; 18: 404–10.
2. Babl F, *et al.* A pilot study of inhaled methoxyflurane for procedural analgesia in children. *Pediatr Anesth* 2007; 17: 148–53.
3. Buntine P, *et al.* Prehospital analgesia in adults using inhaled methoxyflurane. *Emerg Med Australas* 2007; 19: 509–14.
4. Grindlay J, Babl FE. Review article: efficacy and safety of methoxyflurane analgesia in the emergency department and prehospital setting. *Emerg Med Australas* 2009; 21: 4–11.

Adverse Effects

As with other halogenated anaesthetics respiratory depression, hypotension, and malignant hyperthermia have been reported. Methoxyflurane sensitises the myocardium to sympathomimetics to a lesser extent than halothane; arrhythmias appear to be rare.

Methoxyflurane impairs renal function in a dose-related manner that is thought to be due to the effect of the released fluoride on the distal tubule (but see under Pharmacokinetics, p. 1908.1) and may cause polyuric or oliguric renal failure, oxaluria being a prominent feature. Nephrotoxicity is greater with methoxyflurane than with other halogenated anaesthetics because of slower metabolism over several days resulting in prolonged production of fluoride ions, and metabolism to other potentially nephrotoxic substances.

There have also been occasional reports of hepatic dysfunction, jaundice, and fatal hepatic necrosis. Cardiac hypotension, gastrointestinal adverse effects, euphoria, drowsiness, agitation, headache, dizziness, and amnesia have been reported, as have coughing and choking. Blurred vision, diplopia, and nystagmus have been noted.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Precautions

The use of methoxyflurane is limited because of its potential to cause nephrotoxicity and its use as a general anaesthetic is no longer recommended. Methoxyflurane should not be used daily for analgesia and is contra-indicated in the presence of renal impairment.

As with other halogenated anaesthetics it is advisable not to give methoxyflurane to patients who have shown signs of liver damage or fever after previous anaesthesia involving halogenated anaesthetics. Patients with known, or suspected, susceptibility to malignant hyperthermia should not be given methoxyflurane. When used for analgesia, methoxyflurane is also contra-indicated in those with cardiovascular instability, respiratory depression, and head injury or loss of consciousness; it should be used with caution in the elderly.

See also Precautions for General Anaesthetics, p. 1897.3.

Abuse. A 27-year-old nurse suffered from progressive renal disease and painful diffuse and multifocal periostitis, which had developed as a probable consequence of intermittent self-exposure to methoxyflurane possibly over a 9-year period.[1] There has also been a report[2] of hepatitis in a 39-year-old physician who repeatedly self-administered subanaesthetic concentrations of methoxyflurane for insomnia. Inhalation of about 2 mL of methoxyflurane had occurred once or twice almost every day for 6 weeks. A 125-mL bottle of methoxyflurane had been consumed in about 1 month.

1. Klemmer PJ, Hadler NM. Subacute fluorosis: a consequence of abuse of an organofluoride anesthetic. *Ann Intern Med* 1978; 89: 607–11.
2. Okuno T, *et al.* Hepatitis due to repeated inhalation of methoxyflurane in subanaesthetic concentrations. *Can Anaesth Soc J* 1985; 32: 53–5.

Interactions

Care is advised if adrenaline or other sympathomimetics are given to patients also receiving methoxyflurane. The effects of competitive neuromuscular blockers are enhanced by methoxyflurane. The chronic use of hepatic enzyme-inducing drugs, such as barbiturates, may enhance the metabolism of methoxyflurane thereby increasing the risk of nephrotoxicity. Use of nephrotoxic drugs, including certain antibacterials, with methoxyflurane should be avoided; fatal nephrotoxicity has been reported when used with tetracycline.

See also Interactions of General Anaesthetics, p. 1897.3.

Pharmacokinetics

Methoxyflurane is absorbed on inhalation. The blood/gas partition coefficient is high. Methoxyflurane is metabolised to a greater extent than other inhalational anaesthetics. About 50 to 70% of absorbed methoxyflurane undergoes metabolism in the liver to free fluoride, oxalic acid, difluoromethoxyacetic acid, and dichloroacetic acid. Methoxyflurane is very soluble in adipose tissue and excretion may be slow. Peak plasma concentrations of fluoride occur 2 to 4 days after a dose. Methoxyflurane crosses the placenta.

Metabolism. Although fluoride has been thought to be the nephrotoxic metabolite formed during biotransformation of methoxyflurane, studies[1,2] *in vitro* and in *rats* have suggested that dichloroacetic acid, formed with fluoride by *O*-demethylation, may contribute to the nephrotoxic effect.

1. Kharasch ED, *et al.* New insights into the mechanism of methoxyflurane nephrotoxicity and implications for anesthetic development (part 1): identification of the nephrotoxic metabolic pathway. *Anesthesiology* 2006; 105: 726–36.
2. Kharasch ED, *et al.* New insights into the mechanism of methoxyflurane nephrotoxicity and implications for anesthetic development (part 2): identification of nephrotoxic metabolites. *Anesthesiology* 2006; 105: 737–45.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Penthrox; *NZ*: Penthrox; *Ukr.*: Pentrox (Пентрокс).

Nitrous Oxide

Azot oksit; Azote, Protoxyde d'; Azoto Protossido; Azotu(I) tlenek; Diazoto oksidas; Dikväveoxid; Dilämmastikoksiid; Dinitrogen Oxide; Dinitrogenii Oxidum; Dinitrogenoksid; Dinitrogenoxid; Dinitrogén-oxid; Distickstoffmonoxid; Distikstofmonoxide; Dityppioksidi; Dušik suboksid; E942; Gas hilarante; Gaz hilariant; Ilokaasu; Kvælstofforilte; Lachgas; Lattergas; Laughing Gas; Lystgass; Monossido di diazoto; Monóxido de dinitrógeno; Monóxido de nitrógeno; Nitrogen Monoxide; Nitrogen Oxide; Nitrogenii Monoxidum; Nitrogenii Oxidum; Nitrogenium Oxydulatum; Ossido di diazoto; Oxid dusný; Oxid nitrós; Óxido nitroso; Oxidul de azot; Oxyde Nitreux; Oxydum Nitrosum; Podtlenek azotu; Protossido di azoto; Protoxid de azot; Protóxido de azoe; Protóxido de nitrógeno; Stickoxydul; Stikstofoxidule; Диазотен оксид; Закись азота.

N_2O=44.01

CAS — 10024-97-2.

ATC — N01AX13.

ATC Vet — QN01AX13.

UNII — K50XQU1029.

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

Bulb; Buzz bomb; Cartridges; Fall down; Gas; Going to the dentist; Grocery store high; Hippy crack; Hysteria; Laughing gas; Nang; Nie; Nigh; Nitro; Nitrogen; Nitrous; Noss; Pan; Shoot the breeze; Tanks; Whippet; Whippets; Wippets.

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

Ph. Eur. 8: (Nitrous Oxide). A colourless gas. One vol. measured at a pressure of 101 kPa dissolves, at 20 degrees, in about 1.5 vol. of water. Store liquefied under pressure in suitable containers complying with the legal regulations.

The BP 2014 directs that Nitrous Oxide should be kept in approved metal cylinders which are painted blue and carry a label stating 'Nitrous Oxide'. In addition, 'Nitrous Oxide' or the symbol 'N_2O' should be stencilled in paint on the shoulder of the cylinder.

USP 36: (Nitrous Oxide). A colourless gas, without appreciable odour or taste. One litre at 0 degrees and at a pressure of 760 mmHg weighs about 1.97 g. One volume dissolves in about 1.4 volumes of water at 20 degrees and at a pressure of 760 mmHg; freely soluble in alcohol; soluble in ether and in oils.

Flammability. Nitrous oxide supports combustion.

Storage and supply. Nitrous oxide is supplied compressed in metal cylinders. National standards are usually in operation for the labelling and marking of such cylinders.

Cylinders containing 50% nitrous oxide and 50% oxygen should be protected from the cold to prevent separation of the gases. Before use, cylinders should be maintained at a temperature above 10 degrees for at least 24 hours to ensure mixing; cylinders containing up to 700 litres of gas may be used immediately if inverted 3 times beforehand.

Uses and Administration

Nitrous oxide is an anaesthetic given by inhalation. It is a weak anaesthetic with a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) of 110%. It has strong analgesic properties, but produces little muscle relaxation. Nitrous oxide must be given with oxygen, otherwise hypoxia will occur.

Nitrous oxide with oxygen has been used in the induction and maintenance of general anaesthesia (p. 1896.1). However, it is now mainly used as an adjuvant to other inhalational or intravenous anaesthetics, permitting them to be used at significantly lower concentrations. It is also used, with oxygen, in subanaesthetic concentrations for analgesia and sedation in emergency care and obstetric and other painful procedures, including dental procedures (see p. 1032.2).

For maintenance of anaesthesia a mixture containing 50 to 66% nitrous oxide with oxygen is commonly used. Recovery is usually rapid from nitrous oxide anaesthesia.

Nitrous oxide usually 50% v/v with oxygen is used for analgesia; cylinders containing premixed nitrous oxide 50% v/v and oxygen 50% v/v are available in some countries.

Nitrous oxide has also been used occasionally as an insufflating gas for laparoscopy and as a refrigerant in cryosurgery.

Administration in children. Nitrous oxide with oxygen is used in general anaesthesia and for analgesia in children; doses are as for adults (see Uses and Administration, above).

Alcohol withdrawal syndrome. The symptoms of acute alcohol withdrawal (p. 1734.1) are usually managed with benzodiazepines; nitrous oxide has been tried but results have been equivocal.[1,2] More recently, a systematic review[3] found that although nitrous oxide may be a rapidly effective treatment for mild to moderate cases, there was no strong evidence in favour of its use over sedatives due to the small sample sizes of the included studies.

1. Gillman MA. Lichtigfeld FJ. Analgesic nitrous oxide for alcohol withdrawal: a critical appraisal after 10 years' use. *Postgrad Med J* 1990; 66: 543–6.
2. Alho H, *et al.* Long-term effects of and physiological responses to nitrous oxide gas treatment during alcohol withdrawal: a double-blind, placebo-controlled trial. *Alcohol Clin Exp Res* 2002; 26: 1816–22.
3. Gillman MA. *et al.* Psychotropic analgesic nitrous oxide for alcoholic withdrawal states. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 14/01/10).

Pain. A mixture of nitrous oxide 50% v/v and oxygen 50% v/v can provide good relief of pain (see Choice of Analgesic, p. 4.2) without loss of consciousness and is suitable for self-administration. It has been widely used for analgesia and sedation during dental procedures. It is also used for short procedures such as dressing changes,[1,2] venepuncture and biopsy,[3] for pain relief during childbirth,[4] in the management of postoperative pain,[1] as an aid to postoperative physiotherapy, and for acute pain in emergency situations such as in ambulances and in the hospital setting.[3,5–7] It has also been tried successfully for colonoscopy,[8] and bronchoscopy.[9,10] Continuous inhalation of nitrous oxide-oxygen has been tried for periods longer than 24 hours in the management of pain in terminal cancer.[11] However, such a practice is not usually otherwise recommended[1] as it may result in megaloblastic bone-marrow changes.

1. Hull CJ. Control of pain in the perioperative period. *Br Med Bull* 1988; 44: 341–56.
2. Gaukroger PB. Pediatric analgesia: which drug, which dose? *Drugs* 1991; 41: 52–9.
3. Boulland P, *et al.* Mélange équimolaire oxygène-protoxyde d'azote (MEOPA): rappels théoriques et modalités pratiques d'utilisation. *Ann Fr Anesth Reanim* 2005; 24: 1305–12.
4. Brownridge P. Treatment options for the relief of pain during childbirth. *Drugs* 1991; 41: 69–80.
5. O'Sullivan I, Benger J. Nitrous oxide in emergency medicine. *Emerg Med J* 2003; 20: 214–17.
6. Paddy SC, Garlick SR. A systematic review of the safety of analgesia with 50% nitrous oxide: can lay responders use analgesic gases in the prehospital setting? *Emerg Med J* 2005; 22: 901–8.
7. Babl FE, *et al.* Limited analgesic efficacy of nitrous oxide for painful procedures in children. *Emerg Med J* 2008; 25: 717–21.
8. Aboumarzouk OM, *et al.* Nitrous oxide for colonoscopy. Available in The Cochrane Database of Systematic Reviews; Issue 8. Chichester: John Wiley; 2011 (accessed 22/08/11).
9. Fauroux B, *et al.* The efficacy of premixed nitrous oxide and oxygen for fiberoptic bronchoscopy in pediatric patients: a randomized, double-blind, controlled study. *Chest* 2004; 125: 315–21.
10. Aussi K, *et al.* Prefixed equimolar nitrous oxide and oxygen mixture reduces discomfort during flexible bronchoscopy in adult patients: a randomized, controlled, double-blind trial. *Chest* 2005; 128: 863–8.
11. Fosburg MT, Crone RK. Nitrous oxide analgesia for refractory pain in the terminally ill. *JAMA* 1983; 250: 511–13.

Adverse Effects

The main complications after use of nitrous oxide are those due to varying degrees of hypoxia. Prolonged use has been followed by megaloblastic anaemia and myeloneuropathy. Depression of white cell formation may also occur. There is a risk of increased pressure and volume from the diffusion of nitrous oxide into air-containing cavities; prolonged exposure may lead to bowel distension, middle ear damage, and rupture of the ear drum. Malignant hyperthermia has been reported rarely.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Reviews.

1. Louis-Ferdinand RT. Myelotoxic, neurotoxic and reproductive adverse effects of nitrous oxide. *Adverse Drug React Toxicol Rev* 1994; 13: 193–206.
2. Donaldson D, Meechan JG. The hazards of chronic exposure to nitrous oxide: an update. *Br Dent J* 1995; 178: 95–100.
3. Weimann J. Toxicity of nitrous oxide. *Best Pract Res Clin Anaesthesiol* 2003; 17: 47–61.
4. Collado V, *et al.* A review of the safety of 50% nitrous oxide/oxygen in conscious sedation. *Expert Opin Drug Safety* 2007; 6: 559–71.
5. Sanders RD, *et al.* Biologic effects of nitrous oxide: a mechanistic and toxicologic review. *Anesthesiology* 2008; 109: 707–22.

Effects on the blood. Nitrous oxide inactivates vitamin B_{12}, a cofactor for methionine synthase (which converts homocysteine to methionine), thereby increasing plasma-homocysteine concentrations and depleting methionine and tetrahydrofolate. The interference with folate metabolism and DNA synthesis prevents production of both leucocytes and red blood cells by the bone marrow. Megaloblastic changes in bone marrow and impaired granulocyte production are found in patients exposed to anaesthetic concentrations of nitrous oxide for 24 hours. In patients with normal bone marrow, stores of mature granulocytes will normally be adequate to prevent leucopenia during exposure for up to 3 days; in patients exposed to nitrous oxide for longer periods of time, leucopenia will develop and exposure for 4 days or longer can result in agranulocytosis. In general, healthy surgical patients can be given nitrous oxide for up to 24 hours without harm. In situations where nitrous oxide is used for more than 24 hours, folinic acid 30 mg twice daily has been given to protect the haematopoietic system. Repeat exposure to nitrous oxide at intervals of less than 3 days will have a cumulative effect on DNA synthesis and megaloblastic marrow changes have been reported following multiple short-term exposure.[1]

Depletion of methionine has been implicated in the neurological deficit (see Effects on the Nervous System

p. 1909.1) seen mainly after chronic use of nitrous oxide. It may also account for the fetotoxicity seen in *rats*, see Pregnancy, under Precautions, below. For discussion of the effects of hyperhomocysteinaemia, see Effects on the Cardiovascular System, below.

Assessment of vitamin B_{12} levels should be considered before giving nitrous oxide anaesthesia to patients with risk factors for deficiency.[2]

1. Nunn JF. Clinical aspects of the interaction between nitrous oxide and vitamin B_{12}. *Br J Anaesth* 1987; 59: 3–13.
2. MHRA/CHM. Nitrous oxide: neurological and haematological toxic effects, especially with prolonged use. *Drug Safety Update* 2008; 2 (5): 2. Also available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/publication/con033504.pdf (accessed 20/09/11)

Effects on the cardiovascular system. Nitrous oxide is associated with a dose-dependent increase in plasma-homocysteine concentrations due to the inactivation of vitamin B_{12}, a cofactor for methionine synthase which converts homocysteine to methionine (see also Effects on the Blood and the Nervous System, p. 1908.3 and below, respectively). Acute nitrous oxide-induced hyperhomocysteinaemia has been shown[1] to impair endothelial function in patients with cardiovascular disease undergoing noncardiac surgery. A multicentre randomised controlled study[2] in patients undergoing noncardiac surgery found that the incidence of major postoperative complications, including postoperative fever, wound infection, pneumonia, pulmonary atelectasis, and severe nausea and vomiting, was reduced in the nitrous oxide-free group, but not the length of hospital stay. The authors also noted a possible association between nitrous oxide and postoperative myocardial infarction although this was statistically insignificant. (A substudy[3] on some of the patients identified hyperhomocysteinaemia as an independent risk factor for major postoperative complications, attributed to increased rates of cardiovascular complications.) Follow-up[4] after a median of 3.5 years suggested that nitrous oxide anaesthesia was associated with a marginal increase in the long-term risk of myocardial infarction, but not of death or stroke.

Measures to protect against nitrous oxide-induced hyperhomocysteinaemia have been tried. A randomised study[5] found that oral vitamin B-complex given daily for one week before surgery inhibited the increase in postoperative plasma-homocysteine concentrations; however, differences in clinical outcome were not measured. A later randomised placebo-controlled study[6] concluded that a single pre-operative intravenous infusion of vitamin B_{12} and folate did not prevent nitrous oxide-induced hyperhomocysteinaemia.

1. Myles PS, *et al.* Effect of nitrous oxide anesthesia on plasma homocysteine and endothelial function. *Anesthesiology* 2008; 109: 657–63.
2. Myles PS, *et al.* ENIGMA Trial Group. Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial. *Anesthesiology* 2007; 107: 221–31.
3. Myles PS, *et al.* Effect of nitrous oxide on plasma homocysteine and folate in patients undergoing major surgery. *Br J Anaesth* 2008; 100: 780–6.
4. Leslie K, *et al.* Nitrous oxide and long-term morbidity and mortality in the ENIGMA trial. *Anesth Analg* 2011; 112: 387–93.
5. Badner NH, *et al.* Preoperative oral B vitamins prevent nitrous oxide-induced postoperative plasma homocysteine increases. *Anesth Analg* 2001; 93: 1507–10.
6. Rao LK, *et al.* Pre-operative vitamin B infusion and prevention of nitrous oxide-induced homocysteine increase. *Anaesthesia* 2010; 65: 710–15.

Effects on the nervous system. Neurological disorders (mainly myeloneuropathies and neuropathies) have occurred in chronic abusers of nitrous oxide;[1-3] severe myeloneuropathy has been reported after acute use of a high dose.[4] Similar effects have been noted after repeated use of nitrous oxide in hospitalised patients. These neurological effects are considered to be due to nitrous oxide-induced methionine deficiency (see Effects on the Blood and the Cardiovascular System, p. 1908.3 and above, respectively). However, neurological effects can occur without preceding overt haematological changes. Psychosis, responsive to treatment with vitamin B_{12}, has also been reported in a patient abusing nitrous oxide.[5]

In patients with undiagnosed subclinical deficiency of vitamin B_{12} (a cofactor involved in methionine synthesis) neurological manifestations, including those consistent with subacute combined degeneration of the spinal cord, have occurred after a single exposure to nitrous oxide for anaesthesia.[6-8] A literature review[9] of 18 cases found that the onset of symptoms after exposure to nitrous oxide varied from immediately after surgery to about 2 months later; duration of exposure ranged from 60 minutes to 11 hours, at concentrations of 40 to 66%. Acute paralysis, due to degeneration of the spinal cord, has also been reported in a malnourished patient who had been abusing nitrous oxide for 10 days for the self-treatment of a painful sprained ankle.[10]

1. Miller MA, *et al.* Nitrous oxide "whippit" abuse presenting as clinical B12 deficiency and ataxia. *Am J Emerg Med* 2004; 22: 124.
2. Doran M, *et al.* Toxicity after intermittent inhalation of nitrous oxide for analgesia. *BMJ* 2004; 328: 1364–5.
3. Richardson PG. Peripheral neuropathy following nitrous oxide abuse. *Emerg Med Australas* 2010; 22: 88–90.
4. Alt RS, *et al.* Severe myeloneuropathy from acute high-dose nitrous oxide (N_2O) abuse. *J Emerg Med* 2010. Available at: doi:10.1016/j.jemermed.2010.04.020
5. Sethi NK, *et al.* Nitrous oxide "whippit" abuse presenting with cobalamin responsive psychosis. *J Med Toxicol* 2006; 2: 71–4.
6. Schilling RF. Is nitrous oxide a dangerous anesthetic for vitamin B_{12}-deficient subjects? *JAMA* 1986; 255: 1605–6.
7. Nestor PJ, Stark RJ. Vitamin B_{12} myeloneuropathy precipitated by nitrous oxide anaesthesia. *Med J Aust* 1996; 165: 174.
8. Renard D, *et al.* Subacute combined degeneration of the spinal cord caused by nitrous oxide anaesthesia. *Neurol Sci* 2009; 30: 75–6.
9. Singer MA, *et al.* Reversible nitrous oxide-induced myeloneuropathy with pernicious anemia: case report and literature review. *Muscle Nerve* 2008; 37: 125–9.
10. Cartner M, *et al.* Paralysis caused by "nagging". *Med J Aust* 2007; 187: 366–7.

Malignant hyperthermia. An 11-year-old girl whose father had died from malignant hyperthermia after anaesthesia developed hyperthermia after anaesthesia with nitrous oxide and oxygen.[1]

1. Ellis FR, *et al.* Malignant hyperpyrexia induced by nitrous oxide and treated with dexamethasone. *BMJ* 1974; 4: 270–1.

Precautions

Hypoxic anaesthesia is dangerous and nitrous oxide should always be given with at least 21 to 30% oxygen. Nitrous oxide diffuses into gas-filled body cavities and is contra-indicated in patients with any condition where the expansion of trapped gas may be dangerous, such as head injuries with impairment of consciousness, pneumothorax, air embolism, decompression sickness, severe bullous emphysema, gross abdominal distension, intoxication, maxillofacial injuries, and after air encephalography or recent intra-ocular injection of gas. Nitrous oxide should not be used for more than a total of 24 hours, or more frequently than every 4 days, without close supervision and haematological monitoring. Oxygen should be given during emergence from prolonged anaesthesia with nitrous oxide to prevent diffusion hypoxia where the alveolar oxygen concentration is diminished. See also Precautions for General Anaesthetics, p. 1897.3.

Nitrous oxide has been subject to abuse.

Abuse. 'Recreational' use or abuse of nitrous oxide has been referred to as "nagging" or "nanging". For some of the resulting adverse effects of nitrous oxide abuse, see Effects on the Nervous System, above.

Driving. A slight but quantifiable impairment in driving ability was found up to 30 minutes after 15 minutes' inhalation of nitrous oxide/oxygen mixtures for analgesia and sedation;[1] indeed, licensed product information recommends against driving or operating machinery until at least 30 minutes after administration. Similarly, such activities should be avoided until 12 hours after nitrous oxide anaesthesia.

1. Moyes DG, *et al.* Driving after anaesthetics. *BMJ* 1979; 1: 1425.

Epidural anaesthesia. Nitrous oxide diffuses into gas-filled body cavities and can increase the size of any air bubbles injected into the epidural space to determine placement of the needle in epidural anaesthesia.[1] This could result in uneven spread of the local anaesthetic and produce inadequate analgesia. The volume of air injected should be limited or another technique used to determine placement of the needle if nitrous oxide is to be given subsequently.

1. Stevens R, *et al.* Fate of extradural air bubbles during inhalation of nitrous oxide. *Br J Anaesth* 1994; 72: 482P–483P.

Occupational exposure. A scavenging system and effective ventilation may be necessary to control the nitrous oxide pollution that can occur when this gas is used for analgesia or anaesthesia. Risk areas include, in addition to operating theatres, delivery rooms and dental surgeries.[1-3] Occupational exposure can lead to serious toxicity with bone-marrow and neurological impairment.[1,2] Reduced fertility has been reported in female dental workers exposed to high concentrations of nitrous oxide;[4] such women also appear to have a higher rate of spontaneous abortion.[5] It has been suggested that nitrous oxide can also affect male fertility;[6] in one study a dose-related increase in the incidence of spontaneous abortion was found in the wives of men with occupational exposure to nitrous oxide.[7] A later review[8] concluded that although there is some evidence of a causal link between exposure to nitrous oxide and spontaneous abortion and infertility, this evidence was limited. The author noted that most of the studies were conducted before scavenging was widely used, and none included ambient gas sampling, and that most of the data were obtained by questionnaire.

1. Brodsky JB, *et al.* Exposure to nitrous oxide and neurologic disease among dental professionals. *Anesth Analg* 1981; 60: 297–301.
2. Sweeney B, *et al.* Toxicity of bone marrow in dentists exposed to nitrous oxide. *BMJ* 1985; 291: 567–9.
3. Munley AJ, *et al.* Exposure of midwives to nitrous oxide in four hospitals. *BMJ* 1986; 293: 1063–4. Correction. *ibid.*; 1280.
4. Rowland AS, *et al.* Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide. *N Engl J Med* 1992; 327: 993–7.
5. Rowland AS, *et al.* Nitrous oxide and fertility. *N Engl J Med* 1993; 328: 284.
6. Brodsky JB. Nitrous oxide and fertility. *N Engl J Med* 1993; 328: 284–5.
7. Cohen EN, *et al.* Occupational disease in dentistry and chronic exposure to trace anesthetic gases. *J Am Dent Assoc* 1980; 101: 21–31.
8. Olfert SM. Reproductive outcomes among dental personnel: a review of selected exposures. *J Can Dent Assoc* 2006; 72: 821–5.

Pregnancy. Nitrous oxide is fetotoxic in *rats*.[1] However, retrospective reviews,[2] and individual case reports[3] have not shown nitrous oxide anaesthesia to be fetotoxic in humans. See also Occupational Exposure, above.

1. Lane GA, *et al.* Anesthetics as teratogens: nitrous oxide is fetotoxic, xenon is not. *Science* 1980; 210: 899–901.
2. Aldridge LM, Tunstall ME. Nitrous oxide and the fetus: a review and the results of a retrospective study of 175 cases of anaesthesia for insertion of Shirodkar suture. *Br J Anaesth* 1986; 58: 1348–56.
3. Park GR, *et al.* Normal pregnancy following nitrous oxide exposure in the first trimester. *Br J Anaesth* 1986; 58: 576–7.

Vitamin B_{12} deficiency. For reports of neurological dysfunction associated with the use of nitrous oxide in patients with undiagnosed subclinical vitamin B_{12} deficiency, see Effects on the Nervous System, above.

Interactions

Use of nitrous oxide in a high concentration with an inhalational anaesthetic accelerates the uptake of the latter from the lungs. This phenomenon is known as the *second gas effect*. It is due to the disproportionate absorption of nitrous oxide into the blood resulting in an increased alveolar concentration of the second gas.

The use of high doses of opioids such as fentanyl with nitrous oxide may result in a drop in heart rate and cardiac output.

See also Interactions for General Anaesthetics, p. 1897.3.

Methotrexate. Combined use of nitrous oxide and methotrexate may increase some of the adverse effects of methotrexate therapy, see p. 828.2.

Pharmacokinetics

Nitrous oxide is rapidly absorbed on inhalation. The blood/gas partition coefficient is low and most of the inhaled nitrous oxide is rapidly eliminated unchanged through the lungs though small amounts diffuse through the skin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Niontix; *Denm.*: Niontix; *Fin.*: Niontix; *Fr.*: Kinox; *Ger.*: Niontix; *Israel*: Maxicool; *Neth.*: Niontix; *Norw.*: Niontix; *Swed.*: Niontix.

Multi-ingredient Preparations. *Belg.*: Kalinox; *Canad.*: Alnox; Entonox; Liqui-Med; *Cz.*: Entonox; *Denm.*: Kalinox; Livopan; Medimix; *Fin.*: Livopan; *Fr.*: Antasol; Entonox; Kalinox; Oxynox; *Ger.*: Livopan; *IrL.*: Entonox; *Neth.*: Donopa; Relivopan; *Pol.*: Entonox; *S.Afr.*: Entonox; *Spain*: Entonox; Kalinox; *Swed.*: Livopan; Medimix; *Switz.*: Entonox; Kalinox; Medimix†; *UK*: Entonox; Equanox.

Propanidid *(BAN, USAN, rINN)*

Bayer-1420; FBA-1420; Propanidide; Propanididum; TH-2180; WH-5668; Пропанидид.

Propyl 4-diethylcarbamoylmethoxy-3-methoxyphenylacetate.

$C_{18}H_{27}NO_5$=337.4

CAS — 1421-14-3.

ATC — N01AX04.

ATC Vet — QN01AX04.

UNII — AO82L471NS.

Profile

Propanidid has been used as an intravenous anaesthetic for rapid induction and for maintenance of general anaesthesia of short duration.

Commercial preparations of propanidid were provided as a liquid in polyoxyl castor oil. Anaphylactoid reactions associated with the vehicle led to the general withdrawal of propanidid from use.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Progray; *Mex.*: Panitol.

Propofol *(BAN, USAN, rINN)*

Disoprofol; ICI-35868; Propofoli; Propofolis; Propofolum; Пропофол.

2,6-Di-isopropylphenol; 2,6-Bis(1-methylethyl)phenol

$C_{12}H_{18}O$=178.3

CAS — 2078-54-8

ATC — N01AX10

ATC Vet — QN01AX10

UNII — YI7VU623SF

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

Ph. Eur. 8: (Propofol). A colourless or very light yellow, clear liquid. Very slightly soluble in water; miscible with hexane and with methyl alcohol. Store under an inert gas. Protect from light.

USP 36: (Propofol). A clear, colourless to slightly yellowish liquid. Very slightly soluble in water; very soluble in dehydrated alcohol and in methyl alcohol; slightly soluble in cyclohexane and in isopropyl alcohol. Store under an inert gas in airtight containers. Protect from light.

Uses and Administration

Propofol is a short-acting anaesthetic given intravenously for the induction and maintenance of general anaesthesia (p. 1896.1). It is also used for sedation (p. 1032.2) in adult patients undergoing diagnostic procedures, in those undergoing surgery with local or regional anaesthesia, and in ventilated adult patients under intensive care. When used for anaesthesia, induction is rapid, as is recovery. Propofol has no analgesic activity and supplementary analgesia may be required.

Propofol is available as a 1 or 2% emulsion. The 1% emulsion may be given by intravenous injection or infusion, but the 2% emulsion is for infusion only. Infusions and injections should be prepared using aseptic techniques, see Administration, below.

Induction of **anaesthesia** is generally carried out by giving propofol by injection or infusion at a rate of 40 mg every 10 seconds; a rate of 20 mg every 10 seconds may be used in high-risk patients including elderly, neurosurgical, and debilitated patients. Most adults under 55 years of age can be anaesthetised by a dose of 1.5 to 2.5 mg/kg; high-risk patients usually require a dose of 1 to 1.5 mg/kg.

When used for maintenance propofol is infused at a rate of between 4 to 12 mg/kg per hour (or 3 to 6 mg/kg per hour for elderly and debilitated patients); alternatively intermittent bolus injections of 20 to 50 mg may be given; rapid bolus doses should be avoided in high-risk patients.

For dosage in children, see below.

A novel delivery system is also available for the induction and maintenance of anaesthesia in adults. The Diprifusor target-controlled infusion system allows the speed of induction and depth of anaesthesia to be controlled by specifying target blood concentrations of propofol. Initial target concentrations for induction range from 4 to 8 micrograms/mL for patients under 55 years of age; lower initial target concentrations should be used in older and debilitated patients and should be increased gradually thereafter in steps of 0.5 to 1 microgram/mL at intervals of 1 minute to achieve a gradual induction of anaesthesia. Target concentrations for maintenance are 3 to 6 micrograms/mL.

For **sedation** in diagnostic and surgical procedures in adults an initial infusion of 6 to 9 mg/kg per hour may be given for 3 to 5 minutes; alternatively 0.5 to 1 mg/kg may be injected slowly over 1 to 5 minutes. An infusion of 1.5 to 4.5 mg/kg per hour may be used for maintenance of sedation. High-risk patients usually require a 20% reduction in the maintenance dose.

For the sedation of ventilated adults propofol can be given by intravenous infusion in a dose of 0.3 to 4 mg/kg per hour. If the duration of sedation is in excess of 3 days, lipid concentrations should be monitored.

Reviews.

1. Langley MS, Heel RC. Propofol: a review of its pharmacodynamic and pharmacokinetic properties and use as an intravenous anaesthetic. *Drugs* 1988; 35: 334–72.
2. Larijani GE, *et al.* Clinical pharmacology of propofol: an intravenous anesthetic agent. *DICP Ann Pharmacother* 1989; 23: 743–9.
3. Bryson HM, *et al.* Propofol: an update of its use in anaesthesia and conscious sedation. *Drugs* 1995; 50: 513–59.
4. Fulton B, Sorkin EM. Propofol: an overview of its pharmacology and a review of its clinical efficacy in intensive care sedation. *Drugs* 1995; 50: 636–57.
5. Singh H, *et al.* Propofol for sedation during colonoscopy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 15/01/10).
6. Vasilelou I, *et al.* Propofol: a review of its non-anaesthetic effects. *Eur J Pharmacol* 2009; 605: 1–8.
7. Lundström S, *et al.* Propofol. *J Pain Symptom Manage* 2010; 40: 466–70.

Administration. Propofol is formulated as an oil-in-water emulsion for injection. Strict aseptic techniques must be maintained when handling propofol as, in some countries, the parenteral product contains no antimicrobial preservatives and the vehicle can support rapid growth of microorganisms. Aseptic techniques must also be applied to formulations, such as those available in the UK and USA, that contain the microbial-retarding agent disodium edetate, as microbial growth is still possible. An emulsion containing 1% of propofol may be diluted with glucose 5% immediately before use but it should not be diluted to a concentration of less than 2 mg/mL. An emulsion containing 2% of propofol should not be diluted. The use of a 5-micrometre filter needle to withdraw propofol emulsion from an ampoule does not cause significant loss of drug.[1] A reduction in concentration of propofol can occur when the diluted emulsion is run through PVC intravenous tubing.[1] Propofol 1 or 2% may be given into a running intravenous infusion through a Y-site close to the injection site and under these circumstances it is compatible with glucose 5%, sodium chloride 0.9%, lactated Ringer's solution, and glucose with sodium chloride or with lactated Ringer's solution.

Because injection of propofol can be painful, it may be mixed with alfentanil or lidocaine before use. UK licensed product information advises mixing lidocaine 0.5 or 1% injection (without preservatives) in a ratio of 1:20 with propofol injection 1% immediately before use; similarly, alfentanil injection 500 micrograms/mL may be mixed in a ratio of 1:20 to 1:50 with propofol 1%. It advises against mixing the 2% emulsion of propofol with other drugs.

1. Bailey LC, *et al.* Effect of syringe filter and I.V. administration set on delivery of propofol emulsion. *Am J Hosp Pharm* 1991; 48: 2627–30.

Administration in children. In the UK, children aged 1 month and over may be given propofol for the induction and maintenance of anaesthesia. The dose should be adjusted for weight and age, and given slowly until the onset of anaesthesia. Most children aged over 8 years require an induction dose of 2.5 mg/kg; younger children may require a higher dose within the range of 2.5 to 4 mg/kg. Doses of 9 to 15 mg/kg per hour by intravenous infusion or intermittent bolus injections are suitable for maintenance. The 2% emulsion formulation of propofol should only be used in children aged 3 years and over. In the USA, children aged 3 years and over may be given propofol for the induction of anaesthesia; those aged 2 months and over may receive propofol for maintenance of anaesthesia. Doses are similar to those used in the UK.

Propofol is contra-indicated for sedation in children aged 16 years or less. A systematic review[1] found only 1 study of the use of propofol in neonates; although there was some evidence of benefit the numbers were insufficient to establish its role and safety.

1. Shah PS, Shah VS. Propofol for procedural sedation/anaesthesia in neonates. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2011 (accessed 14/04/11).

Nausea and vomiting. It is commonly believed that propofol is associated with less postoperative nausea and vomiting than some other anaesthetics.[1,2] However, a review[3] concluded that any reduction in nausea and vomiting when using propofol anaesthesia may be short term and clinically relevant only for maintenance anaesthesia in procedures with an inherent risk of nausea and vomiting.

There are also reports[4-9] indicating that propofol may have some intrinsic antiemetic action when used in subhypnotic doses although a study[10] of the effect of sedative and non-sedative (sub-hypnotic) doses against apomorphine-induced vomiting has suggested that any antiemetic effect is probably due to sedation.

1. McCollum JSC, *et al.* The antiemetic action of propofol. *Anaesthesia* 1988; 43: 239–40.
2. Woodward WM, *et al.* Comparison of post-operative nausea and vomiting after thiopentone/isoflurane or propofol infusion for 'bat-ear' correction in children. *Br J Anaesth* 1994; 72 (suppl 1): 92.
3. Tramèr M, *et al.* Propofol anaesthesia and postoperative nausea and vomiting: quantitative systematic review of randomized controlled studies. *Br J Anaesth* 1997; 78: 247–55.
4. Borgeat A, *et al.* Adjuvant propofol for refractory cisplatin-associated nausea and vomiting. *Lancet* 1992; 340: 679–80.
5. Törn K, *et al.* Effects of sub-hypnotic doses of propofol on the side effects of intrathecal morphine. *Br J Anaesth* 1994; 73: 411–12.
6. Borgeat A, *et al.* Adjuvant propofol enables better control of nausea and emesis secondary to chemotherapy for breast cancer. *Can J Anaesth* 1994; 41: 1117–19.
7. Ewalenko P, *et al.* Antiemetic effect of subhypnotic doses of propofol after thyroidectomy. *Br J Anaesth* 1996; 77: 463–7.
8. Gan TJ, *et al.* Determination of plasma concentrations of propofol associated with 50% reduction in postoperative nausea. *Anesthesiology* 1997; 87: 779–84.
9. Unal Y, *et al.* Comparison of the efficacy of propofol and metoclopramide in preventing postoperative nausea and vomiting after middle ear surgery. *Saudi Med J* 2009; 30: 778–82.
10. Thörn S-E, *et al.* Propofol effects upon apomorphine induced vomiting. *Br J Anaesth* 1994; 72 (suppl 1): 90.

Pruritus. Propofol is one of many drugs that have been tried in the management of pruritus (p. 1687.3). Sub-hypnotic doses of propofol appear to have an antipruritic action. It has produced conflicting results in the treatment and prophylaxis of pruritus associated with epidural and intrathecal morphine[1-4] although it appears to be able to relieve cholestasis-associated pruritus.[5] It has been suggested that propofol might act by suppression of the spinal transmission of pruritic signals.

1. Borgeat A, *et al.* Subhypnotic doses of propofol relieve pruritus induced by epidural and intrathecal morphine. *Anesthesiology* 1992; 76: 510–12.
2. Törn K, *et al.* Effects of sub-hypnotic doses of propofol on the side effects of intrathecal morphine. *Br J Anaesth* 1994; 73: 411–12.
3. Warwick JP, *et al.* The effect of subhypnotic doses of propofol on the incidence of pruritus after intrathecal morphine for caesarean section. *Anaesthesia* 1997; 52: 270–5.
4. Beilin Y, *et al.* Subhypnotic doses of propofol do not relieve pruritus induced by intrathecal morphine after cesarean section. *Anesth Analg* 1998; 86: 310–3.
5. Borgeat A, *et al.* Subhypnotic doses of propofol relieve pruritus associated with liver disease. *Gastroenterology* 1993; 104: 244–7.

Status epilepticus. General anaesthesia may be used to control refractory tonic-clonic status epilepticus (p. 510.2). A short-acting barbiturate such as thiopental is usually used. Propofol is also used[1-7] although good controlled studies of its efficacy are lacking; in addition, it has caused seizures when used in anaesthesia (see CNS Effects, under Precautions, p. 1912.1) and should be given with caution to patients with epilepsy. The risks of respiratory and cerebral depression, lipid overload with prolonged therapy and propofol infusion syndrome should also be borne in mind. It may induce involuntary movements and care is required to distinguish these from seizures. Nonetheless, it has a rapid onset of action and its effects are maintained while the infusion is maintained; recovery is rapid on stopping. Some guidelines[7] recommend giving an initial intravenous bolus of 2 to 3 mg/kg, with further boluses of 1 to 2 mg/kg until seizures are controlled, followed by a continuous infusion of 4 to 10 mg/kg per hour guided by EEG monitoring. A lower initial bolus dose of 1 mg/kg has also been used.[4] The dose should be gradually reduced and the infusion tapered 12 to 24 hours after seizure activity is halted. Lower doses should be used in the elderly. A study[8] comparing propofol with high-dose barbiturates in patients with refractory status epilepticus concluded that recurrent seizures were common when propofol infusions were suddenly stopped but not when the infusions were gradually tapered.

1. Rossetti AO, *et al.* Propofol treatment of refractory status epilepticus: a study of 31 episodes. *Epilepsia* 2004; 45: 757–63.
2. Marik PE, Varon J. The management of status epilepticus. *Chest* 2004; 126: 582–91.
3. van Gestel JPJ, *et al.* Propofol and thiopental for refractory status epilepticus in children. *Neurology* 2005; 65: 591–2.
4. Kälviäinen R, *et al.* Refractory generalised convulsive status epilepticus: a guide to treatment. *CNS Drugs* 2005; 19: 759–68.
5. Rossetti AO. Which anesthetic should be used in the treatment of refractory status epilepticus? *Epilepsia* 2007; 48 (suppl 8): 52–5. *Correction. ibid.*: 2383.
6. Parviainen I, *et al.* Propofol and barbiturates for the anesthesia of refractory convulsive status epilepticus: pros and cons. *Neurol Res* 2007; 29: 667–71.
7. Meierkord H, *et al.* European Federation of Neurological Societies. EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol* 2010; 17: 348–55.
8. Stecker MM, *et al.* Treatment of refractory status epilepticus with propofol: clinical and pharmacokinetic findings. *Epilepsia* 1998; 39: 18–26.

Tetanus. Sedation with propofol has been used in the treatment of tetanus (p. 2029.2) to control spasms and rigidity.

Adverse Effects

Early studies with propofol used a preparation formulated with polyoxyl castor oil. Because of anaphylactoid reactions the preparation was reformulated with a vehicle of soya oil and purified egg phosphatide. Adverse effects with this preparation include pain on injection, especially if the injection is into a small vein. Local pain may be reduced by injection into a large vein or by injection of intravenous lidocaine. Apnoea may be frequent; apnoea lasting longer than 60 seconds has been reported to occur in 12% of patients. There are isolated reports of pulmonary oedema. Cardiovascular effects include a reduction in blood pressure and bradycardia. There have been reports of convulsions (sometimes delayed in onset) and involuntary movements. Fever and pancreatitis have occurred very rarely. Anaphylactoid reactions have been reported. Discoloration of urine has been reported after prolonged use. Nausea, vomiting, and headache may occur during recovery.

Children given propofol for prolonged sedation have suffered severe reactions and there have been fatalities, and a life-threatening infusion syndrome has also been seen in adults, see Incidence of Adverse Effects, below.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Incidence of adverse effects. In May 1989 the UK CSM commented on the 268 reports of adverse reactions to propofol that it had received since propofol was introduced to the UK market, during which period about 2 million patients had been anaesthetised with the drug.[1] These included reports of:

- seizures (37 cases, 13 in known epileptics)
- involuntary movements (16 cases)
- opisthotonus (10 cases)
- anaphylactic reactions (32 cases)
- cardiac arrest (13 cases)
- delayed recovery (8 cases)

In 1992 the CSM pointed to the risk of **delayed convulsions** with propofol and its particular importance

for day-case surgery.[2] While the incidence of convulsions was low (170 reports), 31% of the reports described the convulsions as delayed.

In June 1992 the CSM commented on the dangers of propofol for the **sedation of children** in intensive care,[3] a use for which it is contra-indicated in the UK. (This prohibition does not apply to its use for the sedation of ventilated adults—but see below—or to propofol's use as an *anaesthetic* in children. Sedation in children undergoing surgical and diagnostic procedures is not contra-indicated but is an unlicensed use, and is not recommended.[4])

The CSM reported that there had been 66 reports worldwide of serious adverse effects in children sedated with propofol, and some fatalities had ensued. The children had suffered neurological, cardiac, and renal effects, hyperlipidaemia, hepatomegaly, and metabolic acidosis. Five deaths had been reported to the CSM. These 5 children[5] were aged 4 weeks to 6 years and doses of propofol ranged from 4 to 10.7 mg/kg per hour. They developed metabolic acidosis, bradyarrhythmia, and progressive myocardial failure resistant to treatment. The latter has been reported by others to be significantly associated with the use of long-term, **high-dose** propofol infusions.[6]

Similar adverse effects resulting in fatalities have also been reported in **adult** patients with head injuries who received high doses of propofol infusion (greater than 5 mg/kg per hour) for long-term sedation.[7] The CSM subsequently reminded prescribers that the recommended dose range for sedation (up to 4 mg/kg per hour) should not be exceeded.[8] There has also been a report of death in a patient with a closed head injury who received propofol infusion at an average dose of 4.1 mg/kg per hour for long-term sedation.[9] Other fatalities reported included an adult patient with a spinal injury who was sedated with a maximum dose of 2.6 mg/kg per hour (mean 1.9 mg/kg per hour) for about 85 hours[10] and an adult patient with multiple fractures who received doses of 1.4 to 5.1 mg/kg per hour for 88 hours.[11]

The Australian Adverse Drug Reactions Advisory Committee[12] stated in December 2004 that it had received a report of lactic acidosis and another of torsade de pointes in adult patients receiving lower doses of propofol infusion, 30 and 100 mg/hour, respectively, for about 24 hours.

The term **propofol infusion syndrome** is used to describe the life-threatening adverse reaction that is characterised by metabolic acidosis, rhabdomyolysis, acute renal failure, hepatomegaly, hyperlipidaemia, and cardiac dysfunction.[13-16] A prospective observational study[17] of 1017 adult intensive care patients receiving propofol for at least 24 hours found that propofol infusion syndrome developed in 11 patients after an average of 3 days post infusion. Of these 11 patients, 2 died and 2 had received a dose of more than 4.98 mg/kg per hour of propofol (one of whom died). However, one commentator[18] has questioned the findings of this study, noting that they were at odds with most published literature and that the authors did not establish a dose-dependent association. It has also been suggested that concomitant use of glucocorticoids or vasopressive catecholamines are risk factors for development of the syndrome.[16]

Recent recommendations[19-21] on the safe use of propofol have reiterated that it should only be used by professionals trained in the provision of general anaesthesia and given in medical settings where resuscitation facilities are available.

1. CSM. Propofol—convulsions, anaphylaxis and delayed recovery from anaesthesia. *Current Problems 26* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024442&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)
2. CSM. Propofol and delayed convulsions. *Current Problems 35* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024453&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)
3. CSM. Serious adverse effects and fatalities in children associated with the use of propofol (Diprivan) for sedation. *Current Problems 34* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024452&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)
4. CSM/MCA. Clarification: propofol (Diprivan) infusion contraindication. *Current Problems* 2002; **28**: 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 17/05/06)
5. Parke TJ, *et al.* Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. *BMJ* 1992; **305**: 613–16.
6. Bray RJ. Propofol infusion syndrome in children. *Paediatr Anaesth* 1998; **8**: 491–9.
7. Cremer OL, *et al.* Long-term propofol infusion and cardiac failure in adult head-injured patients. *Lancet* 2001; **357**: 117–18.
8. CSM/MCA. Long term, high dose propofol (Diprivan) infusion. *Current Problems* 2001; **27**: 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 17/05/06)
9. Ernest D, Prench C. Propofol infusion syndrome: report of an adult fatality. *Anaesth Intensive Care* 2003; **31**: 316–19.
10. Merz TM, *et al.* Propofol infusion syndrome—a fatal case at a low infusion rate. *Anesth Analg* 2006; **103**: 1050.
11. Eriksen J, Povey HMR. A case of suspected non-neurosurgical adult fatal propofol infusion syndrome. *Acta Anaesthesiol Scand* 2006; **50**: 117–19.
12. Adverse Drug Reactions Advisory Committee (ADRAC). Propofol: danger of prolonged and high infusion rates in ICU. *Aust Adverse Drug React Bull* 2004; **23**: 23–4. Also available at: http://www.tga.gov.au/pdf/asdrb-0412.pdf (accessed 20/09/11)
13. Fodale V, La Monaca E. Propofol infusion syndrome: an overview of a perplexing disease. *Drug Safety* 2008; **31**: 293–303.
14. Orsini J, *et al.* Propofol infusion syndrome: case report and literature review. *Am J Health-Syst Pharm* 2009; **66**: 908–15.
15. Fudickar A, Bein B. Propofol infusion syndrome: update of clinical manifestation and pathophysiology. *Minerva Anestesiol* 2009; **75**: 339–44.
16. Laquay N, *et al.* Le syndrome de perfusion du propofol. *Ann Fr Anesth Reanim* 2010; **29**: 377–86.
17. Roberts RJ, *et al.* Incidence of propofol-related infusion syndrome in critically ill adults: a prospective, multicenter study. *Crit Care* 2009; **13**: R169. Available at: http://ccforum.com/content/13/5/R169 (accessed 07/04/11)
18. Cremer OL. The propofol infusion syndrome: more puzzling evidence on a complex and poorly characterized disorder. *Crit Care* 2009; **13**: 1012. Available at: http://ccforum.com/content/13/6/1012 (accessed 07/04/11)
19. American Society of Anesthesiologists. Statement on safe use of propofol (approved 27th October, 2004; amended 21st October, 2009). Also available at: http://www.asahq.org/For-Members/Clinical-Information/~/media/For%20Members/documents/Standards%20Guidelines%20Stmts/Safe%20Use%20of%20Propofol.ashx (accessed 20/09/11)
20. Vargo JJ, *et al.* American Association for the Study of Liver Diseases, American College of Gasteroenterology, American Gastroenterological Association. Position statement: nonanesthesiologist administration of propofol for GI endoscopy. *Gastroenterology* 2009; **137**: 2161–7. Also available at: http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508509017454.pdf (accessed 26/09/11)
21. Dumonceau JM, *et al.* NAAP Task Force Members. European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology guideline: non-anaesthesiologist administration of propofol for GI endoscopy. *Eur J Anaesthesiol* 2010; **27**: 1016–30.

Effects on the cardiovascular system. The main effect of propofol on the cardiovascular system is a fall in both systolic and diastolic blood pressure of 20 to 30%. The compensatory tachycardia seen after a fall in arterial pressure with other intravenous anaesthetics is not usually seen with propofol. Propofol can also decrease systemic vascular resistance, cardiac output, myocardial blood flow, and myocardial oxygen consumption. Bradycardia can occur even in those premedicated with antimuscarinics, and can occasionally be profound and lead to asystole.[1] Despite these cardiodepressant effects propofol in doses of 1.5 to 2.5 mg/kg does not generally cause unacceptable haemodynamic changes in patients with a healthy cardiovascular system although concern has been expressed about its safety in cardiac surgical patients.[2]

Patients (especially children) given propofol for continuous sedation in intensive care units have suffered adverse cardiac reactions with bradyarrhythmia, progressive myocardial failure, and death—see Incidence of Adverse Effects, p. 1910.3.

1. Tramèr MR, *et al.* Propofol and bradycardia: causation, frequency and severity. *Br J Anaesth* 1997; **78**: 642–51.
2. Ginsberg R, Lippmann M. Haemodynamic effects of propofol. *Br J Anaesth* 1994; **72**: 370–1.

Effects on lipids. Prolonged infusion of propofol may be associated with increases in serum triglycerides. In one patient this was believed to have been the cause of necrotising pancreatitis.[1]

1. Metkus AP, *et al.* A firefighter with pancreatitis. *Lancet* 1996; **348**: 1702.

Effects on mental function. There have been anecdotal reports[1] of disinhibited behaviour or sexually orientated hallucinations associated with the use of propofol, but a study using subanaesthetic doses found no evidence that propofol produced euphoria or other mood changes.[2]

1. Canaday BR. Amorous, disinhibited behaviour associated with propofol. *Clin Pharm* 1993; **12**: 449–51.
2. Whitehead C, *et al.* The subjective effects of low-dose propofol. *Br J Anaesth* 1994; **72** (suppl 1): 89.

Effects on the nervous system. See under Precautions, p. 1912.1.

Effects on respiration. See under Precautions, p. 1912.1.

Hypersensitivity. Anaphylactic reactions associated with polyoxyl castor oil used in propofol preparations had prompted a change to the use of soya oil and egg phosphatide in the formulation. A group of workers have reported a patient who had anaphylactic shock when given the reformulated emulsion.[1] A possible case of anaphylaxis to this formulation has also been reported in a child with allergies to egg and peanut oil.[2] Indeed, licensed product information contra-indicates its use in patients with peanut, soya, or egg allergy. However, some[3] have attributed such reactions to propofol itself, in particular its isopropyl and phenol groups.

1. Laxenaire MC, *et al.* Anaphylactic shock due to propofol. *Lancet* 1988; **ii**: 739–40.
2. Hofer KN, *et al.* Possible anaphylaxis after propofol in a child with food allergy. *Ann Pharmacother* 2003; **37**: 398–401.
3. Bradley AED, *et al.* Use of propofol in patients with food allergies. *Anaesthesia* 2008; **63**: 439.

Infection. Between June 1990 and February 1993, 62 cases of postsurgical infections identified in 7 hospitals in the USA were attributed to improper handling of propofol.[1] The infusion was not prepared aseptically and the syringes used in the infusion pumps were reused for several patients. Propofol is formulated as a soybean fat emulsion and the injection contains no antimicrobial preservative although, in the UK and USA, the formulation now contains the microbial-retarding agent, disodium edetate (see Administration, p. 1910.1). However, either formulation still has the potential to support microbial growth. Licensed product information now warns of the importance of aseptic technique in the preparation and use of propofol. Microbial multiplication did not appear to be clinically significant when propofol infusions were prepared and given using conventional aseptic techniques.[2]

1. Bennett SN, *et al.* Postoperative infections traced to contamination of an intravenous anesthetic, propofol. *N Engl J Med* 1995; **333**: 147–54.
2. Farrington M, *et al.* Do infusions of midazolam and propofol pose an infection risk to critically ill patients? *Br J Anaesth* 1994; **72**: 415–17.

Malignant hyperthermia. From an *in-vitro* study it was concluded that propofol does not trigger malignant hyperthermia.[1] There is a report of the safe use of propofol in 19 patients considered susceptible to malignant hyperthermia.[2]

1. Denborough M, Hopkinson KC. Propofol and malignant hyperpyrexia. *Lancet* 1988; **i**: 191.
2. Harrison GG. Propofol in malignant hyperthermia. *Lancet* 1991; **337**: 503.

Pain on injection. Product information suggests the use of lidocaine or alfentanil to reduce the pain associated with injection of conventional formulations of propofol (see Administration, p. 1910.1); alternatively, the larger veins in the forearm and antecubital fossa can be used. Studies indicate that metoclopramide[1] might also be effective. The pain is thought to be caused by the proportion of the propofol dose that is present in the aqueous rather than the oily phase of the emulsion. It has been suggested[2] that the analgesic effect of lidocaine, and possibly metoclopramide, is due to a pH-lowering effect, causing more propofol to be present in the oily phase, but a study showing that lidocaine given by iontophoresis also reduces pain[3] suggests this is not the only mechanism. In another attempt to reduce pain by decreasing the amount of aqueous propofol, a formulation containing a mixture of medium-chain and long-chain triglycerides (*Propofol-Lipuro*), assumed to improve distribution into the lipid phase, has been introduced in some countries. However, studies in adults[4] and children[5] suggest that the reduction in pain with the newer formulation is not as great as that achieved by mixing lidocaine with the conventional long-chain formulation. Licensed product information for this formulation makes similar recommendations for reducing injection pain to those of the conventional formulation. Although some studies in adults[6] and children[7] have suggested that mixing lidocaine with *Propofol-Lipuro* resulted in less injection pain than mixing lidocaine with the conventional formulation, another study in children[8] had found the incidence and intensity of the pain to be similar with both methods. A systematic review and meta-analysis[9] of 177 randomised controlled studies found that about 60% of patients develop pain on injection of propofol alone, and that using an antecubital vein, or pretreating the hand vein with lidocaine along with venous occlusion, were most effective in reducing injection pain. The authors also recommended routine use of a small dose of opioids before induction unless contra-indicated.

1. Ganta R, Fee JPH. Pain on injection of propofol: comparison of lignocaine with metoclopramide. *Br J Anaesth* 1992; **69**: 316–17.
2. Eriksson M, *et al.* Effect of lignocaine and pH on propofol-induced pain. *Br J Anaesth* 1997; **78**: 502–6.
3. Sadler PJ, *et al.* Iontophoretically applied lidocaine reduces pain on propofol injection. *Br J Anaesth* 1999; **82**: 432–4.
4. Adam S, *et al.* Propofol-induced injection pain: comparison of a modified propofol emulsion to standard propofol with premixed lidocaine. *Anesth Analg* 2004; **99**: 1076–9.
5. Nyman Y, *et al.* Propofol injection pain in children: a prospective randomized double-blind trial of a new propofol formulation versus propofol with added lidocaine. *Br J Anaesth* 2005; **95**: 222–5.
6. Mallick A, *et al.* Lidocaine is more efficient than the choice of propofol formulations to reduce incidence of pain on induction. *Eur J Anaesthesiol* 2007; **24**: 403–7.
7. Rochette A, *et al.* Avoiding propofol injection pain in children: a prospective, randomized, double-blinded, placebo-controlled study. *Br J Anaesth* 2008; **101**: 390–4.
8. Varghese E, *et al.* Does the newer preparation of propofol, an emulsion of medium/long chain triglycerides cause less injection pain in children when premixed with lignocaine? *Pediatr Anesth* 2010; **20**: 338–42.
9. Jalota L, *et al.* Prevention of pain on injection of propofol: systematic review and meta-analysis. Abstract: *BMJ* 2011; **342**: 694. Full version: http://www.bmj.com/content/342/bmj.d1110.full.pdf (accessed 12/04/11)

Urine discoloration. A case report of dark green urine in a 16-year-old during a prolonged infusion of propofol.[1] Pink urine that also contained a uric acid precipitate was collected from an obese surgical patient after propofol anaesthesia.[2]

1. Bodenham A, *et al.* Propofol infusion and green urine. *Lancet* 1987; **ii**: 740.
2. Stern AB, *et al.* Pink urine after propofol anesthesia. *Kidney Int* 2010; **78**: 1193.

Precautions

Propofol should not be given to patients known to be allergic to it, or who have peanut, soya, or egg allergy (see Hypersensitivity, p. 1911.2). Propofol should be used with caution in patients with hypovolaemia, epilepsy, or lipid metabolism disorders, and in the elderly. Since there have been reports of delayed convulsions associated with the use of propofol it is recommended that special care should be taken when propofol is used for day-case surgery. When used in patients with increased intracranial pressure it should be given slowly to avoid a substantial decrease in mean arterial pressure and a resultant decrease in cerebral perfusion pressure. It is also recommended that propofol should not be used with ECT. Premedication with an antimuscarinic may be advisable since propofol does not cause vagal inhibition.

Propofol is used to provide continuous sedation for ventilated adult patients under intensive care. Account should be taken of increasing the patient's lipid load. If the duration of sedation is in excess of 3 days, lipid concentrations should be monitored. Children aged 16 years or less should not be sedated in this manner with propofol (see Incidence of Adverse Effects, p. 1910.3). Propofol is not recommended for use in obstetrics including caesarean section.

See also Precautions for General Anaesthetics, p. 1897.3.

For the need for aseptic handling of propofol see Administration, p. 1910.1 and Infection, p. 1911.2.

Abuse. References[1-6] to the abuse of propofol.

1. Kranioti EF, *et al.* Lethal self administration of propofol (Diprivan): a case report and review of the literature. *Forensic Sci Int* 2007; 167: 56–8.
2. Wischmeyer PE, *et al.* A survey of propofol abuse in academic anesthesia programs. *Anesth Analg* 2007; 105: 1066–71.
3. Roussin A, *et al.* Pharmacological and clinical evidences on the potential for abuse and dependence of propofol: a review of the literature. *Fundam Clin Pharmacol* 2007; 21: 459–66.
4. Wilson C, *et al.* The abuse potential of propofol. *Clin Toxicol* 2010; 48: 165–70.
5. Levy RJ. Clinical effects and lethal and forensic aspects of propofol. *J Forensic Sci* 2011; 56 (suppl 1): S142–S147.
6. Monroe T, *et al.* The misuse and abuse of propofol. *Subst Use Misuse* 2011; 46: 1199–1205.

Breast feeding. A patient reported that the first breast milk expressed 8 hours after surgery, performed under an anaesthetic regimen that included propofol, had a bluish-green colour that changed to green on standing. The exact compound responsible for the discoloration could not be identified and any potential risk to a breast-fed infant was unknown.

1. Birkholz T, *et al.* Green breast milk after propofol administration. *Anesthesiology* 2009; 111: 1168–9.

CNS effects. Epileptic activity was seen[1] on the EEGs of 3 patients given propofol and it was suggested that it might be useful in ECT, but others[2,3] found that the duration of seizures was less with propofol anaesthesia than with methohexital anaesthesia. It has been suggested[4] that propofol should not be used with ECT and this is the advice in UK licensed product information.

Some consider that abnormal movements induced by propofol are not associated with cortical seizure activity.[5,6] These appear to be more frequent with low doses of propofol[6] and can be abolished in children by increasing the induction dose of propofol from 3 to 5 mg/kg.

1. Hodkinson BP, *et al.* Propofol and the electroencephalogram. *Lancet* 1987; ii: 1518.
2. Simpson KH, *et al.* Seizure duration after methohexitone or propofol for induction of anaesthesia for electroconvulsive therapy (ECT). *Br J Anaesth* 1987; 59: 1323P–1324P.
3. Rampton AJ, *et al.* Propofol and electroconvulsive therapy. *Lancet* 1988; i: 296–7.
4. Anonymous. Addendum: propofol better avoided with ECT at present. *Drug Ther Bull* 1990; 28: 72.
5. Borgeat A, *et al.* Spontaneous excitatory movements during recovery from propofol anaesthesia in an infant: EEG evaluation. *Br J Anaesth* 1993; 70: 459–61.
6. Borgeat A, *et al.* Propofol and epilepsy: time to clarify. *Anesth Analg* 1994; 78: 198–9.

Impaired respiration. The manufacturer has stated[1] that some patients who have received propofol for sedation in regional anaesthesia have had bradypnoea or hypoxaemia, or both. A reduction in oxygen saturation has also been noted in other patients sedated for endoscopy.[2] Licensed product information therefore recommends that oxygen saturation should be monitored and that oxygen supplementation should be readily available.

1. Arnold BDC. Sedation with propofol during regional anaesthesia. *Br J Anaesth* 1993; 70: 112.
2. Patterson KW, *et al.* Propofol sedation for outpatient upper gastrointestinal endoscopy: comparison with midazolam. *Br J Anaesth* 1991; 67: 108–11.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies propofol 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 04/10/11)

Interactions

The use of propofol with other CNS depressants, including those used in premedication, may increase the sedative, anaesthetic, and cardiorespiratory depressant effects of propofol. It is recommended that propofol is given after opioids so that the dose of propofol can be carefully titrated against the response. The dosage of propofol should be reduced if used with nitrous oxide or halogenated anaesthetics. Although propofol does not potentiate the effects of neuromuscular blockers, bradycardia and asystole have occurred after use of propofol with atracurium or suxamethonium (but see under Adverse Effects, p. 1911.2 for the effects of propofol itself on the cardiovascular system).

See also Interactions of General Anaesthetics, p. 1897.3.

Benzodiazepines. Propofol and *midazolam* have been reported to act synergistically.[1-3]

1. Short TG, Chui PT. Propofol and midazolam act synergistically in combination. *Br J Anaesth* 1991; 67: 539–45.
2. McClune S, *et al.* Synergistic interaction between midazolam and propofol. *Br J Anaesth* 1992; 69: 240–5.
3. Teh J, *et al.* Pharmacokinetic interactions between midazolam and propofol: an infusion study. *Br J Anaesth* 1994; 72: 62–5.

Catecholamines. For the suggestion that use of catecholamines increases the risk of developing the propofol infusion syndrome see Incidence of Adverse Effects, p. 1910.3.

Clonidine. Premedication with clonidine has been reported[1] to reduce intraoperative requirements of propofol.

1. Guglielminotti J, *et al.* Effects of premedication on dose requirements for propofol: comparison of clonidine and hydroxyzine. *Br J Anaesth* 1998; 80: 733–6.

Corticosteroids. For the suggestion that use of *glucocorticoids* increases the risk of developing the propofol infusion syndrome see Incidence of Adverse Effects, p. 1910.3.

Gastrointestinal drugs. The dose of propofol required for induction is reduced in patients given *metoclopramide*.[1]

1. Page VJ, Chhipa JH. Metoclopramide reduces the induction dose of propofol. *Acta Anaesthesiol Scand* 1997; 41: 256–9.

General anaesthetics. Use with *halothane* or *isoflurane* has been reported to increase serum concentrations of propofol.[1] Synergy has been reported between propofol and *etomidate*.[2]

1. Grundmann U, *et al.* Propofol and volatile anaesthetics. *Br J Anaesth* 1994; 72 (suppl 1): 88.
2. Drummond GB, Cairns DT. Do propofol and etomidate interact kinetically during induction of anaesthesia? *Br J Anaesth* 1994; 73: 272P.

Local anaesthetics. A reduction in the amount of propofol required to provide adequate hypnosis[1] or sedation[2] has been reported after *bupivacaine*[1] or *lidocaine*.[1,2] However, lidocaine is often added to propofol emulsions to reduce the pain of injection, see Administration, p. 1910.1.

1. Ben-Shlomo I, *et al.* Hypnotic effect of iv propofol is enhanced by im administration of either lignocaine or bupivacaine. *Br J Anaesth* 1997; 78: 375–7.
2. Mallick A, *et al.* Local anaesthesia to the airway reduces sedation requirements in patients undergoing artificial ventilation. *Br J Anaesth* 1996; 77: 731–4.

Opioids. In a study mean blood concentrations of propofol were higher in patients pretreated with *fentanyl* compared with patients maintained only on nitrous oxide.[1] However, others[2] were unable to confirm this interaction.

1. Cockshott ID, *et al.* Pharmacokinetics of propofol in female patients. *Br J Anaesth* 1987; 59: 1103–10.
2. Dixon J, *et al.* Study of the possible interaction between fentanyl and propofol using a computer-controlled infusion of propofol. *Br J Anaesth* 1990; 64: 142–7.

Pharmacokinetics

The pharmacokinetics of propofol are best described by a 3-compartment model. After a single bolus dose, two distribution phases are seen. The first phase has a half-life of 2 to 4 minutes. This is followed by a second phase with a half-life of 30 to 60 minutes during which significant metabolism of propofol occurs, and then by a slower redistributive phase. The terminal half-life ranges from 3 to 12 hours; with prolonged use, the terminal half-life may be longer. The termination of anaesthetic effect after a single intravenous bolus or maintenance infusion is due to extensive redistribution from the brain to other tissues and to metabolic clearance.

Propofol is over 95% bound to plasma proteins. It undergoes extensive hepatic metabolism to conjugates which are eliminated in the urine. The pharmacokinetics of propofol do not appear to be altered by gender, chronic hepatic cirrhosis, or chronic renal impairment. Propofol crosses the placental barrier and is distributed into breast milk.

References.

1. Saint-Maurice C, *et al.* Pharmacokinetics of propofol in young children after a single dose. *Br J Anaesth* 1989; 63: 667–70.
2. Kanto J, Gepts E. Pharmacokinetic implications for the clinical use of propofol. *Clin Pharmacokinet* 1989; 17: 308–26.
3. Gin T, *et al.* Pharmacokinetics of propofol in women undergoing elective caesarean section. *Br J Anaesth* 1990; 64: 148–53.
4. Servin F, *et al.* Pharmacokinetics of propofol infusions in patients with cirrhosis. *Br J Anaesth* 1990; 65: 177–83.
5. Jones RDM, *et al.* Pharmacokinetics of propofol in children. *Br J Anaesth* 1990; 65: 661–7.
6. Morgan DJ, *et al.* Pharmacokinetics of propofol when given by intravenous infusion. *Br J Clin Pharmacol* 1990; 30: 144–8.
7. Gin T, *et al.* Disposition of propofol at caesarean section and in the postpartum period. *Br J Anaesth* 1991; 67: 49–53.
8. Baille GR, *et al.* Pharmacokinetics of propofol during and after long term continuous infusion for maintenance of sedation in ICU patients. *Br J Anaesth* 1992; 68: 486–91.
9. Altmayer P, *et al.* Propofol binding in human blood. *Br J Anaesth* 1994; 72 (suppl 1): 86.
10. Oei-Lim VLB, *et al.* Pharmacokinetics of propofol during conscious sedation using target-controlled infusion in anxious patients undergoing dental treatment. *Br J Anaesth* 1998; 80: 324–31.
11. Dawidowicz AL, *et al.* Free and bound propofol concentrations in human cerebrospinal fluid. *Br J Clin Pharmacol* 2003; 56: 545–50.
12. Hiraoka H, *et al.* Kidneys contribute to the extrahepatic clearance of propofol in humans, but not lungs and brain. *Br J Clin Pharmacol* 2005; 60: 176–82.
13. Nitsun M, *et al.* Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clin Pharmacol Ther* 2006; 79: 549–57.
14. Peeters MYM, *et al.* Propofol pharmacokinetics and pharmacodynamics for depth of sedation in nonventilated infants after major craniofacial surgery. *Anesthesiology* 2006; 104: 466–74.
15. Kim K-M, *et al.* Pharmacokinetics and pharmacodynamics of propofol microemulsion and lipid emulsion after an intravenous bolus and variable rate infusion. *Anesthesiology* 2007; 106: 924–34.
16. Allegaert K, *et al.* Inter-individual variability in propofol pharmacokinetics in preterm and term neonates. *Br J Anaesth* 2007; 99: 864–70.
17. Bleeker C, *et al.* Recovery and long-term renal excretion of propofol, its glucuronide, and two di-isopropylquinol glucuronides after propofol infusion during surgery. *Br J Anaesth* 2008; 101: 207–12.
18. Peeters MYM, *et al.* Disease severity is a major determinant for the pharmacodynamics of propofol in critically ill patients. *Clin Pharmacol Ther* 2008; 83: 443–51.
19. Han T-H, *et al.* Propofol clearance and volume of distribution are increased in patients with major burns. *J Clin Pharmacol* 2009; 49: 768–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Diprivan; Fresofol; Gobbi fol; Oleo-Lax; *Austral.*: Diprivan; Fresofol; Recofol†; *Austria* Diprivan; *Belg.*: Diprivan; Propolipid; *Braz.*: Diprivan; Porpo van†; Profolen; Propoabbott†; Propotil; Propovan; *Canad.*: Diprivan; *Chile*: Anefol; Diprivan; *China*: Di Shi Ning (迪施宁); Diprivan (得普利麻); Le Wei Jing (乐维静); Li Meng Xin (力蒙欣); Recofol (瑞可富); *Cz.*: Diprivan†; Recofol†; *Denm.*: Diprivan; Propolipid; Recofol; *Fin.*: Propolipid; Recofol†; *Fr.*: Diprivan; *Ger.*: Disoprivan; *Gr.*: Diprivan; Morpheus; Propogen; Recofol; *Hong Kong*: Diprivan; Fresofol; *Hung.*: Diprivan†; *India*: Celofol; Cleofol; Critifol; Diprivan; Fresofol; Hyprc *Indon.*: Diprivan; Fresofol; Proanes; Recofol; Safol; Trivam; *Irl.* Diprivan; Propoven; *Israel*: Diprivan; Diprofol; Propofol Lipure Recofol; *Ital.*: Diprivan; *Malaysia*: Diprivan; Fresofol†; *Mex.* Cryotol; Diprivan; Fresofol; Indufol; Provive†; Recofol; *Neth.* Curtega; Diprivan; Recofol; Ripol; *Norw.*: Diprivan†; Propolipid *NZ*: Diprivan; Fresofol; Provive; *Philipp.*: Diprifol; Diprivan Fresofol; IV-Pro; Lipuro; *Pol.*: Abbofol†; Diprivan; Plofed; *Port.* Diprivan; Provive; *Rus.*: Diprivan (Диприван); Propovan (Пропован); Recofol (Рекофол); *S.Afr.*: Diprivan; Recofol†; *Singapore*: Diprivan†; Fresofol; Recofol; *Spain*: Diprivan; Recofol *Swed.*: Diprivan; Propolipid; *Switz.*: Disoprivan; *Thal.*: Anepol Anesvan; Fresofol; Pofol; Profol; Recofol†; *Turk.*: Diprivan Pofol; Recofol; *UK*: Diprivan; Propoven; *Ukr.*: Diprivan (Дипривал); Diprofol (Дипрофол); *USA*: Diprivan; Propoven *Venez.*: Anespro; Diprivan; Profol.

Pharmacopoeial Preparations

BP 2014: Propofol Injection;
USP 36: Propofol Injectable Emulsion.

Sevoflurane *(BAN, USAN, rINN)*

BAX-3084; MR-654; Sevofluraan; Sevofluraant; Sevofluran; Sévoflurane; Sevoflurano; Sevofluranum; Sewoflüran; Szevoflurán; Севофлуран.

Fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether; 1,1,1,3,3,3-Hexafluoro-2-(fluoromethoxy)-propane.

$C_4H_3F_7O$=200.1

CAS — 28523-86-6.

ATC — N01AB08.

ATC Vet — QN01AB08.

UNII — 38LVP0K73A.

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

Ph. Eur. 8: (Sevoflurane). A clear, colourless, volatile non-flammable liquid. Slightly soluble in water; miscible with alcohol. Store in airtight, stainless-steel containers Protect from light.

USP 36: (Sevoflurane). A clear, colourless, volatile non-flammable liquid. Slightly soluble in water; miscible

with alcohol, with chloroform, and with ether. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Sevoflurane is a volatile halogenated anaesthetic given by inhalation. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p. 1896.1) ranging from 1.4% in the elderly to 3.3% in neonates. It is used for the induction and maintenance of general anaesthesia (p. 1896.1). It is non-flammable. Sevoflurane has a nonpungent odour and does not cause respiratory irritation. It also has muscle relaxant properties which may be sufficient for some surgical procedures to be performed without a neuromuscular blocker. However, it has been reported to possess no analgesic properties (but see Pain, below).

Sevoflurane is given using a calibrated vaporiser. A short-acting barbiturate or other intravenous induction agent may be given before inhaling sevoflurane. For induction in premedicated patients, sevoflurane is given in concentrations of up to 5% v/v in adults, with oxygen or a mixture of oxygen and nitrous oxide; concentrations of up to 7% v/v may be used in children. For induction in unpremedicated patients, concentrations of up to 8% v/v may be used. Induction with sevoflurane is rapid (surgical anaesthesia in less than 2 minutes) and smooth because of its nonpungent odour. Maintenance of anaesthesia is achieved with a concentration of 0.5 to 3% v/v with or without nitrous oxide.

Reviews.

1. Patel SS, Goa KL. Sevoflurane: a review of its pharmacodynamic and pharmacokinetic properties and its clinical use in general anaesthesia. *Drugs* 1996; 51: 658–700.
2. Smith I, *et al.* Sevoflurane—a long-awaited volatile anaesthetic. *Br J Anaesth* 1996; 76: 435–45.
3. Grounds RM, Newman PJ. Sevoflurane. *Br J Hosp Med* 1997; 57: 43–6.
4. Goa KL, *et al.* Sevoflurane in paediatric anaesthesia: a review. *Paediatr Drugs* 1999; 1: 127–53.
5. Ghatge S, *et al.* Sevoflurane: an ideal agent for adult day-case anesthesia? *Acta Anaesthesiol Scand* 2003; 47: 917–31.
6. Sakai EM, *et al.* Inhalation anesthesiology and volatile liquid anesthetics: focus on isoflurane, desflurane, and sevoflurane. *Pharmacotherapy* 2005; 25: 1773–88.

Administration in children. Sevoflurane is used for the induction and maintenance of general anaesthesia in children; for details of doses, see Uses and Administration, above.

Pain. Two small, open-label studies[1,2] found self-administered sevoflurane 0.8% v/v in oxygen to be effective for pain relief during childbirth although an earlier study[3] was unable to confirm that it had an analgesic effect at subanaesthetic concentrations.

1. Yeo ST, *et al.* Analgesia with sevoflurane during labour: I. Determination of the optimum concentration. *Br J Anaesth* 2007; 98: 105–9.
2. Yeo ST, *et al.* Analgesia with sevoflurane during labour: II. Sevoflurane compared with Entonox for labour analgesia. *Br J Anaesth* 2007; 98: 110–15.
3. Tomi K, *et al.* Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans. *Br J Anaesth* 1993; 70: 684–6.

Adverse Effects

As with other halogenated anaesthetics sevoflurane may cause cardiorespiratory depression, hypotension, and malignant hyperthermia. However, the effects of sevoflurane on heart rate have only been seen at higher concentrations and it appears to have little effect on heart rhythm in comparison to other halogenated anaesthetics. Sevoflurane appears to sensitise the myocardium to sympathomimetics to a lesser extent than halothane or enflurane. Other effects seen with sevoflurane include agitation, especially in children, laryngospasm, and increased cough and salivation. Urinary retention and acute renal failure have also been noted, as have changes in liver enzyme values and reports of liver damage. Seizures have occurred in children and young adults, as well as older adults, with and without predisposing risk factors; dystonic movements have also been seen in children. Shivering, nausea, and vomiting have been reported in the postoperative period.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Effects on the cardiovascular system. The cardiovascular effects of sevoflurane are similar to those of isoflurane (see p. 1904.1) but it does not produce coronary steal. Also sevoflurane produces less tachycardia than isoflurane suggesting that it may be preferable in those predisposed to myocardial ischaemia.

Effects on the kidneys. Investigations[1] of the nephrotoxic potential of sevoflurane have found no evidence of renal function impairment despite peak plasma-fluoride ion concentrations greater than 50 nanomol/mL (a level considered to be nephrotoxic) being recorded in some patients at the end of sevoflurane anaesthesia,[2] and clinical experience would tend to support this.[3] The lack of renal toxicity with sevoflurane may be due to low concentrations of intrarenally generated fluoride ions;[4] in comparison, methoxyflurane defluorination in the kidney is much greater, and other metabolites may contribute to its known nephrotoxicity (see p. 1908.1).

Compound A, formed by the degradation of sevoflurane by carbon dioxide absorbents (see under Precautions, below), is nephrotoxic in *rats*.[1] However, studies in humans undergoing sevoflurane anaesthesia have detected no renal impairment postoperatively even when compound A was detected in the anaesthetic circuits.

1. Malan TP. Sevoflurane and renal function. *Anesth Analg* 1995; 81: S39–S45.
2. Kobayashi Y, *et al.* Serum and urinary inorganic fluoride concentrations after prolonged inhalation of sevoflurane in humans. *Anesth Analg* 1992; 74: 753–7.
3. Gentz BA, Malan TP. Renal toxicity with sevoflurane: a storm in a teacup? *Drugs* 2001; 61: 2155–62.
4. Kharasch ED, *et al.* Human kidney methoxyflurane and sevoflurane metabolism: Intrarenal fluoride production as a possible mechanism of methoxyflurane nephrotoxicity. *Anesthesiology* 1995; 82: 689–99.

Effects on the liver. There have been signs of hepatotoxicity in *animal* studies but in studies in humans, markers for hepatocellular dysfunction were no greater after sevoflurane anaesthesia than those after isoflurane.[1] The metabolism of sevoflurane differs from other halogenated anaesthetics in such a way that metabolites implicated in liver toxicity are not formed (see Pharmacokinetics, p. 1914.1). Nevertheless, licensed product information states that there have been postmarketing reports of hepatitis, and fatal cases of hepatic failure[2] and necrosis[3] have been reported. The production of compound A (see Carbon Dioxide Absorbents, under Precautions, below), increased cytosolic free calcium, and activation of free radical metabolising enzymes have been proposed as possible mechanisms of sevoflurane hepatotoxicity.[4]

1. Darling JR, *et al.* Comparison of the effects of sevoflurane with those of isoflurane on hepatic glutathione-S-transferase concentrations after body surface surgery. *Br J Anaesth* 1994; 73: 268P.
2. Lehmann A, *et al.* Case report: fatal hepatic failure after aortic valve replacement and sevoflurane exposure. *Can J Anesth* 2007; 54: 917–21.
3. Turillazzi E, *et al.* A fatal case of fulminant hepatic necrosis following sevoflurane anesthesia. *Toxicol Pathol* 2007; 35: 780–5.
4. Singhal S, *et al.* Sevoflurane hepatotoxicity: a case report of sevoflurane hepatic necrosis and review of the literature. *Am J Ther* 2010; 17: 219–22.

Effects on the nervous system. Sevoflurane has been shown to have a dose-related epileptogenic effect although the mechanism is unknown.[1] Tonic-clonic seizure-like movements associated with induction of anaesthesia using sevoflurane have been reported particularly in children[1-3] with or without a personal and/or family history of epilepsy or seizures, including an infant[4] with a history of tonic-clonic seizures. To minimise the risk, some have suggested[1] using a maximum of 1.5 times the minimum alveolar concentration (MAC) sevoflurane for maintenance of anaesthesia, and avoiding hypocapnia and monitoring cortical activity during the procedure.

1. Constant I, *et al.* Sevoflurane and epileptiform EEG changes. *Pediatr Anesth* 2005; 15: 266–74.
2. Åkeson J, Didriksson I. Convulsions on anaesthetic induction with sevoflurane in young children. *Acta Anaesthesiol Scand* 2004; 48: 405–7.
3. Yano T, *et al.* Two cases with past and family history of febrile convulsion developed seizure-like movements during sevoflurane anesthesia. *Anesthesiology* 2008; 109: 571.
4. Rewari V, Sethi D. Recurrence of focal seizure activity in an infant during induction of anaesthesia with sevoflurane. *Anaesth Intensive Care* 2007; 35: 788–91.

Hypersensitivity. For a report of hypersensitivity reactions, including asthma, associated with occupational exposure to isoflurane and sevoflurane, see under Precautions, below.

Precautions

As with other halogenated anaesthetics, patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with sevoflurane. It should also not be used in those with a history of moderate or severe hepatic impairment associated with halogenated anaesthetics and should be used with caution in those with underlying liver disease. Sevoflurane reduces uterine muscle tone during pregnancy and should be used with caution in obstetrics because of the increased risk of uterine bleeding. Although the effects of sevoflurane on cerebral pressure are minimal in normal patients, safety in those with raised intracranial pressure has not been established and therefore sevoflurane should be used with caution together with techniques to lower intracranial pressure. As emergence and recovery are particularly rapid with sevoflurane patients may require early postoperative pain relief. In children with neuromuscular disease, particularly Duchenne muscular dystrophy, halogenated anaesthetics have been associated with very rare cases of hyperkalaemia resulting in cardiac arrhythmias and death during the postoperative period.

See also Precautions for General Anaesthetics, p. 1897.3.

Abuse. Fatalities have been reported[1-3] with the abuse of sevoflurane. Autopsy revealed pulmonary oedema and frothing in the lung of one victim, suggesting death by asphyxia,[1] and cardiac arrhythmias were considered the cause of death in another 2 victims.[2,3]

1. Rosales CM, *et al.* Sevoflurane concentrations in blood, brain, and lung after sevoflurane-induced death. *J Forensic Sci* 2007; 52: 1408–10.
2. Levine B, *et al.* A fatality from sevoflurane abuse. *J Anal Toxicol* 2007; 31: 534–6.
3. Canturell FL. A fatal case of sevoflurane abuse. *Clin Toxicol* 2008; 46: 918–19.

Carbon dioxide absorbents. During anaesthesia given by circle breathing systems, the degradation of sevoflurane by carbon dioxide absorbents (such as soda lime) results in the formation of pentafluoroisopropenyl fluoromethyl ether (PIFE; compound A), and trace amounts of pentafluoromethoxy isopropyl fluoromethyl ether (PMFE; Compound B). The degree of degradation, absorption, and solubility of volatile anaesthetics is affected by the water content of carbon dioxide absorbents. In the case of sevoflurane, patients may inhale significant amounts of degradation products when the soda lime dries out. Compound A has been shown to be nephrotoxic in *rats* (see under Effects on the Kidneys, above). Even during short exposure times, as required for induction of anaesthesia, use of moist soda lime is important to minimise sevoflurane degradation, which is also aggravated by a high potassium hydroxide content of the soda lime.[1] Licensed product information states that the problem of compound A formation may be greater if barium hydroxide lime is used as a carbon dioxide absorbent rather than soda lime. Newer carbon dioxide absorbents that contain no, or reduced amounts of, potassium and/or sodium hydroxide have been developed and subsequently shown[2-4] to reduce the degradation of sevoflurane.

The use of desiccated carbon dioxide absorbents with sevoflurane has also been associated with rare cases of extreme heat and smoke or fire developing in the anaesthetic apparatus.[5]

1. Funk W, *et al.* Dry soda lime markedly degrades sevoflurane during simulated inhalation induction. *Br J Anaesth* 1999; 82: 193–8.
2. Kobayashi S, *et al.* Amsorb Plus and Drägersorb Free, two new-generation carbon dioxide absorbents that produce a low compound A concentration while providing sufficient CO2 absorption capacity in simulated sevoflurane anesthesia. *J Anesth* 2004; 18: 277–81.
3. Keijzer C, *et al.* Compound A and carbon monoxide production from sevoflurane and seven different types of carbon dioxide absorbent in a patient model. *Acta Anaesthesiol Scand* 2007; 51: 31–7.
4. Marini P, *et al.* Compound A, formaldehyde and methanol concentrations during low-flow sevoflurane anaesthesia: comparison of three carbon dioxide absorbers. *Acta Anaesthesiol Scand* 2007; 51: 625–32.
5. Abbott Laboratories, Canada. Important safety information regarding the use of Sevorane AF (sevoflurane) in conjunction with anesthesia machines (issued 17th November, 2003). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/sevorane_hpc-cps-eng.pdf (accessed 08/08/08)

Occupational exposure. Hypersensitivity reactions, manifesting as asthma, angioedema, or dermatitis, associated with occupational exposure to isoflurane and sevoflurane have been reported[1] in 3 healthcare workers. Of these, one worker with positive response on bronchial provocation testing subsequently had an anaphylactic reaction to sevoflurane during general anaesthesia; indirect exposure to sevoflurane resulted in a late asthmatic reaction in another, and exposure to isoflurane resulted in a rash in the third.

1. Vellore AD, *et al.* Occupational asthma and allergy to sevoflurane and isoflurane in anaesthetic staff. *Allergy* 2006; 61: 1485–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sevoflurane 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 04/10/11)

Interactions

Care is advised if adrenaline or other sympathomimetics are given during sevoflurane anaesthesia. The effects of competitive neuromuscular blockers such as atracurium are enhanced by sevoflurane (see p. 2032.3). The metabolism, and hence toxicity, of sevoflurane may be increased by drugs or compounds that induce cytochrome P450 isoenzyme CYP2E1 including isoniazid and alcohol.

See also Interactions of General Anaesthetics, p. 1897.3.

References.

1. Dale O. Drug interactions in anaesthesia: focus on desflurane and sevoflurane. *Baillieres Clin Anaesthesiol* 1995; 9: 105–17.

Pharmacokinetics

Sevoflurane is absorbed on inhalation. The blood/gas partition coefficient is low. Up to 5% of the absorbed dose of sevoflurane is metabolised in the liver by the cytochrome P450 isoenzyme CYP2E1 and defluorinated to its major metabolites hexafluoroisopropanol (HFIP), inorganic fluoride, and carbon dioxide. HFIP is rapidly conjugated with glucuronic acid and eliminated in the urine. Sevoflurane crosses the placenta.

References.
1. Behne M, *et al.* Clinical pharmacokinetics of sevoflurane. *Clin Pharmacokinet* 1999; 36: 13–26.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Eraldin; Sevocristalia; Sevorane; *Austral.*: Sevorane†; *Austria*: Sevorane; *Belg.*: Sevorane; *Braz.*: Anesevo; Sevocris; Sevorane; *Canad.*: Sevorane; *Chile*: Sevorane; *China*: Kai Te Li (凯特力); QiFuMei (奇弗美); Sevofrane (喜保福宁); Ultane (悦坦); *Cz.*: Sevorane; *Denm.*: Sevorane; *Fin.*: Sevorane; *Fr.*: Sevorane; *Ger.*: Sevorane; *Gr.*: Sevorane; *Hong Kong*: Sevorane; *Hung.*: Sevorane; *Indon.*: Sevorane; Sojourn; *Irl.*: Sevorane; *Israel*: Sevorane; Sojourn; *Ital.*: Sevorane; *Malaysia*: Sevorane; *Mex.*: Floves; Sevorane; Sovener; *Neth.*: Sevorane; *Norw.*: Sevorane; *NZ*: Sevorane; *Philipp.*: Sevo; Sevorane; *Pol.*: Sevorane; *Port.*: Sevorane; *Rus.*: Sevorane (Севоран); *S.Afr.*: Sojourn; Ultane; *Singapore*: Sevorane; *Spain*: Sevorane; *Swed.*: Sevorane; *Switz.*: Sevorane; *Thai.*: Sefether; Sevorane; Sojourn; *Turk.*: Sevorane; Sojourn; *USA*: Sojourn; Ultane; *Venez.*: Sevorane.

Sodium Oxybate (USAN)

JZP-6; NSC-84223; Ossibato di Sodio; Oxibato sódico; Sodium Gamma-hydroxybutyrate; Wy-3478; Натрия Оксибат; Натрия Оксибутират.

Sodium 4-hydroxybutyrate.

$C_4H_7NaO_3$=126.1.

CAS — 502-85-2.

UNII — 7G33012534.

NOTE. The name Rekinla has been used as a trade mark for sodium oxybate.

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

Blue nitro; Blue verve; Caps; Cherry Meth; Date rape drug; Drogue Du Cambriolage Sexuel Parfait; Easy lay; Everclear; EZLay; Fantasy; G; Gamma Oh; Gamma-OH; GBH; Georgia home boy; GHB; Goop; Great hormones at bedtime; Grievous bodily harm; G-riffic Jib; Liquid E; Liquid ecstacy; Liquid ecstasy; Liquid G; Liquid X; Organic quaalude; Salty water; Scoop; Sleep; Sleep-500; Soap; Somatomax; Somatomax PM; Vita-G; Water.

Pharmacopoeias. In *Chin.*

Uses and Administration

Sodium oxybate has hypnotic properties and, in its endogenous form, gamma-hydroxybutyrate (a catabolite of gamma-aminobutyric acid), increases dopamine concentrations in the brain. It is given intravenously usually with an opioid analgesic and a neuroleptic to produce general anaesthesia (p. 1896.1). Skeletal muscle relaxants may also be necessary. Sodium oxybate given orally is used in the treatment of cataplexy in patients with narcolepsy (below); in the USA it is also indicated for the excessive daytime sleepiness associated with narcolepsy.

In general anaesthesia a solution of sodium oxybate equivalent to 20% of the acid is given slowly by intravenous injection, usually in a dose of 60 mg/kg; in children 100 mg/kg may be used. For maintenance, a further dose that is half of the initial dose may be given.

For the management of narcolepsy in adults, sodium oxybate is given in initial oral doses of 4.5 g daily, as two equally-divided doses. The first dose should be taken at bedtime while in bed and at least 2 to 3 hours after food; the second dose should be taken 2.5 to 4 hours later also while sitting in bed. Both doses should be prepared before going to bed; each dose should be diluted with 60 mL of water. The initial dose may be increased in steps of 1.5 g (0.75 g per dose) every 1 to 2 weeks to a maximum dose of 9 g daily. If therapy has been stopped for more than 14 consecutive days, titration should be restarted at the lowest dose. Reduced doses are recommended in patients with hepatic impairment (see below).

References.
1. Puller DE, *et al.* The Xyrem risk management program. *Drug Safety* 2004; 27: 293–306.
2. Snead OC, Gibson KM. γ-Hydroxybutyric acid. *N Engl J Med* 2005; 352: 2721–32. Correction. *ibid.* 2006; 354: 537.
3. Pardi D, Black J. γ-Hydroxybutyrate/sodium oxybate: neurobiology, and impact on sleep and wakefulness. *CNS Drugs* 2006; 20: 993–1018.
4. Castelli MP, Multi-faceted aspects of gamma-hydroxybutyric acid: a neurotransmitter, therapeutic agent and drug of abuse. *Mini Rev Med Chem* 2008; 8: 1188–1202.
5. Benarroch EE. γ-Hydroxybutyric acid and its relevance in neurology. *Neurology* 2009; 72: 282–6.

Administration in children. Sodium oxybate is used in general anaesthesia in children; for details of doses, see Uses and Administration, above.

Administration in hepatic impairment. The recommended initial oral dose of sodium oxybate (see Uses and Administration, above) should be halved in patients with hepatic impairment. Subsequent increases should be monitored against effect.

Alcohol withdrawal syndrome. A systematic review[1] of 13 randomised controlled studies involving 648 patients concluded that oral sodium oxybate 50 mg/kg daily is effective, when compared with placebo, in reducing symptoms of alcohol withdrawal (p. 1734.1) and in helping to prevent relapse for up to 3 months thereafter. It also appeared to be as effective as the benzodiazepines and clomethiazole in the treatment of alcohol withdrawal syndrome, and as effective as naltrexone and disulfiram in the maintenance of abstinence. The most commonly reported adverse effects were dizziness and vertigo. However, the risk of addiction, misuse, and/or abuse of the drug is of concern with this patient group.

1. Leone MA, *et al.* Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2010 (accessed 17/03/11).

Cluster headache. Sodium oxybate has been investigated[1] in the management of patients with cluster headache (p. 670.1).

1. Khatami R, *et al.* Long-term efficacy of sodium oxybate in 4 patients with chronic cluster headache. *Neurology* 2011; 77: 67–70.

Fibromyalgia. Studies[1-3] of the efficacy of sodium oxybate in the management of fibromyalgia, a painful musculoskeletal disorder which usually responds poorly to analgesics (see Soft-tissue Rheumatism, p. 14.2), showed some benefit in the perception of pain and fatigue, and in improving sleep.

1. Russell IJ, *et al.* Oxybate SXB-26 Fibromyalgia Syndrome Study Group. Sodium oxybate relieves pain and improves function in fibromyalgia syndrome: a randomized, double-blind, placebo-controlled, multicenter clinical trial. *Arthritis Rheum* 2009; 60: 299–309.
2. Moldofsky H, *et al.* Effects of sodium oxybate on sleep physiology and sleep/wake-related symptoms in patients with fibromyalgia syndrome: a double-blind, randomized, placebo-controlled study. *J Rheumatol* 2010; 37: 2156–66.
3. Russell IJ, *et al.* Sodium Oxybate 06-008 FM Study Group. Sodium oxybate reduces pain, fatigue, and sleep disturbance and improves functionality in fibromyalgia: results from a 14-week, randomized, double-blind, placebo-controlled study. *Pain* 2011; 152: 1007–17.

Narcoleptic syndrome. Sodium oxybate[1-7] given at night is used to improve cataplexy and excessive daytime sleepiness in patients with narcoleptic syndrome (p. 2314.3).

For a reference to the pharmacokinetics of sodium oxybate in narcoleptic patients, see p. 1915.1.

1. US Xyrem Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. *Sleep* 2002; 25: 42–9.
2. US Xyrem Multicenter Study Group. A 12-month, open-label, multicenter extension trial of orally administered sodium oxybate for the treatment of narcolepsy. *Sleep* 2003; 26: 31–5.
3. Xyrem International Study Group. Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients. *Sleep Med* 2005; 6: 415–21.
4. Xyrem International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. *J Clin Sleep Med* 2005; 1: 391–7.
5. Lemon MD, *et al.* Sodium oxybate for cataplexy. *Ann Pharmacother* 2006; 40: 433–40.
6. Robinson DM, Keating GM. Sodium oxybate: a review of its use in the management of narcolepsy. *CNS Drugs* 2007; 21: 337–54.
7. Black J, *et al.* The nightly use of sodium oxybate is associated with a reduction in nocturnal sleep disruption: a double-blind, placebo-controlled study in patients with narcolepsy. *J Clin Sleep Med* 2010; 6: 596–602.

Adverse Effects

When used in general anaesthesia adverse effects with sodium oxybate include abnormal muscle movements during the induction period and nausea and vomiting. Occasional emergence delirium has been reported. Bradycardia frequently occurs. Respiration may be slowed and hypokalaemia has been reported.

The most common adverse reactions seen in patients taking sodium oxybate orally for the management of narcolepsy are dizziness, headache, and, particularly in women, nausea. Other common reactions include anorexia, vomiting, diarrhoea, peripheral oedema, abnormal dreams and nightmares, sleepwalking, confusion, depression, anxiety, insomnia, paraesthesia, somnolence, tremor, amnesia, blurred vision, sweating, muscle cramps, nocturnal enuresis, urinary incontinence, asthenia, and fatigue. Blood pressure may also be increased. Psychosis, convulsions, hallucinations, agitation, hypersensitivity, and faecal incontinence are less common; rarely, respiratory depression has been reported.

See also Adverse Effects of General Anaesthetics, p. 1896.3.

Effects on electrolyte balance. A report of severe metabolic disorders occurring during therapy with sodium oxybate and tetracosactide in 4 patients with severe head injuries.[1] The disorders consisted of hypernatraemia, hypokalaemia, and metabolic acidosis.

1. Béal JL, *et al.* Troubles métaboliques induits par l'association gamma-hydroxy butyrate de sodium et tétracosactide chez le traumatisé crânien. *Therapie* 1983; 38: 569–71.

Precautions

In general anaesthesia, sodium oxybate should not be given to patients with severe hypertension, bradycardia, conditions associated with defects of cardiac conduction, epilepsy, eclampsia, renal impairment, or alcohol abuse.

Treatment with oral sodium oxybate is contra-indicated in patients with succinic semialdehyde dehydrogenase deficiency, an enzyme involved in its metabolism to succinic acid. Its use is also contra-indicated in patients with epilepsy as safety and efficacy have not been established; convulsions have been reported with sodium oxybate use.

Patients with a history of depression or suicide attempt should be carefully monitored for depressive symptoms while taking sodium oxybate. The high sodium content of sodium oxybate (0.75 g of sodium in a 4.5 g daily dose) should be considered in patients with heart failure, hypertension, or impaired renal function.

Rebound symptoms with an increased frequency of cataplexy may be seen when sodium oxybate is stopped. There have also been rare reports of withdrawal symptoms such as insomnia, headache, dizziness, anxiety, hallucinations, and psychotic disorders following the illicit use of sodium oxybate (see Abuse, below).

See also Precautions for General Anaesthetics, p. 1897.3.

Abuse. Reports[1] of acute poisoning with oral sodium oxybate after illicit use led the FDA to issue warnings[2] about its potential for abuse. It is usually supplied illicitly as the sodium salt under a variety of names (see Street Names, above) and has been promoted for body building, weight loss, as a psychedelic substance, and as a sleep aid. Sodium oxybate has also been abused at social gatherings.[3,4] Adverse effects include vomiting, drowsiness, amnesia, hypotonia, vertigo, respiratory depression, and involuntary movements. Seizure-like activity, bradycardia, hypotension, and respiratory arrest have also been reported. Resolution of symptoms occurs spontaneously over 2 to 96 hours. However, some patients have required hospitalisation and respiratory support; deaths have been reported in several countries.[5-9] Severity of symptoms depends on the dose of sodium oxybate and the presence of other drugs such as alcohol, benzodiazepines, cannabis, or amfetamines; however, fatalities associated with the ingestion of sodium oxybate alone have been reported.[9] Prolonged use of large doses may lead to a withdrawal syndrome on stopping.[3,4,10-12]

Sodium oxybate is available in tasteless and odourless forms, and has occasionally been misused to incapacitate the victim and produce amnesia in sexual assaults and drug-facilitated rape ('date rape').[3,4,13]

Its precursors gamma-butyrolactone (GBL) and 1,4-butanediol are abused similarly.[3,4,7,13] Withdrawal symptoms have also been associated with stopping these 2 substances in abusers.[12]

1. CDC. Multistate outbreak of poisonings associated with illicit use of gamma hydroxy butyrate. *JAMA* 1991; 265: 447–8.
2. FDA. Warning about GHB. *JAMA* 1991; 265: 1802.
3. Smith KM, *et al.* Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and γ-hydroxybutyrate. *Am J Health-Syst Pharm* 2002; 59: 1067–76.
4. National Institute on Drug Abuse. Club drugs (GHB, Ketamine, and Rohypnol) (updated July 2010). Available at: http://www.drugabuse.gov/pdf/Infofacts/ClubDrugs10.pdf (accessed 28/03/11)
5. Anonymous. GBH death indicates increasing problem. *Pharm J* 1996; 256: 441.
6. CDC. Gamma hydroxy butyrate use—New York and Texas, 1995–1996. *JAMA* 1997; 277: 1511.
7. Caldicott DGE, *et al.* Fatalities associated with the use of γ-hydroxybutyrate and its analogues in Australasia. *Med J Aust* 2004; 181: 310–13.
8. Knudsen K, *et al.* Twenty-three deaths with γ-hydroxybutyrate overdose in western Sweden between 2000 and 2007. *Acta Anaesthesiol Scand* 2010; 54: 987–92.
9. Zvosec DL, *et al.* Case series of 226 γ-hydroxybutyrate-associated deaths: lethal toxicity and trauma. *Am J Emerg Med* 2011; 29: 319–32.
10. Galloway GP, *et al.* Physical dependence on sodium oxybate. *Lancet* 1994; 343: 57.
11. Wojtowicz JM, *et al.* Withdrawal from gamma-hydroxybutyrate, 1,4-butanediol and gamma-butyrolactone: a case report and systematic review. *CJEM* 2008; 10: 69–74.
12. van Noorden MS, *et al.* GHB-afhankelijkheid enonthoudingssyndroom: diagnostiek en behandeling. *Ned Tijdschr Geneeskd* 2010; 154: A1286.

13. Németh Z, *et al.* The involvement of gamma-hydroxybutyrate in reported sexual assaults: a systematic review. *J Psychopharmacol* 2010; 24: 1281–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sodium oxybate 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 05/10/11)

Interactions

In anaesthesia, sodium oxybate enhances the effects of opioid analgesics, barbiturates, and competitive neuromuscular blockers. The CNS depressant effects of sodium oxybate may be potentiated by alcohol, sedative-hypnotics, and other CNS depressants. The risk of respiratory depression may also be increased by benzodiazepines.

See also Interactions of General Anaesthetics, p. 1897.3.

Pharmacokinetics

After oral doses sodium oxybate is rapidly but incompletely absorbed from the gastrointestinal tract; absolute bioavailability is about 25%. Peak concentrations are reached within 0.5 to 2 hours. Absorption may be delayed and decreased following a high fat meal. Protein binding is less than 1%. Sodium oxybate is metabolised in the liver via GHB dehydrogenase to succinic semialdehyde, which is then converted to succinic acid via another enzyme, succinic semialdehyde dehydrogenase. Succinic acid enters the Krebs cycle and is metabolised to carbon dioxide, which is expired, and water. Less than 5% of unchanged drug appears in the urine; faecal excretion is also negligible.

References.

1. Palatini P, *et al.* Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers. *Eur J Clin Pharmacol* 1993; 45: 353–6.
2. Scharf MB, *et al.* Pharmacokinetics of gammahydroxybutyrate (GHB) in narcoleptic patients. *Sleep* 1998; 21: 507–14.
3. Borgen LA, *et al.* The influence of gender and food on the pharmacokinetics of sodium oxybate oral solution in healthy subjects. *J Clin Pharmacol* 2003; 43: 59–65.
4. Borgen LA, *et al.* The pharmacokinetics of sodium oxybate oral solution following acute and chronic administration to narcoleptic patients. *J Clin Pharmacol* 2004; 44: 253–7.
5. Brennelsen R, *et al.* Pharmacokinetics and excretion of gamma-hydroxybutyrate (GHB) in healthy subjects. *J Anal Toxicol* 2004; 28: 625–30.
6. Haller C, *et al.* GHB urine concentrations after single-dose administration in humans. *J Anal Toxicol* 2006; 30: 360–4.
7. Abanades S, *et al.* Gamma-hydroxybutyrate (GHB) in humans: pharmacodynamics and pharmacokinetics. *Ann N Y Acad Sci* 2006; 1074: 559–76.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria:*** Alcover; Xyrem; ***Belg.:*** Xyrem; ***Canad.:*** Xyrem; ***Cz.:*** Xyrem; ***Denm.:*** Xyrem; ***Fr.:*** Gamma-OH; Xyrem; ***Ger.:*** Somsanit; Xyrem; ***Irl.:*** Xyrem; ***Ital.:*** Alcover; Xyrem; ***Neth.:*** Xyrem; ***Norw.:*** Xyrem; ***Pol.:*** Xyrem; ***Port.:*** Xyrem; ***Spain:*** Xyrem; ***Swed.:*** Xyrem; ***Switz.:*** Xyrem; ***UK:*** Xyrem; ***USA:*** Xyrem.

Thiamylal Sodium

Tiamilal sódico.

Sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate.

$C_{12}H_{17}N_2NaO_2S$=276.3

CAS — 77-27-0 (thiamylal); 337-47-3 (thiamylal sodium).

UNII — T4L2P3KH7K.

Pharmacopoeias. In *Jpn.*

Profile

Thiamylal sodium is a short-acting intravenous barbiturate anaesthetic. It is possibly slightly more potent than thiopental sodium (below) and has similar actions and uses. It has been used for the production of complete anaesthesia of short duration, for the induction of general anaesthesia, or for inducing a hypnotic state.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn:*** Citosol; Isozol.

Thiopental Sodium *(BANM, rINN)*

Natrium Isopentylaethylthiobarbituricum (cum Natrio Carbonico); Penthiobarbital Sodique; Sodyum Tiopental; Sodyum Tiopenton; Soluble Thiopentone; Thiomebumalnatrium cum Natrii Carbonate; Thiopental et carbonate sodiques; Thiopental-Natrium; Thiopental Sodique; Thiopental Sodium and Sodium Carbonate; Thiopental sodná sůl a uhličitan sodný; Thiopentalum Natricum; Thiopentalum natricum et natrii carbonas; Thiopentobarbitalum Solubile; Thiopentone Sodium; Tiopentaalinatrium; Tiopentaalinatrium ja natriumkarbonaat; Tiopental sódico; Tiopentalio natrio druska ir natrio karbonatas; Tiopentalnatrium; Tiopentál-nátrium és nátrium-karbonát; Tiopentalnatrium och natriumkarbonat; Тиопентал Натрий.

Sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate.

$C_{11}H_{17}N_2NaO_2S$=264.3

CAS — 76-75-5 (thiopental); 71-73-8 (thiopental sodium).

ATC — N01AF03; N05CA19.

ATC Vet — QN01AF03; QN05CA19.

UNII — 49Y44QZL70.

NOTE. The name thiobarbital has been applied to thiopental and has also been used to describe a barbiturate of different composition.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.* Some include thiopental sodium with, some without, anhydrous sodium carbonate; some only include a sterile mixture for injection.

Ph. Eur. 8: (Thiopental Sodium and Sodium Carbonate; Thiopental Sodium BP 2014). A yellowish-white hygroscopic powder. It contains 84 to 87% thiopental and 10.2 to 11.2% sodium. Freely soluble in water; partly soluble in dehydrated alcohol. Store in airtight containers. Protect from light.

USP 36: (Thiopental Sodium). A white to off-white crystalline powder, or yellowish-white to pale greenish-yellow hygroscopic powder. May have a disagreeable odour. Its solutions are alkaline to litmus, decompose on standing, and on boiling, precipitation occurs. Soluble in water and in alcohol; insoluble in ether, in petroleum spirit, and in benzene. Store in airtight containers.

Incompatibility. Solutions of thiopental sodium are incompatible with acidic and oxidising substances including some antibacterials, neuromuscular blockers and analgesics. Compounds commonly listed as incompatible include amikacin sulfate, benzylpenicillin salts, cefapirin sodium, codeine phosphate, ephedrine sulfate, fentanyl citrate, glycopyrronium bromide, morphine sulfate, pentazocine lactate, prochlorperazine edisilate, suxamethonium salts, and tubocurarine chloride. Solutions decompose on standing and precipitation occurs on boiling.

Stability. Loss of thiopental in PVC and cellulose propionate delivery systems has been reported,[1,2] but in another study,[3] no loss of potency was noted. Adsorption has been reported[4] not to occur in polyolefin infusion bags.

1. Kowaluk EA, *et al.* Interactions between drugs and polyvinyl chloride infusion bags. *Am J Hosp Pharm* 1981; 38: 1308–14.
2. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; 39: 460–7.
3. 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.
4. Trissel LA, *et al.* Drug compatibility with new polyolefin infusion solution containers. *Am J Health-Syst Pharm* 2006; 63: 2379–82.

Uses and Administration

Thiopental is a short-acting barbiturate anaesthetic. It is given intravenously, usually for the induction of general anaesthesia (p. 1896.1), but may be used as the sole anaesthetic to maintain anaesthesia for short procedures with minimal painful stimuli. It is also used in anaesthesia as a supplement to other anaesthetics and as a hypnotic in balanced anaesthesia. Thiopental sodium may also be used intravenously in the control of refractory tonic-clonic status epilepticus and in neurosurgical patients to reduce increased intracranial pressure. It has also been given rectally for basal anaesthesia or basal narcosis.

Thiopental does not usually produce excitation and induction of anaesthesia is usually smooth. It has poor muscle relaxant properties and a muscle relaxant must be given before intubation is attempted. Thiopental also has poor analgesic properties and small doses may even lower the pain threshold. Recovery from moderate doses usually occurs within 10 to 30 minutes, but the patient may remain sleepy or confused for several hours. Large doses, repeated smaller doses, or continuous use may markedly delay recovery.

In **anaesthesia**, the dosage of thiopental varies greatly according to the state of the patient and the nature of other drugs being used concurrently (see under Precautions p. 1916.2 and Interactions p. 1916.2 for further details). Thiopental is usually given intravenously as the sodium salt as a 2.5% solution but a 5% solution is occasionally used. UK licensed product information states that a typical dose for inducing anaesthesia is 100 to 150 mg injected over 10 to 15 seconds, repeated after 30 to 60 seconds according to response. It also recommends that the total dosage used should not exceed 500 mg; in pregnant patients the total maximum dose is 250 mg. In some other countries, it has been recommended that induction begin with a test dose of 25 to 75 mg; thereafter, a dose of 50 to 75 mg may be given at intervals of 20 to 40 seconds according to response. Once anaesthesia has been established, additional doses of 25 to 50 mg may be given as necessary. When thiopental is used as the sole anaesthetic, anaesthesia can be maintained by repeat doses as needed or by continuous intravenous infusion of a 0.2 or 0.4% solution.

To **reduce elevations of intracranial pressure** in neurological patients, thiopental sodium is licensed for use as intermittent bolus injections of 1.5 to 3 mg/kg if adequate ventilation is provided (but see also Cerebrovascular Disorders, below). Higher doses have been tried.

For suggested doses in refractory tonic-clonic **status epilepticus**, see Status Epilepticus, p. 1916.1.

For dosage in *children* and the *elderly*, see also below.

References.

1. Russo H, Bressolle F. Pharmacodynamics and pharmacokinetics of thiopental. *Clin Pharmacokinet* 1998; 35: 95–134.

Administration in children. For the *induction of anaesthesia* in children, UK licensed product information recommends that thiopental sodium is given by slow intravenous injection (over 10 to 15 seconds) in a dose of 2 to 7 mg/kg; the dose may be repeated after 1 minute. Intravenous injections are normally given as a 2.5% solution.

In the treatment of prolonged *status epilepticus* (see p. 1916.1), the *BNFC* recommends an initial dose of up to 2 mg/kg in neonates or up to 4 mg/kg in children aged 1 month to 18 years, given as a slow intravenous injection; for all patients, this should then be followed by a continuous intravenous infusion of up to 8 mg/kg per hour, adjusted according to response.

Administration in the elderly. It is usually recommended that the dosage of barbiturate anaesthetics is reduced in the elderly. A study[1] in elderly patients showed that although reducing the rate of intravenous injection reduced the speed of induction, the dosage required was also reduced. Giving thiopental sodium 2.5% solution at a rate of 125 mg/minute induced anaesthesia in a mean of 90.8 seconds and required a mean dose of 2.8 mg/kg. Corresponding values for a rate of 500 mg/minute were 40.8 seconds and 5 mg/kg, respectively.

1. Berthoud MC, *et al.* Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients. *Br J Anaesth* 1993; 70: 423–7.

Anaesthesia. Some of the adverse effects of the neuromuscular blocker suxamethonium may be reduced when thiopental is used as part of the anaesthetic regimen. For a suggestion that thiopental may help to counteract the rise in intra-ocular pressure associated with the use of suxamethonium for intubation, see under Anaesthesia, p. 2028.1.

Cerebrovascular disorders. Barbiturates have been considered as suitable anaesthetics for use in patients with or at risk of raised intracranial pressure. Barbiturate-induced coma (commonly with pentobarbital or thiopental) has been used, both therapeutically and prophylactically, to protect the brain from ischaemia resulting from neurological insults including head injury, stroke, Reye's syndrome, and hepatic encephalopathy.[1-3] Rationale includes the ability of barbiturates to reduce intracranial pressure and to reduce metabolic demands of cerebral tissues. Although thiopental protected patients against the neuropsychiatric complications of cardiopulmonary bypass,[4] the Brain Resuscitation Clinical Trial I Study Group[5] found no cerebral benefit from thiopental in comatose survivors of cardiac arrest. Nor did others[6] observe any benefit from thiopental-induced coma in infants with severe birth asphyxia. A review in 1989 considered that there was no convincing evidence of improvement in neurological outcome to justify the risks of the procedure in conditions causing global ischaemia, although use of barbiturates without necessarily inducing coma might have a limited role in reduction of raised intracranial pressure refractory to other therapy. Use of barbiturates in the setting of regional cerebral ischaemia, including use during cardiopulmonary bypass to prevent focal neurological complications, remained controversial.[1] A systematic review[7] came to similar conclusions, pointing out that although the barbiturates may reduce intracranial pressure their hypotensive effects are likely to offset any beneficial action on cerebral perfusion, perhaps accounting for the lack of evidence for any clinical benefit. In addition, there have been individual case reports of effects on blood-potassium associated with thiopental-induced coma (see Effects on Electrolytes, under Adverse Effects and Treatment, p. 1916.1).

For a discussion of the treatment of raised intracranial pressure, including a mention of the use of barbiturates, see p. 1271.3.

1. Rogers MC, Kirsch JR. Current concepts in brain resuscitation. *JAMA* 1989; 261: 3143–7.

2. Lyons MK, Meyer FB. Cerebrospinal fluid physiology and the management of increased intracranial pressure. *Mayo Clin Proc* 1990; 65: 684–707.
3. Wooster PS, LeBlanc KL. Management of elevated intracranial pressure. *Clin Pharm* 1990; 9: 762–72.
4. Nussmeier NA, *et al.* Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. *Anesthesiology* 1986; 64: 165–70.
5. Abramson NS, *et al.* Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. *N Engl J Med* 1986; 314: 397–403.
6. Eyre JA, Wilkinson AR. Thiopentone induced coma after severe birth asphyxia. *Arch Dis Child* 1986; 61: 1084–9.
7. Roberts I, Sydenham E. Barbiturates for acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 16/06/05).

Status epilepticus. General anaesthesia may be used to control refractory tonic-clonic status epilepticus (p. 510.2). A short-acting barbiturate such as thiopental is usually used.

Doses of thiopental sodium in the treatment of status epilepticus appear to vary widely and may be defined by local clinical protocols. Licensed product information and the *BNF* recommend a dose of 75 to 125 mg intravenously as a 2.5% solution. Other regimens advocate an initial loading dose followed by further intermittent doses or a continuous infusion. European guidelines for the management of status epilepticus in adults suggest thiopental is started with a bolus of 3 to 5 mg/kg, then further boluses of 1 to 2 mg/kg every 2 to 3 minutes until seizures are controlled, followed by continuous intravenous infusion at a rate of 3 to 7 mg/kg per hour, titrated against EEG burst suppression, which should be maintained for at least 24 hours.[1] Recovery may be prolonged.[2]

For the dose of thiopental in children, see Administration in Children, p. 1915.3.

1. Meierkord H, *et al.* European Federation of Neurological Societies. EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol* 2010; 17: 348–55.
2. Parviainen I, *et al.* High-dose thiopental in the treatment of refractory status epilepticus in intensive care unit. *Neurology* 2002; 59: 1249–51.

Adverse Effects and Treatment

As for Phenobarbital, p. 536.3.

Excitatory phenomena such as coughing, hiccuping, sneezing, and muscle twitching or jerking may occur with any of the barbiturate anaesthetics, particularly during induction, but they occur more frequently with methohexital than with thiopental. Symptoms of laryngeal spasm or bronchospasm including cough and sneezing may also occur during induction. The intravenous injection of concentrated solutions of thiopental sodium such as 5% may result in thrombophlebitis. Extravasation of barbiturate anaesthetics may cause tissue necrosis. Intra-arterial injection causes severe arterial spasm with burning pain and may cause prolonged blanching of the forearm and hand and gangrene of digits. Hypersensitivity reactions have been rarely reported. Barbiturate anaesthetics can cause respiratory depression. They depress cardiac output and often cause an initial fall in blood pressure, and overdosage may result in circulatory failure. Arrhythmias may occur. Excessive doses are associated with hypothermia and profound cerebral impairment. Postoperative vomiting is infrequent but shivering may occur and there may be persistent drowsiness, confusion, and amnesia. Other relatively common postoperative effects include anorexia, malaise, fatigue, and dizziness; delirium has been seen in elderly patients. Headache has also been reported.

See also under Adverse Effects of General Anaesthetics, p. 1896.3.

Effects on electrolytes. Although barbiturate-induced coma with intravenous thiopental is used in the management of raised intracranial pressure, it has been associated with reports of hypokalaemia and severe rebound hyperkalaemia.[1-3] Frequent monitoring of serum-potassium concentrations during the first 24 hours after stopping thiopental infusion,[1] and tapering the dose,[2] have been recommended by some.

1. Bouchard PM, *et al.* Thiopental-associated dyskalemia in severe head trauma. *J Trauma* 2008; 64: 838–42.
2. Neil MJE, Dale MC. Hypokalaemia with severe rebound hyperkalaemia after therapeutic barbiturate coma. *Anesth Analg* 2009; 108: 1867–8.
3. Jung JY, *et al.* Sequential occurrence of life-threatening hypokalemia and rebound hyperkalemia associated with barbiturate coma therapy. *Clin Nephrol* 2009; 71: 333–7.

Hypersensitivity. Anaphylactic reactions to thiopental have been reported[1,2] although such reactions are rare. There has also been a report of haemolytic anaemia and renal failure with the development of an anti-thiopental antibody in a patient who had undergone general anaesthesia induced by thiopental.[3]

1. Westacott P, *et al.* Anaphylactic reaction to thiopentone: a case report. *Can Anaesth Soc J* 1984; 31: 434–8.
2. Moneret-Vautrin DA, *et al.* Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases. *Br J Anaesth* 1990; 64: 743–5.
3. Habibi B, *et al.* Thiopental-related immune hemolytic anemia and renal failure: specific involvement of red-cell antigen I. *N Engl J Med* 1985; 312: 353–5. Correction. *ibid.*; 1136.

Intra-arterial injection. Accidental intra-arterial injection of thiopental sodium produces severe arterial spasm with intense burning pain. Anaesthesia, paresis, paralysis, and gangrene may occur. Therapy has concentrated on dilution of injected thiopental, prevention and treatment of arterial spasm, prophylaxis of thrombosis, thrombectomy and other measures to sustain good blood flow. There has been a report[1] of the successful use of urokinase intra-arterially in the management of one patient accidentally given thiopental intra-arterially.

1. Vangerven M, *et al.* A new therapeutic approach to accidental intra-arterial injection of thiopentone. *Br J Anaesth* 1989; 62: 98–100.

Precautions

Barbiturate anaesthetics are contra-indicated in severe shock, dystrophia myotonica, and when there is dyspnoea or respiratory obstruction such as in acute severe asthma or when maintenance of an airway cannot be guaranteed.

Barbiturate anaesthetics should be used with caution in patients with dehydration, hypovolaemia, severe haemorrhage, burns, severe anaemia, hyperkalaemia, toxaemia, myasthenia gravis, myxoedema and other metabolic disorders, or severe renal disease. Caution is also required in those with cardiovascular disease, adrenocortical insufficiency, cachexia, or increased intracranial pressure or blood urea. Reduced doses are required in the elderly and in severe hepatic disease.

See also Precautions for General Anaesthetics, p. 1897.3.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers received thiopental, and the last available guidance from the American Academy of Pediatrics[1] considered that it was therefore usually compatible with breast feeding.

In two groups of 8 women undergoing induction with thiopental, the milk-to-plasma ratio was less than 1 in both groups and it was considered that the effects of thiopental on breast-fed infants would be negligible.[2]

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 26/05/04)
2. Andersen LW, *et al.* Concentrations of thiopentone in mature breast milk and colostrum following an induction dose. *Acta Anaesthesiol Scand* 1987; 31: 30–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies thiopental 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 05/10/11)

Interactions

Producing anaesthesia with the usual dose of barbiturate anaesthetics in patients accustomed to taking alcohol or other CNS depressants may be difficult; additional anaesthetics may be necessary. Patients being treated with phenothiazine antipsychotics may develop increased hypotension. Some phenothiazines, especially promethazine, may also increase the incidence of excitatory phenomena produced by barbiturate anaesthetics; cyclizine may possibly have a similar effect. Opioid analgesics can potentiate the respiratory depressant effect of barbiturate anaesthetics and the dose of the anaesthetic may need to be reduced. Use with nitrous oxide greatly reduces the dose of barbiturate anaesthetics required for anaesthesia. Reduced doses of thiopental may be required in patients receiving sulfafurazole.

See also Interactions of General Anaesthetics, p. 1897.3.

Antidepressants. Potentiation of barbiturate anaesthesia may be expected in patients receiving *tricyclic antidepressants* or *MAOIs* (see Anaesthesia under Precautions of Amitriptyline, p. 404.3 and for Phenelzine, p. 444.1, respectively).

Antipsychotics. For mention of the effect of *droperidol* on thiopental see Gastrointestinal Drugs, below.

Aspirin. Pretreatment with aspirin, a highly protein-bound drug, has been shown to potentiate thiopental anaesthesia.[1]

1. Dundee JW, *et al.* Aspirin and probenecid pretreatment influences the potency of thiopentone and the onset of action of midazolam. *Eur J Anaesthesiol* 1986; 3: 247–51.

Gastrointestinal drugs. *Metoclopramide* profoundly reduced the dose of thiopental required to produce hypnosis in female patients; *droperidol* had a similar effect.[1]

1. Mehta D, *et al.* Metoclopramide decreases thiopental hypnotic requirement. *Anesth Analg* 1993; 77: 784–7.

Probenecid. Pretreatment with probenecid, a highly protein-bound drug, potentiates thiopental anaesthesia.[1]

1. Dundee JW, *et al.* Aspirin and probenecid pretreatment influences the potency of thiopentone and the onset of action of midazolam. *Eur J Anaesthesiol* 1986; 3: 247–51.

Pharmacokinetics

Thiopental is highly lipid soluble and when it is given intravenously as the sodium salt, concentrations sufficient to produce unconsciousness occur in the brain within 30 seconds. Onset of action occurs within 8 to 10 minutes when thiopental sodium is given rectally but absorption may be unpredictable if a suspension rather than a solution is used. Recovery from anaesthesia is also rapid due to redistribution to other tissues, particularly fat. About 80% of thiopental may be bound to plasma proteins, although reports show a wide range of figures. Thiopental is metabolised almost entirely in the liver, but as it is only released slowly from lipid stores this occurs at a very slow rate.

It is mostly metabolised to inactive metabolites but a small amount is desulfurated to pentobarbital. Repeated or continuous use can lead to accumulation of thiopental in fatty tissue and this can result in prolonged anaesthesia and respiratory and cardiovascular depression. Elimination of thiopental after bolus injection can be described by a triexponential curve. The terminal elimination half-life has been reported to be 10 to 12 hours in adults and about 6 hours in children. However, values of 26 to 28 hours have been reported in obese patients and pregnant patients at term. Thiopental readily diffuses across the placenta and is distributed into breast milk.

References.
1. Gaspari F, *et al.* Elimination kinetics of thiopentone in mothers and their newborn infants. *Eur J Clin Pharmacol* 1985; 28: 321–5.
2. Swerdlow BN, Holley FO. Intravenous anaesthetic agents: pharmacokinetic-pharmacodynamic relationships. *Clin Pharmacokinet* 1987; 12: 79–110.
3. Esener Z, *et al.* Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum. *Br J Anaesth* 1992; 69: 586–8.
4. Gedney JA, Ghosh S. Pharmacokinetics of analgesics, sedatives and anaesthetic agents during cardiopulmonary bypass. *Br J Anaesth* 1995; 75: 344–51.
5. Norman E, *et al.* Placental transfer and pharmacokinetics of thiopentone in newborn infants. *Arch Dis Child Fetal Neonatal Ed* 2010; 95: F277–F282.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bensulf; Hipnopento; *Austral.*: Pentothal†; *Belg.*: Pentothal†; *Braz.*: Thionembutal; Thiopentax; *Canad.*: Pentothal†; *Denm.*: Pentothal; *Fin.*: Pentocur; Pentothal; *Fr.*: Pentothal†; *Ger.*: Trapanal; *Gr.*: Pentothal; *Hong Kong*: Pentothal†; *India*: Anesthal; Intraval Sodium; *Indon.*: Pentothal; *Ital.*: Farmotal; Pentothal; *Malaysia*: Pentotex; *Mex.*: Pentarim; Pentothal; Sodipental†; *Neth.*: Pentothal; *Norw.*: Pentothal†; *NZ*: Intraval†; *Philipp.*: Pentazol; Penthal; Pentobrim; Pentothal; *Singapore*: Pentothal; *Spain*: Pentothal; Tiobarbital; *Swed.*: Pentothal†; *Switz.*: Pentothal; *Thai.*: Pentothal†; Thiopen; *Turk.*: Ekipental; Pental; Pentothal†; *USA*: Pentothal†.

Pharmacopoeial Preparations
BP 2014: Thiopental Injection;
USP 36: Thiopental Sodium for Injection.

Tiletamine Hydrochloride *(BANM, USAN, rINNM)*

CI-634; CL-399; CN-54521-2; Hidrocloruro de tiletamina; Tiletamina, hidrocloruro de; Tilétamine, Chlorhydrate de; Tiletamini Hydrochloridum; Тилетамина Гидрохлорид.

2-Ethylamino-2-(2-thienyl)cyclohexanone hydrochloride.

$C_{12}H_{17}NOS,HCl$=259.8

CAS — 14176-49-9 (tiletamine); 14176-50-2 (tiletamine hydrochloride).

UNII — 99TAQ2QWJI.

Pharmacopoeias. In *US* (for veterinary use only.

USP 36: (Tiletamine Hydrochloride). A white to off-white crystalline powder. Freely soluble in water; slightly soluble in chloroform; practically insoluble in ether; soluble in methyl alcohol; freely soluble in 0.1N hydrochloric acid. pH of a 10% solution in water is between 3.0 and 5.0. Store in airtight containers.

Profile

Tiletamine has similar properties to ketamine (p. 1905.1). It is used as the hydrochloride with zolazepam (p. 1116.2) for general anaesthesia in veterinary medicine.

References.
1. Lee CC, *et al.* Movement disorder caused by abuse of veterinary anesthesia containing tiletamine. *Am J Emerg Med* 2009; 27: 1022.e5–6.

Trichloroethylene (*rINN*)

Trichlorethylene; Trichlorethylenum; Trichloroethene; Trichloroéthylène; Trichloroethylenum; Trichloroetylen; Tricloroetileno; Трихлороэтилен.

$CHCl:CCl_2$=131.4

CAS — 79-01-6.

ATC — N01AB05.

ATC Vet — QN01AB05.

UNII — 290YE8AR51.

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

Trichlo.

Stability. NOTE. Trichloroethylene used for anaesthetic purposes contains thymol 0.01% w/v as a stabiliser and is coloured blue for identification. It is non-flammable.

Uses and Administration

Trichloroethylene is a volatile halogenated anaesthetic given by inhalation. It has been used in some countries for the maintenance of light anaesthesia (p. 1896.1) but it has weak anaesthetic properties compared with other halogenated anaesthetics and poor muscle relaxant activity, and safer anaesthetics are generally preferred. It has also been used to supplement anaesthesia with nitrous oxide-oxygen or halothane. Trichloroethylene is a potent analgesic and has been used in subanaesthetic concentrations to provide analgesia for obstetrics, emergency management of trauma, and other acutely painful procedures.

Trichloroethylene is used in industry as a solvent for oils and fats, for degreasing metals, and for dry cleaning. It has also been used in type correction fluids but is no longer included in most brands.

Adverse Effects and Precautions

Trichloroethylene increases the rate and decreases the depth of respiration and may be followed by apnoea. The sensitivity of the heart to beta-adrenergic activity may increase, possibly with ventricular arrhythmias.

Acute exposure to trichloroethylene may be followed by dizziness, lightheadedness, lethargy, nausea, and vomiting; hepatic and renal dysfunction may follow. Fatalities have occurred, although temporary unconsciousness is a more common manifestation.

Chronic poisoning may result in visual disturbances, intolerance to alcohol as manifested by transient redness of the face and neck (degreasers' or trichloroethylene flush), impairment of performance, hearing defects, neuralgia, and mild liver dysfunction. Prolonged contact with trichloroethylene can cause dermatitis, eczema, burns, and conjunctivitis.

Dependence has been reported in medical personnel and factory workers who regularly inhale trichloroethylene vapour.

If trichloroethylene is used as an anaesthetic it should not be used in closed-circuit apparatus since there is a reaction with soda lime to produce a toxic end product that may cause cranial nerve paralysis and possibly death.

See also Adverse Effects and Precautions for General Anaesthetics, p. 1896.3.

Reviews[1-4] of the toxicity of trichloroethylene.

1. Health and Safety Executive. Trichloroethylene. *Toxicity Review* 6. London: HMSO, 1982.
2. WHO. Trichloroethylene. *Environmental Health Criteria 50*. Geneva: WHO, 1985. Available at: http://www.inchem.org/documents/ehc/ehc/ehc50.htm (accessed 26/05/04)
3. Davidson IWF, Bellies RP. Consideration of the target organ toxicity of trichloroethylene in terms of metabolite toxicity and pharmacokinetics. *Drug Metab Rev* 1991; 23: 493–599.
4. Tabrez S, Ahmad M. Toxicity, biomarkers, genotoxicity, and carcinogenicity of trichloroethylene and its metabolites: a review. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 2009; 27: 178–96.

Abuse. Toxicity associated with inhalation of volatile substances including trichloroethylene has been reviewed.[1,2] Trichloroethylene can damage the kidney, liver, heart, and lung. However, in young healthy subjects, organ toxicity becomes apparent only with intensive and protracted abuse of volatile substances and fatalities have been reported.[3,4]

1. Marjot R, McLeod AA. Chronic non-neurological toxicity from volatile substance abuse. *Hum Toxicol* 1989; 8: 301–6.
2. Anonymous. Solvent abuse: little progress after 20 years. *BMJ* 1990; 300: 135–6.
3. Jones GR, Singer PP. An unusual trichloroethanol fatality attributed to sniffing trichloroethylene. *J Anal Toxicol* 2008; 32: 183–6.
4. Takaki A, *et al.* A 27-year-old man who died of acute liver failure probably due to trichloroethylene abuse. *J Gastroenterol* 2008; 43: 239–42.

Carcinogenicity. The use of trichloroethylene in foods, drugs, and cosmetics was banned by the FDA after studies found that hepatocellular carcinomas could be induced in *mice* by chronic exposure to very high doses. However, similar effects have not been found in *rats* and larger species and several epidemiologic studies have failed to show an increased incidence of liver tumours, total mortality, or mortality due to cancer in workers exposed to trichloroethylene. Suggestions that the carcinogenicity of trichloroethylene is due to one of its intermediate metabolites, cloral hydrate, have raised concern over the continuing use of cloral hydrate as a medicine. For further details, see p. 1056.1.

Effects on the liver. References[1,2] to hepatotoxicity after occupational exposure to trichloroethylene. See also Carcinogenicity, above, and Effects on the Skin, below.

1. McCunney RJ. Diverse manifestations of trichloroethylene. *Br J Ind Med* 1988; 45: 122–6.
2. Schattner A, Malnick SDH. Anicteric hepatitis and uveitis in a worker exposed to trichloroethylene. *Postgrad Med J* 1990; 66: 730–1.

Effects on the skin. A hypersensitivity syndrome comprising rashes, fever, hepatitis, and lymphadenopathy has been associated with occupational exposure to trichloroethylene, as have severe skin reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.[1-3] Carriers of the HLA allele HLA-B*1301, which occurs almost exclusively in persons of Asian ancestry, have been suggested to be at increased risk for developing such reactions.[4]

Scleroderma has been reported[5] in 3 patients occupationally exposed to trichloroethylene and, in 2 cases, also to trichloroethane.

1. Kamijima M, *et al.* Occupational trichloroethylene exposure as a cause of idiosyncratic generalized skin disorders and accompanying hepatitis similar to drug hypersensitivities. *Int Arch Occup Environ Health* 2007; 80: 357–70.
2. Kamijima M, *et al.* Trichloroethylene causes generalized hypersensitivity skin disorders complicated by hepatitis. *J Occup Health* 2008; 50: 328–38.
3. Xu X, *et al.* Severe hypersensitivity dermatitis and liver dysfunction induced by occupational exposure to trichloroethylene. *Ind Health* 2009; 47: 107–12.
4. Li H, *et al.* HLA-B*1301 as a biomarker for genetic susceptibility to hypersensitivity dermatitis induced by trichloroethylene among workers in China. *Environ Health Perspect* 2007; 115: 1553–6.
5. Flindt-Hansen H, Isager H. Scleroderma after occupational exposure to trichloroethylene and trichlorethane. *Acta Derm Venereol (Stockh)* 1987; 67: 263–4.

Poisoning. There has been a report[1] of a fatal self-poisoning in a 47-year-old woman with severe anorexia nervosa who ingested 500 mL of trichloroethylene and an unknown quantity of benzodiazepines. Coma developed shortly after ingestion, followed by abdominal distension, perforation, and necrosis, and multiple organ failure.

1. Llotier J, *et al.* A rare cause of abdominal compartment syndrome: acute trichlorethylene overdose. *Clin Toxicol* 2008; 46: 905–7.

Interactions

The arrhythmogenic effects of trichloroethylene may be potentiated by sympathomimetics such as adrenaline. Alcohol consumption after chronic exposure to trichloroethylene may result in a reddening of the skin (see Adverse Effects and Precautions, above).

See also Interactions of General Anaesthetics, p. 1897.3.

Pharmacokinetics

Trichloroethylene is rapidly absorbed by inhalation and ingestion. Percutaneous absorption can occur. Some of the inhaled trichloroethylene is slowly eliminated through the lungs; trichloroethylene is metabolised mainly in the liver, cloral hydrate (see p. 1055.2) being the first stable major metabolite formed; most is then metabolised to trichloroethanol and trichloroacetic acid which are excreted in the urine. The latter may be used as an indicator of industrial exposure. Trichloroethylene diffuses across the placenta.

Xenon

Ksenon; Ksenonas; Ksenons; Ksenon; Senon; Xeanón; Xenó; Xeno; Xenón; Xénon; Xenônio; Xénonum; Ксенон.

Xe=131.293

ATC — N01AX15.

ATC Vet — QN01AX15.

UNII — 3H3U766W84.

Profile

Xenon is a non-explosive gas. Mixtures of 60 or 70% v/v xenon with oxygen have been tried as a general anaesthetic.

References.

1. Rossaint R, *et al.* Multicenter randomized comparison of the efficacy and safety of xenon and isoflurane in patients undergoing elective surgery. *Anesthesiology* 2003; 98: 6–13.
2. Sanders RD, *et al.* Xenon: no stranger to anaesthesia. *Br J Anaesth* 2003; 91: 709–17.
3. Bedi A, *et al.* Use of xenon as a sedative for patients receiving critical care. *Crit Care Med* 2003; 31: 2470–7.
4. Preckel B, Schlack W. Xenon—cardiovascularly inert? *Br J Anaesth* 2004; 92: 786–9.
5. Sanders RD, *et al.* Xenon: elemental anaesthesia in clinical practice. *Br Med Bull* 2005; 71: 115–35.
6. Baskar N, Hunter JD. Xenon as an anaesthetic gas. *Br J Hosp Med* 2006; 67: 658–61.
7. Derwall M, *et al.* Xenon: recent developments and future perspectives. *Minerva Anestesiol* 2009; 75: 37–45.
8. Bronco A, *et al.* Xenon anaesthesia produces better early postoperative cognitive recovery than sevoflurane anaesthesia. *Eur J Anaesthesiol* 2010; 27: 912–16.
9. Jordan BD, Wright EL. Xenon as an anesthetic agent. *AANA J* 2010; 78: 387–92.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: LENOXe; *Fr.*: LENOXe; *Neth.*: LENOXe; *Port.*: LENOXe; *Spain*: LENOXe.

Growth Hormone and its Modulators

Human growth is under a complex system of hormonal controls. Growth hormone is produced by specialised cells (somatotropes) in the anterior pituitary; production and secretion are under a system of double regulation by a release-inhibiting hormone, somatostatin, and a growth hormone-releasing hormone, somatorelin, both produced in the hypothalamus. These in turn are modulated by various stimuli: dopamine, serotonin, hypoglycaemia, stress or emotional excitement, and ingestion of protein-rich meals all stimulate growth hormone release, whereas glucose, free fatty acids, insulin-like growth factor and growth hormone itself all suppress it.

The effects of growth hormone in the body rely on its interaction with a distinct growth hormone receptor; some effects, such as stimulation of lipolysis and gluconeogenesis, are direct but others, including its anabolic and growth-promoting effects, are mediated by induction of insulin-like growth factors (somatomedins).

Included in this chapter are growth hormone itself, now generally given as *recombinant somatropin* (p. 1919.3) or its synthetic methionyl analogue somatrem (p. 1919.3), and somatomedins such as mecasermin (p. 1929.2). Also included are the hypothalamic releasing hormone, somatorelin (p. 1930.1), and its analogue sermorelin (p. 1930.1); the hypothalamic inhibiting hormone, somatostatin (p. 1930.3), and its analogues such as lanreotide (p. 1923.2) and octreotide (p. 1924.1); the growth hormone release stimulant pralmorelin (p. 1929.1); and the growth hormone-receptor antagonist pegvisomant (p. 1928.2). Their use in acromegaly and growth retardation is discussed in more detail below.

Acromegaly and gigantism

Acromegaly and gigantism are syndromes of excess growth hormone secretion, usually associated with a secretory pituitary adenoma (somatropinoma).

Excessive growth hormone secretion in childhood, while the epiphyses of the long bones are open, results in ***gigantism***,[1,2] with a proportional growth spurt and skeletal enlargement. Other common features include obesity, coarse facial features, and disproportionately large hands and feet with thick fingers and toes. Puberty, with the increase in sex hormone secretion that leads to epiphyseal fusion, may be delayed by concomitant hypogonadism, leading to attainment of an even greater ultimate height. If growth hormone excess persists into adulthood, features of acromegaly may be superimposed on gigantism.[1] Treatment is similar to that used in acromegaly, as described below, although radiotherapy is used less often in gigantism because of the potential long-term consequences, such as hypopituitarism, for relatively young patients.[2] There is also more urgency to control the condition and avoid potentially irreversible musculoskeletal deformities and excessively tall stature.

When excess growth hormone secretion develops first in adulthood the condition is known as ***acromegaly***. Signs and symptoms tend to develop slowly and may be missed, sometimes for years. Growth hormone concentrations, and hence those of insulin-like growth factor I (IGF-I), which is produced in the liver in response to growth hormone, are elevated, sometimes markedly. The facial features become coarser, the jaw enlarges (prognathism), and hands and feet become enlarged. Peripheral neuropathy and carpal tunnel syndrome due to nerve entrapment, arthropathy, osteoarthritis, and muscle weakness, abnormal glucose tolerance, hypertension and left ventricular hypertrophy are all common, as is nodular goitre. Daytime somnolence may occur due to sleep apnoea. Acromegalics have an increased mortality if left untreated, largely due to cardiovascular disease.

Diagnosis and monitoring. The biochemical goal of treatment is to normalise growth hormone and IGF-I concentrations in order to reduce some of the signs and symptoms of acromegaly and to reverse the increased risk of mortality.[2,3] Growth hormone may be measured after an oral glucose tolerance test (OGTT); this suppresses growth hormone concentrations in healthy subjects, but not in patients with acromegaly. A growth hormone concentration below 400 nanograms/litre after an OGTT may be used to exclude acromegaly at the initial diagnosis, and in the assessment of surgical efficacy. Growth hormone concentrations taken as random samples may be used during the long-term monitoring of medical therapy for acromegaly; in such circumstances a target concentration below 1 microgram/litre is often used.[2,3] However, the target concentrations that have been suggested have changed over time with the development of more sensitive assays, and results must be interpreted in the context of the method used.[2-4] Random IGF-I concentrations should fall to normal for age and sex.[2,3]

Treatment. As for most pituitary tumours, **surgery** is the mainstay of treatment.[2,5] The success rate depends on surgical expertise and the size and extension of the mass, with success rates higher for microadenomas (75 to 95%) than macroadenomas (40 to 68%) depending on criteria.[5]

Drug therapy for acromegaly is indicated for patients who refuse surgery, have a low probability of a surgical cure, are at increased risk from surgery, have active disease after surgery, or are awaiting the effects of radiotherapy (see below).[2,5]

The *somatostatin analogues*, octreotide and lanreotide, reduce growth hormone secretion in most patients, but not all will have persistent suppression and normalisation of growth hormone levels.[6,7] Reported response rates vary, but effective growth hormone suppression occurs in about 50 to 55% of patients, and IGF-I is normalised in about 50 to 65%. Somatostatin analogues also produce tumour shrinkage, reducing tumour size by more than 20% in about 75% of patients,[5] and improve signs and symptoms of acromegaly, including improvements in cardiac structure and function.[8] Octreotide and lanreotide appear to have similar efficacy in the control of growth hormone and IGF-I concentrations based on limited data, but comparative studies of tumour shrinkage are lacking.[7,9]

There has been increasing interest in the use of somatostatin analogues for primary therapy, but when there is visual or neurological compromise then surgery is preferred because drug therapy may not provide enough tumour shrinkage to relieve pressure on the optic chiasm.[6,10] Guidelines[2,5] consider somatostatin analogues only suitable as first-line treatment for patients with a low likelihood of surgical cure or at high surgical risk. There are some data that suggest pre-operative use of somatostatin analogues could improve cardiovascular, respiratory, and metabolic functions and hence reduce morbidity associated with surgery, but further study is needed.[2,5,7,11] Pre-operative use might also improve surgical remission rates, particularly in patients with macroadenomas, but again further study is needed.[2,7,11]

Dopaminergics can produce a paradoxical reduction in growth hormone secretion in some patients with acromegaly, providing symptomatic relief. Cabergoline may be more effective than bromocriptine, but they are both less effective than somatostatin analogues. They are generally added to somatostatin analogue therapy, but may be considered alone for medical therapy in patients with modest IGF-I elevations when oral therapy is preferred.[2,5]

Pegvisomant is a growth hormone-receptor antagonist that may be used when other therapies have failed or are inappropriate.[2,5,7,12] It is reported[13,14] to lower IGF-I concentrations, improve signs and symptoms of acromegaly, and be well tolerated. Pegvisomant does not reduce growth hormone concentrations so these patients must be monitored by IGF-I measurement.[2,4] The addition of pegvisomant has also been reported to normalise IGF-I concentrations in patients with persistently elevated levels during somatostatin analogue therapy.[2,15]

Tumour regression induced by **radiotherapy** is a possible alternative, usually when surgical and/or medical therapy have failed.[2,5] Although it reduces growth hormone concentrations in most patients, its effects are slow and it often produces hypopituitarism. Since it may take several years for growth hormone concentrations to fall, drug therapy is also given until the effects of radiation therapy are satisfactory.

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Growth retardation

Stature follows a normal (bell-shaped) distribution within the population. Short stature has been defined as a height more than 2 standard deviations below the population mean, but there may be some difficulty in deciding at what point short stature becomes abnormal and to some extent this is determined by cultural as well as physiological norms.

Certain disorders are associated with well-defined deficiencies of growth which may be severe enough to warrant the description ***dwarfism***. Some forms are associated with disorders of bone or cartilage growth (skeletal dysplasias), and many of these result additionally in disproportionate growth, as in the short-limbs and large head characteristic of achondroplasia. Other genetic conditions that feature short stature include Noonan syndrome and SHOX (short stature homeobox-containing gene) deficiency. Other important causes of dwarfism include inadequate production of growth hormone (idiopathic growth hormone deficiency), either alone (isolated growth hormone deficiency) or combined with other pituitary hormone deficiencies as part of hypopituitarism; resistance to circulating growth hormone, as in Laron-type dwarfism, where there is a mutation of the growth hormone receptor; or defects in somatomedin synthesis.

Some other endocrine causes of short stature include hypothyroidism, Cushing's syndrome, and Turner's syndrome. Severe chronic disease in childhood such as asthma, chronic renal failure, or liver disorders can result in some growth retardation as can inadequate nutrition due to malabsorption syndromes such as coeliac disease.

Endocrine causes of growth retardation are significant because they may be treatable by appropriate replacement therapy. Isolated growth hormone deficiency, or growth hormone and gonadotrophin deficiencies, are the commonest congenital forms of hypopituitarism. Since most children with short stature will not have growth hormone deficiency and deficiency is rarely complete, care is required in its **diagnosis**. Although provocative growth hormone tests, which use non-physiological means to stimulate growth hormone secretion, have long been considered the gold standard for diagnosis of growth hormone deficiency they have limitations and some consider measurement of circulating somatomedins (insulin-like growth factors; IGFs) or their binding proteins to be more useful.[1] Different assays may give different results, and it has been advised that therapeutic decisions should be based on a combination of comprehensive clinical and height assessments, biochemical tests, and radiological evaluation.[2,3]

In children with confirmed **growth hormone deficiency** replacement therapy is appropriate, and is given by subcutaneous injections of synthetic human *growth hormone* (somatropin) or its methionyl analogue (somatrem). Treatment improves bone density[4,5] and growth velocity;[6,7] final adult height is also increased but the extent of the benefit is unclear.

A cohort study of French children registered to receive growth hormone between 1973 and 1993 suggested that the eventual outcome was not as good as expected, and treated individuals remained short.[8] However, a large American cohort that included more than 11 000 growth-hormone deficient patients found that although treated patients remained below target heights, many did achieve heights within the normal range for chronological age.[9] Maximum growth rates occurred in the first year of treatment and fell progressively thereafter, with no significant difference between growth rates after 4 years compared with pretreatment rates. A further cohort study[10] from the same French register for 1987 to 1996 found that adult heights were similar whether patients completed treatment or stopped before reaching adult height, and that patients

with severe growth hormone deficiency may respond better than those with less severe deficiency.

Growth hormone treatment regimens have changed over the years, and it appears that with optimal treatment it may be possible for some growth-hormone deficient children to achieve their genetic height potential.[7] An important prognostic factor is age, and for optimum results treatment should be started as early as possible in an attempt to maximise height before the onset of puberty.[2,7]

In patients with multiple pituitary hormone deficiencies, genetic defects in growth hormone synthesis, or severe organic growth hormone deficiency, growth hormone therapy should be continued into adulthood. In other patients, growth hormone deficiency may or may not persist into adult life, and retesting should be done after the patient reaches adult height and after 1 to 3 months without therapy.[2,11-13] In those patients who need continued treatment, the dose of growth hormone should be gradually reduced in order to maintain IGF-I concentrations within the normal range.[11,12]

Somatorelin (*growth hormone-releasing hormone*) or its analogue sermorelin have also been tried to boost growth hormone secretion in patients with growth hormone deficiency. Although there have been reports of improved growth rates, there are limited data directly comparing these with growth hormone. One large study[14] of sermorelin found that, compared with results generally reported for growth hormone therapy, fewer patients responded over a 12-month period and growth responses were poorer.

In patients with Laron dwarfism (**growth hormone resistance or insensitivity**), conventional growth hormone therapy is ineffective because of defects in the growth hormone receptors. However, replacement therapy with *mecasermin*, the recombinant form of insulin-like growth factor-I, may be of substantial benefit in the treatment of this disorder.[15]

The use of growth hormone in **short stature** other than that due to indisputable growth hormone deficiency is controversial. Benefit has been reported from growth hormone therapy in children with chronic renal failure,[16-18] juvenile idiopathic arthritis[19] (p. 12.1), cystic fibrosis (see also p. 1921.1)[20,21] in girls with Turner's syndrome (but see p. 2254.3), in young children (6 months to 3 years of age) with Down's syndrome,[22,23] and in Prader-Willi syndrome[24,25] (p. 2315.2), all of which are associated with marked growth retardation. However, many commentators see such interventions as essentially cosmetic. The treatment of idiopathic short stature in particular, for which no underlying disorder can be identified, poses problems as the risks and also the benefits in terms of final height are uncertain.[26-28] Children who are born small for gestational age usually experience catch-up growth by 2 years of age. In those who do not achieve this, growth hormone therapy can induce catch-up growth and improve childhood height scores; data on adult height are limited, however.[29,30] Guidelines suggest that therapy is justifiable in chronic renal insufficiency,[3,6,31] Turner's syndrome,[3,6,31] Prader-Willi syndrome,[3,31] and for children born small for gestational age.[3,31,32] However, sufficient evidence of benefit is lacking for other disorders including non-growth hormone deficient short stature and growth retardation associated with Down's syndrome, and some[6] consider that growth hormone should not be given to children with constitutional delay of growth.

More recently, growth hormone therapy has improved growth rate and height in children with SHOX deficiency.[31,33] Mutations and deletions of the SHOX gene, a gene involved in bone and cartilage formation, are associated with various short stature conditions such as Léri-Weill dyschondrosteosis, and are now understood to play a role in the short stature of Turner's syndrome and in some cases of idiopathic short stature. Growth hormone therapy can also improve height in children with Noonan syndrome.[34,35] As in other forms of growth retardation, starting treatment early before the onset of puberty might produce better results.

Although *sex hormones* have effects on growth they may also cause premature closure of the epiphyses when given to prepubertal or pubertal children, and this has limited their use. Nonetheless, anabolic drugs such as testosterone and oxandrolone have been used in boys, and oestrogen in girls, who have constitutional delay of growth associated with delayed puberty (see p. 2252.1). Oestrogens are not generally used for growth promotion in girls with Turner's syndrome, but as replacement therapy to promote puberty (see p. 2254.3).

Several *other drugs* have been investigated in growth retardation. Clonidine, which can promote growth hormone-releasing hormone release, has been given to children with growth hormone deficiency as well as to short children without proven deficiency, but results have been contradictory and largely unsatisfactory.[36-38] Gonadorelin analogues have also been given with growth hormone to short girls with or without growth hormone deficiency, in an attempt to slow bone maturation and delay puberty, thereby improving adult height.[39,40] However, a decrease in bone mineral density may outweigh any modest increase in height.[41] Where growth retardation is associated with zinc deficiency, zinc supplementation may be useful (see p. 2127.2).

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Growth Hormone *(BAN)* ⊗

GH; Groeihormoon; Hormon wzrostu; Hormona del crecimiento; Hormone de croissance; Hormônio do crescimento; Kasvuhormoni; Kasvuhormoon; Növekedési hormon; Ormone della crescita; Phyone; Růstový hormon; Somatotrophin; Somatotropiini; Somatotropin; Somatotropina; Somatotropine; STH; Tillväxthormon; Veksthormon; Wachstumshormon; Гормон Роста; Растежен Хормон; Соматропин.

CAS — 9002-72-6.

Somatrem *(BAN, USAN, pINN)* ⊗

Met-HGH; Methionyl Human Growth Hormone; Somatremum; Соматрем.

$C_{995}H_{1537}N_{263}O_{301}S_8$=22256.3

CAS — 82030-87-3.

ATC — H01AC02.

ATC Vet — QH01AC02.

UNII — CU8D464EDW.

Description. Somatrem is an analogue of somatropin containing an additional (methionyl) amino-acid residue. It may be produced in bacteria from recombinant DNA. Sometribove (*BAN*) is methionyl bovine growth hormone. Sometripor (*BAN*) is methionyl porcine growth hormone.

Somatropin *(BAN, USAN, rINN)* ⊗

CB-311; HGH; Human Growth Hormone; LY-137998; Somatropiini; Somatropina; Somatropinas; Somatropine; Somatropinum; Szomatropin; Соматропин.

$C_{990}H_{1528}N_{262}O_{300}S_7$=22125.1

CAS — 12629-01-5.

ATC — H01AC01.

ATC Vet — QH01AC01.

UNII — NQX9KB6PCL.

Description. Somatropin is synthetic human growth hormone having the normal structure of the major (22K) component of natural human pituitary growth hormone. It consists of a single polypeptide chain of 191 amino acids with disulfide linkages between positions 53 and 165 and between 182 and 189. For labelling purposes, the name may carry in parentheses an approved code in lower case letters indicative of the method of production: (epr) indicates production by enzymatic conversion of a precursor produced by a bacterium genetically modified by recombinant DNA technology; (rbe) indicates production from bacteria genetically modified by recombinant DNA technology; (rmc) indicates production from genetically engineered and transformed mammalian (mouse) cells.

Somidobove (*BAN*) is synthetic bovine growth hormone.

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

Ph. Eur. 8: (Somatropin). A protein having the structure (191 amino acid residues) of the major component of growth hormone produced by the human pituitary. A white or almost white powder, containing not less than 2.5 units/mg. Store at 2 degrees to 8 degrees in airtight containers.

Ph. Eur. 8: (Somatropin Concentrated Solution). A clear or slightly turbid, colourless solution. It may contain buffer

salts and other auxiliary substances. Store at -20 degrees in airtight containers. Avoid repeated freezing and thawing.

USP 36: (Somatropin). A protein hormone consisting of 191 amino acid residues, and its structure corresponds to the major component of the growth hormone extracted from human pituitary glands. It is produced as a lyophilised powder or bulk solution by methods based on recombinant DNA technology. The lyophilised powder contains not less than 910 micrograms of somatropin per mg, calculated on the anhydrous basis. The bulk solution contains not less than 910 micrograms of somatropin per mg of total protein.

Store at -25 degrees to -10 degrees in airtight containers.

Units

4.4 units of human growth hormone (somatropin) are contained in 1.75 mg of freeze-dried purified human growth hormone, with 20 mg of glycine, 2 mg of mannitol, 2 mg of lactose, and 2 mg of sodium bicarbonate, in one ampoule of the first International Standard (1987).

The second International Standard for Somatropin (2000), rDNA-derived human growth hormone, has a defined content of 1.95 mg of protein per ampoule, with a specific activity of 3.0 units/mg. One mg of anhydrous Somatropin USP is equivalent to 3.0 USP Somatropin Units. Commercial preparations vary somewhat in the number of units/mg.

Uses and Administration

Growth hormone is an anabolic hormone secreted by the anterior lobe of the pituitary, varying in size and amino-acid sequence between animal species. It promotes growth of skeletal, muscular, and other tissues, stimulates protein anabolism, and affects fat and mineral metabolism. The hormone has a diabetogenic action on carbohydrate metabolism. Secretion is pulsatile and dependent on neural and hormonal influences including a hypothalamic release-inhibiting hormone (see Somatostatin, p. 1930.3), and a hypothalamic releasing hormone (see Somatorelin, p. 1930.1). Sleep, hypoglycaemia, and physical or emotional stress result in increased secretion of growth hormone. The effects of growth hormone on skeletal growth are mediated by the somatomedins (see p. 1929.1). Somatropin is synthetic human growth hormone and somatrem its methionyl analogue.

Somatropin is given to children with open epiphyses for the treatment of short stature due to growth hormone deficiency (pituitary dwarfism) following assessment of pituitary function. Somatrem has been used similarly but is no longer generally available. Somatropin is also used in children with some other forms of growth retardation, such as that associated with Turner's syndrome, Noonan syndrome, SHOX (short stature homeobox-containing gene) deficiency, or chronic renal insufficiency, in short children born small for gestational age, and in idiopathic short stature. In Prader-Willi syndrome, somatropin is given to improve growth and body composition (but see also under Adverse Effects and Precautions, p. 1922.3). In adults, somatropin is given for confirmed growth hormone deficiency. It is also used in the management of wasting or cachexia associated with AIDS. In short bowel syndrome, somatropin is used to increase intestinal absorption of water, electrolytes, and nutrients from specialised nutritional support.

Doses in **growth retardation** should be individualised for each patient. Manufacturers vary somewhat in their estimates of the number of units/mg for somatropin and although some countries specify labelling in mg, others require labelling in units or both.

- In *children with growth hormone deficiency*, the usual daily dose in the UK is 25 to 35 micrograms/kg (0.07 to 0.1 units/kg), or 0.7 to 1 mg/m^2 (2 to 3 units/m^2). Doses are usually given by subcutaneous injection although some preparations are also licensed for intramuscular use; needle-free delivery systems are also available. Some licensed product information also suggests that doses should be given in the evening. Similar doses are used in other countries, where the total weekly dose may be divided into 3, 6, or 7 doses.
  When children with growth hormone deficiency reach their final height they should be re-assessed for the need to continue therapy, usually after at least 4 weeks without treatment. During *transition into adulthood* a subcutaneous dose of 200 to 500 micrograms daily may be used, and adjusted as required to maintain IGF-I concentrations in the normal range.
- In *Turner's syndrome* (gonadal dysgenesis), a subcutaneous daily dose of 45 to 50 micrograms/kg (0.14 units/kg), or 1.4 mg/m^2 (4.3 units/m^2), is generally used, although higher doses of up to 67 micrograms/kg daily may be needed.
- Doses of up to 66 micrograms/kg daily have been used for growth retardation related to *Noonan syndrome*.
- Daily doses of 45 to 50 micrograms/kg may be used in children with growth retardation due to *chronic renal insufficiency* or *SHOX deficiency*.
- In children with growth retardation who were *born small for gestational age*, the licensed daily dose in the UK is 35 micrograms/kg by subcutaneous injection (0.1 units/kg), or 1 mg/m^2 (3 units/m^2). In the USA, the licensed dose is somewhat higher, at 480 micrograms/kg weekly, divided into 6 or 7 doses.
- In children with *idiopathic short stature* somatropin is given subcutaneously in a weekly dose of up to 300 to 470 micrograms/kg divided into 6 or 7 doses.
- In children with *Prader-Willi syndrome*, a daily dose of about 35 micrograms/kg, or 1 mg/m^2, is given subcutaneously; daily doses should not exceed 2.7 mg.

In patients with **adult-onset growth hormone deficiency** lower doses are recommended. The initial dose is not more than 6 micrograms/kg (0.018 units/kg) subcutaneously daily. The dose can then be gradually increased according to patient response, to a usual maximum of 12.5 micrograms/kg daily. Alternatively, an initial dose in the range of 100 to 300 micrograms daily (0.3 to 0.9 units) in the evening is increased gradually at monthly intervals, based on clinical response, to a maintenance dose that is usually no more than 1 mg daily. Dosage requirements may decline with increasing age. In the UK, it has been recommended that treatment should be re-assessed 9 months after starting therapy.

In the treatment of **HIV-associated wasting or cachexia** somatropin is given in doses of 100 micrograms/kg daily by subcutaneous injection at bedtime, to a maximum of 6 mg daily. A starting dose of 100 micrograms/kg on alternate days may be considered for patients who are at increased risk of adverse effects.

In **short bowel syndrome** somatropin is given subcutaneously in a dose of about 100 micrograms/kg daily (to a maximum of 8 mg daily) for 4 weeks.

Sustained-release injections and inhalation formulations of growth hormone are also under investigation.

Administration in children. For details of somatropin doses in children with growth retardation, see Uses and Administration, above. See also below for doses that have been tried in those with severe burns.

Administration in adults. Growth hormone continues to be secreted in adult life, although secretion and activity gradually decline with increasing age, and it appears to play a role in maintaining skeletal and lean body-mass amongst other things. In adults with growth hormone deficiency (usually secondary to pituitary adenoma or its treatment) replacement therapy with growth hormone is reported to decrease body fat and abdominal adiposity, increase lean body-mass, and improve lipid profiles.[1-5] It may also increase bone density,[1,3] but many studies have been uncontrolled and of short duration, and any beneficial effect on bone density appears to be small.[6] Strength[7] and exercise capacity[8] can also be improved, although prolonged growth hormone therapy and physical training may be required to increase muscle performance.[3] Cardiac structure and function can be adversely affected by growth hormone deficiency, and replacement therapy in adults can have a positive effect on some cardiac parameters.[9] There are also some reports of improvements in quality of life;[3] although a study[10] using general standardised psychometric tests found no benefit, another[11] using a questionnaire developed for adults with hypopituitarism reported long-term benefits. Long-term data are not yet available to determine whether growth hormone therapy reduces the mortality rate in this group of patients, but it may provide some protection against myocardial infarction.[12] Guidelines on the use of growth hormone in adults with growth hormone deficiency have been issued.[13-16]

Less well established is the use of growth hormone in otherwise healthy elderly patients. Considerable controversy has attended suggestions that growth hormone therapy may retard or reverse some of the metabolic effects of ageing, and there is some concern that these patients may be at increased risk of adverse effects.[17] Studies[18] have shown that growth hormone can increase lean body-mass and decrease body fat, but functional ability does not necessarily improve and common adverse effects include peripheral oedema, carpal tunnel syndrome, arthralgias, and gynaecomastia.

Other uses for growth hormone in adult patients are discussed below. For mention of managing the transition to adulthood of children with growth hormone deficiency, see above and under Growth Retardation, p. 1918.3.

1. Götherström G, *et al.* A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. *J Clin Endocrinol Metab* 2001; **86**: 4657–65.
2. Attanasio AF, *et al.* Human growth hormone replacement in adult hypopituitary patients: long-term effects on body composition and lipid status—3-year results from the HypoCCS Database. *J Clin Endocrinol Metab* 2002; **87**: 1600–6.
3. Verhelst J, Abs R. Long-term growth hormone replacement therapy in hypopituitary adults. *Drugs* 2002; **62**: 2399–2412.
4. Maison P, *et al.* Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a metaanalysis of blinded, randomized, placebo-controlled trials. *J Clin Endocrinol Metab* 2004; **89**: 2192–9.
5. Götherström G, *et al.* A 10-year, prospective study of the metabolic effects of growth hormone replacement in adults. *J Clin Endocrinol Metab* 2007; **92**: 1442–5.
6. Davidson P, *et al.* Growth hormone replacement in adults and bone mineral density: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 2004; **60**: 92–8.
7. Götherström G, *et al.* Ten years of growth hormone (GH) replacement normalizes muscle strength in GH-deficient adults. *J Clin Endocrinol Metab* 2009; **94**: 809–16.
8. Widdowson WM, Gibney J. The effect of growth hormone replacement on exercise capacity in patients with GH deficiency: a metaanalysis. *J Clin Endocrinol Metab* 2008; **93**: 4413–17.
9. Maison P, Chanson P. Cardiac effects of growth hormone in adults with growth hormone deficiency: a meta-analysis. *Circulation* 2003; **108**: 2648–52.
10. Baum HBA, *et al.* Effects of physiological growth hormone (GH) therapy on cognition and quality of life in patients with adult-onset GH deficiency. *J Clin Endocrinol Metab* 1998; **83**: 3184–9.
11. Rosilio M, *et al.* Long-term improvement of quality of life during growth hormone (GH) replacement therapy in adults with GH deficiency, as measured by questions on life satisfaction-hypopituitarism (QLS-H). *J Clin Endocrinol Metab* 2004; **89**: 1684–93.
12. Svensson J, *et al.* Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. *J Clin Endocrinol Metab* 2004; **89**: 3306–12.
13. NICE. Human growth hormone (somatropin) in adults with growth hormone deficiency: Technology Appraisal 64 (issued August 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/TA64_HGHadults_fullguidance.pdf (accessed 20/08/08)
14. Ho KKY. 2007 GH Deficiency Consensus Workshop Participants. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. *Eur J Endocrinol* 2007; **157**: 695–700. Also available at: http://www.ghresearchsociety.org/files/2007_Consensus_AGHD.pdf (accessed 08/12/08)
15. Cook DM, *et al.* American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in growth hormone-deficient adults and transition patients—2009 update. *Endocr Pract* 2009; **15** (suppl 2): 1–29. Also available at: https://www.aace.com/sites/default/files/GrowthHormoneGuidelines.pdf (accessed 26/09/11)
16. Molitch ME, *et al.* Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011; **96**: 1587–1609. Also available at: http://www.endo-society.org/guidelines/upload/Evaluation-treatment-of-Adult-Growth-Hormone-Deficiency-Clinical-Practice-Guideline-NonCME.pdf (accessed 26/09/11)
17. Vance ML. Can growth hormone prevent aging? *N Engl J Med* 2003; **348**: 779–80.
18. Liu H, *et al.* Systematic review: the safety and efficacy of growth hormone in the healthy elderly. *Ann Intern Med* 2007; **146**: 104–15.

Burns. Growth hormone has been studied as a possible treatment to increase the rate of wound healing after severe burns. In a small study[1] of children with severe burns requiring skin grafts, subcutaneous somatropin 100 micrograms/kg daily, given from the first autograft until donor-site healing, was ineffective. However, a higher dose of somatropin 200 micrograms/kg daily by intramuscular injection, given throughout hospitalisation, reduced donor-site healing times and the length of hospital stay. There has been some concern that growth hormone therapy might increase hypertrophic scar formation, but studies[2,3] of subcutaneous somatropin given daily from hospital discharge until 1 year after burning have not found this. Somatropin treatment given during hospitalisation has also been reported to ameliorate burn-induced growth delays in such children; those injured during non-growth-spurt years may benefit most.[4,5] Long-term therapy given for 1 year after wound healing may also improve weight, linear growth, lean body-mass, and bone mineral content.[3,6] However, the manufacturers have recommended that somatropin should not be used to treat acute catabolic states in critically ill and burn patients, as there is some evidence in adults that mortality may be increased.[7] The management of burns is described on p. 1683.1.

1. Herndon DN, *et al.* Effects of recombinant human growth hormone on donor-site healing in severely burned children. *Ann Surg* 1990; **212**: 424–9.
2. de Oliveira GV, *et al.* Growth hormone effects on hypertrophic scar formation: a randomized controlled trial of 62 burned children. *Wound Repair Regen* 2004; **12**: 404–11.
3. Branski LK, *et al.* Randomized controlled trial to determine the efficacy of long-term growth hormone treatment in severely burned children. *Ann Surg* 2009;**250**: 514–23.
4. Low JFA, *et al.* Effect of growth hormone on growth delay in burned children: a 3-year follow-up study. *Lancet* 1999; **354**: 1789.
5. Low JFA, *et al.* The effect of short-term growth hormone treatment on growth and energy expenditure in burned children. *Burns* 2001; **27**: 447–52.
6. Hart DW, *et al.* Attenuation of posttraumatic muscle catabolism and osteopenia by long-term growth hormone therapy. *Ann Surg* 2001; **233**: 827–34.
7. Takala J, *et al.* Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med* 1999; **341**: 785–92.

Cachexia and lipodystrophy. Treatment with subcutaneous growth hormone has been reported to reverse weight loss and improve body wasting in subjects with HIV disease (p. 959.1).[1,2] It can have beneficial effects on

physical function, body-weight, lean body-mass, and measures of health-related quality of life.

Some benefit has been reported[3] with growth hormone therapy in HIV-associated lipodystrophy. However, the optimal dose of growth hormone for these patients has yet to be found. Studies using subcutaneous doses of 6 mg daily, although very effective in reducing visceral adipose fat, led to supraphysiological levels of IGF-I and treatment-limiting adverse effects in particular decreased insulin sensitivity. The use of lower doses such as 4 mg on alternate days had a more favourable adverse effect profile and produced acceptable decreases in visceral fat; physiological doses of growth hormone (about 1 mg daily) did not adversely affect insulin sensitivity but had modest effects on body composition. Furthermore, the effect of growth hormone on visceral fat is not sustained once treatment is withdrawn.

Growth hormone therapy has also been reported to improve metabolic indicators of malnutrition in some[4] but not other[5] studies of patients undergoing haemodialysis.

1. Goldsmith DR, Wagstaff AJ. Mammalian cell-derived somatropin: a review of its use in the management of HIV-associated wasting. *Drugs* 2006; 66: 387–401.
2. Gelato M, *et al.* Role of recombinant human growth hormone in HIV-associated wasting and cachexia: pathophysiology and rationale for treatment. *Clin Ther* 2007; 29: 2269–88.
3. Stanley TL, Grinspoon SK. GH/GHRH axis in HIV lipodystrophy. *Pituitary* 2009; 12: 143–52.
4. Johannsson G, *et al.* Double-blind, placebo-controlled study of growth hormone treatment in elderly patients undergoing chronic hemodialysis: anabolic effect and functional improvement. *Am J Kidney Dis* 1999; 33: 709–17.
5. Kotzmann R, *et al.* One-year growth hormone therapy improves granulocyte function without major effects on nutritional and anthropometric parameters in malnourished hemodialysis patients. *Nephron Clin Pract* 2003; 93: c75–82.

Cardiovascular disorders. A few small uncontrolled studies have reported improvements in heart failure (p. 1262.3) with the use of growth hormone.[1] A meta-analysis[2] of 12 studies using growth hormone in adults with chronic heart failure, including 8 placebo-controlled studies, also found evidence for improvement in several cardiovascular measures; however, individual results have been mixed and further study of long-term high-dose therapy is needed. A small underpowered study[3] of 6 months of treatment in children with dilated cardiomyopathy found only a trend towards improved cardiac function. Retrospective analysis[4] of a group of childhood cancer survivors found that growth hormone used to treat deficiency had some beneficial effects on anthracycline-induced left ventricular dysfunction, but that these diminished when growth hormone therapy was stopped.

1. Volterrani M, *et al.* Role of growth hormone in chronic heart failure: therapeutic implications. *Drugs* 2000; 60: 711–19.
2. Le Corvoisier P, *et al.* Cardiac effects of growth hormone treatment in chronic heart failure: a meta-analysis. *J Clin Endocrinol Metab* 2007; 92: 180–5.
3. McElhinney DB, *et al.* Recombinant human growth hormone treatment for dilated cardiomyopathy in children. Abstract: *Pediatrics* 2004; 114: 1074–5. Full version: http://pediatrics.aappublications.org/cgi/content/full/114/4/e452 (accessed 16/09/05)
4. Lipshultz SE, *et al.* Cardiac changes associated with growth hormone therapy among children treated with anthracyclines. *Pediatrics* 2005; 115: 1613–22.

Cystic fibrosis. The use of growth hormone has been investigated in several small studies in patients with cystic fibrosis (p. 177.2). A review[1] of studies in children, adolescents, and young adults found improvements in measures of pulmonary function, height, and weight in those treated with growth hormone, usually without a comparator. However, further study is needed to determine whether there are significant effects on pulmonary exacerbations or infections, bone fractures, or death. The typical dose used was 300 micrograms/kg per week [subcutaneously], and treatment was generally given for 6 months to 1 year.

1. Phung OJ, *et al.* Recombinant human growth hormone in the treatment of patients with cystic fibrosis. Abstract: *Pediatrics* 2010; 126: 1000. Full version: http://pediatrics.aappublications.org/cgi/reprint/126/5/e1211 (accessed 22/03/11)

Fibromyalgia. Symptomatic improvement after daily subcutaneous growth hormone injection has been reported in women with fibromyalgia,[1-3] a painful form of soft-tissue rheumatism (p. 14.2), and low levels of insulin-like growth factor I (IGF-I).

1. Bennett RM, *et al.* A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia. *Am J Med* 1998; 104: 227–31.
2. Cuatrecasas G, *et al.* Growth hormone as concomitant treatment in severe fibromyalgia associated with low IGF-1 serum levels: a pilot study. *BMC Musculoskelet Disord* 2007; 8: 119. Available at: http://www.biomedcentral.com/content/pdf/1471-2474-8-119.pdf (accessed 08/04/09)
3. Cuatrecasas G. Fibromyalgic syndromes: could growth hormone therapy be beneficial? *Pediatr Endocrinol Rev* 2009; 6 (suppl 4): 529–33.

Growth retardation. Growth hormone is a mainstay of the management of growth retardation (see p. 1918.3).

Reviews.

1. Harris M, *et al.* Growth hormone treatment in children: review of safety and efficacy. *Pediatr Drugs* 2004; 6: 93–106.
2. Richmond E, Rogol AD. Current indications for growth hormone therapy for children and adolescents. *Endocr Dev* 2010; 18: 92–108.
3. Collett-Solberg PF. Update in growth hormone therapy of children. *J Clin Endocrinol Metab* 2011; 96: 573–9.

Infertility. Growth hormone appears to sensitise the ovary to stimulation by gonadotrophins and it has been suggested that somatropin may have a role in the management of female infertility. However, studies of somatropin added to gonadotrophin regimens have generally been small, used different treatment protocols and outcome measures, and studied mixed groups of women in terms of the cause of infertility. Studies in women with poor response to ovarian stimulation have shown mixed results, and response may depend on the cause of infertility. Mixed results have also been reported in women with polycystic ovary syndrome. Benefits may be most likely in women with hypogonadotrophic hypogonadism,[1] or those considered to be poor responders,[2] but there is no additional benefit for women who have a normal ovarian response to gonadotrophins.[1,2] UK guidelines[3] for the treatment of infertility do not recommend its use. Growth hormone has also been tried similarly to enhance spermatogenesis in infertile men unresponsive to conventional therapy, but studies have been small, and despite some encouraging reports[4] others have found no benefit.[5,6]

For a discussion of infertility and the more usual drugs used in its management, see p. 2253.1.

1. Artini PG, *et al.* Growth hormone cotreatment with gonadotropins in ovulation induction. *J Endocrinol Invest* 1996; 19: 763–79.
2. Duffy JMN, *et al.* Growth hormone for in vitro fertilization. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 28/04/10).
3. NICE. Fertility: assessment and treatment for people with fertility problems (issued February 2013). Available at: http://www.nice.org.uk/nicemedia/live/14078/62769/62769.pdf (accessed 30/10/13)
4. Shoham Z, *et al.* Cotreatment with growth hormone for induction of spermatogenesis in patients with hypogonadotropic hypogonadism. *Fertil Steril* 1992; 57: 1044–51.
5. Ovesen PG, *et al.* Vaeksthormonbehandling af maend med nedsat saedkvalitet. *Ugeskr Laeger* 1998; 160: 176–80.
6. Giagulli VA. Absence of effect of recombinant growth hormone to classic gonadotropin treatment on spermatogenesis of patients with severe hypogonadotropic hypogonadism. *Arch Androl* 1999; 43: 47–53.

Osteogenesis imperfecta. For reference to possible benefit from growth hormone therapy in patients with osteogenesis imperfecta, see p. 1167.3.

Osteomalacia. As mentioned on p. 1168.1, there has been some interest in the use of growth hormone in children with hypophosphataemic rickets.

Prader-Willi syndrome. Growth hormone treatment may be of benefit in the management of children with Prader-Willi syndrome (p. 2315.2). It increases growth velocity and improves body composition, by reducing fat mass and increasing muscle mass. However, there is limited information about long-term efficacy, and the effect on growth velocity is reported to wane after 1 to 3 years of therapy. There are also specific contra-indications and precautions relating to the use of growth hormone in these patients (see under Adverse Effects and Precautions, p. 1922.3). Growth hormone treatment may also improve body composition in adults with Prader-Willi syndrome.

References.

1. Carrel AL, *et al.* Growth hormone improves body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome: a controlled study. *J Pediatr* 1999; 134: 215–21.
2. Myers SE, *et al.* Sustained benefit after 2 years of growth hormone on body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome. *J Pediatr* 2000; 137: 42–9.
3. Burman P, *et al.* Endocrine dysfunction in Prader-Willi syndrome: a review with special reference to GH. *Endocr Rev* 2001; 22: 787–99.
4. Carrel AL, *et al.* Benefits of long-term GH therapy in Prader-Willi syndrome: a 4-year study. *J Clin Endocrinol Metab* 2002; 87: 1581–5.
5. Whitman BY, *et al.* The behavioral impact of growth hormone treatment for children and adolescents with Prader-Willi syndrome: a 2-year, controlled study. Abstract: *Pediatrics* 2002; 109: 308–9. Full version: http://pediatrics.aappublications.org/cgi/content/full/109/2/e35 (accessed 16/09/05)
6. Paterson WF, Donaldson MDC. Growth hormone therapy in the Prader-Willi syndrome. *Arch Dis Child* 2003; 88: 283–5.
7. Carrel AL, *et al.* Growth hormone improves mobility and body composition in infants and toddlers with Prader-Willi syndrome. *J Pediatr* 2004; 145: 744–9.
8. Craig ME, *et al.* Growth hormone treatment and adverse events in Prader-Willi syndrome: data from KIGS (the Pfizer International Growth Database). *Clin Endocrinol (Oxf)* 2006; 65: 178–85.
9. Myers SE, *et al.* Two years of growth hormone therapy in young children with Prader-Willi syndrome: physical and neurodevelopmental benefits. *Am J Med Genet A* 2007; 143: 443–8.
10. Mogul HR, *et al.* Growth hormone treatment of adults with Prader-Willi syndrome and growth hormone deficiency improves lean body mass, fractional body fat, and serum triiodothyronine without glucose impairment: results from the United States multicenter trial. *J Clin Endocrinol Metab* 2008; 93: 1238–45.
11. de Lind van Wijngaarden RFA, *et al.* Efficacy and safety of long-term continuous growth hormone treatment in children with Prader-Willi syndrome. *J Clin Endocrinol Metab* 2009; 94: 4205–15.
12. Carrel AL, *et al.* Long-term growth hormone therapy changes the natural history of body composition and motor function in children with Prader-Willi syndrome. *J Clin Endocrinol Metab* 2010; 95: 1131–6.
13. Sode-Carlsen R, *et al.* One year of growth hormone treatment in adults with Prader-Willi syndrome improves body composition: results from a randomized, placebo-controlled study. *J Clin Endocrinol Metab* 2010; 95: 4943–50.

Short bowel syndrome. A combination of growth hormone, glutamine, and dietary modification may improve intestinal absorption of fluid, electrolytes, and other nutrients, and thus reduce parenteral nutrition requirements in patients with short bowel syndrome.[1] However, studies have produced conflicting results, and benefit may depend on several factors including the type and length of remaining bowel, the presence or absence of mucosal disease, and the doses of somatropin and glutamine.[2] Additionally the beneficial effects may be short-lived, returning to baseline if therapy is stopped.[3]

1. Keating GM, Wellington K. Somatropin (Zorbtive®) in short bowel syndrome. *Drugs* 2004; 64: 1375–81.
2. Matarese LE, *et al.* Growth hormone, glutamine, and modified diet for intestinal adaptation. *J Am Diet Assoc* 2004; 104: 1265–72.
3. Wales PW, *et al.* Human growth hormone and glutamine for patients with short bowel syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 6. Chichester: John Wiley; 2010 (accessed 08/12/10).

Veterinary and agricultural use. Bovine growth hormone or bovine somatotrophin (bovine somatotropin; BST) can increase milk yield in dairy cows. There has been considerable debate about both animal welfare and human food safety, and although it is approved in the USA[1] its use is banned in the EU.

1. FDA. CVM Update. Update on human safety of BST (issued 5th February, 1999). Available at: http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm130356.htm (accessed 12/08/10)

Adverse Effects and Precautions

Antibodies to growth hormone have been formed in some patients but these rarely seem to affect growth. There may be redness, itching, lumps, or lipoatrophy at the site of injection. Transient dose-related fluid retention with peripheral oedema and carpal tunnel syndrome has occurred; headache, muscle and joint pain, paraesthesia, and cases of benign intracranial hypertension have been reported. Although growth hormone has diabetogenic effects, high acute dosage has been associated with hypoglycaemia followed by hyperglycaemia. Growth hormone therapy may further increase the risk of ear disorders and otitis media in patients with Turner's syndrome, who are already at increased risk of ear and hearing disorders.

Growth hormone therapy is contra-indicated in patients with active neoplasms or intracranial lesions and should be stopped if evidence of tumour growth develops. Growth hormones should not be used for growth promotion in patients with closed epiphyses. Patients with scoliosis should be monitored during growth hormone therapy because of the risk of progression of scoliosis that can occur with rapid growth. Because of the diabetogenic effect of growth hormone it should be given with care to patients with diabetes mellitus; adjustment of antidiabetic therapy may be necessary. Somatropin is contra-indicated in patients with proliferative or preproliferative diabetic retinopathy. Hypothyroidism may develop during treatment, and may result in suboptimal response. Secondary hypoadrenalism may be unmasked by somatropin treatment, requiring glucocorticoid replacement therapy (see also Interactions, p. 1923.1). Growth hormone should not be used in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see also p. 1922.3). For the suggestion that growth hormone should not be used to treat acute catabolic states, as in patients with severe burns or who are otherwise critically ill, see Burns, under Uses and Administration, p. 1920.3.

Reviews.

1. Growth Hormone Research Society. Critical evaluation of the safety of recombinant human growth hormone administration: statement from the Growth Hormone Research Society. *J Clin Endocrinol Metab* 2001; 86: 1868–70.
2. Quigley CA, *et al.* Safety of growth hormone treatment in pediatric patients with idiopathic short stature. *J Clin Endocrinol Metab* 2005; 90: 5188–96.
3. Bolar K, *et al.* Long-term safety of recombinant human growth hormone in Turner syndrome. *J Clin Endocrinol Metab* 2008; 93: 344–51.
4. Poduval A, Saenger P. Safety and efficacy of growth hormone treatment in small for gestational age children. *Curr Opin Endocrinol Diabetes Obes* 2008; 15: 376–82.
5. Bell J, *et al.* Long-term safety of recombinant human growth hormone in children. *J Clin Endocrinol Metab* 2010; 95: 167–77.

Abuse. Growth hormone has been subject to abuse in sport for its anabolic effects.[1,2] Limited study data suggest that it may increase lean body-mass,[3,4] however, it has minimal effect on strength and athletic performance, and may worsen exercise capacity.[3]

1. Ehrnborg C, Rosén T. Physiological and pharmacological basis for the ergogenic effects of growth hormone in elite sports. *Asian J Androl* 2008; 10: 373–83.
2. Holt RIG. Is human growth hormone an ergogenic aid? *Drug Test Anal* 2009; 1: 412–18.
3. Liu H, *et al.* Systematic review: the effects of growth hormone on athletic performance. *Ann Intern Med* 2008; 148: 747–58.
4. Meinhardt U, *et al.* The effects of growth hormone on body composition and physical performance in recreational athletes: a randomized trial. *Ann Intern Med* 2010; 152: 568–77.

Benign intracranial hypertension. Benign intracranial hypertension (pseudotumor cerebri) has been described[1,2] in patients given growth hormone treatment. In an analysis[3] of a postmarketing surveillance database (1985 to 2000) of almost 40 000 children and adolescents who had been treated with growth hormone for various conditions, benign intracranial hypertension was more common than in the general paediatric population. The incidence in new patients starting growth hormone therapy was estimated to be about 30 in 100 000, and it had occurred more frequently in patients with renal failure or Turner's syndrome. Headache and papilloedema were the most common symptom and sign, but these did not occur in all patients, and most cases had an onset of a few months. The condition was effectively managed by stopping growth hormone. A small number of patients were rechallenged after the benign intracranial hypertension had resolved, and most could be treated with doses that were 25 to 50% of the original dose. Another surveillance database[4] of nearly 58 000 children and adolescents found an overall incidence of 27.7 per 100 000 treatment years; the incidence was highest in patients with chronic renal impairment, and lowest in those with idiopathic growth hormone deficiency. The median onset of benign intracranial hypertension also varied between diagnostic groups, ranging from about 4 days to 1.3 years. Headache alone is a commonly reported adverse effect of growth hormone treatment, and this study found an incidence of 793.5 per 100 000 treatment years. It has been pointed out that diagnosis of benign intracranial hypertension may be complicated by the occurrence of headaches, which usually resolve spontaneously.[5]

1. Malozowski S, *et al.* Growth hormone, insulin-like growth factor I, and benign intracranial hypertension. *N Engl J Med* 1993; 329: 665–6.
2. Malozowski S, *et al.* Benign intracranial hypertension in children with growth hormone deficiency treated with growth hormone. *J Pediatr* 1995; 126: 996–9.
3. Reeves GD, Doyle DA. Growth hormone treatment and pseudotumor cerebri: coincidence or close relationship? *J Pediatr Endocrinol Metab* 2002; 15 (suppl 2): 723–30.
4. Darendeliler F, *et al.* Headache, idiopathic intracranial hypertension and slipped capital femoral epiphysis during growth hormone treatment: a safety update from the KIGS database. *Horm Res* 2007; 68 (suppl 5): 41–7.
5. Price DA, *et al.* Benign intracranial hypertension induced by growth hormone treatment. *Lancet* 1995; 345: 458–9.

Carcinogenicity. Despite fears to the contrary, studies in children given growth hormone after cranial irradiation for brain tumours or CNS leukaemia have found no evidence that therapy with growth hormone increased the *relapse* rate.[1-3]

Cases of acute *leukaemia* have been reported among patients treated with growth hormones. An international workshop convened in 1988 to review known leukaemia cases in patients treated with growth hormones in Europe, North America, Japan, and Australia since 1959 found the incidence of leukaemia in growth hormone-treated patients represented a twofold increase over the expected rate.[4] It was concluded that there may be a small increase in leukaemia incidence associated with growth hormone treatment of growth hormone-deficient patients, but that it was not clear that this was actually attributable to growth hormone. A later study involving 6284 patients treated with growth hormone between 1963 and 1985 in the USA confirmed an increase of about 2.5-fold in the incidence of leukaemia in this population, but noted that many of the patients had other risk factors for leukaemia.[5] It has been suggested that growth hormone deficiency is itself a risk factor for leukaemia and that perhaps this, rather than growth hormone treatment, is related to the increased incidence of leukaemia in these patients.[6] If there is any risk it is relatively small, and in view of the essential nature of growth hormone therapy in growth hormone-deficient children it was considered inappropriate and unwise to withhold it.[4] Further large cohort studies of survivors of childhood cancers[3] or patients treated for idiopathic growth hormone deficiency[7] have found that the use of growth hormone was not associated with an increased risk of leukaemia.

There is some evidence to suggest that growth hormone may increase the risk of *solid tumours*. The risk of secondary solid tumours was increased in a cohort of childhood cancer survivors, but the authors considered that the risk was probably quite small compared with the benefits of growth hormone therapy in these patients.[3] Extended follow-up of this group also suggested that the elevation of risk diminished with time.[8] Another cohort of patients who had been treated for idiopathic growth hormone deficiency showed increased risks in the incidence and mortality of colorectal cancer.[7]

Further reports of malignancies associated with growth hormone therapy include two children with Bloom's syndrome (a rare chromosomal disorder affecting DNA replication), one of whom developed B-cell non-Hodgkin's lymphoma and the other stem-cell leukaemia.[9]

Continued surveillance of patients who have received growth hormone therapy has been encouraged.[10,11]

1. Packer RJ, *et al.* Growth hormone replacement therapy in children with medulloblastoma: use and effect on tumor control. *J Clin Oncol* 2001; 19: 480–7.
2. Swerdlow AJ, *et al.* Growth hormone treatment of children with brain tumors and risk of tumor recurrence. *J Clin Endocrinol Metab* 2000; 85: 4444–9.
3. Sklar CA, *et al.* Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab* 2002; 87: 3136–41.
4. Fisher DA, *et al.* Leukaemia in patients treated with growth hormone. *Lancet* 1988; i: 1159–60.
5. Pradkin JE, *et al.* Risk of leukemia after treatment with pituitary growth hormone. *JAMA* 1993; 270: 2829–32.
6. Rapaport R, *et al.* Relationship of growth hormone deficiency and leukemia. *J Pediatr* 1995; 126: 759–61.
7. Swerdlow AJ, *et al.* Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959–85: a cohort study. *Lancet* 2002; 360: 273–7.
8. Ergun-Longmire B, *et al.* Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. *J Clin Endocrinol Metab* 2006; 91: 3494–8.
9. Brock PR, *et al.* Malignant disease in Bloom's syndrome children treated with growth hormone. *Lancet* 1991; 337: 1345–6.
10. Ogilvy-Stuart AL, Gleeson H. Cancer risk following growth hormone use in childhood: implications for current practice. *Drug Safety* 2004; 27: 369–82.
11. Jenkins PJ, *et al.* Does growth hormone cause cancer? *Clin Endocrinol (Oxf)* 2006; 64: 115–21.

Creutzfeldt-Jakob disease. Reports in 1985 of a small number of deaths from Creutzfeldt-Jakob disease in patients under 40 years of age who had received growth hormone extracted from human pituitary glands resulted in the suspension of the distribution of pituitary-derived growth hormone by the licensing authorities in a number of countries, including Australia, Canada, the Netherlands, the UK, and the USA. Preparations of non-pituitary-derived growth hormone are now available that are free from contamination with Creutzfeldt-Jakob agent. However, because of the long incubation period of the disease, cases have been reported in patients who had received pituitary-derived growth hormone years previously.[1-5]

1. Brown P, *et al.* Iatrogenic Creutzfeldt-Jakob disease at the millennium. *Neurology* 2000; 55: 1075–81.
2. Croes EA, *et al.* Creutzfeldt-Jakob disease 38 years after diagnostic use of human growth hormone. *J Neurol Neurosurg Psychiatry* 2002; 72: 792–3.
3. Swerdlow AJ, *et al.* Creutzfeldt-Jakob disease in United Kingdom patients treated with human pituitary growth hormone. *Neurology* 2003; 61: 783–91.
4. Hirst C. Iatrogenic Creutzfeldt-Jakob disease presenting 24 years after human growth hormone administration. *Br J Hosp Med* 2005; 66: 592–3.
5. Furtner M, *et al.* Iatrogenic Creutzfeldt-Jakob disease 22 years after human growth hormone therapy: clinical and radiological features. *J Neurol Neurosurg Psychiatry* 2008; 79: 229–31.

Effects on carbohydrate metabolism. A retrospective analysis[1] of data from a pharmacoepidemiological survey of children treated with growth hormone found a higher incidence of type 2 diabetes, compared with that found in untreated children. The researchers speculated that growth hormone treatment might precipitate the onset of type 2 diabetes in predisposed patients, and proposed that patients with risk factors for diabetes, including Turner's syndrome, Prader-Willi syndrome, or intra-uterine growth retardation, be monitored. Studies of growth hormone have reported rises in serum concentrations of insulin, fasting and postprandial blood-glucose, and glycosylated haemoglobin, although these changes were generally small.[2] It has been noted that these effects appear to regress during treatment, but not always, and in some patients glucose intolerance or diabetes mellitus are not reversible after withdrawal of growth hormone.

Nonketotic hyperglycaemia developed within weeks of beginning growth hormone therapy in a 22-month-old child, leading to convulsions and metabolic acidosis; the patient died despite correction of the hyperglycaemia.[3]

1. Cutfield WS, *et al.* Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. *Lancet* 2000; 355: 610–13.
2. Jeffcoate W. Growth hormone therapy and its relationship to insulin resistance, glucose intolerance and diabetes mellitus: a review of recent evidence. *Drug Safety* 2002; 25: 199–212.
3. Garg AK. Hyperglycemia during replacement growth hormone therapy. *J Pediatr* 1994; 125: 329.

Effects on immune function. Growth hormone is generally considered to interact with the immune system although there is a lack of evidence that this is clinically significant.[1-4] There has been a report of acute renal transplant rejection in 2 children receiving treatment for growth retardation with somatropin.[5] In both children renal function of the transplant was stable for several years before somatropin was started, and growth hormone therapy had continued for some months before rejection occurred. It was suggested that during the first months of growth hormone therapy in transplant recipients, immunosuppressive therapy should be increased and transplant function carefully monitored. However, in subsequent studies[6,7] the use of growth hormone did not affect the incidence of rejection.

1. Church JA, *et al.* Immune functions in children treated with biosynthetic growth hormone. *J Pediatr* 1989; 115: 420–3.
2. Rapaport R, Oleske J. Immune function during growth hormone therapy. *J Pediatr* 1990; 116: 669–70.
3. Rekers-Mombarg LTM, *et al.* Immunologic studies in children with idiopathic short stature before and during growth hormone therapy. *Horm Res* 1995; 44: 203–7.
4. Lebl J, *et al.* Immune system in adults with childhood-onset growth hormone deficiency: effect of growth hormone therapy. *Endocr Regul* 2000; 34: 169–73.
5. Tydén G, *et al.* Acute renal graft rejection after treatment with human growth hormone. *Lancet* 1990; 336: 1455–6.
6. Maxwell H, Rees L. Randomised controlled trial of recombinant human growth hormone in prepubertal and pubertal renal transplant recipients. *Arch Dis Child* 1998; 79: 481–7.
7. Maxwell H, *et al.* Growth hormone and markers of immune function in children with renal transplants. *Pediatr Nephrol* 2000; 14: 473–5.

Effects on mortality. The EMEA[1] and FDA[2] are conducting safety reviews of growth hormone after a long-term French epidemiological study of patients who had received treatment during childhood for short stature showed an increased mortality risk for patients given growth hormone compared with the general population. Until the reviews have been completed somatropin should be used according to licensed indications and doses, and the EMEA has issued a reminder that the recommended daily dose of 50 micrograms/kg should not be exceeded.[1]

1. EMEA. Update on somatropin-containing medicines (issued 16th December, 2010). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/12/WC500099936.pdf (accessed 22/09/11)
2. FDA. Safety review update of recombinant human growth hormone (somatropin) and possible increased risk of death (issued 4th August, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm265865.htm (accessed 22/09/11)

Effects on the pancreas. A report of acute pancreatitis on starting growth hormone treatment in a patient with pseudohypoparathyroidism and growth hormone deficiency.[1] Ten further cases of acute pancreatitis associated with growth hormone treatment had been reported to the FDA at the time of writing.

1. Malozowski S, *et al.* Acute pancreatitis associated with growth hormone therapy for short stature. *N Engl J Med* 1995; 332: 401–2.

Effects on skeletal muscle. Mild inflammatory myositis, with myalgia and muscle weakness, has been reported in 2 patients receiving growth hormone therapy.[1] It was suggested that the effect might be due to *m*-cresol used as a preservative in the preparation.

1. Yordam N. Myositis associated with growth hormone therapy. *J Pediatr* 1994; 125: 671.

Gynaecomastia. A report of 22 cases of prepubertal gynaecomastia diagnosed during growth hormone treatment.[1]

1. Malozowski S, Stadel BV. Prepubertal gynecomastia during growth hormone therapy. *J Pediatr* 1995; 126: 659–61.

Hypersensitivity. Generalised urticaria in a patient given somatropin was overcome by a desensitisation regimen.[1] The patient was subsequently maintained uneventfully on daily injections of somatropin.

1. Walker SB, *et al.* Systemic reaction to human growth hormone treated with acute desensitization. *Pediatrics* 1992; 90: 108–9.

Iron deficiency. The view has been expressed[1] that given the increased production of haemoglobin and the prevalence of iron deficiency in patients treated with growth hormone, supplementation with iron should be considered in patients receiving growth hormone treatment.

1. Vihervuori H, *et al.* Increases in hemoglobin concentration and iron needs in response to growth hormone treatment. *J Pediatr* 1994; 125: 242–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies somatropin 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 24/10/11)

Prader-Willi syndrome. Somatropin is used in children diagnosed with Prader-Willi syndrome to improve growth and body composition (see Uses and Administration, p. 1920.1). One US manufacturer of somatropin (*Pharmacia*) has stated that as of April 2003 it was aware of 7 reports of death in children with Prader-Willi syndrome treated with growth hormone.[1] The patients shared one or more of the following risk factors: severe obesity, a history of respiratory impairment or sleep apnoea, or unidentified respiratory infection. It was recommended that patients with Prader-Willi syndrome should be evaluated for upper airway obstruction, before beginning treatment, and if signs of such obstruction, for example snoring, developed during treatment therapy should be suspended. Somatropin was considered contra-indicated in these patients if

they were severely obese or had severe respiratory impairment; licensed product information had been amended accordingly. Early diagnosis and aggressive treatment of respiratory infections was also recommended. A few cases have been described in the literature.[2-4]

Children with Prader-Willi syndrome appear to have a higher incidence of respiratory problems such as sleep apnoea, hypoventilation, and infections than healthy children.[5] A prospective study[6] of 25 patients reported that sleep-disordered breathing had actually improved in most of them after 6 weeks of growth hormone therapy. However, there was a subgroup of 6 patients in which obstructive sleep apnoea and hypopnoea worsened; 4 of them had developed upper respiratory-tract infections and enlarged tonsils, and 2 had high serum concentrations of insulin-like growth factor I (IGF-I) and enlarged tonsils.

1. Pharmacia, USA. Safety alert: Genotropin (somatropin [rDNA origin] for injection) (issued May 2003). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm168411.htm (accessed 12/08/10)
2. Eiholzer U, *et al.* Fatal outcome of sleep apnoea in PWS during the initial phase of growth hormone treatment: a case report. *Horm Res* 2002; 58 (suppl 3): 24–6.
3. Van Vliet G, *et al.* Sudden death in growth hormone-treated children with Prader-Willi syndrome. *J Pediatr* 2004; 144: 129–31.
4. Craig ME, *et al.* Growth hormone treatment and adverse events in Prader-Willi syndrome: data from KIGS (the Pfizer International Growth Database). *Clin Endocrinol (Oxf)* 2006; 65: 178–85.
5. Eiholzer U. Deaths in children with Prader-Willi syndrome: a contribution to the debate about the safety of growth hormone treatment in children with PWS. *Horm Res* 2005; 63: 33–9.
6. Miller J, *et al.* Short-term effects of growth hormone on sleep abnormalities in Prader-Willi syndrome. *J Clin Endocrinol Metab* 2006; 91: 413–17.

Interactions

High doses of corticosteroids may inhibit the growth promoting effects of growth hormone. For the effects of growth hormone on corticosteroids, see p. 1620.2. Doses of growth hormone may need to be increased in women receiving oral oestrogen replacement therapy, and may require adjustment if the route of oestrogen administration is changed.

Pharmacokinetics

Somatropin is well absorbed after subcutaneous or intramuscular injection with a bioavailability varying from about 60 to 80%; peak serum concentrations may not be achieved for several hours. After intravenous injection it has a half-life of about 20 to 30 minutes but after subcutaneous or intramuscular doses serum concentrations decline with a half-life of 3 to 5 hours, due to more prolonged release from the injection site. It is metabolised in the liver and kidneys and excreted in bile.

Absorption. Studies of the pharmacokinetics of somatropin after transdermal jet injection from 2 devices in healthy subjects suggested that absorption was more rapid and peak serum concentration higher than after conventional subcutaneous injection of the same dose.[1,2] However, this did not seem to result in any difference in the total amount absorbed, nor in the biological effect. Other needle-free devices[3,4] provided have similar concentration-time profiles for somatropin compared with conventional injection in healthy subjects. When studied in children with growth hormone deficiency, however, one device[3] was considered to cause more bleeding, pain, soreness, and bruising at the injection site than a needle-injection pen device.

1. Verhagen A, *et al.* Pharmacokinetics and pharmacodynamics of a single dose of recombinant human growth hormone after subcutaneous administration by jet-injection: comparison with conventional needle-injection. *Eur J Clin Pharmacol* 1995; 49: 69–72.
2. Agersø H, *et al.* Pharmacokinetics and pharmacodynamics of a new formulation of recombinant human growth hormone administered by ZomaJet 2 Vision, a new needle-free device, compared to subcutaneous administration using a conventional syringe. *J Clin Pharmacol* 2002; 42: 1262–8.
3. Dörr HG, *et al.* Are needle-free injections a useful alternative for growth hormone therapy in children? Safety and pharmacokinetics of growth hormone delivered by a new needle-free injection device compared to a fine gauge needle. *J Pediatr Endocrinol Metab* 2003; 16: 383–92.
4. Brearley C, *et al.* Pharmacokinetics of recombinant human growth hormone administered by cool.click 2, a new needle-free device, compared with subcutaneous administration using a conventional syringe and needle. *BMC Clin Pharmacol* 2007; 7: 10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Biotropin; Genotropin; HHT; Hutrope; Norditropin; Saizen; ***Austral.***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; SciTropin; Zomacton; ***Austria***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Zomacton; ***Belg.***: Genotonorm; Humatrope; Norditropin; NutropinAq; Omnitrope; Zomacton; ***Braz.***: Eutropin; Genotropin; Hormotrop; Humatrope; Norditropin; Omnitrope; Saizen; Somatrop; ***Canad.***: Humatrope; Norditropin; Nutropin; Omnitrope; Saizen; Serostim; ***Chile***: Genotonorm; HHT; Humatrope; Hutrope; Norditropin; Saizen; ***China***: An Su Meng (安苏萌); Genheal (珍怡); Genotropin (健高宁); Hai Zhi Yuan (海之元); Humatrope (优猛茁); Jintropin (赛增); Norditropin (诺泽); Sai Gao Lu (赛高路); Saizen (思真); ***Cz.***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Valtropin†; Zomacton; ***Denm.***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Zomacton; ***Fin.***: Genotropin; Humatrope; Norditropin; NutropinAq; Saizen; Zomacton; ***Fr.***: Genotonorm; Maxomat†; Norditropine; NutropinAq; Omnitrope; Saizen; Umatrope; Zomacton; ***Ger.***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Zomacton; ***Gr.***: Genotropin; Humatrope; Norditropin; Nutropin; Saizen; Zomacton; ***Hong Kong***: GenLei Jintropin; Genotropin; Humatrope†; Norditropin†; Saizen; SciTropin†; Serostim†; Zomacton; ***Hung.***: Genotropin; Humatrope; Norditropin; NutropinAq; Saizen; ***India***: Genotropin; Humatrope; LG Eutropin; Norditropin; Saizen; ***Indon.***: Eutropin; Genotropin; Norditropin; Saizen; ***Irl.***: Genotropin; Norditropin; Nutropin; Omnitrope; Saizen; Valtropin†; Zomacton; ***Israel***: Bio-Tropin; Genotropin; Norditropin; Nutropin; Saizen†; ***Ital.***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Zomacton; ***Jpn***: Growject; Norditropin; ***Malaysia***: Genotropin; Norditropin; Saizen; ***Mex.***: Cryo-Tropin; Genotropin; HHT†; Humatrope; Norditropin; Saizen; Serostim†; Xerendip; ***Neth.***: Genotropin; Humatrope; Norditropin; Nutropin; Omnitrope; Zomacton; ***Norw.***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Zomacton; ***NZ***: Genotropin; Norditropin; Saizen; ***Philipp.***: GenHeal; Humatrope†; Norditropin; Saizen; SciTropin; ***Pol.***: Genotropin; Norditopin; NutropinAq; Omnitrope; Valtropin†; ***Port.***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Valtropin†; Zomacton; ***Rus.***: Genotropin (Генотропин); Humatrope (Хуматроп); Jintropine (Джинтропин); Norditropin (Нордитропин); Rastan (Растан); Saizen (Сайзен); ***S.Afr.***: Genotropin; Humatrope; Norditropin; ***Singapore***: Genotropin; Norditropin; Saizen; SciTropin; ***Spain***: Genotonorm; Humatrope; Norditropin; Nutropin; Omnitrope; Saizen; Zomacton; ***Swed.***: Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Zomacton; ***Switz.***: Genotropin; Humatrope; Norditropine; Omnitrope; Saizen; ***Thai.***: Eutropin; GenHeal; Genotropin; Norditropin; Saizen; ***Turk.***: Genotropin; Humatrope; Norditropin; Saizen; Zomacton; ***UK***: Genotropin; Humatrope; Norditropin; Nutropin; Omnitrope; Saizen; Zomacton; ***Ukr.***: Biorostan (Биоростан); Genotropin (Генотропин); Norditropin (Нордитропин); ***USA***: Genotropin; Humatrope; Norditropin; Nutropin; Omnitrope; Saizen; Serostim; Tev-Tropin; Zorbtive; ***Venez.***: Genotropin; Humatrope; Saizen.

Multi-ingredient Preparations. ***Ukr.***: Nutropin (Нутропин Aq).

Pharmacopoeial Preparations

BP 2014: Somatropin Injection;
Ph. Eur.: Somatropin for Injection;
USP 36: Somatropin for Injection.

Lanreotide *(BAN, rINN)*

Angiopeptin; BIM-23014; BN-52030; DC-13-116; Lanreotid; Lanreotida; Lanréotide; Lanreotidi; Lanreotidum; Lanreotyd; Ланреотид.

3-(2-Naphthyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide cyclic (2→7)-disulfide.

$C_{54}H_{69}N_{11}O_{10}S_2$=1096.3
CAS — 108736-35-2.
ATC — H01CB03.
ATC Vet — QH01CB03.
UNII — 0G3DE8943Y.

Lanreotide Acetate *(BANM, USAN, rINNM)*

Acetato de lanreotida; BIM-23014C; Lanreotida, acetato de; Lanréotide, Acétate de; Lanreotidi Acetas; Ланреотида Ацетат.

$C_{54}H_{69}N_{11}O_{10}S_2 x (C_2H_4O_2)$
CAS — 127984-74-1.
ATC — H01CB03.
ATC Vet — QH01CB03.
UNII — IEU56G3J9C.

Uses and Administration

Lanreotide is a somatostatin analogue with similar properties to those of octreotide (p. 1924.1). It is given, as a long-acting depot injection, in the treatment of acromegaly (p. 1918.1) and thyrotrophic adenoma, as well as in the symptomatic management of neuroendocrine tumours, particularly carcinoid syndrome (p. 716.3).

Lanreotide is given as the acetate, but doses are usually expressed in terms of the base. The usual starting dose of one **intramuscular** depot injection (*Somatuline LA; Ipsen, UK*) is equivalent to lanreotide 30 mg every 14 days. In acromegaly and symptomatic neuroendocrine tumours, this may be increased if necessary to 30 mg every 7 to 10 days; in thyrotrophic adenoma it may be increased to 30 mg every 10 days.

An alternative preparation (*Somatuline Autogel; Ipsen, UK*) for acromegaly and symptomatic neuroendocrine tumours may be given by deep **subcutaneous** injection.

In acromegaly, an initial dose of 60 mg once every 28 days may be used in treatment-naive patients. For patients already receiving the intramuscular formulation, the same total dose of lanreotide that would have been given over 28 or 30 days may be replaced by a single dose of the subcutaneous preparation once every 28 days. In patients who respond to treatment, lanreotide may be gradually reduced to subcutaneous maintenance doses of 120 mg given at intervals of up to 56 days. In those who are not adequately controlled, a maximum dose of 120 mg once every 28 days may be used. Doses are adjusted according to symptoms and concentrations of growth hormone and IGF-I.

In patients with neuroendocrine tumours, the preparation for deep subcutaneous injection may be given in doses of 60 to 120 mg once every 28 days, and adjusted according to symptomatic relief.

In the USA, a preparation for deep subcutaneous injection (*Somatuline Depot; Tercica, USA*) may be given for acromegaly in initial doses of 90 mg once every 28 days for 3 months, then adjusted to between 60 and 120 mg every 28 days as necessary. Alternatively, for maintenance therapy a dose of 120 mg every 42 or 56 days may be appropriate.

For doses in hepatic and renal impairment, see below.

Lanreotide has been tried for the prevention of restenosis in coronary blood vessels following angioplasty (see Reperfusion and Revascularisation Procedures, p. 1259.2).

References.

1. Wymenga ANM, *et al.* Efficacy and safety of prolonged-release lanreotide in patients with gastrointestinal neuroendocrine tumors and hormone-related symptoms. *J Clin Oncol* 1999; 17: 1111–17.
2. Kuhn JM, *et al.* Evaluation of the treatment of thyrotropin-secreting pituitary adenomas with a slow release formulation of the somatostatin analog lanreotide. *J Clin Endocrinol Metab* 2000; 85: 1487–91.
3. Ruszniewski P, *et al.* Rapid and sustained relief from the symptoms of carcinoid syndrome: results from an open 6-month study of the 28-day prolonged-release formulation of lanreotide. *Neuroendocrinology* 2004; 80: 244–51.
4. Freda PU, *et al.* Long-acting somatostatin analog therapy of acromegaly: a meta-analysis. *J Clin Endocrinol Metab* 2005; 90: 4465–73.
5. Croxtall JD, Scott LJ. Lanreotide Autogel: a review of its use in the management of acromegaly. *Drugs* 2008; 68: 711–23.
6. Khan MS, *et al.* Long-term results of treatment of malignant carcinoid syndrome with prolonged release lanreotide (Somatuline Autogel). *Aliment Pharmacol Ther* 2011; 34: 235–42.

Administration in hepatic and renal impairment. The clearance of lanreotide, given by intravenous bolus, was significantly reduced in patients with severe chronic renal impairment requiring haemodialysis.[1] However, the authors of this study suggested that considering the wide therapeutic window of lanreotide, depot formulations may be given at the usual initial dose, with further doses adjusted according to response. Clearance of lanreotide was only slightly reduced in patients with moderate to severe hepatic impairment (Child-Pugh category B and C).[2]

The UK licensed product information for one depot **subcutaneous** formulation (*Somatuline Autogel; Ipsen, UK*) given every 28 days recommends that dose adjustment is not necessary in renal or hepatic impairment. Product information for a similar US preparation (*Somatuline Depot; Tercica, USA*) advises that in moderate and severe renal or hepatic impairment, an initial dose of 60 mg instead of 90 mg should be given by deep subcutaneous injection once every 28 days for 3 months, then adjusted as needed. Product information for another preparation (*Somatuline LA; Ipsen, UK*) usually given **intramuscularly** every 14 days suggests that it is not necessary to adjust the starting dose in hepatic or renal impairment.

1. Barbanoj M, *et al.* Pharmacokinetics of the somatostatin analog lanreotide in patients with severe chronic renal insufficiency. *Clin Pharmacol Ther* 1999; 66: 485–91.
2. Tomlinson B, *et al.* Pharmacokinetic profile of the somatostatin analogue lanreotide in individuals with chronic hepatic insufficiency. *Clin Pharmacokinet* 2006; 45: 1003–11.

Adverse Effects and Precautions

As for Octreotide Acetate, p. 1927.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lanreotide 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 24/10/11)

Interactions

As for Octreotide Acetate, p. 1927.3.

Pharmacokinetics

After intravenous injection lanreotide has a terminal half-life of about 2.5 hours. Lanreotide is available as injectable depot preparations, and after subcutaneous or intramuscular use of these an initial rapid liberation of the drug is followed by more prolonged release with an apparent half-

life of about 5 to 30 days. The absolute bioavailability is stated to range from about 55 to 80%, depending on the product.

References.
1. Hu M, Tomlinson B. Pharmacokinetic evaluation of lanreotide. *Expert Opin Drug Metab Toxicol* 2010; 6: 1301–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Somatuline; *Austral.*: Somatuline; *Austria*: Somatuline; *Belg.*: Somatuline; *Canad.*: Somatuline; *China*: Somatuline (赛马杜林); *Cz.*: Somatuline; *Denm.*: Ipstyl; *Fin.*: Somatuline; *Fr.*: Somatuline; *Ger.*: Somatuline; *Gr.*: Somatuline; *Hong Kong*: Somatuline; *Hung.*: Somatuline; *Irl.*: Somatuline; *Israel*: Somatuline; *Ital.*: Ipstyl; *Jpn*: Somatuline; *Neth.*: Somatuline; *Norw.*: Ipstyl; *Pol.*: Somatuline; *Port.*: Somatulina; *Rus.*: Somatuline (Соматулин); *Singapore*: Somatuline; *Spain*: Somatulina; *Swed.*: Somatuline; *Switz.*: Somatuline; *Turk.*: Somatuline; *UK*: Somatuline; *Ukr.*: Somatuline (Соматулин); *USA*: Somatuline.

Octreotide Acetate *(BANM, USAN, rINNM)*

Acetato de octreotida; Octreotida, acetato de; Octréotide, Acétate d'; Octreotidi Acetas; SMS-201-995 (octreotide); Октреотида Ацетат.

2-(D-Phenylalanyl-L-cystyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cystyl)-(2*R*,3*R*)-butane-1,3-diol acetate; D-Phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-*N*-[(1*R*,2*R*)-2-hydroxy-1-(hydroxymethyl)propyl]-L-cysteinamide cyclic (2→7) disulphide acetate.

$C_{49}H_{66}N_{10}O_{10}S_2.xC_2H_4O_2$=1019.2 (octreotide)

CAS — 83150-76-9 (octreotide); 79517-01-4 (octreotide acetate).

ATC — H01CB02.

ATC Vet — QH01CB02.

UNII — 75R0U2568I.

Incompatibility. Apparent loss of insulin has been reported from a total parenteral nutrient solution containing octreotide; there may be an incompatibility.[1] Also the manufacturers had suggested that octreotide might be adsorbed onto plastics. However, a solution containing octreotide 200 micrograms/mL as the acetate was reported to be stable at 5 degrees or -20 degrees for up to 60 days when stored in polypropylene syringes.[2]

1. Rosen GH. Potential incompatibility of insulin and octreotide in total parenteral nutrient solutions. *Am J Hosp Pharm* 1989; 46: 1128.
2. Ripley RG, *et al.* Stability of octreotide acetate in polypropylene syringes at 5 and -20 degreesC. *Am J Health-Syst Pharm* 1995; 52: 1910–11.

Uses and Administration

Octreotide is an octapeptide analogue of somatostatin (p. 1930.3) with similar properties but a longer duration of action.

It is used as the acetate in the symptomatic management of neuroendocrine tumours such as carcinoid tumours, VIPomas, and glucagonomas. Octreotide acetate is also used in the treatment of acromegaly and the prevention of complications after pancreatic surgery, and may be used in the treatment of other disorders including variceal haemorrhage and HIV-associated diarrhoea. It has also been investigated in a variety of other disorders.

In the management of **secretory neoplasms** octreotide acetate is given subcutaneously in an initial dose equivalent to 50 micrograms of octreotide once or twice daily gradually increased, according to response, to up to 600 micrograms daily in 2 to 4 divided doses. Higher doses have been used. If there is no benefit within a week of starting treatment for carcinoid tumour, continued therapy is not recommended.

Where a rapid response is required, the initial dose may be given by the intravenous route. In the UK, licensed product information states that it should be diluted not less than 1 in 1 or not more than 1 in 9 in sodium chloride 0.9%, but in the USA, product information permits the use of the undiluted solution as an intravenous bolus in emergencies; alternatively, the dose may be given by intermittent infusion over 15 to 30 minutes, diluted in 50 to 200 mL of sodium chloride 0.9% or glucose 5%.

Once control has been established maintenance therapy with a depot preparation may be possible; initially 20 mg by intramuscular injection every 4 weeks is suggested. Subcutaneous injection with a rapid-acting preparation should be continued for 2 weeks after the first depot injection to provide symptomatic cover, and may be added to therapy when necessary thereafter. Maintenance doses of the depot preparation may be adjusted after 2 or 3 months to between 10 and 30 mg every 4 weeks, as necessary.

In **acromegaly**, the usual dose is the equivalent of 100 to 200 micrograms of octreotide three times daily by subcutaneous injection. In the USA it is suggested that dosage begin with 50 micrograms three times daily in order to minimise gastrointestinal disturbance. If there is no relevant reduction in growth hormone concentrations and no improvement in clinical symptoms within 3 months of starting treatment, octreotide should be stopped. Once control has been established maintenance therapy with a depot preparation is possible; an initial dose equivalent to 20 mg of octreotide given intramuscularly once every 4 weeks has been recommended for patients with acromegaly, adjusted after 3 months to between 10 and 30 mg every 4 weeks. For patients who are not adequately controlled on 30 mg, the dose may be further increased to 40 mg every 4 weeks. The depot preparation may also be used for short-term treatment before pituitary surgery, but the last dose should be given at least 3 to 4 weeks before surgery to ensure successful endocrine testing for tumour removal 5 to 6 weeks after surgery.

For the prevention of complications after **pancreatic surgery** the equivalent of 100 micrograms of octreotide may be given three times daily by subcutaneous injection of a rapid-acting preparation; treatment is given for 7 consecutive days, beginning at least 1 hour before laparotomy on the day of operation.

In the management of **variceal haemorrhage** in patients with cirrhosis, octreotide is given as a continuous intravenous infusion at a dose equivalent to octreotide 25 micrograms/hour for 48 hours. Doses up to 50 micrograms/hour have been used. Patients at high risk of rebleeding may continue treatment for up to 5 days. For octreotide doses in oesophageal or gastric variceal bleeding in children, see below.

HIV-associated diarrhoea may be treated with an initial dose of octreotide 100 micrograms three times daily, given subcutaneously. If the diarrhoea is not controlled after a week, the dose may be increased to 250 micrograms three times daily, but if this is not effective after one further week then octreotide therapy should be stopped.

For doses in hepatic and renal impairment, see below.

General reviews of octreotide.

1. Anthony L, Preda PU. From somatostatin to octreotide LAR: evolution of a somatostatin analogue. *Curr Med Res Opin* 2009; 25: 2989–99.

Administration in children. Although octreotide is not licensed in the UK for oesophageal or gastric variceal bleeding in children, the *BNFC* includes a dose of 1 microgram/kg per hour by continuous intravenous infusion for children aged from 1 month to 18 years. Higher doses may be needed initially, to a maximum dose of 50 micrograms/hour. The dose should be reduced gradually over 24 hours once there is no active bleeding.

For other uses of octreotide in children see Chylous Effusion, below, Hyperinsulinism, p. 1926.1, and Obesity, p. 1926.3.

Administration in hepatic and renal impairment. The clearance of octreotide may be reduced in patients with hepatic or renal impairment. US licensed product information suggests that intramuscular depot therapy should be started at a dose of octreotide 10 mg once every 4 weeks in patients with established liver cirrhosis or renal failure requiring dialysis. Patients with lesser degrees of renal impairment may be given normal doses (see above).

Acromegaly. Although surgery remains the most important method of treatment, octreotide has a useful role in the management of acromegaly (p. 1918.1), particularly as adjuvant therapy when there is still active disease after surgery, as primary therapy when surgery is not possible, or while awaiting the full effects of radiotherapy. Octreotide can reduce growth hormone concentrations, normalise IGF-I concentrations, reduce tumour size, and improve signs and symptoms.[1] There is also some evidence that it may improve cardiac function, which is usually compromised in these patients.[1,2] Octreotide can be given subcutaneously and this route is generally used initially to determine patient response and tolerance, but it must be given three times daily making it unattractive for long-term use. Intramuscular sustained-release octreotide is effective for maintenance therapy. There is also increasing interest in the role of octreotide for primary therapy of acromegaly, instead of surgery[3-5] and a meta-analysis[6] suggested that tumour shrinkage was greatest when somatostatin analogues were given as primary rather than secondary therapy. Additionally, pre-operative treatment with octreotide might improve surgical cure rates in patients with macroadenomas.[7]

1. Yang LPH, Keating GM. Octreotide long-acting release (LAR): a review of its use in the management of acromegaly. *Drugs* 2010; 70: 1745–69.
2. Colao A, *et al.* Effects of initial therapy for five years with somatostatin analogs for acromegaly on growth hormone and insulin-like growth factor-I levels, tumor shrinkage, and cardiovascular disease: a prospective study. *J Clin Endocrinol Metab* 2009; 94: 3746–56.
3. Bevan JS, *et al.* Primary medical therapy for acromegaly: an open, prospective, multicenter study of the effects of subcutaneous and intramuscular slow-release octreotide on growth hormone, insulin-like growth factor-I, and tumor size. *J Clin Endocrinol Metab* 2002; 87: 4554–63.
4. Cozzi R, *et al.* Primary treatment of acromegaly with octreotide LAR: a long-term (up to nine years) prospective study of its efficacy in the control of disease activity and tumor shrinkage. *J Clin Endocrinol Metab* 2006; 91: 1397–1403.
5. Colao A, *et al.* Octreotide LAR vs. surgery in newly diagnosed patients with acromegaly: a randomized, open-label, multicentre study. *Clin Endocrinol (Oxf)* 2009; 70: 757–68.
6. Preda PU, *et al.* Long-acting somatostatin analog therapy of acromegaly: a meta-analysis. *J Clin Endocrinol Metab* 2005; 90: 4465–73.
7. Carlsen SM, *et al.* Preoperative octreotide treatment in newly diagnosed acromegalic patients with macroadenomas increases cure short-term postoperative rates: a prospective, randomized trial. *J Clin Endocrinol Metab* 2008; 93: 2984–90.

Cardiovascular disorders. There have been reports of benefit from octreotide in patients with postprandial hypotension and orthostatic hypotension (p. 1634.3) associated with autonomic neuropathy.[1-6] Octreotide has also produced cardiac improvement in patients with acromegaly (see above). Promising results have been reported in patients with primary hypertrophic cardiomyopathy.[7,8] Benefit has also been reported in a few patients with dilated cardiomyopathy.[9] For the usual management of cardiomyopathies, see p. 1261.3.

1. Hoeldtke RD, *et al.* Treatment of autonomic neuropathy with a somatostatin analogue SMS-201-995. *Lancet* 1986; II: 602–5.
2. Hoeldtke RD, Israel BC. Treatment of orthostatic hypotension with octreotide. *J Clin Endocrinol Metab* 1989; 68: 1051–9.
3. Woo J, *et al.* Treatment of severe orthostatic hypotension with the somatostatin analogue octreotide. *Aust N Z J Med* 1990; 20: 822–3.
4. Bordet R, *et al.* Octreotide in the management of orthostatic hypotension in multiple system atrophy: pilot trial of chronic administration. *Clin Neuropharmacol* 1994; 17: 380–3.
5. Hoeldtke RD, *et al.* Treatment of orthostatic hypotension with midodrine and octreotide. *J Clin Endocrinol Metab* 1998; 83: 339–43.
6. Hoeldtke RD, *et al.* Treatment of autonomic neuropathy, postural tachycardia and orthostatic syncope with octreotide LAR. *Clin Auton Res* 2007; 17: 334–40.
7. Günal AI, *et al.* Short term reduction of left ventricular mass in primary hypertrophic cardiomyopathy by octreotide injections. *Heart* 1996; 76: 418–21.
8. Demirtaş B, *et al.* Effects of octreotide in patients with hypertrophic obstructive cardiomyopathy. *Jpn Heart J* 1998; 39: 173–81.
9. Eryol NK, *et al.* The effects of octreotide in dilated cardiomyopathy: an open-label trial in 12 patients. *Jpn Heart J* 2004; 45: 613–21.

Chylous effusion. Chylous effusion results in accumulation of a milky lymphatic fluid containing raised concentrations of white blood cells, triglycerides, and cholesterol. Chylothorax, when the effusion affects the pleural cavity, is generally a complication of malignancy or chest surgery or may be idiopathic. Treatment usually involves catheter drainage and dietary modification; surgery is used when these measures fail. Octreotide has been used successfully in several cases to treat chylothorax,[1-5] although there are also reports of it being ineffective.[6] Doses have generally been 50 to 100 micrograms subcutaneously 3 times daily. Octreotide has also been used for treating chylothorax in paediatric patients, particularly after cardiothoracic surgery. Doses noted in reviews[7-9] have ranged from 7 to 240 micrograms/kg daily by intravenous infusion, or around 4 to 40 micrograms/kg daily by subcutaneous injection. Octreotide has also been used in chyloperitoneum[10-15] and for cervical chylous fistula.[16]

1. Demos NJ, *et al.* Somatostatin in the treatment of chylothorax. *Chest* 2001; 119: 964–6.
2. Demos NJ. Octreotide in the treatment of chylothorax. *Chest* 2002; 121: 2080–1.
3. Evans J, *et al.* Chylous effusions complicating lymphoma: a serious even with octreotide as a treatment option. *Hematol Oncol* 2003; 21: 77–81.
4. Makrilakis K, *et al.* Successful octreotide treatment of chylous pleural effusion and lymphedema in the yellow nail syndrome. *Ann Intern Med* 2004; 141: 246–7.
5. Mincher L, *et al.* The successful treatment of chylous effusions in malignant disease with octreotide. *Clin Oncol (R Coll Radiol)* 2005; 17: 118–21.
6. Mikroulis D, *et al.* Octreotide in the treatment of chylothorax. *Chest* 2002; 121: 2079–80.
7. Roehr CC, *et al.* Somatostatin or octreotide as treatment options for chylothorax in young children: a systematic review. *Intensive Care Med* 2006; 32: 650–7.
8. Helin RD, *et al.* Octreotide therapy for chylothorax in infants and children: a brief review. *Pediatr Crit Care Med* 2006; 7: 576–9.
9. Caverly L, *et al.* Octreotide treatment of chylothorax in pediatric patients following cardiothoracic surgery. *Congenit Heart Dis* 2010; 5: 573–8.
10. Bhatia C, *et al.* Octreotide therapy: a new horizon in treatment of iatrogenic chyloperitoneum. *Arch Dis Child* 2001; 85: 234–5.
11. Leong RWL, *et al.* Chylous ascites caused by portal vein thrombosis treated with octreotide. *J Gastroenterol Hepatol* 2003; 18: 1211–13.
12. Hwang J-B, *et al.* Resolution of refractory chylous ascites after Kasai portoenterostomy using octreotide. *J Pediatr Surg* 2004; 39: 1806–7.
13. Qi J, *et al.* Management of postoperative chyloretroperitoneum in adults. *Singapore Med J* 2009; 50: e338–e341.
14. Zhou DX, *et al.* The effectiveness of the treatment of octreotide on chylous ascites after liver cirrhosis. *Dig Dis Sci* 2009; 54: 1783–8.
15. Soylu A, *et al.* Resolution of chyloperitoneum in a preterm with octreotide, diet and cessation of dialysis. *Pediatr Nephrol* 2010; 25: 363–6.
16. Suver DW, *et al.* Somatostatin treatment of massive lymphorrhea following excision of a lymphatic malformation. *Int J Pediatr Otorhinolaryngol* 2004; 68: 845–50.

Cushing's syndrome. Cushing's syndrome (p. 2559.1) can be caused by excessive secretion from an ectopic ACTH secreting tumour. Many of these ectopic tumours express somatostatin receptors and it has been suggested that octreotide may be useful in the diagnosis, and possibly the treatment, of selected patients.[1] However, there are

types of somatostatin receptor,[2,3] and responses to octreotide have been variable,[4] even in the same patient.[3,5]

1. de Herder WW, Lamberts SWJ. Is there a role for somatostatin and its analogs in Cushing's syndrome? *Metabolism* 1996; 45 (suppl): 83–5.
2. de Herder WW, Lamberts SWJ. Octapeptide somatostatin-analogue therapy of Cushing's syndrome. *Postgrad Med J* 1999; 75: 65–6.
3. Uwaifo GI, *et al.* Is there a therapeutic role for octreotide in patients with ectopic Cushing's syndrome? *J Endocrinol Invest* 2003; 26: 710–17.
4. Woodhouse NJY, *et al.* Acute and long-term effects of octreotide in patients with ACTH-dependent Cushing's syndrome. *Am J Med* 1993; 95: 305–8.
5. Gill GV, *et al.* Carcinoid-associated ectopic ACTH syndrome with variable response to octreotide. *Postgrad Med J* 1999; 75: 98–101.

Diabetes mellitus. Although octreotide has been reported to impair glucose tolerance, and even precipitate frank diabetes (see Effects on Carbohydrate Metabolism, under Adverse Effects, p. 1927.2), its variable effects on blood glucose and insulin have led to investigations[1,2] of its ability to induce beta cell rest in patients with diabetes mellitus (p. 458.2) who still have residual insulin secretion. There is also some suggestion that it may be of benefit in the treatment or prevention of diabetic nephropathy[3,4] and retinopathy.[5–7] Benefit has been reported from the use of octreotide in patients with diabetic diarrhoea—see Diarrhoea, under Gastrointestinal Disorders, below.

1. Björk E, *et al.* Induction of β-cell rest in type 1 diabetes. *Diabetes Care* 1998; 21: 427–30.
2. Vondra K, *et al.* Somatostatin: beneficial effects on remission in young adult patients with newly diagnosed diabetes mellitus type 1. *Physiol Res* 2004; 53: 115–17.
3. Serri O, *et al.* Somatostatin analogue, octreotide, reduces increased glomerular filtration rate and kidney size in insulin-dependent diabetes. *JAMA* 1991; 265: 888–92.
4. Clemens A, *et al.* Octreotide (somatostatin analog) treatment reduces endothelial cell dysfunction in patients with diabetes mellitus. *Metabolism* 1999; 48: 1236–40.
5. Grant MB, *et al.* The efficacy of octreotide in the therapy of severe nonproliferative and early proliferative diabetic retinopathy: a randomized controlled trial. *Diabetes Care* 2000; 23: 504–9.
6. Boehm BO, *et al.* Octreotide reduces vitreous hemorrhage and loss of visual acuity risk in patients with high-risk proliferative diabetic retinopathy. *Horm Metab Res* 2001; 33: 300–306.
7. Grant MB, Caballero S. Somatostatin analogues as drug therapies for retinopathies. *Drugs Today* 2002; 38: 783–91.

Diagnosis and testing. Radiolabelled octreotide or other somatostatin analogues such as pentetreotide and depreotide may be used to visualise various malignant neoplasms which express somatostatin receptors.[1–5]

Octreotide may also have a role in the diagnosis of Cushing's syndrome, see p. 1924.3.

1. Basu S, *et al.* PET imaging in neuroendocrine tumors: current status and future prospects. *Minerva Endocrinol* 2008; 33: 257–75.
2. Kwekkeboom DJ, *et al.* ENETS consensus guidelines for the standards of care in neuroendocrine tumors: somatostatin receptor imaging with ^{111}In-pentetreotide. *Neuroendocrinology* 2009; 90: 184–9. Also available at: http://www.enets.org/d.1.52.pdf (accessed 19/10/11)
3. Kwekkeboom DJ, *et al.* Somatostatin receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. *Endocr Relat Cancer* 2010; 17: R53–R73.
4. Bombardieri E, *et al.* Oncology Committee of the EANM. ^{111}In-pentetreotide scintigraphy: procedure guidelines for tumour imaging. *Eur J Nucl Med Mol Imaging* 2010; 37: 1441–8. Also available at: http://www.eanm.org/publications/guidelines/EJNMMI_111In-Pentetreotide_GL.pdf (accessed 19/10/11)
5. Virgolini I, *et al.* Procedure guidelines for PET/CT tumour imaging with ^{68}Ga-DOTA-conjugated peptides: ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TATE. *Eur J Nucl Med Mol Imaging* 2010; 37: 2004–10. Also available at: http://www.eanm.org/publications/guidelines/gl_Ga68DOTA-X.pdf (accessed 19/10/11)

Eye disorders. There are reports of response to octreotide in patients with cystoid macular oedema, a refractory form of retinal oedema.[1–4] The problem recurred when octreotide was withdrawn[1,3,4] but responded to resumption of octreotide therapy.[1]

1. Kuijpers RWAM, *et al.* Treatment of cystoid macular edema with octreotide. *N Engl J Med* 1998; 338: 624–6.
2. Hernaez-Ortega MC, *et al.* Sandostatin LAR for cystoid diabetic macular edema: a 1-year experience. *Diabetes Res Clin Pract* 2004; 64: 71–2.
3. Missotten T, *et al.* Octreotide long-acting repeatable for the treatment of chronic macular edema in uveitis. *Am J Ophthalmol* 2007; 144: 838–843.
4. Hogewind BF, *et al.* Octreotide acetate in dominant cystoid macular dystrophy. *Eur J Ophthalmol* 2008; 18: 99–103.

Gastrointestinal disorders. Somatostatin inhibits gastric and intestinal secretion and the production of various active substances in the gastrointestinal tract. It also reduces splanchnic arterial blood flow and portal and gastric mucosal blood flow. These properties are made use of, usually in the form of octreotide, in the management of several gastrointestinal disorders including bleeding, refractory diarrhoea, fistulae, dumping syndrome, and nausea and vomiting secondary to bowel obstruction (see below).

Octreotide is used particularly in the treatment of carcinoid syndrome arising from endocrine tumours (see Neuroendocrine Tumours, p. 716.3).

BLEEDING. There have been mixed results with octreotide in the treatment of **nonvariceal** upper gastrointestinal bleeding. Although a large multicentre study[1] showed that octreotide had no benefit compared with placebo in the management of bleeding upper gastrointestinal ulcers, a meta-analysis that included somatostatin and octreotide suggested there might be some benefit.[2] Nevertheless, a later study[3] found that octreotide, given as an adjunct to endoscopic haemostasis using noradrenaline, did not seem to provide any additional benefit, and it is not recommended in the management of nonvariceal bleeding associated with peptic ulcer (p. 1813.2). A review suggested that octreotide was useful in patients with acquired gastrointestinal angiodysplasia with refractory bleeding, and might be considered for use particularly in those with inaccessible lesions or at high risk from other interventions.[4]

Octreotide may be used in the management of **variceal haemorrhage** (see under Monoethanolamine, p. 2563.1). There is some evidence that octreotide is as effective as sclerotherapy in the control of acute bleeding.[5] A meta-analysis[6] of studies comparing octreotide with other therapies (including vasopressin, terlipressin, sclerotherapy, or balloon tamponade) for the control of acute variceal bleeding found that octreotide had a similar effect to sclerotherapy in the prevention of rebleeding and was more effective and associated with fewer major complications than vasopressin or terlipressin. However, there was no evidence of mortality benefit associated with octreotide use. A systematic review[7] of studies comparing somatostatin or its analogues with either placebo or no drug treatment also found that although there was a small benefit in controlling bleeding, it was doubtful whether this benefit was worthwhile, and that deaths were not reduced. A third systematic review[8] found that sclerotherapy was associated with more frequent and severe adverse effects than drug therapy, including octreotide.

Controlled studies have suggested that *combination* of octreotide infusion for 5 days with endoscopic ligation[9] or sclerotherapy[10,11] reduces the risk of rebleeding. In another study,[12] sclerotherapy with 48 hours of octreotide infusion was more effective at controlling bleeding than sclerotherapy alone, and octreotide was as effective as sclerotherapy in those with evidence of recent bleeding. However, another study[13] found that octreotide given subcutaneously for up to 29 days after sclerotherapy did not affect the rate of early rebleeding. Octreotide has also produced some benefit (combined with regular sclerotherapy), in the long-term management of patients with cirrhotic portal hypertension.[14]

1. Christiansen J, *et al.* Placebo-controlled trial with the somatostatin analogue SMS 201-995 in peptic ulcer bleeding. *Gastroenterology* 1989; 97: 568–74.
2. Imperiale TF, Birgisson S. Somatostatin or octreotide compared with H_2 antagonists and placebo in the management of acute nonvariceal upper gastrointestinal hemorrhage: a meta-analysis. *Ann Intern Med* 1997; 127: 1062–71. Correction. *ibid.* 1998; 128: 245.
3. Nikolopoulou VN, *et al.* The effect of octreotide as an adjunct treatment in active nonvariceal upper gastrointestinal bleeding. *J Clin Gastroenterol* 2004; 38: 243–7.
4. Brown C, *et al.* Somatostatin analogues in the treatment of recurrent bleeding from gastrointestinal vascular malformations: an overview and systematic review of prospective observational studies. *Dig Dis Sci* 2010; 55: 2129–34.
5. Jenkins SA, *et al.* A multicentre randomised trial comparing octreotide and injection sclerotherapy in the management and outcome of acute variceal haemorrhage. *Gut* 1997; 41: 526–33.
6. Corley DA, *et al.* Octreotide for acute esophageal variceal bleeding: a meta-analysis. *Gastroenterology* 2001; 120: 946–54.
7. Gøtzsche PC, Hróbjartsson A. Somatostatin analogues for acute bleeding oesophageal varices. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 21/08/08).
8. D'Amico G, *et al.* Emergency sclerotherapy versus vasoactive drugs for bleeding oesophageal varices in cirrhotic patients. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2010 (accessed 28/04/10).
9. Sung JJY, *et al.* Prospective randomised study of effect of octreotide on rebleeding from oesophageal varices after endoscopic ligation. *Lancet* 1995; 346: 1666–9.
10. Besson I, *et al.* Sclerotherapy with or without octreotide for acute variceal bleeding. *N Engl J Med* 1995; 333: 555–60.
11. Zuberi BF, Baloch Q. Comparison of endoscopic variceal sclerotherapy alone and in combination with octreotide in controlling acute variceal hemorrhage and early rebleeding in patients with low-risk cirrhosis. *Am J Gastroenterol* 2000; 95: 768–71.
12. Freitas DS, *et al.* Octreotide in acute bleeding esophageal varices: a prospective randomized study. *Hepatogastroenterology* 2000; 47: 1310–14.
13. Primignani M, *et al.* Sclerotherapy plus octreotide versus sclerotherapy alone in the prevention of early rebleeding from esophageal varices: a randomized, double-blind, placebo-controlled, multicenter trial. *Hepatology* 1995; 21: 1322–7.
14. Jenkins SA, *et al.* Randomised trial of octreotide for long term management of cirrhosis after variceal haemorrhage. *BMJ* 1997; 315: 1338–41.

DIARRHOEA. Octreotide has been tried for its effects on gastrointestinal secretion and intestinal transit time in the management of severe refractory diarrhoea associated with a variety of conditions. A review[1] found that studies were generally small, and that although there appeared to be an overall benefit associated with the use of octreotide, response was influenced by the cause of diarrhoea. There are reports of octreotide controlling diarrhoea associated with amyloidosis,[2–4] diabetes mellitus,[5–11] and bone marrow transplantation.[12,13] Although octreotide was reported to be useful in a case of microvillous atrophy,[14] others have not found it to be effective.[15] There have been reports of benefit in refractory AIDS-associated diarrhoea,[16] and it has been licensed for this use in some countries, but a double-blind, controlled study found octreotide to be no more beneficial than placebo.[17] Octreotide has also been used successfully for symptomatic treatment of chronic diarrhoea associated with cytomegalovirus colitis.[18] In patients with the short bowel syndrome and jejunostomies or ileostomies, octreotide may be useful in decreasing faecal mass[19] or jejunal efflux,[20] and increasing small bowel transit time.[21] Octreotide has also been used with some benefit in refractory diarrhoea associated with chemotherapy, particularly with regimens that include fluorouracil[22,23] and irinotecan.[24] In a small series of patients[25] the use of depot octreotide controlled most episodes of diarrhoea, and allowed the continuation of chemotherapy in some cases.

1. Szilagyi A, Shrier I. Systematic review: the use of somatostatin or octreotide in refractory diarrhoea. *Aliment Pharmacol Ther* 2001; 15: 1889–97.
2. O'Connor CR, O'Dorisio TM. Amyloidosis, diarrhea, and a somatostatin analogue. *Ann Intern Med* 1989; 110: 665–6.
3. Gilanders IA, *et al.* Octreotide therapy for diarrhoea. *Postgrad Med J* 1997; 73: 62.
4. Jeong Y-S, *et al.* Successful treatment of protein-losing enteropathy due to AA amyloidosis with somatostatin analogue and high dose steroid in ankylosing spondylitis. *Clin Exp Rheumatol* 2000; 18: 619–21.
5. Tsai S-T, *et al.* Diabetic diarrhea and somatostatin. *Ann Intern Med* 1986; 104: 894.
6. Michaels PE, Cameron RB. Octreotide is cost-effective therapy in diabetic diarrhea. *Arch Intern Med* 1991; 151: 2469.
7. Mourad FH, *et al.* Effective treatment of diabetic diarrhoea with somatostatin analogue, octreotide. *Gut* 1992; 33: 1578–80.
8. Nakabayashi H, *et al.* Marked improvement of diabetic diarrhea with the somatostatin analogue octreotide. *Arch Intern Med* 1994; 154: 1863–7.
9. Virally-Monod ML, *et al.* Variable efficacy of octreotide in diabetic diarrhea. *Diabetes Metab* 1996; 22: 356–8.
10. Murao S, *et al.* Severe diabetic diarrhea successfully treated with octreotide, a somatostatin analogue. *Endocr J* 1999; 46: 477–8.
11. Meyer C, *et al.* Octreotide treatment of severe diabetic diarrhoea. *Intern Med J* 2003; 33: 617–8.
12. Crouch MA, *et al.* Octreotide acetate in refractory bone marrow transplant-associated diarrhea. *Ann Pharmacother* 1996; 30: 331–6.
13. Ippoliti C, *et al.* Use of octreotide in the symptomatic management of diarrhea induced by graft-versus-host disease in patients with hematological malignancies. *J Clin Oncol* 1997; 15: 3350–4.
14. Couper RTL, *et al.* Clinical response to the long acting somatostatin analogue SMS 201-995 in a child with congenital microvillus atrophy. *Gut* 1989; 30: 1020–4.
15. Beck NS, *et al.* Microvillus inclusion disease in two Korean infants. *J Korean Med Sci* 1997; 12: 452–6.
16. Montaner JSG, *et al.* Octreotide therapy in AIDS-related, refractory diarrhea: results of a multicentre Canadian-European study. *AIDS* 1995; 9: 209–10.
17. Simon DM, *et al.* Multicenter trial of octreotide in patients with refractory acquired immunodeficiency syndrome–associated diarrhea. *Gastroenterology* 1995; 108: 1753–60. Correction. *ibid.*; 109: 1024.
18. Bartels MC, Mergenhagen KA. Octreotide for symptomatic treatment of diarrhea due to cytomegalovirus colitis. *Ann Pharmacother* 2011; 45: e4.
19. Ladefoged K, *et al.* Effect of a long acting somatostatin analogue SMS 201-995 on jejunostomy effluents in patients with severe short bowel syndrome. *Gut* 1989; 30: 943–9.
20. Nightingale JMD, *et al.* Jejunal efflux in short bowel syndrome. *Lancet* 1990; 336: 765–8.
21. Nehra V, *et al.* An open trial of octreotide long-acting release in the management of short bowel syndrome. *Am J Gastroenterol* 2001; 96: 1494–8.
22. Goumas P, *et al.* Octreotide acetate in the treatment of fluorouracil-induced diarrhea. *Oncologist* 1998; 3: 50–3.
23. Zidan J, *et al.* Octreotide in the treatment of severe chemotherapy-induced diarrhea. *Ann Oncol* 2001; 12: 227–9.
24. Barbounis V, *et al.* Control of irinotecan-induced diarrhea by octreotide after loperamide failure. *Support Care Cancer* 2001; 9: 258–60.
25. Rosenoff S. Resolution of refractory chemotherapy-induced diarrhea (CID) with octreotide long-acting formulation in cancer patients: 11 case studies. *Support Care Cancer* 2004; 12: 561–70.

FISTULAE. Octreotide has been used in the management of postoperative small-bowel fistulae. There have been mixed reports, but some have found reduced fistula output,[1,2] with the time to spontaneous fistula closure either reduced[1] or unchanged.[2] Octreotide has also been reported to accelerate healing of pancreatic cutaneous fistulae of various causes,[3] but others[4] have found no benefit from octreotide in preventing pancreatic fistula formation after pancreaticoduodenectomy. A systematic review[5] of controlled studies commented on the variation in study methods and conflicting results, but concluded that there is probably benefit in giving octreotide pre-operatively to prevent complications of pancreatic surgery, and that in established postoperative fistulae it may have a limited role in reducing fistula output and reducing the time to fistula closure. In a series of 5 patients[6] with Crohn's disease who were treated for 8 weeks with high-dose octreotide, enterocutaneous fistulae closed in 4 cases.

1. Nubiola-Calonge P, *et al.* Blind evaluation of the effect of octreotide (SMS 201-995), a somatostatin analogue, on small-bowel fistula output. *Lancet* 1987; ii: 672–4.
2. Alivizatos V, *et al.* Evaluation of the effectiveness of octreotide in the conservative treatment of postoperative enterocutaneous fistulas. *Hepatogastroenterology* 2002; 49: 1010–12.
3. Prinz RA, *et al.* Treatment of pancreatic cutaneous fistulas with a somatostatin analog. *Am J Surg* 1988; 155: 36–42.
4. Barnett SP, *et al.* Octreotide does not prevent postoperative pancreatic fistula or mortality following pancreaticoduodenectomy. *Am Surg* 2004; 70: 222–7.
5. Li-Ling J, Irving M. Somatostatin and octreotide in the prevention of postoperative pancreatic complications and the treatment of enterocutaneous pancreatic fistulas: a systematic review of randomized controlled trials. *Br J Surg* 2001; 88: 190–9.
6. Lavy A, Yasin K. Octreotide for enterocutaneous fistulas of Crohn's disease. *Can J Gastroenterol* 2003; 17: 555–8.

OTHER GASTROINTESTINAL DISORDERS. Further gastrointestinal disorders in which octreotide might be useful include

dumping syndrome[1-3] (p. 1806.2). One report[4] suggested that preprandial subcutaneous doses produce higher peak serum concentrations and might therefore be more effective than a long-acting intramuscular formulation. Other disorders include reactive (or postprandial) hypoglycaemia,[5] and protein-losing enteropathy associated with intestinal lymphangiectasia.[6,7] Nausea and vomiting secondary to bowel obstruction in patients terminally ill with cancer may also be relieved by octreotide.[8,9] The *BNF* states that in palliative care a dose of 250 to 500 micrograms (sometimes up to 750 micrograms or occasionally higher) may be given by subcutaneous infusion over 24 hours to reduce intestinal secretions and to reduce vomiting due to bowel obstruction.

1. Vecht J, *et al.* Long-term results of octreotide-therapy in severe dumping syndrome. *Clin Endocrinol (Oxf)* 1999; 51: 619–24.
2. Li-Ling J, Irving M. Therapeutic value of octreotide for patients with severe dumping syndrome—a review of randomised controlled trials. *Postgrad Med J* 2001; 77: 441–2.
3. Arts J, *et al.* Efficacy of the long-acting repeatable formulation of the somatostatin analogue octreotide in postoperative dumping. *Clin Gastroenterol Hepatol* 2009; 7: 432–7.
4. Didden P, *et al.* Octreotide therapy in dumping syndrome: analysis of long-term results. *Aliment Pharmacol Ther* 2006; 24: 1567–75.
5. Lehnert H, *et al.* Treatment of severe reactive hypoglycemia with a somatostatin analogue (SMS 201-995). *Arch Intern Med* 1990; 150: 2401–2.
6. Klingenberg RD, *et al.* Type I intestinal lymphangiectasia treated successfully with slow-release octreotide. *Dig Dis Sci* 2003; 48: 1506–9.
7. Lee HL, *et al.* Successful treatment of protein-losing enteropathy induced by intestinal lymphangiectasia in a liver cirrhosis patient with octreotide: a case report. *J Korean Med Sci* 2004; 19: 466–9.
8. Ripamonti C, *et al.* The role of somatostatin and octreotide in bowel obstruction: pre-clinical and clinical results. *Tumori* 2001; 87: 1–9.
9. Mystakidou K, *et al.* Comparison of octreotide administration vs conservative treatment in the management of inoperable bowel obstruction in patients with far advanced cancer: a randomized, double-blind, controlled clinical trial. *Anticancer Res* 2002; 22: 1187–92.

Hypercalcaemia. There have been individual reports of hypercalcaemia associated with raised plasma concentrations of parathyroid hormone-related protein (hypercalcaemia of malignancy—p. 1167.2) being successfully controlled with octreotide in patients with malignant pancreatic endocrine tumours[1-3] and adrenal phaeochromocytoma.[4] Octreotide also resolved hypercalcaemia occurring in a patient with VIPoma and vasoactive intestinal peptide concentrations declined.[5] In 2 patients with a parathyroid hormone-related protein secreting carcinoid tumour, octreotide reduced protein concentrations in both patients[6,7] but controlled hypercalcaemia in only one.[7] Octreotide also normalised calcium concentrations in a patient with hypercalcaemia related to B cell lymphoma.[8] In many of these cases, hypercalcaemia had previously been resistant to treatment with bisphosphonates.

1. Wynick D, *et al.* Treatment of a malignant pancreatic endocrine tumour secreting parathyroid hormone related protein. *BMJ* 1990; 300: 1314–15.
2. Dodwell D, *et al.* Treatment of a pancreatic tumour secreting parathyroid hormone related protein. *BMJ* 1990; 300: 1653.
3. Müssig K, *et al.* Somatostatin receptor expression in a parathyroid hormone-related peptide-secreting pancreatic neuroendocrine tumour causing severe hypercalcaemia. *Eur J Gastroenterol Hepatol* 2007; 19: 719–23.
4. Harrison M, *et al.* Somatostatin analogue treatment for malignant hypercalcaemia. *BMJ* 1990; 300: 1313–14. Correction. *ibid.*; 301: 97 [dosage error].
5. Venkatesh S, *et al.* Somatostatin analogue: use in the treatment of vipoma with hypercalcaemia. *Am J Med* 1989; 87: 356–7.
6. Mantzoros CS, *et al.* Intractable hypercalcaemia due to parathyroid hormone-related peptide secretion by a carcinoid tumour. *Clin Endocrinol (Oxf)* 1997; 46: 373–5.
7. Barhoum M, *et al.* Intractable hypercalcemia due to a metastatic carcinoid secreting parathyroid hormone-related peptide and interleukin-6: response to octreotide. *Am J Med Sci* 1999; 318: 203–5.
8. Pezzilli R, *et al.* Octreotide for the treatment of hypercalcemia related to B cell lymphoma. *Oncology* 1997; 54: 517–18.

Hyperinsulinism. As well as reactive hypoglycaemia (see under Other Gastrointestinal Disorders, p. 1925.3), octreotide has been used to control inappropriate insulin secretion, both in the short-term and long-term, in children with hypoglycaemia of infancy,[1-4] or nesidioblastosis.[5-7] Although not licensed in the UK for children, the *BNFC* includes a dose of octreotide for persistent hyperinsulinaemic hypoglycaemia (p. 1554.3) unresponsive to diazoxide and glucose. For neonates an initial dose of 2 to 5 micrograms/kg may be given every 6 to 8 hours subcutaneously and adjusted according to response. For children aged from 1 month to 18 years, an initial dose of 1 to 2 micrograms/kg every 4 to 6 hours may be used. Doses up to 7 micrograms/kg every 4 hours may be required in rare cases.

Octreotide has also been used to treat a patient with hyperinsulinaemia induced by quinine.[8,9] For mention of investigations of octreotide for the reverse effect, see Diabetes Mellitus, p. 1925.1.

1. Kirk JMW, *et al.* Somatostatin analogue in short term management of hyperinsulinism. *Arch Dis Child* 1988; 63: 1493–4.
2. DeClue TJ, *et al.* Linear growth during long-term treatment with somatostatin analog (SMS 201-995) for persistent hyperinsulinemic hypoglycemia of infancy. *J Pediatr* 1990; 116: 747–50.
3. Thornton PS, *et al.* Short- and long-term use of octreotide in the treatment of congenital hyperinsulinism. *J Pediatr* 1993; 123: 637–43.
4. Aynsley-Green A, *et al.* Practical management of hyperinsulinism in infancy. *Arch Dis Child Fetal Neonatal Ed* 2000; 82: F98–F107.
5. Hindmarsh P, Brook CGD. Short-term management of nesidioblastosis using the somatostatin analogue SMS 201-995. *N Engl J Med* 1987; 316: 221–2.
6. Delemarre-van de Waal HA, *et al.* Long-term treatment of an infant with nesidioblastosis using a somatostatin analogue. *N Engl J Med* 1987; 316: 222–3.
7. Behrens R, *et al.* Unusual course of neonatal hyperinsulinaemic hypoglycaemia (nesidioblastosis). *Arch Dis Child* 1998; 78: F156.
8. Phillips RE, *et al.* Effectiveness of SMS 201-995, a synthetic, long-acting somatostatin analogue, in treatment of quinine-induced hyperinsulinaemia. *Lancet* 1986; i: 713–16.
9. Phillips RE, *et al.* Hypoglycaemia and counterregulatory hormone responses in severe falciparum malaria: treatment with Sandostatin. *Q J Med* 1993; 86: 233–40.

Malignant neoplasms. See also Neuroendocrine Tumours, below. For mention of the use of octreotide to treat nausea and vomiting associated with malignant gastrointestinal obstruction see under Other Gastrointestinal Disorders, p. 1925.3. Octreotide has also proved of benefit in some patients with cancer pain (see Pain, below). An unconventional regimen using octreotide or somatostatin with melatonin, bromocriptine, and a solution of retinoids (the Di Bella regimen) was investigated in patients with a variety of advanced malignancies and found to be ineffective.[1,2]

1. Italian Study Group for the Di Bella Multitherapy Trials. Evaluation of an unconventional cancer treatment (the Di Bella multitherapy): results of phase II trials in Italy. *BMJ* 1999; 318: 224–8.
2. Bulatti E, *et al.* Results from a historical survey of the survival of cancer patients given Di Bella multitherapy. *Cancer* 1999; 86: 2143–9.

HEPATOCELLULAR CARCINOMA. In a study in 58 patients with advanced hepatocellular carcinoma (p. 709.3) treatment with octreotide was associated with prolongation of survival compared with no treatment.[1] In a further case report[2] cancer regression occurred in a patient given octreotide, and a study[3] found better survival in patients treated with octreotide and tamoxifen compared with fluorouracil and mitomycin. However, other studies of octreotide in patients with advanced hepatocellular carcinoma failed to show any benefit.[4-7] A systematic review of randomised studies[8] concluded that octreotide did not improve survival.

1. Kouroumalis E, *et al.* Treatment of hepatocellular carcinoma with octreotide: a randomised controlled study. *Gut* 1998; 42: 442–7.
2. Slveke JT, *et al.* Complete regression of advanced HCC with long acting octreotide. *Gut* 2003; 52: 1531. Correction. *ibid.*; 1800.
3. Pan D-Y, *et al.* Tamoxifen combined with octreotide or regular chemotherapeutic agents in treatment of primary liver cancer: a randomized controlled trial. *Hepatobiliary Pancreat Dis Int* 2003; 2: 211–15.
4. Yuen M-F, *et al.* A randomized placebo-controlled study of long-acting octreotide for the treatment of advanced hepatocellular carcinoma. *Hepatology* 2002; 36: 687–91.
5. Lersch C, *et al.* Treatment of HCC with pravastatin, octreotide, or gemcitabine - a critical evaluation. *Hepatogastroenterology* 2004; 51: 1099–1103.
6. Becker G, *et al.* HECTOR Study Group. Long-acting octreotide versus placebo for treatment of advanced HCC: a randomized controlled double-blind study. *Hepatology* 2007; 45: 9–15.
7. Verset G, *et al.* Efficacy of the combination of long-acting release octreotide and tamoxifen in patients with advanced hepatocellular carcinoma: a randomised multicentre phase III study. *Br J Cancer* 2007; 97: 582–8.
8. Jia W-D, *et al.* Octreotide therapy for hepatocellular carcinoma: a systematic review of the evidence from randomized controlled trials. *Hepatogastroenterology* 2010; 57: 292–9.

MENINGIOMA. Octreotide has been reported to suppress headaches and visual disturbances associated with meningioma in a small number of patients.[1-3] Doses were generally started at 100 micrograms three times daily subcutaneously, but were increased to 500 micrograms three times daily in some cases because of tolerance. Although it was thought that octreotide may have had a beneficial effect on the meningioma size in one case,[1] others found no evidence of tumour shrinkage.[2,3] A pilot study[4] examined the effects of octreotide in 16 patients with recurrent meningioma that overexpressed somatostatin receptors. There were 5 partial responses, 5 cases of stable disease, and 6 cases of progressive disease after the first 3 treatment cycles; progression-free survival at 6 months was 44% (7 patients).

1. Rünzi MW, *et al.* Successful treatment of meningioma with octreotide. *Lancet* 1989; i: 1074.
2. García-Luna PP, *et al.* Clinical use of octreotide in unresectable meningiomas: a report of three cases. *J Neurosurg Sci* 1993; 37: 237–41.
3. Jaffrain-Rea M-L, *et al.* Visual improvement during octreotide therapy in a case of episellar meningioma. *Clin Neurol Neurosurg* 1998; 100: 40–3.
4. Chamberlain MC, *et al.* Recurrent meningioma: salvage therapy with long-acting somatostatin analogue. *Neurology* 2007; 69: 969–73. Correction. *ibid.* 2008; 70: 325.

NEUROENDOCRINE TUMOURS. For a discussion of neuroendocrine tumours and other secretory neoplasms, including reference to the role of octreotide, see p. 716.3.

References.

1. Öberg K, *et al.* Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. *Ann Oncol* 2004; 15: 966–73.
2. Delaunoit T, *et al.* Somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine tumors. *Mayo Clin Proc* 2005; 80: 502–6.
3. Kwekkeboom DJ, *et al.* ENETS consensus guidelines for the standards of care in neuroendocrine tumors: peptide receptor radionuclide therapy with radiolabeled somatostatin analogs. *Neuroendocrinology* 2009; 90: 220–6.
4. Colao A, *et al.* Somatostatin analogues: treatment of pituitary and neuroendocrine tumors. *Prog Brain Res* 2010; 182: 281–94.
5. Öberg KE, *et al.* Role of somatostatins in gastroenteropancreatic neuroendocrine tumor development and therapy. *Gastroenterology* 2010; 139: 742–53.

THYMOMA. A patient with thymoma and pure red cell aplasia, in whom corticosteroids alone failed to control anaemia, had complete remission after treatment with octreotide and prednisone, and subsequently remained well on long-term maintenance therapy with octreotide 500 micrograms twice daily subcutaneously and prednisone 200 micrograms/kg daily.[1] In a study[2] that included 32 patients with thymoma and a positive octreotide scan, octreotide therapy alone (500 micrograms subcutaneously three times daily for up to 1 year) or with prednisone (600 micrograms/kg daily) had modest activity: there were 2 complete and 10 partial responses overall.

1. Palmieri G, *et al.* Successful treatment of a patient with a thymoma and pure red-cell aplasia with octreotide and prednisone. *N Engl J Med* 1997; 336: 263–5. Correction. *ibid.*; 1039.
2. Loehrer PJ, *et al.* Octreotide alone or with prednisone in patients with advanced thymoma and thymic carcinoma: an Eastern Cooperative Oncology Group phase II trial. *J Clin Oncol* 2004; 22: 293–9. Correction. *ibid.*; 2261.

Nesidioblastosis. For reference to the use of octreotide in nesidioblastosis, see Hyperinsulinism, above.

Obesity. Hypothalamic obesity can be a complication of hypothalamic damage caused by insults such as head trauma, brain tumours, and cranial surgery or irradiation. Octreotide has improved body-weight, body-mass index, and regulation of insulin secretion in small studies of children with hypothalamic obesity.[1-3] Additionally octreotide has produced a small amount of weight loss in some obese adults with insulin hypersecretion.[4,5] Octreotide is also under investigation in the treatment of Prader-Willi syndrome (p. 2315.2).[6]

1. Lustig RH, *et al.* Hypothalamic obesity caused by cranial insult in children: altered glucose and insulin dynamics and reversal by a somatostatin agonist. *J Pediatr* 1999; 135: 162–8.
2. Lustig RH, *et al.* Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2003; 88: 2586–92.
3. Tzotzas T, *et al.* Use of somatostatin analogues in obesity. *Drugs* 2008; 68: 1963–73.
4. Velasquez-Mieyer PA, *et al.* Suppression of insulin secretion is associated with weight loss and altered macronutrient intake and preference in a subset of obese adults. *Int J Obes Relat Metab Disord* 2003; 27: 219–26.
5. Lustig RH, *et al.* A multicenter, randomized, double-blind, placebo-controlled, dose-finding trial of a long-acting formulation of octreotide in promoting weight loss in obese adults with insulin hypersecretion. *Int J Obes (Lond)* 2006; 30: 331–41.
6. Haqq AM, *et al.* Circulating ghrelin levels are suppressed by meals and octreotide therapy in children with Prader-Willi syndrome. *J Clin Endocrinol Metab* 2003; 88: 3573–6.

Pain. Octreotide 120 to 480 micrograms daily was given by continuous intrathecal infusion to 6 patients with cancer pain that had been poorly controlled by opioid analgesics.[1] All patients obtained good pain relief, 3 reporting pain to be totally absent. Sustained decrease in incapacitating bone pain has also been reported in a patient with skeletal metastasis of a gastrinoma who was given subcutaneous octreotide 100 micrograms three times daily.[2] The pain of hypertrophic pulmonary osteoarthropathy (a paraneoplastic syndrome of periostitis, arthropathy, and gynaecomastia seen particularly with squamous cell lung cancer) has also been reported to respond to octreotide.[3] However, a controlled study of octreotide in cancer pain found that it was no better than placebo in most patients.[4] (General guidelines for the management of cancer pain are discussed on p. 7.1.) Octreotide has also been reported to ease headache associated with meningioma (above), and pituitary adenoma (see Acromegaly, p. 1924.2, and Pituitary Adenoma, p. 1927.1).

The use of intrathecal octreotide has also been described[5] in 2 patients with severe intractable non-malignant pain. During 5 years of treatment, octreotide provided a beneficial degree of pain relief and allowed a reduction in opioid dosage. However, the dose of octreotide had to be gradually increased, suggesting tolerance to the analgesic effect; one patient was receiving a daily dose of 648 micrograms.

1. Penn RD, *et al.* Octreotide: a potent new non-opiate analgesic for intrathecal infusion. *Pain* 1992; 49: 13–19.
2. Burgess JR, *et al.* Effective control of bone pain by octreotide in a patient with metastatic gastrinoma. *Med J Aust* 1996; 164: 725–7.
3. Johnson SA, *et al.* Treatment of resistant pain in hypertrophic pulmonary osteoarthropathy with subcutaneous octreotide. *Thorax* 1997; 52: 298–9.
4. De Conno F, *et al.* Subcutaneous octreotide in the treatment of pain in advanced cancer patients. *J Pain Symptom Manage* 1994; 9: 34–8.
5. Paice JA, *et al.* Intrathecal octreotide for relief of intractable nonmalignant pain: 5-year experience with two cases. *Neurosurgery* 1996; 38: 203–7.

Pancreatic disorders. Octreotide has been tried in the treatment of acute pancreatitis, but was found to be ineffective.[1] Prophylactic octreotide has also been studied for the prevention of pancreatitis following endoscopic retrograde cholangiopancreatography with some positive results,[2,3] but a meta-analysis concluded that it was ineffective.[4] Others[5,6] have suggested that it might only be

effective at total doses of more than 500 micrograms, although the optimal route and timing are unclear.[5] For reference to the use of octreotide in the management of pancreatic endocrine tumours, see under Neuroendocrine Tumours (p. 716.3); for its use in pancreatic fistulae, see under Gastrointestinal Disorders, p. 1925.3.

1. Uhl W, *et al.* A randomised, double blind, multicentre trial of octreotide in moderate to severe acute pancreatitis. *Gut* 1999; 45: 97–104.
2. Thomopoulos KC, *et al.* Twenty-four hour prophylaxis with increased dosage of octreotide reduces the incidence of post-ERCP pancreatitis. *Gastrointest Endosc* 2006; 64: 726–31.
3. Li Z-S, *et al.* Effect of octreotide administration in the prophylaxis of post-ERCP pancreatitis and hyperamylasemia: a multicenter, placebo-controlled, randomized clinical trial. *Am J Gastroenterol* 2007; 102: 46–51.
4. Bai Y, *et al.* Prophylactic octreotide administration does not prevent post-endoscopic retrograde cholangiopancreatography pancreatitis: a meta-analysis of randomized controlled trials. *Pancreas* 2008; 37: 241–6.
5. Zhang Y, *et al.* Meta-analysis: octreotide prevents post-ERCP pancreatitis, but only at sufficient doses. *Aliment Pharmacol Ther* 2009; 29: 1155–64.
6. Omata F, *et al.* Meta-analysis: somatostatin or its long-acting analogue, octreotide, for prophylaxis against post-ERCP pancreatitis. *J Gastroenterol* 2010; 45: 885–95.

Pituitary adenoma. Octreotide has a role in the management of pituitary adenomas that cause acromegaly (see p. 1924.2). It has also been used in the management of rare tumours such as thyrotropin-secreting pituitary adenomas, usually when surgery or radiotherapy have failed. Octreotide may reduce concentrations of thyrotropin and normalise thyroid hormones in most patients; tumour shrinkage also occurs in at least a third of cases.[1-4] Octreotide has also been tried in the management of other rare adenomas such as clinically nonfunctioning adenomas, but results have been mixed; in a few cases there has been relief of symptoms such as headache without any change in tumour volume.[5]

1. Chanson P, *et al.* Octreotide therapy for thyroid-stimulating hormone-secreting pituitary adenomas: a follow-up of 52 patients. *Ann Intern Med* 1993; 119: 236–40.
2. Caron P, *et al.* Efficacy of the long-acting octreotide formulation (octreotide-Lar) in patients with thyrotropin-secreting pituitary adenomas. *J Clin Endocrinol Metab* 2001; 86: 2849–53.
3. Beck-Peccoz P, Persani L. Medical management of thyrotropin-secreting pituitary adenomas. *Pituitary* 2002; 5: 83–8.
4. Sodn HV, *et al.* The changing spectrum of TSH-secreting pituitary adenomas: diagnosis and management in 43 patients. *Eur J Endocrinol* 2003; 148: 433–42.
5. Colao A, *et al.* Somatostatin analogs in treatment of non-growth hormone-secreting pituitary adenomas. *Endocrine* 2003; 20: 279–83.

Polycystic kidney and liver diseases. Octreotide[1-3] and lanreotide[4] have been investigated in autosomal dominant polycystic kidney and liver diseases. Small studies, usually lasting 6 or 12 months, suggest that treatment may slow the rate of increase in kidney volume and may decrease liver volume.

1. Ruggenenti P, *et al.* Safety and efficacy of long-acting somatostatin treatment in autosomal-dominant polycystic kidney disease. *Kidney Int* 2005; 68: 206–16.
2. Hogan MC, *et al.* Randomized clinical trial of long-acting somatostatin for autosomal dominant polycystic kidney and liver disease. *J Am Soc Nephrol* 2010; 21: 1052–61.
3. Caroli A, *et al.* Reducing polycystic liver volume in ADPKD: effects of somatostatin analogue octreotide. *Clin J Am Soc Nephrol* 2010; 5: 783–9.
4. van Keimpema L, *et al.* Lanreotide reduces the volume of polycystic liver: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2009; 137: 1661–8.

Pretibial myxoedema. Pretibial myxoedema (deposition of glycosaminoglycans in the subcutaneous tissue of the shins) is associated with Graves' disease (see Hyperthyroidism, p. 2332.2). There are reports of apparent benefit from the use of octreotide for this condition. In one case,[1,2] octreotide given for 6 months after surgical removal of the myxoedematous tissue may have prevented its recurrence. In another,[3] octreotide injected intralesionally was reported to improve and control the condition. However, in other cases[4] subcutaneous octreotide has been ineffective.

1. Derrick EK, *et al.* Successful surgical treatment of severe pretibial myxoedema. *Br J Dermatol* 1995; 133: 317–18.
2. Felton J, *et al.* Successful combined surgical and octreotide treatment of severe pretibial myxoedema reviewed after 9 years. *Br J Dermatol* 2003; 148: 825–6.
3. Shinohara M, *et al.* Refractory pretibial myxoedema with response to intralesional insulin-like growth factor 1 antagonist (octreotide): downregulation of hyaluronic acid production by the lesional fibroblasts. *Br J Dermatol* 2000; 143: 1083–6.
4. Rotman-Pikielny P, *et al.* Lack of effect of long-term octreotide therapy in severe thyroid-associated dermopathy. *Thyroid* 2003; 13: 465–70.

Raised intracranial pressure. For reference to octreotide being tried in idiopathic intracranial hypertension, see p. 1271.3.

Sulfonylurea overdose. Octreotide has been used in the treatment of severe refractory cases of sulfonylurea-induced hypoglycaemia (see Treatment of Adverse Effects, p. 502.1).

Adverse Effects and Precautions

There may be a transient local reaction at the site of injection of octreotide. Systemic adverse effects are mainly gastrointestinal and may include anorexia, nausea, vomiting, diarrhoea and steatorrhoea, abdominal discomfort, and flatulence. Use between meals or at bedtime may reduce these gastrointestinal effects. Hypersensitivity reactions and hair loss have been reported rarely.

Gallstones may develop on long-term therapy; there have been isolated reports of hepatic dysfunction and of biliary colic associated with drug withdrawal. Checks should be made for gallstones before prolonged therapy and at 6- to 12-month intervals during treatment. There have also been isolated reports of pancreatitis and of hepatic dysfunction without cholestasis. Hypoglycaemia may occur, especially in patients with insulinomas, but there is also a risk of hyperglycaemia or impaired glucose tolerance. Thyroid function should be monitored during octreotide therapy because of the possibility of hypothyroidism. Pituitary tumours that secrete growth hormone can expand during treatment, causing serious complications; patients should be monitored for signs of tumour expansion, such as visual field defects. Cardiac rhythm should be monitored during intravenous use of octreotide. Doses may need to be adjusted in patients with liver cirrhosis or end-stage renal failure, in whom the clearance of octreotide is reduced.

In women with acromegaly, the normalisation of growth hormone and IGF-I concentrations by octreotide may restore fertility. Licensed product information for octreotide advises that contraception be used during treatment, but see also Pregnancy, below.

Effects on the biliary tract. Octreotide has an inhibitory effect on gallbladder motility and bile secretion, accounting for the development of gallstones and biliary colic.[1-6]

1. Redfern JS, Fortuner WJ. Octreotide-associated biliary tract dysfunction and gallstone formation: pathophysiology and management. *Am J Gastroenterol* 1995; 90: 1042–52.
2. Tauber JP, *et al.* The impact of continuous subcutaneous infusion of octreotide on gallstone formation in acromegalic patients. *J Clin Endocrinol Metab* 1995; 80: 3262–6.
3. Hussaini SH, *et al.* Roles of gall bladder emptying and intestinal transit in the pathogenesis of octreotide induced gall bladder stones. *Gut* 1996; 38: 775–83.
4. Trendle MC, *et al.* Incidence and morbidity of cholelithiasis in patients receiving chronic octreotide for metastatic carcinoid and malignant islet cell tumors. *Cancer* 1997; 79: 830–4.
5. Moschetta A, *et al.* Severe impairment of postprandial cholecystokinin release and gall-bladder emptying and high risk of gallstone formation in acromegalic patients during Sandostatin LAR. *Aliment Pharmacol Ther* 2001; 15: 181–5.
6. Hofmann AF. Increased deoxycholic acid absorption and gall stones in acromegalic patients treated with octreotide: more evidence for a connection between slow transit constipation and gall stones. *Gut* 2005; 54: 575–8.

Effects on carbohydrate metabolism. Changes in glucose tolerance may occur in patients with acromegaly who are treated with somatostatin analogues. A meta-analysis of studies of the use of octreotide or lanreotide in acromegaly concluded that somatostatin analogues had a marginal impact on glucose homoeostasis. There was evidence for a decrease in fasting plasma-insulin, but without significant effect on fasting plasma-glucose or glycated haemoglobin ($HbA1_c$). Nevertheless, a significant adverse effect may occur in individual patients and glycaemic monitoring was recommended.[1]

There has been a report of deterioration in glucose tolerance leading to death from diabetic ketoacidosis when octreotide treatment was stopped in a patient with acromegaly and insulin-resistant diabetes mellitus.[2]

See also Diabetes Mellitus and Hyperinsulinism under Uses and Administration, p. 1925.1 and p. 1926.1.

1. Mazziotti G, *et al.* Effects of somatostatin analogs on glucose homeostasis: a metaanalysis of acromegaly studies. *J Clin Endocrinol Metab* 2009; 94: 1500–8.
2. Abrahamson MJ. Death from diabetic ketoacidosis after cessation of octreotide in acromegaly. *Lancet* 1990; 336: 318–19.

Effects on the hair. Diffuse loss of scalp hair has been reported in 4 of 7 women who received octreotide; after withdrawal of octreotide in 3 of the women there was a complete recovery of scalp hair.[1] Other similar cases have also been reported. In one case, diffuse alopecia in a male patient was completely reversed when octreotide was replaced with lanreotide.[2]

1. Jönsson A, Manbem P. Octreotide and loss of scalp hair. *Ann Intern Med* 1991; 115: 913.
2. Lami M-C, *et al.* Hair loss in three patients with acromegaly treated with octreotide. *Br J Dermatol* 2003; 149: 655–6.

Effects on the liver. Hepatitis occurred in 2 acromegalic patients treated with octreotide 300 micrograms daily subcutaneously.[1,2] In both cases liver enzyme values returned to normal within 1 to 2 months of withdrawing octreotide, and recurred on rechallenge.

1. Arosio M, *et al.* Acute hepatitis after treatment of acromegaly with octreotide. *Lancet* 1988; ii: 1498.
2. González-Martín JA, *et al.* Acute liver injury and octreotide. *Am J Gastroenterol* 1996; 91: 2434–5.

Effects on mental function. A woman with acromegaly developed manic symptoms on 2 separate occasions 2 months after starting treatment with octreotide.[1]

1. Fernández-Real J-M, *et al.* Octreotide-induced manic episodes in a patient with acromegaly. *Ann Intern Med* 2006; 144: 704.

Effects on the pancreas. There have been reports of pancreatitis associated with octreotide[1-4] and lanreotide.[4] It has been suggested that octreotide-induced pancreatitis may result from spasm of the sphincter of Oddi, resulting in retention of activated pancreatic enzymes due to outflow obstruction.[3]

1. Predenrich A, *et al.* Acute pancreatitis after short-term octreotide. *Lancet* 1991; 338: 52–3.
2. Sadoul J-L, *et al.* Acute pancreatitis following octreotide withdrawal. *Am J Med* 1991; 90: 763–4.
3. Bodemar G, Hjortswang H. Octreotide-induced pancreatitis: an effect of increased contractility of Oddi sphincter. *Lancet* 1996; 348: 1668–9.
4. Cannavò S, *et al.* Octreotide and lanreotide treatment in active acromegaly. *J Clin Endocrinol Metab* 1997; 82: 2376–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies octreotide 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 24/10/11)

Pregnancy. There have been reports of women given lanreotide[1,2] or octreotide[2-7] during pregnancy. Most were being treated for acromegaly, although there is also a report[6] of octreotide use during pregnancy in a woman treated for nesidioblastosis. In most cases, the somatostatin analogue was stopped early in the pregnancy, but in some cases octreotide was continued to term. No maternal complications or congenital anomalies were described, although several cases[2] of babies born small for gestational age have been seen.

1. de Menis E, *et al.* Uneventful pregnancy in an acromegalic patient treated with slow-release lanreotide: a case report. *J Clin Endocrinol Metab* 1999; 84: 1489.
2. Caron P, *et al.* Acromegaly and pregnancy: a retrospective multicenter study of 59 pregnancies in 46 women. *J Clin Endocrinol Metab* 2010; 95: 4680–7.
3. Neal JM. Successful pregnancy in a woman with acromegaly treated with octreotide. *Endocr Pract* 2000; 6: 148–50.
4. Fassnacht M, *et al.* Octreotide LAR treatment throughout pregnancy in an acromegalic woman. *Clin Endocrinol (Oxf)* 2001; 55: 411–15.
5. Mikhail N. Octreotide treatment of acromegaly during pregnancy. *Mayo Clin Proc* 2002; 77: 297–8.
6. Boulanger C, *et al.* Normal pregnancy in a woman with nesidioblastosis treated with somatostatin analog octreotide. *J Endocrinol Invest* 2004; 27: 465–70.
7. Maffei P, *et al.* Effects of octreotide exposure during pregnancy in acromegaly. *Clin Endocrinol (Oxf)* 2010; 72: 668–77. Correction. *ibid.*: 856.

Interactions

Octreotide has been associated with alterations in nutrient absorption and there is a theoretical possibility that it may affect the oral absorption of other drugs. Patients receiving insulin or oral hypoglycaemics may require dose adjustments of these drugs if octreotide is also used. The bioavailability of bromocriptine is increased by octreotide. It has been suggested that dosage of beta blockers, calcium-channel blockers, or drugs to control fluid and electrolyte balance may also need to be adjusted.

Ciclosporin. For a reference to octreotide reducing serum concentrations of ciclosporin, see p. 1954.3.

Pharmacokinetics

Octreotide is rapidly absorbed after subcutaneous injection, with peak plasma concentrations reached about 25 to 40 minutes after a dose, and is distributed to body tissues. About 40 to 65% of the octreotide in the circulation is bound to plasma proteins. It is said to show non-linear pharmacokinetics, with reduced clearance at high doses. Octreotide has a plasma elimination half-life of about 1.5 hours; half-life is prolonged in elderly patients, renal impairment, and liver cirrhosis. About a third of a dose is excreted unchanged in the urine. Octreotide diffuses across the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Sandostatin; *Austral.*: Sandostatin; *Austria*: Sandostatin; *Belg.*: Sandostatine; *Braz.*: Octride; Sandostatin; *Canad.*: Sandostatin; *Chile*: Sandostatin; *China*: Jin Di Lin (金迪林); Li Er Ning (力尔宁); Li Te Xin (力特辛); Octride (启文); PeiXin (培新); Sandostatin (善宁); Sheng Ao Ding (生奥定); Tai Ruo Tan (太若坦); Xing An Yi (星安忆); Yi Pu Bi Shan (依普比善); Yi Pu Ning (益谱宁); *Cz.*: Sandostatin; *Denm.*: Sandostatin; *Fin.*: Sandostatin; *Fr.*: Sandostatine; Sirectid; *Ger.*: Bendatreotid†; Sandostatin; *Gr.*: Sandostatin; *Hong Kong*: Sandostatin; *Hung.*: Sandostatin; *India*: Actide; Octate; Octide; Octride; Octronis; Okeron; Otide; Sandostatin; *Indon.*: Sandostatin; *Irl.*: Sandostatin; *Israel*:

Sandostatin; *Ital.*: Longastatina; Samilstin; Sandostatina; *Malaysia*: Sandostatin; *Mex.*: Acroken; Cryostatin; Proclose; Sandostatina; *Neth.*: Sandostatine; *Norw.*: Sandostatin; *NZ*: Sandostatin; *Philipp.*: Sandostatin; *Pol.*: Sandostatin; Sirocttid; *Port.*: Octrayne; Sandostatina; *Rus.*: Genfastat (Генфастат); Octride (Октрид); Sandostatin (Сандостатин); *S.Afr.*: Sandostatin; *Singapore*: Sandostatin; *Spain*: Oktidel; Sandostatin; *Swed.*: Sandostatin; *Switz.*: Sandostatine; *Thai.*: Octride; Sandostatin; *Turk.*: Sandostatin; *UK*: Sandostatin; *Ukr.*: Octra (Октра); Octrestatin (Октрестатин); Octrin (Октрин); Sandostatin (Сандостатин); *USA*: Sandostatin; *Venez.*: Sandostatin.

Pasireotide *(USAN, rINN)*

Pasireotida; Pasiréotide; Pasireotidum; SOM-230; Пасиреотид.

Cyclo[(4*R*)-4-(2-aminoethylcarbamoyloxy)-L-prolyl-L-phenylglycyl-D-tryptophyl-L-lysyl-4-O-benzyl-L-tyrosyl-L-phenylalanyl-].

$C_{58}H_{66}N_{10}O_9$=1047.2

CAS — 396091-73-9 (pasireotide); 396091-76-2 (pasireotide acetate).

ATC — H01CB05.

ATC Vet — QH01CB05.

UNII — 98H1T17066.

Pasireotide Aspartate *(rINNM)*

Aspartato de pasireotida; Pasireotide L-aspartate; Pasiréotide, Aspartate de; Pasireotidi Aspartas; SOM-230B; Пасиреотида Аспартат.

$C_{58}H_{66}N_{10}O_9.C_4H_7NO_4$

CAS — 396091-77-3 (pasireotide x aspartate).

ATC — H01CB05.

ATC Vet — QH01CB05.

Uses and Administration

Pasireotide is a somatostatin analogue that binds to 4 of the 5 human somatostatin (hsst) receptors, especially hsst-5 which is expressed at high levels in corticotropin (ACTH)-producing adenomas. The resulting inhibition of ACTH secretion is used in the treatment of Cushing's disease (p. 2559.1), particularly when surgery is not an option or has failed.

It is given as the diaspartate ($C_{58}H_{66}N_{10}O_9.2C_4H_7NO_4$ = 1313.4) but doses are expressed in terms of the base; 125 micrograms of pasireotide diaspartate is equivalent to about 100 micrograms of pasireotide. An initial dose equivalent to 600 micrograms of pasireotide is given twice daily by subcutaneous injection. Clinical benefit should be assessed after two months and the dose may be increased to 900 micrograms twice daily if necessary, according to the reduction in urinary free cortisol. If no response is seen after two months, treatment discontinuation should be considered. Adverse effects may be managed by a temporary reduction in dose by decrements of 300 micrograms twice daily. For doses in hepatic impairment, see below.

Pasireotide is also under investigation in the treatment of acromegaly and carcinoid tumours.

References.
1. Boscaro M, *et al.* Treatment of pituitary-dependent Cushing's disease with the multireceptor ligand somatostatin analog pasireotide (SOM230): a multicenter, phase II trial. *J Clin Endocrinol Metab* 2009; **94:** 115–22.
2. Petersenn S, *et al.* Pasireotide (SOM230) demonstrates efficacy and safety in patients with acromegaly: a randomized, multicenter, phase II trial. *J Clin Endocrinol Metab* 2010; **95:** 2781–9.
3. Feelders RA, *et al.* Pasireotide alone or with cabergoline and ketoconazole in Cushing's disease. *N Engl J Med* 2010; **362:** 1846–8.
4. Colao A, *et al.* Pasireotide B2305 Study Group. A 12-month phase 3 study of pasireotide in Cushing's disease. *N Engl J Med* 2012; **366:** 914–24. Correction. *ibid.*; **367:** 780.

Administration in hepatic impairment. Higher exposure to pasireotide has been seen in subjects with moderate and severe hepatic impairment.[1] Licensed product information suggests that dose adjustment is not required in mild hepatic impairment (Child-Pugh class A). For patients with moderate hepatic impairment (Child-Pugh class B) the initial dose of subcutaneous pasireotide should be 300 micrograms twice daily with a maximum dose of 600 micrograms twice daily. Pasireotide should not be used in severe hepatic impairment (Child-Pugh class C).

1. Horsmans Y, *et al.* Effect of hepatic impairment on the pharmacokinetics of pasireotide (SOM230): results from a multicenter phase I study. *J Clin Pharmacol* 2012; **52:** 552–8.

Adverse Effects, Treatment, and Precautions

As for Octreotide Acetate, p. 1927.1. Other common adverse effects include anaemia, headache, hypotension, myalgia and arthralgia, and fatigue.

Hyperglycaemia is very commonly reported in patients given pasireotide for the management of Cushing's disease. Glycated haemoglobin (HbA_{1c}) has been reported to increase significantly and stabilise during therapy, then decrease but not return to baseline values after stopping pasireotide. Fasting plasma glucose and HbA_{1c} should be assessed before starting pasireotide then monitored weekly for the first 2 to 3 months of therapy and periodically thereafter. Fasting plasma glucose should be measured 4 weeks, and HbA_{1c} at 3 months, after stopping treatment. If hyperglycaemia remains uncontrolled by antidiabetic therapy, the dose of pasireotide should be adjusted or it should be stopped.

Mild transient elevations of liver enzymes commonly occur in patients given pasireotide. Rare cases of more significant increases in liver enzymes and bilirubin have been reported, usually developing within 10 days of starting therapy, with full recovery after stopping pasireotide. Monitoring of liver function is recommended before using pasireotide, after 1, 2, 4, 8, and 12 weeks during treatment, and thereafter as clinically indicated.

Bradycardia and QT prolongation have been reported and it is recommended that ECG should be monitored before and 1 week after starting pasireotide treatment, and thereafter as clinically indicated. Hypokalaemia and/or hypomagnesaemia should be corrected before treatment and monitored periodically during therapy.

Pasireotide causes rapid suppression of corticotropin (ACTH) secretion in Cushings' disease, and complete or near-complete suppression can cause transient adrenocortical insufficiency. Dose reduction or withdrawal of pasireotide with glucocorticoid replacement therapy may be needed. Pasireotide may also inhibit other pituitary hormones, and monitoring of pituitary function is recommended.

Interactions

Pasireotide is a P-glycoprotein (PgP) substrate so there is potential for strong PgP inhibitors to increase the concentrations of pasireotide; however, the clinical implications are unknown. Pasireotide should be used with caution with other drugs that prolong the QT interval or have bradycardic effects. Dose adjustment of insulin and other antidiabetic medicines may be required in patients given pasireotide.

Pharmacokinetics

Pasireotide is rapidly absorbed after subcutaneous injection, with peak plasma concentrations reached about 15 to 30 minutes after a dose. Pasireotide is mostly distributed in the plasma and plasma protein binding is about 88%. Pasireotide is eliminated mainly by hepatic clearance and is mostly found, unchanged, in the faeces (48%) and urine (8%). The half-life in healthy subjects is about 12 hours and increases in hepatic impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Signifor; *Fr.*: Signifor; *Neth.*: Signifor; *Norw.*: Signifor; *Switz.*: Signifor; *UK*: Signifor; *USA*: Signifor.

Pegvisomant *(BAN, USAN, rINN)*

B2036-PEG; Pegvisomanto; Pegvisomantti; Pegvisomantum; Pegwisomant; Пегвизомант.

18-L-Aspartic acid-21-L-asparagine-120-L-lysine-167-L-asparagine-168-L-alanine-171-L-serine-172-L-arginine-174-L-serine-179-L-threonine growth hormone (human), reaction product with polyethylene glycol.

CAS — 218620-50-9.

ATC — H01AX01.

ATC Vet — QH01AX01.

UNII — N824AOU5XV.

Uses and Administration

Pegvisomant is a protein of recombinant DNA origin to which several polyethylene glycol polymers are covalently bound. It is an analogue of human growth hormone that acts as an antagonist at growth hormone receptors, and is used in the treatment of acromegaly (below). A loading dose of 40 or 80 mg is given subcutaneously, followed by 10 mg daily. Further dose adjustments, in increments of 5 mg, are made according to serum concentrations of IGF-I, which should be measured every 4 to 6 weeks. The maintenance dose should not exceed 30 mg daily.

Reviews.
1. Muller AF, *et al.* Growth hormone receptor antagonists. *J Clin Endocrinol Metab* 2004; **89:** 1503–11.
2. Thankamony GN, *et al.* Pegvisomant: current and potential novel therapeutic applications. *Expert Opin Biol Ther* 2009; **9:** 1553–63.

Administration in children. For administration of pegvisomant in children with pituitary gigantism, see below.

Acromegaly. Pegvisomant may be used in patients with acromegaly (p. 1918.1) who have not responded adequately to surgery, radiotherapy, or somatostatin analogues, or when these therapies are unsuitable or not tolerated. The combination of pegvisomant with a somatostatin analogue is also under investigation in patients whose response to a somatostatin analogue alone is inadequate. Pegvisomant has also been tried in a small number of younger patients with gigantism (see below).

References.
1. Trainer PJ, *et al.* Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. *N Engl J Med* 2000; **342:** 1171–7.
2. van der Lely AJ, *et al.* Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. *Lancet* 2001; **358:** 1754–9.
3. Feenstra J, *et al.* Combined therapy with somatostatin analogues and weekly pegvisomant in active acromegaly. *Lancet* 2005; **365:** 1644–6. Correction. *ibid.*; 1620.
4. Jehle S, *et al.* Alternate-day administration of pegvisomant maintains normal serum insulin-like growth factor-I levels in patients with acromegaly. *J Clin Endocrinol Metab* 2005; **90:** 1588–93.
5. Colao A, *et al.* Efficacy of 12-month treatment with the GH receptor antagonist pegvisomant in patients with acromegaly resistant to long-term, high-dose somatostatin analog treatment: effect on IGF-I levels, tumor mass, hypertension and glucose tolerance. *Eur J Endocrinol* 2006; **154:** 467–77.
6. Pivonello R, *et al.* Treatment with growth hormone receptor antagonist in acromegaly: effect on cardiac structure and performance. *J Clin Endocrinol Metab* 2007; **92:** 476–82. Correction. *ibid.*; 1605.
7. Neggers SJCMM, *et al.* Long-term efficacy and safety of combined treatment of somatostatin analogs and pegvisomant in acromegaly. *J Clin Endocrinol Metab* 2007; **92:** 4598–4601.
8. Ghigo E, *et al.* Comparison of pegvisomant and long-acting octreotide in patients with acromegaly naive to radiation and medical therapy. *J Endocrinol Invest* 2009; **32:** 924–33.
9. Trainer PJ. ACROSTUDY: the first 5 years. *Eur J Endocrinol* 2009; **161** (suppl): S19–S24.

Gigantism. Several case reports have described the use of pegvisomant in children and adolescents in the treatment of pituitary gigantism (p. 1918.1).[1-4] The condition had been previously uncontrolled by other treatments (surgery, octreotide, or dopamine agonists). Generally daily subcutaneous injections of pegvisomant 10 mg were given initially, and the youngest patient[3] was aged 5 years and 6 months.

1. Rix M, *et al.* Pegvisomant therapy in pituitary gigantism: successful treatment in a 12-year-old girl. *Eur J Endocrinol* 2005; **153:** 195–201.
2. Müssig K, *et al.* Pegvisomant treatment in gigantism caused by a growth hormone-secreting giant pituitary adenoma. *Exp Clin Endocrinol Diabetes* 2007; **115:** 198–202.
3. Goldenberg N, *et al.* Treatment of pituitary gigantism with the growth hormone receptor antagonist pegvisomant. *J Clin Endocrinol Metab* 2008; **93:** 2953–6.
4. Bergamaschi S, *et al.* Eight-year follow-up of a child with a GH/prolactin-secreting adenoma: efficacy of pegvisomant therapy. *Horm Res Paediatr* 2010; **73:** 74–9.

Adverse Effects and Precautions

Adverse effects commonly reported with the use of pegvisomant include gastrointestinal disturbances, elevated liver function tests, flu-like symptoms, fatigue, injection site reactions, arthralgia, myalgia, peripheral oedema, headache, dizziness, somnolence, tremor, sweating, pruritus, rash, sleep disorders, hypercholesterolaemia, weight gain, hyperglycaemia, hunger, and hypertension.

Liver function should be tested before starting pegvisomant, then every 4 to 6 weeks for the first 6 months of therapy. US licensed product information recommends that further testing take place twice in the next 6 months and then twice in the following year.

Pegvisomant is structurally similar to growth hormone and may cause assays to overestimate growth hormone concentrations.

Breast feeding. The distribution of pegvisomant into breast milk has been examined (see Pregnancy, below).

Effects on the skin. Lipohypertrophy has been described in patients who have consistently injected pegvisomant into the same subcutaneous area.[1-3] Lipohypertrophy regressed on stopping the drug.[3] The efficacy of pegvisomant was also reduced in one case, but lipohypertrophy resolved and pegvisomant efficacy improved when the patient used the recommended technique of injection site rotation.[2] Licensed product information recommends that a different injection site is used daily to help prevent lipohypertrophy.

1. Maffei P, *et al.* Lipohypertrophy in acromegaly induced by the new growth hormone receptor antagonist pegvisomant. *Ann Intern Med* 2006; **145:** 310–12.
2. Marazuela M, *et al.* Pegvisomant-induced lipohypertrophy: report of a case with histopathology. *Ann Intern Med* 2007; **147:** 741–3.
3. Bonert VS, *et al.* Lipodystrophy in patients with acromegaly receiving pegvisomant. *J Clin Endocrinol Metab* 2008; **93:** 3515–18.

Pregnancy. A women receiving pegvisomant for acromegaly continued therapy during pregnancy.[1] The dose of pegvisomant needed to be increased from 15 mg subcutaneously daily to 20 mg daily one month after conception, and to 25 mg daily at 3 months of gestation. Normal fetal growth milestones were achieved and a normal child was delivered at week 40 by caesarean section. The baby girl

was reported to be healthy and normal at 6 months of age. Transplacental passage of pegvisomant was considered to be either absent or minimal, based on samples of maternal and cord blood. There was also no evidence of substantial secretion into breast milk, and the authors suggested that any that might be ingested would be likely to undergo rapid gastric hydrolysis.

There is also a report of a woman who continued to receive pegvisomant during a single cycle of IVF and until a positive pregnancy test, with no apparent adverse effect on the fetus. The child was reported to be normal at 1 year of age.[2]

1. Brian SR, *et al.* Treatment of acromegaly with pegvisomant during pregnancy: maternal and fetal effects. *J Clin Endocrinol Metab* 2007; **92:** 3374–7.
2. Qureshi A, *et al.* IVF/ICSI in a woman with active acromegaly: successful outcome following treatment with pegvisomant. *J Assist Reprod Genet* 2006; **23:** 439–42.

Interactions

Pegvisomant may increase insulin sensitivity. In patients with diabetes, doses of insulin or oral hypoglycaemics may need to be decreased because of the increased risk of hypoglycaemia. Patients taking opioid analgesics may require higher serum concentrations of pegvisomant to achieve appropriate IGF-I suppression.

Pharmacokinetics

Pegvisomant is absorbed slowly after subcutaneous injection, and peak serum concentrations occur after about 33 to 77 hours. It is slowly eliminated from serum, with a half-life estimated to range from 74 to 172 hours. Renal clearance of pegvisomant is negligible.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Somavert; ***Austria***: Somavert; ***Belg.***: Somavert; ***Braz.***: Somavert; ***Canad.***: Somavert; ***Cz.***: Somavert; ***Denm.***: Somavert; ***Fin.***: Somavert; ***Fr.***: Somavert; ***Ger.***: Somavert; ***Gr.***: Somavert; ***Hung.***: Somavert; ***Irl.***: Somavert; ***Israel***: Somavert; ***Ital.***: Somavert; ***Mex.***: Somavert; ***Neth.***: Somavert; ***Norw.***: Somavert; ***Pol.***: Somavert; ***Port.***: Somavert; ***Singapore***: Somavert; ***Spain***: Somavert; ***Swed.***: Somavert; ***Switz.***: Somavert; ***Turk.***: Somavert; ***UK***: Somavert; ***Ukr.***: Somavert (Сомаверт)†; ***USA***: Somavert.

Pralmorelin Dihydrochloride *(USAN, rINNM)* ⊗

Dihidrocloruro de pralmorelina; GHRP-2 (pralmorelin); Growth Hormone-releasing Peptide-2 (pralmorelin); KP-102 (pralmorelin); Pralmoréline, Dichlorhydrate de; Pralmorelini Dihydrochloridum; WAY-GPA-748; Пральморелина Дигидрохлорид.

D-Alanyl-3-(2-naphthyl)-D-alanyl-L-alanyl-L-tryptophyl-D-phenylalanyl-L-lysinamide dihydrochloride.

$C_{45}H_{55}N_9O_6.2HCl$=890.9

CAS — 158861-67-7 (pralmorelin); 158827-34-0 (pralmorelin dihydrochloride).

UNII — R4AVR27MM8.

Profile

Pralmorelin is a small synthetic peptide that stimulates the release of growth hormone. It is used in the diagnosis of growth hormone deficiency; it has also been tried in the treatment of growth retardation (p. 1918.3).

References.

1. Mericq V, *et al.* Effects of eight months treatment with graded doses of a growth hormone (GH)-releasing peptide in GH-deficient children. *J Clin Endocrinol Metab* 1998; **83:** 2355–60.
2. Mahajan T, Lightman SL. A simple test for growth hormone deficiency in adults. *J Clin Endocrinol Metab* 2000; **85:** 1473–6.
3. Gondo RG, *et al.* Growth hormone-releasing peptide-2 stimulates GH secretion in GH-deficient patients with mutated GH-releasing hormone receptor. *J Clin Endocrinol Metab* 2001; **86:** 3279–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: GHRP.

Somatomedins ⊗

Fattori di crescita insulino-simili; IGFs; Insuliininkaltaiset kasvutekijät; Insulinähnliche Wachstumsfaktoren; Insuline-achtige groeifactoren; Insulin-like Growth Factors; Somatomedinas; Somatomédine; Somatomediner; Sulphation Factors; Соматомедины.

Description. Somatomedins are a group of polypeptide hormones related to insulin and usually known individually as insulin-like growth factors (IGFs), with molecular weights of about 7000 to 8000. They are synthesised in the liver, kidney, muscle, and other tissues.

Mecasermin *(BAN, USAN, rINN)* ⊗

CEP-151; FK-780; IGF-1; IGF-I; Insulin-like growth factor I (human); Mecasermina; Mécasermine; Mecaserminum; rhIGF-1; Somatomedin C; Somatomedina C; Меказермин.

$C_{331}H_{512}N_{94}O_{101}S_7$=7648.7

CAS — 68562-41-4; 67763-96-6.

ATC — H01AC03.

ATC Vet — QH01AC03.

UNII — 7GR9I2683O.

Mecasermin Rinfabate *(USAN, rINN)* ⊗

Mecasermina rinfabato; Mécasermine Rinfabate; Mecasermini Rinfabas; rhIGF-I/rhIGFBP-3; Меказермин Ринфабат.

A complex of insulin-like growth factor I (human) with insulin-like growth factor-binding protein IGFBP-3 (human).

CAS — 478166-15-3.

ATC — H01AC05.

ATC Vet — QH01AC05.

UNII — NZ8M50KKRG.

Uses and Administration

The somatomedins are a group of polypeptide hormones, some of which are involved in mediating the effects of growth hormone in the body. Insulin-like growth factor I (IGF-I) is believed to be responsible for many of the anabolic effects of growth hormone. It is secreted primarily by the liver, regulated principally by growth hormone and insulin secretion; IGF-I may also be secreted in other tissues, where it may exert local hormonal (paracrine) effects. In the circulation, IGF-I is almost completely protein bound; 6 binding proteins have been identified and production of some of these is also under the control of growth hormone. In addition to its anabolic effects IGF-I, which is structurally related to insulin, also has potent hypoglycaemic properties.

IGF-I is available as mecasermin, a product of recombinant DNA technology. It is used in the treatment of growth failure in children and adolescents with severe primary IGF-I deficiency or with growth hormone gene deletion who have developed neutralising antibodies to growth hormone (see Growth Retardation, below). However, it is not recommended for children less than 2 years of age because of a lack of data. The starting dose of mecasermin is 40 to 80 micrograms/kg twice daily by subcutaneous injection. After 1 week, if this dose is tolerated, it may be increased by 40 micrograms/kg per dose to a maximum of 120 micrograms/kg twice daily. Mecasermin should be given within 20 minutes before or after food, to minimise hypoglycaemia. The dose should be reduced if hypoglycaemia occurs with recommended doses despite adequate food intake. If the patient is unable to eat for any reason, the dose of mecasermin should be withheld.

Mecasermin rinfabate is a recombinant protein complex of IGF-I and its most abundant binding protein, insulin-like growth factor binding protein-3 (IGFBP-3). It has been investigated for the management of amyotrophic lateral sclerosis and myotonic muscular dystrophy. It is also under investigation in the prevention of complications in preterm neonates that may be associated with low endogenous concentrations of IGF-I, such as retinopathy of prematurity.

IGF-II (IGF-2) is thought to play an important role in fetal growth, although its function in adults is uncertain. It is closely related in structure to IGF-I, but is not under the control of growth hormone.

General reviews.

1. Laron Z. Somatomedin-1 (insulin-like growth factor-I) in clinical use: facts and potential. *Drugs* 1993; **45:** 1–8.
2. Bondy CA, *et al.* Clinical uses of insulin-like growth factor I. *Ann Intern Med* 1994; **124:** 593–601.
3. Le Roith D. Insulin-like growth factors. *N Engl J Med* 1997; **336:** 633–40.
4. Laron Z. Insulin-like growth factor 1 (IGF-1): a growth hormone. *Mol Pathol* 2001; **54:** 311–16.
5. Kemp SF, *et al.* Efficacy and safety of mecasermin rinfabate. *Expert Opin Biol Ther* 2006; **6:** 533–8.
6. Keating GM. Mecasermin. *BioDrugs* 2008; **22:** 177–88.

Administration in children. For details of mecasermin doses in children see Uses and Administration, above and Growth Retardation, below.

Diabetes mellitus. Patients with type 1 diabetes mellitus (p. 459.1) have low circulating levels of insulin-like growth factor I (IGF-I), and there has been considerable interest in the therapeutic potential of mecasermin in these patients.[1] Randomised studies[2,3] have found that mecasermin 40 micrograms/kg once or twice daily by subcutaneous injection improves metabolic control in the short term when added to insulin therapy. Insulin doses can also be reduced in some patients.[3] However, the role of IGF-I in the development of diabetic complications is unclear and there has been some concern about its proliferative effect in diabetic retinopathy.[1] Optic disc swelling and worsening of retinopathy have been reported with higher doses of mecasermin.[3] Mecasermin rinfabate has been tried in an attempt to limit adverse effects such as oedema, jaw pain, headache, Bells' palsy, and retinal oedema.[4]

Mecasermin has also been reported to improve insulin sensitivity and to lower concentrations of insulin, glucose, and C-peptide in patients with syndromes of severe insulin resistance or type 2 diabetes mellitus.[1]

1. Thrailkill KM. Insulin-like growth factor-I in diabetes mellitus: its physiology, metabolic effects, and potential clinical utility. *Diabetes Technol Ther* 2000; **2:** 69–80.
2. Acerini CL, *et al.* Randomised placebo-controlled trial of human recombinant insulin-like growth factor I plus intensive insulin therapy in adolescents with insulin-dependent diabetes mellitus. *Lancet* 1997; **350:** 1199–1204.
3. Thrailkill KM, *et al.* Cotherapy with recombinant human insulin-like growth factor I and insulin improves glycemic control in type 1 diabetes. *Diabetes Care* 1999; **22:** 585–92.
4. Clemmons DR, *et al.* The combination of insulin-like growth factor I and insulin-like growth factor-binding protein-3 reduces insulin requirements in insulin-dependent type 1 diabetes: evidence for in vivo biological activity. *J Clin Endocrinol Metab* 2000; **85:** 1518–24.

Growth retardation. Mecasermin is used in the treatment of growth retardation (p. 1918.3) including Laron-type dwarfism (growth hormone resistance or insensitivity). It is given to children and adolescents with severe primary IGF-I deficiency, which includes patients with mutations in the growth hormone receptor or post-growth hormone receptor signalling pathway, and IGF-I gene defects. They have low concentrations of IGF-I and normal or elevated concentrations of growth hormone; they are not growth hormone deficient and cannot be expected to respond to growth hormone therapy. It is also used in children with growth hormone gene deletion who have developed neutralising antibodies to growth hormone. Mecasermin has stimulated linear growth and normalised biochemical abnormalities in these patients.[1] One study[2] found the effect on growth velocity in the first year to be dose dependent. The beneficial effect persisted during up to 8 years of treatment, but growth velocity gradually declined over this time. During long-term use, growth hormone and insulin are persistently suppressed, preventing hypoglycaemia and stabilising blood-glucose concentrations.[3] There is also an increase in the production of the insulin-like growth factor binding protein-3, which prolongs the half-life of mecasermin so that a progressive dose reduction is needed to avoid overdosage and adverse effects.[3]

Some children with idiopathic short stature have a low concentration of IGF-I of no apparent cause, which is less severe than IGF-I deficiency from genetic causes. It has been suggested that these patients, who have normal concentrations of growth hormone, might have a degree of growth hormone insensitivity, and a study[4] of IGF-I treatment reported improvements in height velocity, dependent on dose and age. However, this premise for IGF-I therapy has been criticised and a role for IGF-I treatment in idiopathic short stature requires further study.[5]

1. Laron Z. The essential role of IGF-I: lessons from the long-term study and treatment of children and adults with Laron syndrome. *J Clin Endocrinol Metab* 1999; **84:** 4397–4404.
2. Chernausek SD, *et al.* GH Insensitivity Syndrome Collaborative Group. Long-term treatment with recombinant insulin-like growth factor (IGF)-I in children with severe IGF-I deficiency due to growth hormone insensitivity. *J Clin Endocrinol Metab* 2007; **92:** 902–10.
3. Laron Z. Laron syndrome (primary growth hormone resistance or insensitivity): the personal experience 1958–2003. *J Clin Endocrinol Metab* 2004; **89:** 1031–44.
4. Midyett LK, *et al.* Recombinant insulin-like growth factor (IGF)-I treatment in short children with low IGF-I levels: first-year results from a randomized clinical trial. *J Clin Endocrinol Metab* 2010; **95:** 611–19.
5. Colleu-Solberg PF, Misra M. Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. The role of recombinant human insulin-like growth factor-I in treating children with short stature. *J Clin Endocrinol Metab* 2008; **93:** 10–18.

Motor neurone disease. Mecasermin has been investigated for the management of amyotrophic lateral sclerosis, a form of motor neurone disease (p. 2605.2). A review of 2 studies concluded that there was not enough evidence to assess the clinical efficacy of mecasermin.[1] A later study found no benefit from mecasermin.[2]

1. Mitchell JD, *et al.* Recombinant human insulin-like growth factor I (rhIGF-I) for amyotrophic lateral sclerosis/motor neuron disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 21/08/08).
2. Sorenson EJ, *et al.* Subcutaneous IGF-1 is not beneficial in 2-year ALS trial. *Neurology* 2008; **71:** 1770–5.

Osteoporosis. Mecasermin[1] and mecasermin rinfabate[2] have been investigated as stimulants of bone formation in osteoporosis (p. 1168.1). Some beneficial effects on bone density have been reported.

1. Grinspoon S, *et al.* Effects of recombinant human IGF-1 and oral contraceptive administration on bone density in anorexia nervosa. *J Clin Endocrinol Metab* 2002; **87:** 2883–91.
2. Boonen S, *et al.* Musculoskeletal effects of the recombinant human IGF-I/IGF binding protein-3 complex in osteoporotic patients with proximal femoral fracture: a double-blind, placebo-controlled pilot study. *J Clin Endocrinol Metab* 2002; **87:** 1593–9.

Adverse Effects and Precautions

Since the somatomedins are considered to be responsible for many of the actions of growth hormone similar adverse effects (see p. 1921.3) might be expected, and have been seen with mecasermin. Hypoglycaemia is common but symptoms can generally be avoided if mecasermin is given within 20 minutes of food. Tonsillar hypertrophy can develop; patients should be monitored for complications such as snoring, sleep apnoea, and chronic middle ear effusions. Thickening of the soft tissues of the face can also occur. Cardiomegaly and valvulopathy have been reported in a few patients. Although a relationship between cardiac changes and mecasermin therapy has not been confirmed, echocardiogram monitoring has been recommended. Injection site hypertrophy may occur, but can be avoided or resolved by proper rotation of injection sites. Cases of hypersensitivity, urticaria, pruritus, and erythema have also been reported.

Effects on the eyes. For concerns about an increased risk of retinopathy in diabetic patients receiving mecasermin, see under Diabetes Mellitus, p. 1929.2.

Intravenous administration. Syncope in the absence of hypoglycaemia has been reported in patients given mecasermin by intravenous bolus, accompanied in some cases by convulsions, asystole, bradycardia, hypotension, or dizziness.[1] Reports appear to have ceased since recommendations that mecasermin should not be given intravenously at rates greater than 24 micrograms/kg per hour. Arthralgia, nerve palsies, and hypophosphataemia and dyspnoea have been associated with high-dose intravenous bolus therapy.[2] Mecasermin is now given by subcutaneous injection (see Uses and Administration, p. 1929.2).

1. Maloczowski S, Stadel B. Risks and benefits of insulin-like growth factor. *Ann Intern Med* 1994; 121: 549.
2. Usala A-L. Risks and benefits of insulin-like growth factor. *Ann Intern Med* 1994; 121: 550.

Pharmacokinetics

After subcutaneous injection, mecasermin has a bioavailability of almost 100% in healthy subjects. In the circulation it is bound to 6 binding proteins, with more than 80% bound to binding protein 3 (IGFBP-3). However, IGFBP-3 is greatly reduced in patients with severe primary IGF-I deficiency, such that there is an increase in the clearance of mecasermin. Mecasermin is metabolised in the liver and the kidney, and has a terminal half-life of about 6 hours in children with severe primary IGF-I deficiency.

After subcutaneous injection of mecasermin rinfabate in children with severe primary IGF-I deficiency, the half-life of free IGF-I is prolonged to about 13 hours and IGFBP-3 has a half-life of about 54 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Increlex; ***Belg.***: Increlex; ***Cz.***: Increlex; ***Denm.***: Increlex†; ***Fr.***: Increlex; ***Ger.***: Increlex; ***Gr.***: Increlex; ***Irl.***: Increlex; ***Israel***: Increlex; ***Ital.***: Increlex; ***Neth.***: Increlex; ***Norw.***: Increlex; ***Pol.***: Increlex; ***Port.***: Increlex; ***Spain***: Increlex; ***Swed.***: Increlex; ***UK***: Increlex; ***USA***: Increlex.

Somatorelin *(rINN)* ⊗

GHRF; GHRH; GRF; GRF-44; Growth Hormone-releasing Factor (Human); Growth Hormone-releasing Hormone; Hormone de libération de l'hormone de croissance; Somatocrinina; Somatocrinine; Somatokrinin; Somatoliberin; Somatolibérine; Somatoliberyna; Somatorelíni; Somatorelina; Somatoreline; Somatorelinum; Wachstumshormon-Releasing-Hormon; Соматотропин-освобождающ Хормон; Соматорелин.

$C_{215}H_{358}N_{72}O_{66}$=5039.7

CAS — 83930-13-6.

ATC — V04CD05.

ATC Vet — QV04CD05.

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

Acetato de sermorelina; GRF(1-29)NH_2 (sermorelin); Growth Hormone-releasing Factor (Human)-(1-29)-peptide Amide (sermorelin); Sermorelina, acetato de; Sermoréline, Acétate de; Sermorelini Acetas; Серморелина Ацетат.

Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2 acetate hydrate.

$C_{149}H_{246}N_{44}O_{42}S.C_2H_4O_2.yH_2O$=3357.9 (sermorelin)

CAS — 86168-78-7 (sermorelin); 114466-38-5 (sermorelin acetate).

ATC — H01AC04; V04CD03.

ATC Vet — QH01AC04; QV04CD03.

UNII — 00IBG87IQW.

Uses and Administration

Somatorelin is a peptide, secreted by the hypothalamus, that promotes the release of growth hormone from the anterior pituitary. It exists as 44-, 40-, and 37-amino acid peptides; the 44-amino acid form may possibly be converted to the smaller forms but all are reported to be active, the activity residing in the first 29 amino acid residues. Sermorelin is a synthetic peptide corresponding to the 1–29 amino acid sequence of somatorelin.

Somatorelin acetate is used for the diagnosis of growth hormone deficiency. The usual dose is the equivalent of somatorelin 50 micrograms by intravenous injection, given after the patient has fasted. In highly overweight adults and in children, a dose of 1 microgram/kg is given. Plasma or serum concentrations of growth hormone are measured before the dose of somatorelin and usually 30 minutes after, but additional measurements may be taken at 15, 45, 60, and 90 minutes for a better assessment of growth hormone release. The test can distinguish between pituitary and hypothalamic disorders but is not suitable as a screening test for growth hormone deficiencies.

Sermorelin acetate has been used similarly for the diagnosis of growth hormone deficiency. It has also been used for the treatment of growth retardation in children with growth hormone deficiency (see below).

Sermorelin has also been tried as an adjunct to gonadotrophin therapy in the induction of ovulation and has been investigated in the treatment of HIV-associated wasting.

Diagnostic use. Somatorelin (in its 40- or 44-amino acid forms) has been used in the assessment of growth hormone deficiency.[1-3] It has usually been given as a single intravenous injection in doses of 1 microgram/kg or total doses of up to 200 micrograms. Subsequent normal or exaggerated increases in serum-growth hormone concentrations have occurred in healthy subjects,[1,2] and in patients with hypothalamic tumours[3] or acromegaly,[2] but not in patients with hypopituitarism.[2] A synthetic 29-amino-acid sequence of somatorelin, sermorelin acetate has also been used for the diagnosis of growth hormone deficiency. However, it has been suggested that the test is not useful for screening as it does not test the hypothalamic-pituitary axis, and that it should not be used in routine clinical practice.[4] The use of sermorelin with the synthetic hexapeptide growth-hormone-releasing peptide-6 has also been reported.[5,6]

1. Thorner MO, *et al.* Human pancreatic growth-hormone-releasing factor selectively stimulates growth-hormone secretion in man. *Lancet* 1983; i: 24–8. Correction. *ibid.*: 256.
2. Wood SM, *et al.* Abnormalities of growth hormone release in response to human pancreatic growth hormone releasing factor (GRF (1-44)) in acromegaly and hypopituitarism. *BMJ* 1983; 286: 1687–91.
3. Grossman A, *et al.* Growth-hormone-releasing factor in growth hormone deficiency: demonstration of a hypothalamic defect in growth hormone release. *Lancet* 1983; ii: 137–8.
4. Hindmarsh PC, Swift PGF. An assessment of growth hormone provocation tests. *Arch Dis Child* 1995; 72: 362–8.
5. Popovic V, *et al.* GH-releasing hormone and GH-releasing peptide-6 for diagnostic testing in GH-deficient adults. *Lancet* 2000; 356: 1137–42.
6. Leal A, *et al.* A single growth hormone (GH) determination is sufficient for the diagnosis of GH-deficiency in adult patients using the growth hormone releasing hormone plus growth hormone releasing peptide-6 test. *Clin Endocrinol (Oxf)* 2002; 57: 377–84.

Growth retardation. Sermorelin has been studied in children with growth hormone deficiency (p. 1918.3), usually in doses of 30 micrograms/kg subcutaneously daily. Although there have been reports of improved growth rates,[1-3] there are few direct comparisons with growth hormone. One large study[4] of sermorelin found that, compared with results generally reported for growth hormone therapy, fewer patients responded over a 12-month period and growth responses were poorer.

1. Neyzi O, *et al.* Growth response to growth hormone-releasing hormone (1—29)-NH_2 compared with growth hormone. *Acta Paediatr Suppl* 1993; 388: 16–21.
2. Lanes R, *et al.* Long term therapy with a single daily subcutaneous dose of growth hormone releasing hormone (1-29) in prepubertal growth hormone deficient children. *J Pediatr Endocrinol* 1994; 7: 303–8.
3. Ogilvy-Stuart AL, *et al.* Treatment of radiation-induced growth hormone deficiency with growth hormone-releasing hormone. *Clin Endocrinol (Oxf)* 1997; 46: 571–8.
4. Thorner M, *et al.* Once daily subcutaneous growth hormone-releasing hormone therapy accelerates growth in growth hormone-deficient children during the first year of therapy. *J Clin Endocrinol Metab* 1996; 81: 1189–96.

Lipodystrophy. In a placebo-controlled study[1] of 31 men with HIV-related lipodystrophy, insulin-like growth factor I (IGF-I) concentrations and body composition measures were improved in those given sermorelin 1 mg twice daily subcutaneously for 12 weeks.

1. Koutkia P, *et al.* Growth hormone-releasing hormone in HIV-infected men with lipodystrophy: a randomized controlled trial. *JAMA* 2004; 292: 210–18.

Adverse Effects and Precautions

Adverse effects of somatorelin acetate injection fo diagnostic use include a transient sense of warmth c flushing of the head, neck, and upper body. There may als be taste and smell disturbances. Similar effects have bee reported with sermorelin, as well as pain at the injectio site, headache, nausea and vomiting, and tightness in th chest. Antibodies to somatorelin often develop on repeate use of sermorelin.

Uncontrolled thyroid disorders, obesity, hyperglycaemia, or elevated plasma fatty acids may impair response t somatorelin or sermorelin. Sermorelin should also be use with care in patients with epilepsy. Sermorelin should nc be used to treat growth retardation in children whos growth hormone response to stimulation tests is inadequate. Treatment should cease once the epiphyses have closed.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) an the Porphyria Centre Sweden, classifies sermorelin fo diagnostic use as not porphyrinogenic; it may be used as 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 24/10/11)

Interactions

Drugs that affect the secretion of growth hormone ma interfere with the diagnostic efficacy of somatorelin o sermorelin; these include growth hormone itself (whic should be stopped at least 1 week before testing, somatostatin and its analogues, insulin, corticosteroids, and cyclo-oxygenase inhibitors such as aspirin an indometacin. Growth hormone concentrations may b raised by clonidine and levodopa. The response t somatorelin or sermorelin may also be reduced b antimuscarinic drugs such as atropine, and by antithyroi drugs such as propylthiouracil.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: GHRH; ***Fr.***: Stimu-GH; ***Ger.***: GHRH; ***Gr.***: Esfarase; Geref; ***Irl.***: Geref†; ***Ital.***: Geref; GHRH; ***Neth.***: GHRH; ***Spain***: GHRH; ***Switz.***: GHRH; ***UK***: GHRH; ***USA***: Geref†.

Somatostatin *(BAN, rINN)*

GH-RIF; GHRIH; Growth-hormone-release-inhibiting Hormone; Somatostatiini; Somatostatina; Somatostatinas; Somatostatine; Somatostatinum; Somatostatyna; Somatotrophin release-inhibiting Factor; Szomatosztatin; Соматостатин.

Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys cyclic (3→14) disulphide.

$C_{76}H_{104}N_{18}O_{19}S_2$=1637.9

CAS — 38916-34-6.

ATC — H01CB01.

ATC Vet — QH01CB01.

UNII — 6E20216Q0L.

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

Ph. Eur. 8: (Somatostatin). A cyclic tetradecapeptide havin the structure of the hypothalamic hormone that inhibits th release of human growth hormone. It is produced b chemical synthesis and contains not more than 15% w/w c acetic acid. A white amorphous powder. Freely soluble i water and in acetic acid; practically insoluble i dichloromethane. Store in airtight containers at temperature of 2 degrees to 8 degrees. Protect from ligh and moisture.

Somatostatin Acetate *(BANM, rINNM)*

Acetato de somatostatina; Somatostatiiniasetaatti; Somatostatin Asetat; Somatostatinacetat; Somatostatine, Acétate de Somatostatini Acetas; Соматостатина Ацетат.

ATC — H01CB01.

ATC Vet — QH01CB01.

Uses and Administration

Somatostatin is a polypeptide obtained from the hypothalamus or by synthesis. The naturally occurring form has cyclic structure. Although somatostatin derived from th hypothalamus is a 14-amino-acid peptide, a longer, 28-amino-acid form also exists in some tissues. Five differen receptors for somatostatin have been identified. Somatostatin inhibits the release of growth hormone (p. 1919.3) from the anterior pituitary. It also inhibits the release of thyrotrophin (p. 2346.1) and corticotropin (p. 1628.3) fror the pituitary, glucagon and insulin from the pancreas, an appears to have a role in the regulation of duodenal an

gastric secretions. In the CNS it appears to play a role in the perception of pain.

It has been tried in a variety of disorders such as upper gastrointestinal haemorrhage including variceal haemorrhage (see under Monoethanolamine, p. 2563.1), insulin resistance, and the management of hormone-secreting tumours and other hypersecretory disorders. However, it has a very short duration of action and several analogues of somatostatin have been produced in an attempt to prolong its activity as well as making its inhibitory effects more specific. Octreotide (p. 1924.1) and lanreotide (p. 1923.2) are such analogues.

Somatostatin is usually given as the acetate. In the treatment of gastrointestinal haemorrhage, such as acute bleeding from oesophageal varices, somatostatin acetate equivalent to somatostatin 250 micrograms has been given by intravenous bolus over 3 to 5 minutes, followed by a continuous infusion of 250 micrograms/hour (about 3.5 micrograms/kg per hour) until the bleeding has stopped, which is usually within 12 to 24 hours. The infusion may then be continued for a further 48 to 72 hours to prevent recurrent bleeding. In some cases, the infusion may be continued to a maximum of 120 hours.

Malignant neoplasms. Somatostatin given with melatonin, bromocriptine, and a solution of retinoids (the Di Bella regimen) was ineffective in the treatment of advanced malignancies (see Malignant Neoplasms, under Uses and Administration of Octreotide, p. 1926.2).

Adverse Effects and Precautions

Abdominal discomfort, flushing, nausea, and bradycardia have been associated with too rapid infusion. Because of the short half-life of somatostatin adverse effects are generally transitory on stopping or reducing the infusion. Giving with parenteral nutrition has been suggested because of the inhibitory effects of somatostatin on intestinal absorption; blood glucose should be monitored since somatostatin may interfere with the secretion of insulin and glucagon. Allergic reactions have also been reported.

Effects on the kidneys. Somatostatin has been reported to have an inhibitory effect on renal function[1,2] and severe water retention and hyponatraemia have been reported.[3]

1. Walker BJ, *et al.* Somatostatin and water excretion. *Lancet* 1983; i: 1101–2.
2. Vora JP, *et al.* Effect of somatostatin on renal function. *BMJ* 1986; 292: 1701–2.
3. Halmo C, *et al.* Life-threatening water intoxication during somatostatin therapy. *Ann Intern Med* 1987; 107: 518–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Somatin; *Braz.*: Stilamin; *Canad.*: Stilamin†; *China*: Etaxene (忆太欣); Hening (赫宁); Lizhixue (丽枝雪); Modustatine (赛得); Shishitai (时士太); Stilamin (思他宁); *Fr.*: Modustatine†; *Gr.*: Atostan; Eklivan; Sadolin; Somabion; Somargen; Somaritin; Somastin; Sonafrine; Stilamin; *Hong Kong*: Stilamin; *India*: Ikestatina; Somastin; Stilamin; *Indon.*: Stilamin; *Ital.*: Etaxene; Ikestatina; Modustatina; Nastoren; Resurmide; Stilamin; *Malaysia*: Stilamin; *S.Afr.*: Stilamin; *Singapore*: Stilamin; *Spain*: Somonal†; *Switz.*: Stilamin; *Thai.*: Etaxene†; Stilamin; *Turk.*: Somatosan; Stilamin†; *Venez.*: Ikestatina; Stilamin.

Tesamorelin Acetate *(USAN, rINNM)*

Acetato de tesamorelina; Tésamoréline, Acétate de; Tesamorelini Acetas; TH-9507; Тезаморелина Ацетат.

(3*E*)-Hex-3-enoylsomatoliberin (human) acetate.

$C_{221}H_{366}N_{72}O_{67}S.xC_2H_4O_2$=5135.9 (tesamorelin).

CAS — 901758-09-6.

UNII — LGW5H38VE3.

Uses and Administration

Tesamorelin is a synthetic analogue of somatorelin (p. 1930.1) used for the reduction of excess abdominal fat in HIV-associated lipodystrophy. It is given subcutaneously as the acetate in a dose equivalent to 2 mg of tesamorelin daily.

References.

1. Falutz J, *et al.* Metabolic effects of a growth hormone-releasing factor in patients with HIV. *N Engl J Med* 2007; 357: 2359–70.
2. Falutz J, *et al.* Effects of tesamorelin, a growth hormone-releasing factor, in HIV-infected patients with abdominal fat accumulation: a randomized placebo-controlled trial with a safety extension. *J Acquir Immune Defic Syndr* 2010; 53: 311–22.
3. Falutz J, *et al.* Effects of tesamorelin (TH9507), a growth hormone-releasing factor analog, in human immunodeficiency virus-infected patients with excess abdominal fat: a pooled analysis of two multicenter, double-blind placebo-controlled phase 3 trials with safety extension data. *J Clin Endocrinol Metab* 2010; 95: 4291–4304.
4. Dhillon S. Tesamorelin: a review of its use in the management of HIV-associated lipodystrophy. *Drugs* 2011; 71: 1071–91.
5. Spooner LM, Olin JL. Tesamorelin: a growth hormone-releasing factor analogue for HIV-associated lipodystrophy. *Ann Pharmacother* 2012; 46: 240–7.
6. Stanley TL, *et al.* Reduction in visceral adiposity is associated with an improved metabolic profile in HIV-infected patients receiving tesamorelin. *Clin Infect Dis* 2012; 54: 1642–51.

Adverse Effects and Precautions

Tesamorelin may cause hypersensitivity reactions such as rash and urticaria and adverse effects associated with released growth hormone such as arthralgia, extremity pain, peripheral oedema, hyperglycaemia, and carpal tunnel syndrome may occur. Additionally, injection site reactions can include erythema, pruritus, pain, urticaria, irritation, swelling, and haemorrhage.

Tesamorelin is contra-indicated in active malignancy and any pre-existing malignancy should be inactive and treatment complete before starting tesamorelin. It is also contra-indicated in patients with disruption of the hypothalamic-pituitary axis due to hypophysectomy, hypopituitarism, pituitary tumour or surgery, head irradiation, or head trauma. Tesamorelin is contra-indicated in pregnancy.

Insulin-like growth factor I should be monitored and tesamorelin stopped if the former becomes persistently elevated. Impaired glucose metabolism has been reported and therefore also requires monitoring. Stopping tesamorelin should be considered in the event of critical illness.

References.

1. Falutz J, *et al.* Long-term safety and effects of tesamorelin, a growth hormone-releasing factor analogue, in HIV patients with abdominal fat accumulation. *AIDS* 2008; 22: 1719–28.

Interactions

Since tesamorelin stimulates growth hormone production, they may have similar interactions (see p. 1923.1).

Pharmacokinetics

The absolute bioavailability of tesamorelin after a 2-mg subcutaneous dose was less than 4% in healthy adults. The mean elimination half-life of tesamorelin was 26 minutes in healthy subjects and 38 minutes in HIV-infected patients.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Egrifta.

Vapreotide *(BAN, USAN, rINN)*

BMY-41606; RC-160; Vapreotida; Vapréotide; Vapreotidum; Вапреотид.

D-Phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-tryptophanamide cyclic (2→7)-disulfide.

$C_{57}H_{70}N_{12}O_9S_2$=1131.4

CAS — 103222-11-3.

ATC — H01CB04.

ATC Vet — QH01CB04.

UNII — 2PK59M9GFF.

Vapreotide Acetate *(BANM, USAN, rINNM)*

Acetato de vapreotida; BMY-41606; DP-05-094; RC-160; Vapréotide, Acétate de; Vapreotidi Acetas; Вапреотида Ацетат.

D-Phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-tryptophanamide cyclic (2→7)-disulfide acetate salt (1:*n*).

$C_{57}H_{70}N_{12}O_9S_2.nC_2H_4O_2$

CAS — 849479-74-9.

ATC — H01CB04.

ATC Vet — QH01CB04.

UNII — 5562377HFV.

NOTE. The names Docrised, Octastatin, and Sanvar have been used as trade marks for vapreotide acetate.

Profile

Vapreotide is a somatostatin analogue similar to octreotide (p. 1924.1). It has been investigated in the management of various disorders, including bleeding oesophageal varices, gastrointestinal and pancreatic fistulas, acromegaly, carcinoid tumours, and for the prevention of postoperative complications after pancreatic surgery.

References.

1. Eriksson B, *et al.* The use of new somatostatin analogues, lanreotide and octastatin, in neuroendocrine gastro-intestinal tumours. *Digestion* 1996; 57 (suppl 1): 77–80.
2. Calès P, *et al.* Early administration of vapreotide for variceal bleeding in patients with cirrhosis. *N Engl J Med* 2001; 344: 23–8.
3. Anonymous. Vapreotide: BMY 41606, RC 160, Sanvar. *Drugs R D* 2003; 4: 326–30.
4. Fortune BE, *et al.* Vapreotide: a somatostatin analog for the treatment of acute variceal bleeding. *Expert Opin Pharmacother* 2009; 10: 2337–42.

Immunosuppressants

Asthma, p. 1932
Blood disorders, p. 1932
Diabetes mellitus, p. 1932
Gastrointestinal disorders, p. 1932
Inflammatory bowel disease, p. 1932
Liver disorders, p. 1932
Lung disorders, p. 1932
Interstitial lung disease, p. 1932
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Ocular disorders, p. 1932
Organ and tissue transplantation, p. 1932
Corneal transplantation, p. 1933
Haematopoietic stem cell transplantation, p. 1933
Heart transplantation, p. 1934
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Kidney transplantation, p. 1935
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Lung transplantation, p. 1937
Pancreatic transplantation, p. 1938
Renal disorders, p. 1938
Rheumatoid arthritis, p. 1938
Sarcoidosis, p. 1938
Scleroderma, p. 1938
Skin and connective tissue disorders, p. 1939

The compounds described in this chapter are used in diseases considered to have an auto-immune component, and in organ and tissue transplantation. Some other important drugs used for their immunosuppressant properties are described under Antineoplastics, p. 691.1 and Corticosteroids, p. 1597.1. The choice of an immunosuppressant is discussed below.

Choice of Immunosuppressant

Asthma

Immunosuppressant drugs do not play a role in the regular management of asthma (p. 1195.2). In individual patients requiring oral corticosteroids for chronic severe asthma immunosuppressants have however been investigated for their anti-inflammatory and corticosteroid-sparing properties.

Blood disorders

For the use of immunosuppressants in aplastic anaemia, see p. 1121.3.

Diabetes mellitus

For mention of the use of immunosuppressants in recent-onset type 1 diabetes, see Prevention of Diabetes Mellitus, p. 460.3. See also Pancreatic Transplantation, p. 1938.1.

Gastrointestinal disorders

Inflammatory bowel disease. A number of immunosuppressants have been tried in inflammatory bowel disease (p. 1808.3), with some success, but the mainstays of drug therapy remain the aminosalicylates and the corticosteroids. Immunosuppressants may be valuable in some circumstances for their corticosteroid-sparing effect and for chronic active disease refractory to other treatments.

Liver disorders

For a discussion of the role of immunosuppressants, and particularly azathioprine, in the management of chronic active hepatitis, see p. 1602.3. For the use of immunosuppressants in primary biliary cirrhosis see under Ursodeoxycholic Acid, p. 2638.3.

Lung disorders

Interstitial lung disease. Corticosteroids have been used with azathioprine (or occasionally cyclophosphamide), for the treatment of various forms of interstitial lung disease (p. 1607.1).

Neurological disorders

Multiple sclerosis. Immunosuppressants have been tried in the treatment of multiple sclerosis (p. 996.3), although in some studies the benefit obtained may have been outweighed by toxicity.

Myasthenia gravis. Patients with myasthenia gravis (p. 684.1) who require immunosuppression are usually treated with corticosteroids. Other immunosuppressants such as azathioprine, ciclosporin, mycophenolate mofetil, and tacrolimus have been tried mainly for their corticosteroid-sparing effect but may also be of use when corticosteroids are contra-indicated or when response to their use alone is insufficient.

Ocular disorders

Immunosuppressants have been used with some success in ocular disorders with inflammatory or immunological components. In *scleritis* and *uveitis* (see p. 1612.3 and p. 1615.1) corticosteroids, given topically, intra-ocularly, or systemically are widely used when treatment is needed, but in unresponsive disease, or in patients with unacceptable adverse effects, immunosuppressants such as azathioprine, ciclosporin, or mycophenolate mofetil, may be given. Daclizumab, leflunomide, sirolimus, and tacrolimus have also been tried in uveitis. Immunosuppressants may be valuable in the management of *Behçet's disease*, *rheumatoid arthritis*, or *Wegener's granulomatosis*, (see p. 1601.1, p. 13.2, and p. 1615.2, respectively), including their associated ocular lesions. Ciclosporin or azathioprine have been used with corticosteroids in the management of both ocular and vascular symptoms of *Cogan's syndrome* (p. 1603.2). Ciclosporin has also been used topically in corneal ulceration, see p. 1947.1.

Ciclosporin or methotrexate may be options in the treatment of *Graves' ophthalmopathy* (see under Hyperthyroidism, p. 2332.2).

Reviews.

1. McCluskey PJ, *et al.* Management of chronic uveitis. *BMJ* 2000; **320**: 555–8.
2. Jabs DA, *et al.* Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol* 2000; **130**: 492–513.
3. Kulkarni P. Review: uveitis and immunosuppressive drugs. *J Ocul Pharmacol Ther* 2001; **17**: 181–7.
4. Dunn JP. Review of immunosuppressive drug therapy in uveitis. *Curr Opin Ophthalmol* 2004; **15**: 293–8.
5. Hemady RK, *et al.* Immunosuppressive agents and nonsteroidal anti-inflammatory drugs for ocular immune and inflammatory disorders. *Ophthalmol Clin North Am* 2005; **18**: 511–28.
6. Jap A, Chee S-P. Immunosuppressive therapy for ocular diseases. *Curr Opin Ophthalmol* 2008; **19**: 535–40.

Organ and tissue transplantation

Although surgical techniques suitable for the removal of organs and tissues from a donor, and their engraftment into a host, have existed for many years, such grafts would not normally survive for long. The host's CD4+ T-cells recognise foreign antigens from donor cells. A CD4+ cell is then activated by antigen-presenting cells to secrete interleukin-2 and induce T-cell proliferation. Activated T-cells mediate a rejection response, by increasing the activity and function of B-cells, cytotoxic CD8+ T-cells, and macrophages, either directly, or by cytokine release. Only from the 1960s with the development of drugs capable of attenuating or suppressing this response, did transplantation start to become a feasible mode of treatment.

The drugs available vary in their mechanisms of action, and are often combined for optimum effect. **Corticosteroids** (glucocorticoids) act at several points in the immune cascade, including antigen recognition and production of lymphokines. The **calcineurin inhibitors** ciclosporin and tacrolimus prevent formation of cytotoxic T-cells by inhibiting calcineurin activation, an important step in the release of interleukin-2 from helper T-cells, while polyclonal or monoclonal **antibodies** such as antilymphocyte immunoglobulins and muromonab-CD3 bind to and deplete T-cell populations. Basiliximab and daclizumab function as **interleukin-2 receptor antagonists**. **Antiproliferative drugs** such as azathioprine and mycophenolate mofetil act by preventing cell division of lymphocytes. Sirolimus and everolimus are **proliferation signal inhibitors** that inhibit the T-cell response to cytokines.

Immunosuppressant regimens may be divided into those aimed at:

- prevention of rejection in the early period after transplantation
- long-term maintenance prophylaxis
- treatment of acute episodes of rejection.

In haematopoietic stem cell transplantation, where an immunologically competent tissue is transplanted, it is the donor cells which attack host tissues (graft-versus-host disease), and immunosuppression is required for prophylaxis of this condition.

Because of the critical nature of the early stage, when the organ or tissue must recover normal function, and perhaps to permit better long-term tolerance, initial immunosuppressant regimens tend to use higher doses than maintenance therapy. Standard protocols are usually based around ciclosporin or tacrolimus, combined with corticosteroids and an anti-proliferative agent (triple therapy). Where appropriate, a course of monoclonal or polyclonal antibodies is added to the standard regimen for induction (quadruple therapy). This is usually only required in individuals at increased risk of acute rejection, such as children or patients with a previous transplant or pregnancy, multiple blood transfusions, or a poor HLA-matching. However, it also enables delayed introduction of ciclosporin or tacrolimus in patients at risk of nephrotoxicity, and the use of low-dose regimens, allowing for withdrawal of corticosteroids.

No one immunosuppressive regimen has been identified as being superior to others in pregnancy, and although there are known theoretical risks to mother and fetus, successful pregnancies are now common in transplant recipients. The incidence of structural malformation has not been noted to be increased compared with the general population, but newer regimens have yet to be evaluated.

Since immunosuppressant therapy must in most cases be given for the lifetime of the graft, in long-term maintenance the toxicity of the drugs used, and the risks of infection, neoplasia, post-transplant diabetes mellitus, gout, hyperlipidaemia, and osteoporosis, must be considered. Doses and numbers of drugs used tend to be reduced, and in particular there is a tendency to taper or even eliminate the doses of corticosteroids used in maintenance regimens because of the potential sequelae of prolonged corticosteroid use. Post-transplant cardiovascular disease is a leading cause of death and graft loss. The risk varies between types of transplant, and specific recommendations for prophylaxis may differ.

The use of less intensive maintenance regimens must be balanced against the risk of an acute rejection episode, and the likelihood of its responding to therapy. High-dose corticosteroids and polyclonal or monoclonal antibodies often play a role in the rescue therapy of patients with acute rejection episodes, although much depends upon the severity of the reaction, and whether such episodes have occurred previously.

The management of immunosuppression for the transplantation of particular organs is discussed in more detail below. With the use of suitable immunosuppressant regimens long-term graft survival can be obtained after transplantation. Ultimately, however, the complications of chronic rejection are likely to lead to loss of the graft: the induction of specific tolerance to the donor organ remains the goal of much research. In allogeneic haematopoietic stem cell transplantation, where the aim of immunosuppression is prevention of graft-versus-host disease rather than rejection, immunosuppressant therapy can often be tapered off and eventually withdrawn.

Much interest has been aroused by the possibility of organ transplants from *animals* genetically modified to reduce complement-mediated hyperacute rejection. It is not clear whether such xenotransplantation will require modified immunosuppressive regimens.

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Corneal transplantation. For reference to the use of immunosuppressants to treat graft rejection after corneal transplant see Corneal Graft Rejection, p. 1603.3.

Haematopoietic stem cell transplantation. Haematopoietic stem cell transplantation (HSCT) is used in the treatment of a variety of malignancies, notably leukaemias and lymphomas; to permit the use of very high-dose chemotherapy in the management of some solid tumours (bone marrow rescue); and to treat some other serious disorders affecting the bone marrow, such as aplastic anaemia and the haemoglobinopathies.[1,2]

HSCT may be **autologous**, in which case the patient's own stem cells are harvested or **allogeneic**, where stem cells are harvested from a healthy donor matched as closely as possible for HLA type.[3,4] The haematopoietic stem cells themselves may be derived from:

- bone marrow (classical bone marrow transplantation, BMT)
- peripheral blood (peripheral blood stem cell transplantation, PBSCT)
- umbilical cord blood

PBSCT is convenient as collection does not require hospitalisation or general anaesthesia for the donor, and clinical studies have shown more rapid engraftment of neutrophils and platelets compared with BMT.[2,5-7] However, allogeneic PBSCT appears to increase the risk of graft-versus-host disease[1,2,6-10] (see below). Allogeneic PBSCT was associated with decreased relapse rates and improved disease-free survival but similar overall survival in adults, when compared with BMT.[6] However, in children, allogeneic PBSCT was associated with higher mortality and treatment failure than BMT although relapse rates were similar; advanced disease status and use of colony-stimulating factor were also associated with poorer outcome.[7] Use of umbilical cord blood is associated with slightly delayed engraftment,[2,11-13] and hence, perhaps, an increased risk of fatal infection,[2,11] but a lower risk[2,12,14] of graft-versus-host disease (see below). A meta-analysis[15] confirmed these findings, but found a similar relapse rate, and equivalent survival for cord blood transplantation compared with unrelated BMT. It has mainly been used for transplants in children, since the total number of stem cells in a donation often falls short of the levels deemed necessary for engraftment in an adult.[1,2,5,13] However, cord blood is increasingly used for transplants in adults.[16] Since cell dose correlated with outcome in most studies, strategies have been developed to increase progenitor cell numbers in the cord blood units; techniques include pooled or sequential cord blood transplantation, or expansion of the cord blood cells with cytokines. Combination cord blood and bone marrow transplants, and reduced intensity regimens are under investigation.[16-18]

With autologous HSCT problems of **compatibility** do not arise, but if abnormal cell clones are present in the marrow (as in leukaemia) or stem cells they may be transferred back into the patient and cause disease relapse.[1] Allogeneic HSCT requires immunosuppression for about 6 months[19] to prevent graft-versus-host disease (see below) until a new immunological balance is achieved.

The patient is normally prepared by **conditioning** with total body irradiation, or myeloablative chemotherapy with drugs such as cyclophosphamide or busulfan, or more often both, in order to destroy host bone marrow cells.[5,20] In autologous procedures, harvesting of bone marrow or peripheral blood must be carried out before conditioning. Bone marrow is aspirated from the donor, and infused into the recipient via an indwelling catheter or directly into a peripheral vein. Peripheral blood stem cells are collected by cell separation after mobilisation, which is best achieved by a combination of chemotherapy and granulocyte or granulocyte-macrophage colony-stimulating factor.[1,2,5] Infection is a major cause of morbidity and mortality after transplantation, so prophylactic cover with antimicrobials[2,21,22] and normal immunoglobulins has been recommended,[21] although the value of the latter has been questioned.[23] A subsequent systematic review[24] found no advantage for immunoglobulin prophylaxis in terms of survival or infection prevention; they increased the risk for veno-occlusive disease (VOD), but decreased the rate of interstitial pneumonitis. The authors concluded the evidence did not support the routine use of immunoglobulin prophylaxis for HSCT. Granulocyte colony-stimulating factors are sometimes used after allogeneic transplants to hasten haematopoietic recovery. While a meta-analysis found no evidence for an increase in risk for acute or chronic graft-versus-host disease,[25] a large study found delayed platelet engraftment, increased graft-versus-host disease, and increased mortality in those given growth factors after allogeneic bone marrow transplants; these effects were not seen in patients given allogeneic PBSCT.[26]

In addition to such supportive care, patients who have received allogeneic transplants require immunosuppressive therapy aimed at the prevention of **graft-versus-host disease** (GVHD). GVHD is usually characterised as *acute* or *chronic* depending on the manifestations, and the time of presentation[1,4,5,10,27-30] (by convention acute disease occurs within a hundred days of transplantation, and chronic disease after this time, although in practice there is considerable overlap).

The organ systems mainly affected are skin, liver, lung, and gastrointestinal tract. Both forms are marked by maculopapular rashes, which in severe disease may progress to bullous lesions and epidermal necrolysis. Liver disease may include cholestatic jaundice (usually in the acute form) and hepatitis; symptoms may need to be distinguished from the VOD which sometimes complicates bone marrow transplantation and is due to the pre-transplant conditioning regimen (VOD may respond to treatment with antithrombin III[31] or defibrotide[32,33]). Ursodeoxycholic acid has been found to be of benefit for the prophylaxis of hepatic complications.[34] The main symptom of gastrointestinal GVHD is diarrhoea, often severe and painful. In patients with chronic GVHD other manifestations may include arthritis, mucositis, lung disease (bronchiolitis *obliterans*), and scleroderma.

Most modern regimens for the *prophylaxis* of GVHD after allogeneic HSCT are based on ciclosporin. Although GVHD still occurs in many ciclosporin-treated patients, morbidity is much reduced and survival improved. Combination regimens have been tried for prophylaxis, particularly ciclosporin or tacrolimus with methotrexate, but also combinations with other drugs including antilymphocyte immunoglobulins, corticosteroids, mycophenolate mofetil, and sirolimus.[9,19,35] After allogeneic myeloablative HSCT, adding corticosteroids to the prophylactic regimen has been found to reduce the incidence of moderately severe acute GVHD, but no benefit has been noted for survival.[36] Monoclonal antibodies have been used to produce T-cell depletion or reduce the effects of circulating cytokines,[9,28] and it has been suggested that RNA interference may have a potential role.[37]

Acute GVHD is usually *treated* mainly by the addition of corticosteroids (usually methylprednisolone) to the existing regimen until symptoms are controlled, followed by gradual tapering of the dose. Mycophenolate mofetil, antilymphocyte immunoglobulins, interleukin-2 receptor antibodies, etanercept, and infliximab have also been tried.[2,9,19,38-40] PUVA therapy and extracorporeal photopheresis have been used[2,9,30] and infusion of mesenchymal stem cells is also under investigation.[9,30,41]

Chronic GVHD has no specific standard therapy; most centres use a combination of corticosteroids and a calcineurin inhibitor (ciclosporin or tacrolimus).[2,10,19,30,42,43] Drugs that have been tried for salvage therapy include mycophenolate mofetil, sirolimus, daclizumab, thalidomide, pentostatin, etanercept, infliximab, and rituximab.[10,19,39,42] PUVA therapy with extracorporeal photopheresis has also been used, with good response rates,[10,42] and recommendations for use have been published in the UK.[44] Mesenchymal stem cell infusion may be a potential therapy.[10] Octreotide is recommended for the symptomatic treatment of diarrhoea.[45]

Donor T-cells reactive to recipient minor histocompatibility antigens can inhibit the growth of abnormal cells, and may also target aberrantly expressed proteins, provoking a 'graft-versus-tumour' effect, which reduces relapse, both after allogeneic transplantation and among patients in whom GVHD develops.[1] Indeed, many leukaemia patients who relapse after allogeneic transplant can be reinduced into remission by an additional infusion of donor lymphocytes.[2] Consequently, too effective an immunosuppressant regimen may not always be desirable, and leukaemic patients given bone marrow transplants purged of T-cells, which virtually abolishes GVHD, do not have a better survival rate than those given conventional prophylaxis (engraftment too is reduced in the absence of all T-cells). Specific donor marrow T-cell depletion has been investigated as the sole form of GVHD prophylaxis.[46] In a multicentre randomised study, marrow T-cell depletion was found to reduce but not abolish the incidence of acute GVHD, accelerate neutrophil recovery and reduce toxicity compared with transplantation with T-cell replete marrow; however, disease-free survival at 3 years did not differ due to higher rates of relapse in some patients, and a higher incidence of serious infection in T-cell depleted marrow recipients.[47] The observation of graft-versus-malignancy effects has led to the development of low-dose non-myeloablative conditioning regimens (with or without donor lymphocyte infusions) for elderly or more sensitive patients who might have been unable to receive the standard aggressive therapy.[1-3,15,48-52] Fludarabine is commonly used in reduced-intensity conditioning regimens, often combined with other drugs such as busulfan or melphalan, or with low-dose total body irradiation.[53] Safety and efficacy of these reduced-intensity regimens has led to wider application;[1] however, the lower mortality rate may be offset by a higher relapse rate,[1] and poor engraftment.[2]

An uncommon complication of HSCT is **transplantation-associated thrombotic microangiopathy** which is a thrombotic thrombocytopenic purpura that presents as a microangiopathic haemolytic anaemia. Calcineurin inhibitors have been linked to its development, and initial treatment involves replacing ciclosporin or tacrolimus with alternative immunosuppressants. Improvement has been reported when daclizumab has replaced a calcineurin inhibitor; defibrotide and rituximab have also been used in small numbers of patients.[54]

The combination of irradiation, chemotherapy, and immunosuppression can cause the development of **secondary malignancies** in long-term survivors of HSCT.[1,55-58]

Intracoronary injection of haematopoietic stem cells into the heart is under investigation for cardiac disease,[59] **intramuscular** injection has also been investigated in peripheral vascular disease.[60] There is also interest in HSCT in some auto-immune disorders.[60]

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Heart transplantation. Marked improvements have been seen in the outcome of heart transplantation since the introduction of ciclosporin, which has resulted in a reduced incidence and severity of rejection episodes.[1] The 1-year survival rate is about 80%.[1,2]

A common **immunosuppressive regimen** consists of triple therapy with ciclosporin or tacrolimus, azathioprine or mycophenolate, and corticosteroids.[3–6] Some centres also use induction therapy with antilymphocyte immunoglobulins (polyclonal antibodies) or muromonab-CD3.[4,7]

Induction therapy increases the risk of infection and lymphoproliferative disorders, but does delay the first rejection episode and allows transplantation in higher risk groups. It also enables calcineurin inhibitor use to be delayed in patients with initial poor renal function[7] and corticosteroids to be stopped as maintenance therapy in some groups of patients.[8] Muromonab-CD3 may be associated with a higher incidence of adverse reactions than polyclonal antibodies. Sensitisation to muromonab-CD3 is strongly associated with vascular rejection, and this and the dose-related propensity for lymphoproliferative disease with muromonab-CD3 have led to a decline in its use; some consider it should be abandoned in favour of polyclonal preparations.[7,9] The interleukin-2 receptor antibodies basiliximab and daclizumab have also been used for induction therapy.[2,7,10,11] However, daclizumab use has been associated with an increased risk of death due to infection, mostly in patients given additional immunosuppressive treatment with antilymphocyte drugs for early postoperative complications.[11] The interleukin-2 receptor antibodies have not as yet been associated with an additional risk of malignancies.[7] Alemtuzumab is under investigation for induction therapy in heart transplantation.[7,9]

There does not seem to be any great clinical benefit of tacrolimus over ciclosporin in heart transplant patients,[9,12,13] although some have reported reduced rates of histological rejection,[14,15] and there is evidence that patients of Afro-Caribbean origin in particular may be more prone to acute rejection with ciclosporin than with tacrolimus.[16] It has been suggested that tacrolimus be substituted for ciclosporin in those patients suffering persistent rejection, or adverse effects associated with ciclosporin,[17] or with hyperlipidaemia or hypertension.[18] Microemulsifying ciclosporin may be associated with less rejection than the oil-based formulation.[19]

The use of mycophenolate mofetil instead of azathioprine in triple therapy has been shown to reduce mortality and rejection in the first year after heart transplantation,[20] and a retrospective review[21] concluded that the advent of mycophenolate mofetil has contributed to improved survival in cardiac transplant recipients. Although lower mycophenolic acid (MPA) concentrations may be associated with an increased allograft rejection,[22] there appears to be no benefit in monitoring MPA concentrations beyond the first year in heart transplant recipients,[23] and MPA levels may be affected by concomitant immunosuppression, see Immunosuppressants under Interactions of Mycophenolate, p. 1964.2.

Many variations of regimens exist, and different drugs have been substituted or used adjunctively in order to decrease the doses, and thus alleviate the adverse effects associated with calcineurin inhibitors and/or corticosteroids. Substituting cyclophosphamide for azathioprine for 6 weeks after transplantation is reported to reduce the development of anti-muromonab-CD3 antibodies from induction therapy.[24] Substitution of mycophenolate mofetil with intravenous pulse cyclophosphamide for 4 months post-transplantation appeared to decrease the risk of rejection in a small, non-randomised study in sensitised allograft recipients.[25]

Alternative adjunctive therapies are the proliferation signal inhibitors, sirolimus and everolimus,[2,9] which allow for use of lower doses of calcineurin inhibitors, thus preserving renal function; however, long-term data are limited, and there is little experience with these drugs in paediatric patients. Use of sirolimus with ciclosporin and corticosteroids markedly reduced the incidence of acute rejection in a small open-label study.[26] However, the use of sirolimus with mycophenolate mofetil was associated with a higher than expected incidence of acute rejection in cardiac transplant patients switched from calcineurin inhibitors to this combination.[27]

It has been suggested that the high doses of corticosteroids used increase the risk of cardiac adverse events in the longer term, and protocols that wean patients from corticosteroids after 6 months postoperatively have been used,[28,29] without apparent increases in infection or rejection. Corticosteroid avoidance or early withdrawal regimens are feasible in many, if not most, paediatric heart transplant recipients.[9]

In the early post-transplant period, the most significant causes of **morbidity** are infection and rejection episodes.[8,9] Other complications post-transplant include right ventricular failure and cardiac arrhythmias.[30] Co-trimoxazole is used to protect against *Pneumocystis jirovecii* infection, and ganciclovir as prophylaxis against CMV.[3] Rejection is usually treated with corticosteroids, but other drugs have been used for corticosteroid-resistant cases,[8] including antilymphocyte immunoglobulins and muromonab-CD3.[4,29] In repetitive rejection, tacrolimus may be substituted for ciclosporin, and mycophenolate mofetil for azathioprine.[4,5] Adjunctive methotrexate, total lymphoid irradiation and photopheresis have all been tried.[8]

In the late post-transplant period, malignancy and coronary artery disease are the most significant problems.[3,7,8] About 5% of paediatric heart transplant recipients have been reported to develop post-transplant lymphoproliferative disease (PTLD).[2,31] The strongest risk factor for PTLD is the development of primary Epstein-Barr virus infection after transplantation although children who are seropositive for the virus are not necessarily protected from this complication.[2,9] Despite treatment with chemotherapy or a reduction in immunosuppression, PTLD is associated with significant morbidity and mortality; acute rejection may occur in those whose immunosuppression is reduced.[2] Rituximab and cellular immunotherapy are novel therapeutic approaches for PTLD.[9] Cardiac allograft vasculopathy (also termed coronary artery vasculopathy, or chronic rejection) is a major cause of death and prevention of its progression is a major therapeutic goal.[2,3,9,32,33] It is thought to be mainly an immunological response, but can be accelerated by recipient risk factors such as age, gender, obesity, hyperlipidaemia, hypertension, smoking, diabetes mellitus, pretransplant heart disease, postoperative CMV infection, and immunosuppression itself as well as donor risk factors such as age, gender, and hypertension.[3,6,8,34,35] Long-term use of calcineurin inhibitors is associated with renal dysfunction and also contributes to hypertension and hyperlipidaemia, all of which may exacerbate cardiac allograft vasculopathy.[33] Calcium-channel blockers have been used to decrease the incidence of coronary artery disease, but it has remained a difficult complication to treat.[34] HMG-CoA reductase inhibitors such as pravastatin and simvastatin are recommended[34,37] for the treatment of hyperlipidaemia: pravastatin or atorvastatin have been used in paediatric heart transplant patients.[2] There is evidence that statin therapy substantially improves survival.[38] Fibric acid derivatives may be considered in those patients with hypertriglyceridaemia not controlled by diet alone.[37] Supplementation with antioxidant vitamins such as C or E may reduce the progression of arteriosclerosis after transplantation,[39] and a small study[40] found that omega-3 fatty acids improved blood pressure control in hypertensive transplant recipients. There is some suggestion that sirolimus[26,41] and everolimus[42] may be of benefit in preventing cardiac allograft vasculopathy in adults; data are lacking in paediatric patients.[2,9] Retransplantation for graft failure due to cardiac allograft vasculopathy may be necessary.[33]

Improved surgical techniques and the use of ciclosporin have also made possible successful combined *heart-lung* transplants, although these may require enhanced or modified immunosuppression to prevent obliterative bronchiolitis, a possible manifestation of chronic rejection.[43] Early rejection after transplantation is the most important risk factor for the development of bronchiolitis obliterans syndrome although pathogenesis is unclear.[44] Lung infection,[43] or oxidative stress and lack of glutathione[44] may be factors in the aggravation or onset of bronchiolitis obliterans syndrome.

Donor-specific tolerance, whereby the patient permanently accepts their graft without the need for long-term immunosuppression, while remaining immunocompetent, remains the ultimate goal in cardiac transplantation.[6,9]

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Intestinal transplantation. Transplantation of the *small bowel* is becoming more common, especially in children.[1] There are 3 types of intestinal allograft: the isolated intestine, combined liver and intestine, and the multivisceral graft, which can also include the pancreas, stomach, liver, and kidneys.[2–5] Combined liver and small intestine transplants are used for patients dependent on parenteral nutrition and with irreversible intestinal and hepatic failure, while intestine-only transplants tend to be used for intestinal failure in patients with severe progressive complications of parenteral nutrition, such as recurring sepsis and impending loss of central venous access.[1,5–8] Multivisceral transplants are most common in patients with diffuse gastrointestinal motility disorders.[3,4] Transplantation of the *colon* is avoided because of poorer outcomes and increased risk of sepsis.[9] Overall patient and graft survival varies according to the type of intestinal allograft, and between transplant centres, but is reported to be about 50% at 5 years post-transplant;[1,10] more recent 1-year survival rates of over 90% at the most experienced centres may translate into improved longer-term survival.[10]

Tacrolimus and tapered corticosteroid doses[1,2,9,11–14] are the basis of the standard immunosuppressive regimen. In some centres, corticosteroid-free protocols are used, with induction therapy, and tacrolimus alone as maintenance.[5,14] Prostaglandins[8,9] such as alprostadil may also be given to augment mucosal immunosuppression, and improve splanchnic and renal blood flow. Induction therapy with antilymphocyte immunoglobulins or the interleukin-2 receptor antibodies basiliximab and daclizumab is used to prevent rejection.[1,9,12,14–16] Alemtuzumab has also been used.[13,14,16]

Adjunctive immunosuppressants have been added to the maintenance regimen. Azathioprine has been used.[5,12] Sirolimus has also been tried,[1,4,8,9,15] but combining tacrolimus with sirolimus does not have additional benefit over tacrolimus alone.[16] Sirolimus maintenance monotherapy, after induction, is increasingly favoured.[16] Any role for mycophenolate mofetil in intestinal transplantation is questionable,[13,15,17] owing to its gastrointestinal toxicity and poor absorption in intestinal transplant recipients, particularly during rejection.

Substantial morbidity occurs with intestinal transplants and acute rejection, manifested by diarrhoea, fever, and ileus, is common.[1,2,5,9] Initial treatment is with corticosteroids, and most centres increase the dose of tacrolimus as well. Antilymphocyte immunoglobulins or muromonab-CD3 may be used for severe or corticosteroid-unresponsive episodes.[1,2,7,9,14,16] Azathioprine, sirolimus, or mycophenolate mofetil have also been used adjunctively for treatment of rejection,[1,7] although concerns persist about the use of mycophenolate in intestinal transplantation (see above). Chronic rejection, a common cause of late graft dysfunction, is more difficult to treat.[1,9,17] Infliximab has been tried.[18]

Bacterial, viral, and fungal infections are also common post-transplant,[1,2,9,17] and may be confused with rejection.[4,17] Protocols for antimicrobial prophylaxis and treatment are similar to those used for other solid organ transplants. Selective gastrointestinal decontamination with non-absorbable oral antibacterials is usually performed during the first fortnight after transplantation, and during moderate to severe rejection episodes.[11,12] The high level of immunosuppression necessary in intestinal transplantation makes recipients particularly susceptible to post-transplant lymphoproliferative disease associated with Epstein-Barr virus infection.[1,2,4,6,17] Controlling rejection by more potent immunosuppression is difficult because of these complications, so the induction of immune tolerance through adjunctive bone marrow infusion is being investigated.[1,2,13,15] Graft-versus-host disease (see Haematopoietic Stem Cell Transplantation, p. 1933.1) may occur and there may be a recurrence of the original disease.[2]

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Kidney transplantation. The transplantation of kidneys is now established as the ultimate therapy for end-stage renal disease. There is no single generally accepted immunosuppressant regimen, and different centres have achieved good results with a variety of strategies.[1] Therapy should be tailored to the individual patient. Several factors affect the intensity of immunotherapy required, including the donor source (living or cadaveric) and degree of HLA histocompatibility, and the age, race and panel reactive antibody titre of the recipient.[1]

A widely used approach consists of **triple therapy** with a *calcineurin inhibitor* (ciclosporin or tacrolimus), an *antiproliferative* (azathioprine or mycophenolate mofetil), and a *corticosteroid* (prednisolone).[2,3] Triple therapy is popular because it allows the use of lower doses of nephrotoxic calcineurin inhibitors, and the eventual tapering or even elimination of corticosteroids in some patients.[1]

Many variations of triple therapy regimens have been used.

- Azathioprine has largely been replaced by mycophenolate mofetil, which lowers the incidence of acute rejection and reduces the risk of chronic allograft failure.[4–6] This has been challenged, however, by a study[7] in which mycophenolate mofetil was found to be no better than azathioprine in prevention of acute rejection. The drugs were given with microemulsifying ciclosporin and corticosteroids, and ciclosporin dosage was targeted to plasma trough concentrations. The authors noted that previous studies attesting greater efficacy with mycophenolate mofetil had been carried out using the older standard ciclosporin formulation, and that the possibility of better activity with mycophenolate mofetil could not be excluded in patients in whom target ciclosporin concentrations are not achieved.
- Tacrolimus has been substituted for ciclosporin because it appeared to be more effective in preventing acute rejection than either the older oil-based formulation,[4] or the newer microemulsifying formulation.[8,9] Although it has been suggested that this does not lead to improved survival of either patients or grafts,[10] a systematic review[11] concluded that use of tacrolimus did improve graft survival, with a 44% reduction in graft loss within the first 6 months of transplantation; acute rejection was reduced by almost a third and severe rejection by half. The benefit in graft survival diminished with higher concentrations of tacrolimus. However, although tacrolimus may have a better cardiovascular risk profile than ciclosporin,[8,12,13] patients are two to three times more likely to develop diabetes and to have neurological adverse effects.[13] Choice of calcineurin inhibitor is therefore strongly influenced by adverse effect profiles.[10,14,15]
- There is some evidence of synergism between sirolimus and ciclosporin[16] and *addition* of sirolimus to ciclosporin-based regimens may reduce the incidence of acute rejection.[4,17] Combining sirolimus with tacrolimus instead of ciclosporin may be even more effective.[4] However, sirolimus may augment the nephrotoxicity of both ciclosporin[2] and tacrolimus,[3] and its use with full-dose calcineurin inhibitors has been associated with significantly reduced rates of allograft survival.[18] In an attempt to reduce the chronic allograft nephropathy (see below) associated particularly with calcineurin inhibitors, sirolimus has been given with azathioprine or mycophenolate mofetil, as an *alternative* to ciclosporin-based protocols. Comparable rejection rates and better renal function have been reported, although the use of sirolimus may increase the risk of cardiovascular-related morbidity and mortality, and safety has not been established.

Sequential quadruple therapy, in which antibody-based induction therapy is given postoperatively, in addition to triple therapy,[2,14] is also used. The antibodies are usually stopped once good graft function is achieved.[1] The regimen may improve long-term graft survival in patients with delayed graft function.[19]

Polyclonal lymphocyte-depleting antibodies are associated with a low incidence of rejection but evidence of their benefit in terms of graft survival is lacking; rabbit antilymphocyte immunoglobulin appears to be better than that of equine origin. Use of muromonab-CD3 has declined because of poor tolerability and an increased risk of lymphoproliferative disease.[20] The more specific interleukin-2 receptor antibodies basiliximab and daclizumab are widely used and appear to reduce the incidence of rejection episodes without increased toxicity.[4–6,19–22] Alemtuzumab has also been used, but data for this drug are comparatively limited.[20,23,24]

Some consider the interleukin-2 receptor antibodies to be the first-line choice for induction therapy because of their superior safety profile.[6] While there appears to be no difference between rabbit antilymphocyte immunoglobulins and interleukin-2 receptor antibodies in terms of efficacy, acute rejection in high-risk patients appears to occur less often with rabbit antilymphocyte immunoglobulins, which may be the preferred choice in patients who are *highly sensitised* or receiving a second transplant.[20] Basiliximab or daclizumab, used as part of a ciclosporin-based regimen, are recommended in the UK as options for induction therapy in children and adolescents undergoing renal transplantation, irrespective of immunological risk.[15]

As immunosuppressant regimens have developed the role of corticosteroids has come to be questioned, mainly because of the adverse effects associated with their prolonged use.[4,10,25,26] Studies indicate that corticosteroid

withdrawal is feasible in many patients initially given triple therapy,[1,27] and complete avoidance of corticosteroids may be possible with induction therapy using interleukin-2 receptor antibodies.[26] There has been debate about the long-term consequences of this for graft survival,[4,26,28,29] with a possible increased risk of acute or chronic rejection, and a high proportion of patients who need to resume corticosteroid therapy. A 2009 systematic review of 30 studies[30] found no increase in mortality or graft loss with corticosteroid avoidance or withdrawal strategies despite an increase in acute rejection. The authors concluded that safe corticosteroid avoidance or elimination may be feasible a few days after kidney transplantation if antibody induction treatment is used, or after 3 to 6 months if such induction is not used. However, it is crucial to individualise therapy, and caution is advised for high-risk patients, such as African Americans, sensitised, previously transplanted patients, or those with previous acute rejection episodes. Some consider the best approach to rapid corticosteroid withdrawal to be induction therapy (with antilymphocyte immunoglobulins in high-risk patients), calcineurin inhibitors, and mycophenolate mofetil.[26] Protocols that withdraw, minimise, or avoid calcineurin inhibitors have also been investigated.[29,31-35] Ciclosporin withdrawal is considered by some[32] to be more feasible for patients treated with mycophenolate mofetil than those given azathioprine. However, the most effective regimen in terms of patient and graft survival benefit, and minimisation of rejection and adverse effects, remains to be determined.[29] Data on long-term outcomes are lacking.[29,31,33]

Where an **acute rejection** episode occurs treatment is likely to be with high-dose corticosteroids, or with drugs such as antilymphocyte immunoglobulins, or muromonab-CD3, which are potent and effective reversers of rejection.[1,2,14] European guidelines recommend that the antibody preparations be reserved for corticosteroid-resistant rejection or more severe episodes,[19] but approaches remain varied.[1] Some guidelines[6] suggest tacrolimus should be substituted for ciclosporin; mycophenolate mofetil,[4] sirolimus,[36] and gusperimus[3,23] have also been effective in reversing acute rejection episodes. Ciclosporin and azathioprine are ineffective in treating established rejection. Interleukin-2 receptor antibodies have not been shown to reverse established rejection episodes.[3] There has also been evidence that asymptomatic CMV infection may be associated with episodes of late acute rejection;[37] ganciclovir is reported to improve graft function in such circumstances. However, augmented or rescue immunosuppressive therapy predisposes the patient to infections such as CMV, which may itself mimic late acute rejection, and contribute to chronic rejection.[38]

Severe, recurrent, late episodes of acute rejection are considered to be a major risk factor for the development of **chronic rejection**. Manifested clinically by declining renal function, hypertension, and low-grade proteinuria, the term chronic allograft nephropathy is used.[4] Long-term calcineurin inhibitor treatment and inadequate immunosuppression may contribute to this, but there is some suggestion that the addition of mycophenolate mofetil can delay this process.[4] Protocols that use sirolimus to reduce or replace calcineurin inhibitors have been investigated;[18,39-41] improved renal function has been reported, but use of sirolimus may increase the risk of coronary artery disease, and long-term results are lacking.

Although newer drugs have decreased the incidence of acute rejection, there is only limited evidence that this has improved **longer-term graft survival.**[42-44] The one-year cadaveric graft survival is about 88% and about 60% at 10 years.[45] Recurrence of the original disease or *de novo* renal disease may also cause graft failure.[46] Pentoxifylline[47] and gusperimus[48] may improve graft survival.

Cardiovascular disease is a major cause of **death** in renal transplant patients.[49] Corticosteroids and ciclosporin can impair endothelial function, cause hypertension, and hyperlipidaemia. Sirolimus has also been implicated in hyperlipidaemia.[49] Dyslipidaemia occurs in about 60% of patients after renal transplantation;[13,49] HMG-CoA reductase inhibitors (statins) and dietary modification have been recommended as first-line treatment by some,[13] whereas others[50] recommend drug treatment with various lipid-lowering drugs only if lifestyle changes are insufficient. Modification of the immunosuppressive protocols, as discussed above, may also be effective.[13] Hypertension affects up to 75% of kidney transplant recipients and is associated with premature death and graft loss. Calcium-channel blockers have been reported to reduce the risk of graft loss by about 25% compared with placebo or no treatment, and patients taking calcium-channel blockers also had a higher glomerular filtration rate on average. These effects appeared to be independent of hypertension and so it has been suggested that calcium-channel blockers should be considered for all patients after kidney transplantation. There is less evidence for ACE inhibitors in kidney transplant patients, and results from studies are inconclusive. A reduced risk of graft failure in patients taking an ACE inhibitor and/or an angiotensin receptor antagonist has been reported, and some have suggested that early treatment with an ACE inhibitor in patients without signs of glomerulosclerosis may have a beneficial effect on kidney function. However, treatment of proteinuria with an ACE inhibitor may not be effective in those with existing renal damage,[51] and a systematic review noted ACE inhibitors have some detrimental effects on graft function when compared with calcium-channel blockers.[52]

Hyperuricaemia is a common problem among renal transplant recipients;[53] the use of ciclosporin is an independent risk factor for new-onset gout after transplantation.[54] Use of sirolimus is also associated with an increased risk, whereas use of tacrolimus and mycophenolate mofetil carries a lower risk. Hyperuricaemia, besides having direct deleterious effects on the graft, may potentiate chronic renal dysfunction induced by calcineurin inhibitors, and contribute to chronic allograft nephropathy.[53] New-onset gout after transplantation may also be associated with hypertension, cardiovascular disease, and death.[54]

Morbidity and mortality have improved with reductions in cardiac, vascular and infectious complications, but there has been no decrease in death from **malignancy**, and the risk of developing cancer has been estimated to be about 100% by 30 years post-transplant.[55] Compared with the general population, renal transplant recipients have a three- to fivefold higher risk of malignancy; cancers tend to be more aggressive in transplant recipients, and solid organ tumours have a poorer prognosis. The most common malignancies include non-melanoma skin cancers and post-transplant lymphoproliferative disease (PTLD).[56,57] While not all malignancies are a consequence of transplantation or immunosuppressive therapy,[56] both the duration and intensity of immunosuppression have been linked to this increased incidence.[57] Other risk factors include increasing age, male gender,[58] sun exposure, and cigarette smoking.[56]

It is difficult to assess the impact of individual drugs on cancer risk.[56] Some studies have found an increased incidence in patients given muromonab-CD3 or calcineurin inhibitors;[58,59] azathioprine is not thought to be as carcinogenic as the calcineurin inhibitors.[59] Data are conflicting on the carcinogenic effects of mycophenolate.[56,59] Proliferation signal inhibitors such as sirolimus and everolimus have been reported to carry less of a risk, possibly as a result of their mode of action.[56-60] Although long-term data are needed, some have suggested that conversion from calcineurin inhibitors to proliferation signal inhibitors should be considered in high-risk patients,[57,58,60] or those with Kaposi's sarcoma.[6]

Nonmyeloablative conditioning regimens allowing for the development of immunological **tolerance** specific to the donor remain the ultimate goal of renal transplantation.[4,61] There are reports of the development of chimerism and tolerance allowing withdrawal of all immunosuppression in a few patients in whom kidney transplants were combined with haematopoietic stem cell transplantation.[62,63]

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Liver transplantation. Marked improvements have occurred in the outcome and reliability of liver transplan-

tation and it is now seen as standard therapy for acute and chronic hepatic failure, regardless of aetiology,[1-3] and some metabolic disorders.[4] The 1-year patient and graft survival rates[2,4,5] are about 90%.

The liver induces some tolerance and liver transplant recipients usually require less immunosuppression than other solid organ transplant patients.[6] **Immunosuppressive regimens** generally combine a calcineurin inhibitor (ciclosporin or tacrolimus) with a corticosteroid and azathioprine or mycophenolate mofetil; such triple therapy prevents acute rejection episodes in the majority of cases.[7-9] Double therapy with ciclosporin or tacrolimus and corticosteroids is also used,[8,10] and monotherapy with a calcineurin inhibitor alone has also been used, allowing for complete corticosteroid withdrawal or avoidance.[10]

A review of corticosteroid-free strategies in liver transplantation concluded that up to 50% of patients can avoid corticosteroids with little modification of their maintenance immunosuppressive regimen; adding mycophenolate mofetil and/or induction therapy with antibodies can increase this percentage, although over-immunosuppression may be a problem. Although data are weak and limited, corticosteroid avoidance is not advised with calcineurin inhibitor monotherapy, nor with calcineurin inhibitors and azathioprine; it may be feasible with tacrolimus and mycophenolate mofetil, or with calcineurin inhibitors and antibodies. Benefits of corticosteroid avoidance are seen in growth rates in children, diabetes mellitus, dyslipidaemia, CMV infection, and possibly other infections.[11] A meta-analysis of 19 studies[12] found that corticosteroid-free regimens did not increase the risk of death, graft loss, or bacterial infection compared with corticosteroid-based regimens. When corticosteroids were replaced with another immunosuppressant such as an interleukin-2 receptor antibody, antilymphocyte immunoglobulin, or mycophenolate mofetil, the risk of diabetes and rejection was markedly lower with the corticosteroid-free regimens. Patients with underlying auto-immune hepatitis or inflammatory bowel disease may be relatively refractory to corticosteroid withdrawal.[13]

Although some consider the evidence for one calcineurin inhibitor over another to be equivocal,[14] a systematic review concluded that tacrolimus is better than ciclosporin at preventing acute rejection in liver transplantation. It is also marginally better at preventing patient death and graft loss, but it increases the risk of post-transplant diabetes.[15] Studies of different formulations of ciclosporin found a reduced incidence of rejection with the microemulsifying formulation compared with the older oil-based product.[5]

The use of azathioprine in liver transplant patients has been limited due to its possible hepatotoxicity.[10] Mycophenolate mofetil has been used in place of azathioprine, to reduce the dose of the calcineurin inhibitor or corticosteroid used, and possibly prevent rejection.[2,8] Calcineurin inhibitors have been replaced with mycophenolate mofetil in an attempt to improve renal function,[10] although small studies have suggested that this monotherapy carries a high risk of rejection.[14] The long-term efficacy of calcineurin inhibitor minimisation or avoidance has yet to be determined.[16] The role of sirolimus in liver transplantation has yet to be evaluated.[3] There have been reports of efficacy when used with a calcineurin inhibitor,[1,9] which might allow dose reduction[9] or withdrawal of therapy[5] in patients with toxicity from tacrolimus or ciclosporin, but excess mortality, graft loss, and hepatic artery thrombosis has been associated with such use. A regimen of everolimus, a sirolimus derivative, and reduced-dose tacrolimus, plus a corticosteroid, has similar efficacy and better renal function that a standard-dose tacrolimus regimen.[17]

Induction therapy with antilymphocyte immunoglobulins or muromonab-CD3 is associated with a high incidence of infection and lymphoproliferative disease, and they have been generally reserved for the treatment of corticosteroid-resistant acute rejection.[2,4,8,9] However, interest in the use of antilymphocyte immunoglobulins as induction therapy has increased as it allows avoidance of calcineurin inhibitors early after transplantation, improving renal function without increasing rejection risk.[14] The use of interleukin-2 receptor antibodies, basiliximab, and daclizumab, is also increasing;[10] initial studies suggest they reduce the number of rejection episodes.[8,9] It has been suggested that they may be of benefit in those with pre-transplant renal impairment by allowing for delayed introduction or lower doses of calcineurin inhibitors,[18] although complete withdrawal of calcineurin inhibitors has been reported to lead to high rates of rejection.[14] The use of alemtuzumab has also been investigated.[10,14,16]

The induction of complete immune **tolerance** remains the ultimate goal in liver transplantation.[10,19,20] It may be feasible to reduce or stop all immunosuppression in long-term stable liver transplant patients.[6,21] The term 'operational tolerance' is used to define stable graft function without features of rejection and without immunosuppressive treatment; 'prope tolerance' refers to stable graft function in patients with minimal immunosuppression.[10,21] Although it is not uncommon for rejection to eventually occur in those withdrawn from immunosuppression, this may be reversed by resumption of therapy, with a small rate of graft loss. Favourable markers for successful withdrawal appear to be at least 2 years of post-transplant follow-up, low incidence of previous rejection episodes, non-autoimmune primary liver disease, and possibly minimal post-transplant immunosuppression.[21]

Most **acute rejection** episodes occur during the first 3 to 6 months of therapy.[13] Early acute rejection does not affect patient or graft survival[6,22,23] and, if mild, may be associated with increased survival.[1] Late acute rejection, occurring after 30 days post-transplant may be related to reduction or withdrawal of immunosuppressive therapy.[24] It has a worse prognosis, with reports of up to half of patients developing graft loss.[23] Corticosteroids are used in the first-line treatment of acute rejection.[11,25] For corticosteroid-resistant rejection, muromonab-CD3 or antilymphocyte immunoglobulins are used, and increasing the dose of tacrolimus, or conversion from ciclosporin to tacrolimus, may also be effective.[2,4,9] Interleukin-2 receptor antibodies may also be used. Mycophenolate mofetil or sirolimus have been added to treat recurrent acute rejection.[25] **Chronic rejection** is almost always preceded by one or more episodes of corticosteroid-resistant acute rejection,[23,24] and although its incidence has decreased[5,23-25] to less than 5%, it remains difficult to treat. Corticosteroids are generally ineffective; conversion from ciclosporin to tacrolimus has been reported to be effective,[23] as has addition of mycophenolate mofetil to tacrolimus, followed by interleukin-2 receptor antibodies, and then sirolimus in non-responsive patients.[25]

The main **complications** encountered with liver transplants are infection in the early post-transplant period, vascular and biliary complications, recurrent disease (particularly viral recurrence), and adverse effects due to immunosuppressants.[4,6,24,25]

Sepsis is an important cause of death in the early post-transplant period.[6,26,27] Patients at increased risk, including those with malnutrition, fulminant liver failure, or renal insufficiency, require particularly cautious immunosuppression and more aggressive antibacterial and antifungal prophylaxis regimens.

Recurrence of hepatitis B infection is common.[28] Although the introduction of hepatitis B immunoglobulins and lamivudine have improved the prospects for these patients, combination antiviral therapy and a modified immunosuppression protocol are usually needed.[3,6,7,22,23] Hepatitis C recurrence is almost universal in infected patients,[11,23,29] with a probable reduction in long-term graft survival.[7,22,23] The use of corticosteroids and muromonab-CD3 appears to be associated with more severe recurrence of hepatitis C. Treatment with interferon alfa plus ribavirin appears promising.[28-30]

Nephrotoxicity from ciclosporin or tacrolimus can be a significant problem after long-term therapy.[31] Long-term renal function is affected by the function in the early post-transplant period, so serum creatinine concentrations at 1 and 3 months are often used to predict toxicity.[7] Cardiovascular complications may follow metabolic abnormalities such as diabetes mellitus, hypertension, hyperlipidaemia, and obesity. Dose reduction or change of the calcineurin inhibitor used, corticosteroid withdrawal, or use of statins could minimise the cardiovascular risk post-transplantation.[32-34] Malignancy may occur after prolonged immunosuppression.[4,22,25]

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Lung transplantation. Lung transplantation has become accepted therapy[1-4] for end-stage pulmonary disease such as pulmonary hypertension, cystic fibrosis, emphysema, and pulmonary fibrosis, with a 1-year survival of 70% or more.[2] The rate of death is highest in the first year after transplantation, with infection and primary graft failure the leading causes of early death.[1,5]

Immunosuppressant therapy is usually with a triple therapy regimen of ciclosporin or tacrolimus, azathioprine or, increasingly, mycophenolate mofetil, and a corticosteroid.[1-12] Some centres also use induction therapy with polyclonal or monoclonal antibodies, although its use is controversial.[10,12] While induction therapy may reduce the incidence and severity of acute rejection, and allow for a delay in calcineurin inhibitor therapy, there is an increased risk of infection and of post-transplant lymphoproliferative disease.[2,3,5,13] Antilymphocyte immunoglobulins and muromonab-CD3 have been used; the interleukin-2 receptor antibodies basiliximab and daclizumab are increasingly used,[1,2,13] although experience with these drugs in lung transplantation is limited.[14] Alemtuzumab is under investigation for induction;[1,2,10,11,13,14] preliminary results are promising. Corticosteroids remain a mainstay in lung transplantation,[5,10,11,13-15] although corticosteroid-free regimens have been investigated, with promising results, and further study is warranted.[14,15] Sirolimus has been investigated in lung transplantation, but its early use as a primary immunosuppressant is not recommended[1,2,11] due to its potent antifibrotic effects; sirolimus may also induce pulmonary toxicity.[10,11,13] Cases of fatal anastomotic dehiscence have been reported, and concerns about wound healing complications have led to recommendations to only use sirolimus after initial airway bronchial wound healing is completed, or not until at least 3 months after transplant.[12,13] Everolimus is also under investigation for adjunctive use in lung transplantation.[11-14]

Acute rejection occurs more frequently with lung transplants than with other solid organ transplants;[1,16] from early reports in 60 to 100% of cases, incidence has apparently decreased to about 35% in those receiving induction therapy and about 45% in those without induction therapy,[13] although some centres have reported figures as high as 85%.[16] High doses of intravenous corticosteroids are generally used to control acute episodes of rejection.[3,7,13,16] Corticosteroid-refractory rejection demands further intervention, although no consensus exists. Evidence supports the conversion of ciclosporin to tacrolimus for patients with persistent acute rejection.[13] Other therapies include the use of monoclonal or polyclonal antibodies, plasmapheresis, and total lymphoid irradiation.[13,16] Inhaled ciclosporin has also been used to treat refractory acute rejection.[1,13]

Lung transplant recipients are at high risk of **infection** as a result of impaired pulmonary defence mechanisms, and post-transplant antibacterial prophylaxis is routine.[2] Patients at risk for CMV should be given ganciclovir.[2,7,15] There is no consensus on standard antifungal prophylaxis after lung transplant, but some centres use oral azole therapy or inhaled amphotericin.[2] Respiratory viruses pose a substantial risk to the lung allograft,[2,4,15] and may contribute to chronic rejection. The main complication encountered in the long term and major cause of late mortality is **chronic rejection** manifesting as bronchiolitis

obliterans syndrome (obliterative bronchiolitis).[1,2,7,16] This is characterised by progressive airway obstruction and may be present in up to 40% of patients at 2 years, and in 60 to 70% who survive for 5 years.[7] Young children and living donor lung transplant recipients may have a lower risk for the development of this syndrome.[5] The frequency and severity of acute rejection episodes are the main risk factors for the development of bronchiolitis obliterans, but CMV infection, airway ischaemia and HLA mismatching may also play a part.[1,4,6,7,15-18] There are no proven effective therapies,[4] and the prognosis is poor, with 40% mortality within 3 years of diagnosis.[7] Augmentation of immunosuppression is often tried, but may exacerbate the risk of infection.[4] Some centres change the maintenance regimen, converting ciclosporin to tacrolimus, and azathioprine to mycophenolate mofetil, along with a short course of high-dose corticosteroids.[13,16] Inhaled ciclosporin has also been used, with reports of a trend towards survival benefit.[13] Improvement in pulmonary function has been seen with maintenance azithromycin.[13,16,18] Statins may decrease the risk of developing bronchiolitis obliterans syndrome,[12] and promising results have been reported with the use of total lymphoid irradiation.[16] Re-transplantation may be necessary.[4,16]

Post-transplant lymphoproliferative disorders (PTLD) occur in lung transplant recipients, often in association with a primary Epstein-Barr virus infection.[3,4,15] The incidence is high in paediatric patients, ranging from 13 to 20%. Initial treatment involves a reduction in immunosuppression, or chemotherapy with rituximab.[3,15]

The induction of immune tolerance remains the ultimate goal in lung transplantation.[1,14]

Combined *heart-lung* transplants have also been performed, see under Heart Transplantation, p. 1934.2.

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Pancreatic transplantation. Transplantation of the pancreas may be considered in some diabetic patients. In the vast majority of cases, pancreatic grafts have been transplanted with a kidney (simultaneous pancreas-kidney or SPK) in patients with end-stage diabetic nephropathy, which has produced better graft survival than transplanting the pancreas alone.[1-3] However, pancreas transplants after renal allografting (PAK), or solitary pancreatic transplantation (PTA), are becoming more common,[3] and approaching comparable survival rates.[2,4] Advances in surgical and preservation techniques, and new immunosuppressants, have helped to improve survival.[1] Overall patient survival has been estimated to be about 98% at 1 year, with graft survival of about 78%.[5]

The pancreas is a highly immunogenic organ, so extensive **immunosuppression** is required. Standard treatment often consists of quadruple therapy.[2,6,7] Induction therapy is followed by maintenance therapy with a calcineurin inhibitor (ciclosporin or tacrolimus), corticosteroids, and azathioprine or mycophenolate mofetil.[2,7,8] Induction therapy reduces rejection rates, and may allow for corticosteroid withdrawal, but patient or graft survival is not altered.[6,7] The use of induction therapy varies between centres,[9] and may be dependent on the type of pancreatic transplant.[10] The interleukin-2 receptor antibodies basiliximab and daclizumab are increasingly favoured. Rabbit antilymphocyte immunoglobulins are also used, but the use of muromonab-CD3 has declined.[7] Alemtuzumab is under investigation.[5]

Tacrolimus is usually preferred to ciclosporin[2,4,6-8,10] as it appears to allow for rapid tapering or even complete withdrawal of corticosteroids, causes less rejection, and may increase graft survival and reduce the risk of pancreatic thrombosis. Mycophenolate mofetil is now preferred to azathioprine,[2,6,7,9,10] as it decreases rejection rates, although patient and graft survival rates are comparable.[6,7,10] Early withdrawal of corticosteroids appears to be safe and feasible in pancreatic transplantation,[6,7] without an increase in rejection rates; patients may, however, require slightly higher doses of calcineurin inhibitors, which increases the risk of nephrotoxicity.[7] Although the precise role of sirolimus in pancreatic transplantation has yet to be defined, it may be used with a low-dose calcineurin inhibitor, thus mitigating renal dysfunction,[2] or as a substitute for an antimetabolite,[7,10] or as the chief drug in a calcineurin inhibitor-free maintenance protocol, or for episodes of rejection.[7] Sirolimus used with tacrolimus may allow for rapid withdrawal of corticosteroids.[10]

Episodes of rejection are treated with corticosteroids or antilymphocyte immunoglobulins.[2,7] Conversion to tacrolimus from ciclosporin is used, and for those patients on tacrolimus, sirolimus has been tried.[2]

Pancreatic transplantation facilitates normal carbohydrate metabolism and has the potential to improve patient survival and reduce the incidence of diabetic nephropathy. However, there has been concern over the long-term complications of immunosuppression,[11] and whether islet-cell autoantibodies might produce diabetes in the transplanted graft (although this is certainly not inevitable with adequate immunosuppression).[12] The incidence of hyperglycaemia induced by immunosuppressive regimens after transplantation appears to be less in pancreatic transplants than in recipients of other organs.[5] Explanations for the absence of a higher diabetogenic effect of tacrolimus after pancreatic transplantation compared with other solid organ transplants may include a more cautious dose of tacrolimus in diabetic patients, the use of tacrolimus with corticosteroid-free protocols, and the use of pancreatic grafts from young donors who may be more resistant to a diabetogenic effect.[10]

One possible alternative to complete pancreatic transplantation is an **islet-cell** graft. These have rarely been successful,[1,13] with insulin independence at 1 year[5] only in about 10% of cases. However, the use of carefully prepared islet cells from more than one donor and a modified immunosuppressant protocol[14] has produced greatly improved results. In this 'Edmonton Protocol', corticosteroids were completely avoided because of diabetogenic effects. Induction therapy with daclizumab was used, followed by maintenance with sirolimus and low-dose tacrolimus.[14] Short-term follow-up data indicated that patients with unstable type I diabetes benefited in terms of glucose control from islet transplantation.[15] Reported insulin independence was 80% at 1 year after use of the 'Edmonton protocol'[16] and 10% at 5 years post-transplant.[17] Thus, engrafting an adequate beta-cell mass appears to be the critical factor for transplant success.[9] Insulin independence has been reported with single organs from cadaveric donors.[18] Further study of the 'Edmonton protocol' confirmed that islet-cell transplantation may successfully restore endogenous insulin production and glycaemic stability in patients with type I diabetes mellitus. Insulin independence is gradually lost again in most cases, but persistent islet function without insulin independence confers benefit in terms of glycaemic control, provided the patient can tolerate the immunosuppressive regimen. Islet transplantation may be best for highly selected patients with severe hypoglycaemia or labile type I diabetes mellitus, provided all other attempts to stabilise glycaemic control have been tried. For patients seeking long-term insulin independence, whole pancreas transplantation is a better option at present.[19] See also under Management of Diabetes Mellitus, p. 459.1.

The induction of tolerance,[3,5,11,20] the possibility of neogenesis of beta cells from pancreatic stem or precursor cells,[11,20,21] less toxic immunosuppressive therapy, and enhanced islet engraftment[19] remain focuses of investigation in islet transplantation.

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Renal disorders

Corticosteroids and immunosuppressants are commonly used in the treatment of glomerular kidney disease (p. 1604.3).

Rheumatoid arthritis

Disease-modifying antirheumatic drugs (DMARDs) including immunosuppressants may be given to patients with rheumatoid arthritis (p. 13.2) in an attempt to modify the course of the disease. Ciclosporin appears to be effective, but adverse effects have been a problem. The use of low-dose regimens may help to minimise nephrotoxicity. Use of ciclosporin with methotrexate has produced clinical improvement in patients who had only partial responses to methotrexate alone, but some investigators found that a combination of methotrexate, ciclosporin and intra-articular corticosteroids was no more effective than standard DMARD therapy. Tacrolimus is licensed in some countries for use in refractory rheumatoid arthritis.

Azathioprine has been used, with beneficial short-term effects, but is reported to be no more effective than other DMARDs and significantly more toxic; it may however be useful with prednisone in rheumatoid vasculitis. Mycophenolate mofetil may be effective in rheumatoid arthritis, but further studies are needed.

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Sarcoidosis

Where drug therapy is required for sarcoidosis (p. 1612.2), corticosteroids are the usual treatment. In patients in whom these are ineffective or poorly tolerated, immunosuppressants have been given, with variable results.

Scleroderma

The term scleroderma has been used for both systemic sclerosis, an uncommon multisystem disease characterised by collagen proliferation and fibrosis throughout the body, and for localised fibrotic changes of the skin (morphea) which rarely progresses to involve other organs. In systemic sclerosis, Raynaud's syndrome secondary to vascular involvement usually precedes skin changes; oedema is followed by thickening and tightening of the skin of hands and face, and sometimes limbs and trunk, before progressing to atrophy and contractures. Cutaneous changes may be limited or take a more aggressive diffuse form. Decreased gastrointestinal motility, dysphagia and gastro-oesophageal reflux, arthritis, muscle weakness, and cardiac involvement may occur. Among the most serious potential symptoms, which may result in death, are pulmonary disease and renal failure with malignant hypertension.[1-8]

Many treatments have been tried for localised scleroderma.[4,5] Symptomatic therapies include emollients and topical and systemic antipruritics. Topical, intralesional, and systemic corticosteroids may be useful, especially in early inflammatory stages. Other treatments include topical and systemic vitamin D analogues, topical tacrolimus, and imiquimod cream. Oral therapies used include ciclosporin, colchicine, hydroxychloroquine, interferon gamma, penicillamine, phenytoin, and methotrexate. Phototherapy with UV light, with or without psoralens, has also been reported to be of benefit.

There is a paucity of adequately controlled studies for systemic scleroderma: no treatment has been clearly shown to affect the progression of the disease, and much management is essentially symptomatic. Immunosuppres-

sants are probably appropriate in the early oedematous stages of diffuse scleroderma.[1,6,9,10] Antilymphocyte immunoglobulins have been tried as an induction therapy in early stages of the disease.[9] Ciclosporin has been found to be beneficial, both for skin and visceral manifestations, but its use has been limited by nephrotoxicity and hypertension.[1,3,9,11,12] Tacrolimus has also been tried, though again adverse effects limit its benefit.[9,11,12] Mycophenolate mofetil has been tried after antilymphocyte immunoglobulins with reports of significant skin improvement.[12] Cyclophosphamide with or without corticosteroids has been shown to improve skin thickening, stabilise pulmonary function, and increase survival, especially in early disease, in some studies,[7] but a meta-analysis[13] considered that there was no evidence of a clinically significant improvement in lung function in patients with interstitial lung disease caused by systemic sclerosis. Other novel immunosuppressive strategies include bone marrow ablation followed by peripheral blood stem cell transplantation (see Haematopoietic Stem Cell Transplantation, p. 1933.1),[1,3,5,9,10] photopheresis with a psoralen, and the induction of oral tolerance with native bovine type I collagen.[9] Rituximab is under investigation.[10,12]

Penicillamine has been widely used as an antifibrotic drug, but with variable effects. Observational studies have reported improvements in skin, renal, cardiac, and pulmonary symptoms;[14] however, others have found that usual doses of penicillamine were no more effective than lower doses,[1,9,15] and it is considered by some to be no more effective than placebo.[5] Interferons alfa and gamma have also produced variable results;[5,9] the latter is under investigation for pulmonary fibrosis.[5] Some other drugs have been investigated for their antifibrotic properties, including halofuginone, minocycline and relaxin.[9,15] There is some evidence that oxidative stress is involved in the pathogenesis of scleroderma, so antoxidants like probucol may also be useful.[9] Other drugs that have been investigated include imatinib,[10] potassium aminobenzoate, and thymopentin.

Many patients will require therapy for organ-specific symptoms.

- *Skin* flexibility may be maintained by emollients,[16] and systemic antihistamines can relieve itching, an early feature of diffuse cutaneous scleroderma.[9] Methotrexate has been used with some benefit.[1,3,5,7,9,15]
- Most progress has been made in the management of *vascular* symptoms. ACE inhibitors are considered to be the standard treatment for patients with renal ischaemia,[3,5,6,17] although some 30% of patients will still eventually require renal replacement therapy.[9] For patients who develop pulmonary arterial hypertension the prostaglandins epoprostenol, iloprost, or treprostinil may be given intravenously;[1,3,5,6,9] some have also been investigated subcutaneously[6] or by inhalation.[3,5,6] Sildenafil, bosentan or ambrisentan are also used.[3,5-7,10,18] There is some evidence that epoprostenol and bosentan may be associated with improved survival as well as symptomatic improvement.[3]
  Treatment of Raynaud's syndrome (see under Vasospastic Arterial Disorders, p. 1275.3) unresponsive to nonpharmacological therapy involves the use of calcium-channel blockers such as nifedipine or diltiazem.[1,3,16] Topical nitrates have been used, and intravenous epoprostenol or iloprost are used in acute attacks.[1,3,6,9] Oral iloprost has been tried with variable results.[6] Bosentan can prevent the development of new digital ulcers but may not speed the healing of existing ones.[3] Calcitonin gene-related peptide is being investigated as an alternative to iloprost.[1] Because elevated levels of serotonin have been found in patients with Raynaud's phenomenon, SSRIs and ketanserin have been used.[1] Atorvastatin[6] and sildenafil[10,17] have been reported to be helpful. Dietary supplementation with antoxidant vitamins, fish oils, and evening primrose oil has been of anecdotal benefit.[1,9,19] Acetylcysteine has also been reported to be of benefit in Raynaud's syndrome.[6,19]
  Cardiac involvement may be underdiagnosed;[9] ACE inhibitors or digoxin may be used.[1]
- *Lung* fibrosis is usually treated with cyclophosphamide,[1,3,5,9,20] with or without a corticosteroid such as prednisolone. There is no evidence for corticosteroids alone in lung scleroderma, and high dose may precipitate scleroderma renal crisis, leading to irreversible renal failure.[7] As mentioned above, interferon gamma is under investigation.
- In patients with *gastrointestinal* disease, proton pump inhibitors such as omeprazole, sometimes with prokinetic drugs, are extremely effective for oesophageal involvement, and broad spectrum antibacterials are helpful for small bowel bacterial overgrowth.[1,6,9]

NSAIDs and corticosteroids must be used with care in scleroderma because of the risk of exacerbating renal and other problems.[1,9]

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Skin and connective tissue disorders

Immunosuppressants are used in various skin and connective tissue disorders, including Behçet's syndrome (p. 1601.1), eczema (p. 1684.1), pemphigus and pemphigoid (p. 1687.1), polymyositis (p. 1611.1), psoriasis (p. 1688.1), SLE (p. 1613.3), and the various vasculitic syndromes (p. 1615.2). See also Scleroderma, p. 1938.3.

Antilymphocyte Immunoglobulins

Inmunoglobulinas antilinfocitarias; Иммуноглобулины Антилимфоцитарные.

ATC — L04AA03 (antilymphocyte immunoglobulin, horse); L04AA04 (antilymphocyte immunoglobulin, rabbit).

ATC Vet — QL04AA03 (antilymphocyte immunoglobulin, horse); QL04AA04 (antithymocyte immunoglobulin, rabbit).

UNII — 475247QF1Z (equine thymocyte immunoglobulin); D7RD81HE4W (lapine thymocyte immunoglobulin).

Description. Antilymphocyte immunoglobulins are polyclonal antibodies to human lymphocytes produced by the purification of sera from appropriately immunised animals. The term antilymphocyte immunoglobulin (ALG; lymphocyte immune globulin) implies a product raised against all lymphocyte subsets. The term antithymocyte immunoglobulin (antithymocyte gammaglobulin; antithymocyte globulin; ATG) implies specificity for T-cells (thymus lymphocytes or thymocytes). However, in practice the nomenclature does not seem to be used consistently, and both terms tend to be used for antibodies raised against T-cells. Nomenclature normally includes an indication of the animal source of the immunoglobulin e.g. antithymocyte immunoglobulin (horse), or antithymocyte immunoglobulin (rabbit).

In addition to the purified immunoglobulins the native sera (antilymphocyte serum and antithymocyte serum, sometimes referred to as lymphocytic antiserum and thymitic antiserum) have also been used as immunosuppressants.

Pharmacopoeias. *Eur.* (see p. vii) includes an anti-T lymphocyte immunoglobulin.

Ph. Eur. 8: (Anti-T Lymphocyte Immunoglobulin for Human Use, Animal; Immunoglobulinum Anti-T Lymphocytorum ex Animale ad Usum Humanum). A sterile liquid or freeze-dried preparation containing immunoglobulins, obtained from serum or plasma of animals, mainly rabbits or horses, immunised with human lymphocytic antigens. It has the property of diminishing the number and function of immunocompetent cells, in particular T-lymphocytes. It contains principally immunoglobulin G, and may contain antibodies against other lymphocyte subpopulations and against other cells. It is intended for intravenous administration, after dilution with a suitable diluent where applicable. It may contain excipients such as stabilisers. Protect from light.

Uses and Administration

Antilymphocyte immunoglobulins are antibodies, raised in *animals*, which act against lymphocytes, and in particular against T-cells, to produce suppression of cell-mediated immunity.

They may be added to existing immunosuppressant regimens to treat acute rejection episodes in patients who have undergone organ or tissue transplantation. Alternatively, they may be given prophylactically as part of a combination immunosuppressant regimen with several other agents. For discussion of the role of antilymphocyte immunoglobulins in transplantation, see p. 1932.2 *et seq.*

Antilymphocyte immunoglobulins are also used in the treatment of aplastic anaemia (p. 1121.3) in patients unsuitable for bone marrow transplantation, and have been tried in other immunological disorders. They are under investigation for the treatment of myelodysplastic syndromes (p. 694.3). The dose used in **transplantation** depends on the indication and the combination of immunosuppressants used and may vary between countries.

In the UK, *rabbit* antilymphocyte immunoglobulin is used at the following doses for:

- prophylaxis of rejection after heart transplantation: 1 to 2.5 mg/kg daily for 3 to 5 days
- prophylaxis of rejection after kidney transplantation: 1 to 1.5 mg/kg daily for 3 to 9 days
- treatment of corticosteroid-resistant renal graft rejection: 1.5 mg/kg daily for 7 to 14 days

In the USA, *rabbit* antilymphocyte immunoglobulin is used at the following dose for:

- treatment of acute renal graft rejection: 1.5 mg/kg daily for 7 to 14 days

The *rabbit* product is diluted in sodium chloride 0.9% or glucose 5% (usually using 50 mL per vial, to obtain a total volume ranging from 50 to 500 mL), and given by intravenous infusion using a 0.22 micrometre in-line filter, into a vein with rapid blood flow. The first dose is given over at least 6 hours, and over at least 4 hours on subsequent occasions.

In the USA and Canada, *horse* antilymphocyte immunoglobulin is used at the following doses for:

- prophylaxis of renal graft rejection: 15 mg/kg daily for 14 days, then every other day for 14 days, to a total of 21 doses in 28 days; the first dose is given within 24 hours before or after the transplant
- treatment of renal graft rejection: 10 to 15 mg/kg daily for 14 days; additional alternate-day therapy, up to a total of 21 doses, can be given

For the treatment of **aplastic anaemia**, the recommended dose of *horse* antilymphocyte immunoglobulin is 10 to 20 mg/kg daily for 8 to 14 days; additional alternate-day therapy, up to a total of 21 doses, can be given.

The *horse* product is diluted in an appropriate infusion solution (including sodium chloride 0.9% or glucose 5% plus sodium chloride at either 0.225% or 0.45%); the final concentration should not exceed 4 mg/mL. The infusion is given over at least 4 hours, via an in-line filter (0.2 to 1 micrometre), into a vein with rapid blood flow. A skin sensitivity test is recommended before the first infusion, see Adverse Effects, Treatment, and Precautions, p. 1940.2.

For children's doses, see Administration in Children, below.

Administration in children. Although data in children are limited, licensed product information in the USA states that doses of *horse* antilymphocyte immunoglobulin for renal graft rejection in paediatric **transplantation** patients have ranged from 5 to 25 mg/kg daily. The children's dose for *rabbit* antilymphocyte immunoglobulin is the same as for adults, see above.

For **aplastic anaemia**, doses of *horse* antilymphocyte immunoglobulin have also been comparable to those used in adults, see above.

Aplastic anaemia. The British Committee for Standards in Haematology (BCSH) issued an alert[1] in July 2011 to haematologists concerning the unexpectedly low response rate and survival seen in a study[2] of aplastic anaemia patients treated with *rabbit* antilymphocyte immunoglobulin for the first course of immunosuppressive therapy. In 2007, the *horse* product had been withdrawn in the UK and replaced by the rabbit product, which had previously been used for a second course of therapy in patients who had relapsed or were refractory to a first course of horse antilymphocyte immunoglobulin. The European Blood and Marrow Transplant Severe Aplastic Anaemia Working Party (EBMT SAAWP) requested that the horse antilymphocyte immunoglobulin be made available in Europe,

and offered the following guidance, supported by the BCSH:

- *horse* antilymphocyte immunoglobulin is recommended as first-line immunosuppressive therapy for aplastic anaemia patients ineligible for HLA-identical sibling haematopoietic stem cell transplantation (HSCT)
- if *horse* antilymphocyte immunoglobulin is unavailable, treatment with the *rabbit* product may be considered. The EBMT SAAWP recommended a lower intravenous dose, of 2.5 mg/kg daily for 5 days (instead of 3.75 mg/kg for 5 days) until more data were available, and that the *rabbit* product only be used in experienced centres
- alternative first-line options include ciclosporin monotherapy; data with alemtuzumab as first-line therapy in aplastic anaemia are limited
- early unrelated donor HSCT using fludarabine-based conditioning regimens may also be an option, and may be considered as first-line treatment in children

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Organ and tissue transplantation. The use of antilymphocyte immunoglobulins in organ and tissue transplantation has been reviewed.[1] Although antilymphocyte immunoglobulin products may be derived from various species, much of the experience in transplantation seems to be with a product of *rabbit* origin. In kidney transplantation (p. 1935.2), rabbit antilymphocyte immunoglobulin is considered effective for both prevention and treatment of acute graft rejection. It has been found to be more effective than the *horse* product in treating acute rejection and preventing recurrent rejection in adults; graft survival rates and the incidence of infection did not differ significantly. Induction therapy with rabbit antilymphocyte immunoglobulin has been used successfully in both adults[2,3] and paediatric[4,5] renal transplant recipients. In children, the incidence of acute rejection was lower in rabbit immunoglobulin recipients than in those given the horse product;[6] however, rates of Epstein-Barr virus (EBV) infection were higher with the rabbit product. Patient and graft survival rates, incidence of chronic rejection, EBV lymphoma, or other infection did not differ significantly between the 2 groups.

In adult renal transplant recipients considered to be at high risk for acute rejection or delayed graft function, induction with rabbit antilymphocyte immunoglobulin reduced the incidence and severity of acute rejection (but not the incidence of delayed graft function) compared with basiliximab induction. Patients receiving antilymphocyte immunoglobulin had a greater incidence of infection but a lower incidence of CMV disease; patient and graft survival were similar in the 2 groups after 1 year.[7] After 5 years, the antilymphocyte immunoglobulin group was found to have a lower incidence of acute rejection, and of the combined end-point of acute rejection, graft loss, and death; rates of CMV infection also remained lower in this group.[8]

Induction therapy with antilymphocyte immunoglobulins has also been shown to be beneficial in other solid organ transplants, with lower rates of rejection reported in liver (p. 1936.3), pancreas (p. 1938.1), kidney-pancreas, heart (p. 1934.2), and heart-lung transplantation. Use in lung transplantation remains controversial due to a higher incidence of CMV infection.[9] Induction protocols differ between institutions.

In haematopoietic stem cell transplant recipients (p. 1933.1), those given rabbit antilymphocyte immunoglobulin before a matched unrelated donor (MUD) transplant had comparable outcomes to those given matched related donor (MRD) transplants but no antilymphocyte immunoglobulin; the authors supposed that the use of antilymphocyte immunoglobulin caused MUD recipients to behave clinically like MRD recipients.[10] A review of the use of antilymphocyte immunoglobulins in haematopoietic stem cell transplantation concluded that it significantly reduces the severity and incidence of acute graft-versus-host disease (GVHD) and chronic GVHD. This protective effect is dependent on the dose, the timing of infusion, and the brand used. However, antilymphocyte immunoglobulin induction therapy delays immune reconstitution and there is an increased risk of infection; the use of an antilymphocyte immunoglobulin is a risk factor for EBV reactivation.[11]

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11. Bacigalupo A. Antithymocyte globulin for prevention of graft-versus-host disease. *Curr Opin Hematol* 2005; 12: 457–62.

Adverse Effects, Treatment, and Precautions

Common adverse effects of *rabbit* and *horse* antilymphocyte immunoglobulins include fever, chills, myalgia, arthralgia, and skin reactions including rash, pruritus, and urticaria. Premedication with antihistamines and/or corticosteroids may prevent or reduce the intensity of adverse effects. Leucopenia and thrombocytopenia are also common. Although usually transient, dose adjustment may be needed if they become severe or prolonged. Platelet infusions may be needed in aplastic anaemia patients. Other common effects are gastrointestinal disturbances, headache, dyspnoea, hypotension, and pain. Hypertension, tachycardia, oedema, dizziness, malaise, and weakness can also occur. Infusion site reactions include pain, swelling, or redness; thrombophlebitis can be avoided by infusion into a vein with rapid blood flow.

As with other immunosuppressive drugs, infection (including CMV), reactivation of infection, and secondary malignancies (including lymphoma and post-transplant lymphoproliferative disease) have been reported.

Manifestations of serum sickness can occur, especially in aplastic anaemia patients; prophylaxis or treatment with corticosteroids may decrease the frequency of this reaction. Anaphylaxis is uncommon but serious; fatalities have been reported. The infusion should be stopped immediately and the patient managed accordingly (see p. 1293.2).

Aside from anaphylaxis, other serious immune-mediated reactions have been reported with *rabbit* antilymphocyte immunoglobulins including acute infusion-associated reactions, which have been attributed to the release of cytokines and can be fatal; premedication and reducing the infusion rate may minimise reaction incidence and intensity, and the first dose should be infused over a minimum of 6 hours into a vein with rapid blood flow. Hyperkalaemia has also been reported with the *rabbit* product.

To identify those at risk of anaphylaxis with *horse* antilymphocyte immunoglobulin, a skin sensitivity test is recommended before the first infusion, although the predictive value of this test is clinically unproven and reactions can occur after a negative test. However, if the test is positive, alternative therapy should be considered. Respiratory distress may indicate an anaphylactoid reaction, in which case the infusion should be stopped.

Other adverse effects that can occur with the *horse* product commonly include stomatitis, chest and/or back pain, and night sweats. Arteriovenous fistulas may clot. Pulminant haemolysis has been reported rarely; erythrocyte transfusion and appropriate treatment may be necessary, and the infusion stopped if haemolysis is severe or unremitting. Other adverse effects include laryngospasm, lymphadenopathy, paraesthesia, bradycardia, myocarditis, congestive heart failure, hepatosplenomegaly, seizures, toxic epidermal necrolysis, and wound dehiscence. Iliac vein obstruction, renal artery or deep-vein thrombosis, abnormal renal and/or liver function tests, acute renal failure, and proteinuria can also occur. A burning sensation in the soles or palms, soreness of the mouth or throat, and abnormal involuntary movements, tremor, or rigidity have also been reported.

Intra-uterine contraceptive devices should be used with caution during immunosuppressive treatment as there is an increased risk of infection. Use of live vaccines should generally be avoided for the same reason.

For the suggestion that use of *rabbit* rather than *horse* antilymphocyte immunoglobulins in the treatment of aplastic anaemia may be associated with reduced survival, and precautions for such use, see under Uses and Administration, p. 1939.3.

Effects on the kidneys. Acute renal failure has been reported after the use of antilymphocyte immunoglobulins.[1,2] Prolonged anuria requiring haemodialysis has occurred.[2]

1. Levine JM, *et al.* Antithymocyte globulin-induced acute renal failure. *Am J Kidney Dis* 1999; 34: 1155.
2. Barakat RK, *et al.* Prolonged renal failure secondary to antithymocyte globulin treatment in severe aplastic anemia. *Ann Pharmacother* 2007; 41: 895–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies *rabbit* antilymphocyte immunoglobulin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients. *Horse* antilymphocyte immunoglobulin is not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Linfoglobulina†; Timoglobulina: *Austral.*: Atgam; *Austria*: Thymoglobuline; *Belg.*: ATG; Thymoglobuline; *Braz.*: Thymoglobuline; *Canad.*: Atgam; Thymoglobulin; *Chile*: Linfoglobulina†; Thymogam; Timoglobulina; *China*: ATG (抗人T); Thymoglobuline (即复宁); *Cz.*: ATG; Thymoglobuline; *Denm.*: Thymoglobuline; *Fin.*: Thymoglobuline; *Fr.*: Lymphoglobuline†; Thymoglobuline; *Ger.*: Thymoglobulin; *Gr.*: ATG; Lymphoglobuline; Thymoglobuline: *Hong Kong*: ATG; Atgam; Thymoglobuline; *Hung.*: ATG; Thymoglobulin: *India*: Atgam; Lymphoglobuline: Thymoglobuline; *Irl.*: ATG: Thymoglobulin; *Israel*: ATG; Lymphoglobuline†; Thymoglobuline; *Ital.*: Thymoglobuline; *Jpn*: Thymoglobuline; *Malaysia*: Atgam; Thymoglobuline; *Mex.*: Atgam; Tecelac†; *Neth.*: ATG; Lymphoglobuline†; Thymoglobuline; *Norw.*: Thymoglobuline; *NZ*: Atgam; *Philipp.*: Thymogam; Thymoglobuline; *Pol.*: ATG; Lymphoglobuline†; Tecelac†; Thymoglobuline: *Port.*: Timoglobulina; *Rus.*: Antilipholine (Антилимфолин); ATG (АТГ); Atgam (Атгам); Thymoglobulin (Тимоглобулин); *S.Afr.*: Atgam†; Lymphoglobuline†; Thymoglobuline†; *Singapore*: ATG; Atgam; Thymoglobuline; *Spain*: Atege; Timoglobulina; *Swed.*: ATG; Thymoglobuline; *Switz.*: ATG; Lymphoglobuline†; Thymoglobuline; *Thai.*: ATG; Thymoglobuline; *Turk.*: ATG; Lymphoglobuline; Thymoglobuline; *UK*: Thymoglobuline; *Ukr.*: Atgam (Атгам)†; Thymoglobuline (Тимоглобулин)†; *USA*: Atgam; *Venez.*: Atgam.

Pharmacopoeial Preparations

Ph. Eur.: Anti-T Lymphocyte Immunoglobulin for Human Use, Animal.

Azathioprine *(BAN, USAN, rINN)*

Atsatiopriinl; Azathioprin; Azathioprinum; Azatioprin; Azatioprina; Azatioprinas; Azatiopryna; BW-57322; NSC-39084; Азатиоприн.

6-(1-Methyl-4-nitroimidazol-5-ylthio)purine.

$C_9H_7N_7O_2S$=277.3

CAS — 446-86-6.

ATC — L04AX01.

ATC Vet — QL04AX01.

UNII — MRK240IY2L.

NOTE. The abbreviation AZT, which has sometimes been used for azathioprine, has also been used to denote the antiviral zidovudine.

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

Ph. Eur. 8: (Azathioprine). A pale yellow powder. Practically insoluble in water and in alcohol; soluble in dilute solutions of alkali hydroxides; sparingly soluble in dilute mineral acids. Protect from light.

USP 36: (Azathioprine). A pale yellow, odourless powder. Insoluble in water; very slightly soluble in alcohol and in chloroform; sparingly soluble in dilute mineral acids; soluble in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Uses and Administration

Azathioprine is an immunosuppressive antimetabolite with similar actions to those of mercaptopurine (p. 820.3), to which it is converted in the body. Its effects may not be seen for several weeks after a dose. It is given orally, but where this is not feasible it may be given by slow intravenous injection or by infusion as azathioprine sodium. If given by infusion, the required dose should be diluted to a concentration of 0.25 to 2.5 mg/mL in sodium chloride 0.9% or glucose 5%, and infused over 30 to 60 minutes.

Azathioprine is mainly used as an immunosuppressant for the prevention of rejection in **organ and tissue transplantation** (p. 1932.2). The dose for this purpose, given orally or intravenously, varies from 1 to 5 mg/kg daily and depends partly on the regimen used; the higher doses are used initially, adjusted according to clinical response and haematological tolerance.

Azathioprine is also used in diseases with an **autoimmune or inflammatory** component, see below. The usual dose of azathioprine, given orally or intravenously, in these conditions is in the range of 1 to 3 mg/kg daily. If no improvement is seen after 3 to 6 months, therapy may be stopped.

For doses in children, see Administration in Children, p. 1941.1.

Use of azathioprine with a corticosteroid (p. 1597.3) may have a corticosteroid-sparing effect.

Blood counts should be carried out regularly during treatment and azathioprine withdrawn or the dosage reduced at the first indication of bone-marrow depression. Measurement of thiopurine methyltransferase (TPMT) activity may be used to identify patients at risk of haematological toxicity, although this cannot substitute for blood count monitoring.

Administration in children. UK licensed product information for azathioprine allows for the same doses in children as those used in adults (see Uses and Administration, p. 1940.3), both in organ and tissue transplantation and for diseases with an auto-immune or inflammatory component. The *BNFC* recommends that children aged 1 month to 18 years be given an oral or intravenous maintenance dose of 1 to 3 mg/kg once daily for suppression of **transplant rejection**; alternatively, the total daily dose may be given in 2 divided doses. For **severe ulcerative colitis and Crohn's disease**, the *BNFC* states that azathioprine may be given to children aged 2 to 18 years in an oral dose of 2 mg/kg (if necessary increased up to 2.5 mg/kg) once daily. For diseases with an **autoimmune** component such as SLE and vasculitis, the *BNFC* advises that azathioprine is usually used when corticosteroids alone are ineffective; children from 1 month to 18 years of age are given oral azathioprine in similar doses to those used in adults.

Administration in hepatic or renal impairment. UK licensed product information states that controlled studies have not supported the suggestion that toxicity of azathioprine might be enhanced in the presence of renal impairment. Nevertheless, doses used should be at the lower end of the normal range, and haematological response should be carefully monitored. US licensed product information also recommends low doses, while stating that relatively oliguric patients, especially those with tubular necrosis in the immediate post-cadaveric transplant period, may have delayed clearance of azathioprine and/or its metabolites.

UK licensed product information states that the metabolism of azathioprine may be impaired in patients with hepatic dysfunction; regular blood counts and liver function tests should be performed and the dosage of azathioprine reduced if hepatic or haematological toxicity occurs.

Blood disorders. Immunosuppressants such as azathioprine are occasionally tried in auto-immune haemolytic anaemia (p. 1122.2) refractory to other treatment and may permit reduction of corticosteroid dosage. Similarly in patients with immune thrombocytopenia (p. 1606.1), azathioprine may be tried as a second-line treatment option. Azathioprine with a corticosteroid has been tried in the rare condition of acquired haemophilia (p. 1126.3).

Cogan's syndrome. Azathioprine has been used with corticosteroids for severe Cogan's syndrome with large-vessel vasculitis (see p. 1603.2).

Connective tissue and muscular disorders. Azathioprine is one of many drugs tried for disease control in Behçet's syndrome[1] (p. 1601.1) and SLE[2] (p. 1613.3). In polymyositis (p. 1611.1), combined therapy with azathioprine and a corticosteroid has been found to be better than a corticosteroid alone for maintenance long-term.[3] However, there is also some evidence that methotrexate may be more effective in refractory polymyositis than azathioprine.[4]

1. Yazici H, *et al.* A controlled trial of azathioprine in Behçet's syndrome. *N Engl J Med* 1990; **322:** 281–5.
2. Abu-Shakra M, Shoenfeld Y. Azathioprine therapy for patients with systemic lupus erythematosus. *Lupus* 2001; **10:** 152–3.
3. Bunch TW. Prednisone and azathioprine for polymyositis: long-term followup. *Arthritis Rheum* 1981; **24:** 45–8.
4. Joffe MM, *et al.* Drug therapy of the idiopathic inflammatory myopathies: predictors of response to prednisone, azathioprine, and methotrexate and a comparison of their efficacy. *Am J Med* 1993; **94:** 379–87.

Inflammatory bowel disease. Azathioprine, or its metabolite mercaptopurine, is used to induce remission in chronically active inflammatory bowel disease (p. 1808.3), and to maintain remission, particularly in Crohn's disease.[1-3] They have a useful corticosteroid-sparing effect. Azathioprine may also be useful as a postoperative maintenance treatment in Crohn's disease.[4] In patients with ulcerative colitis, azathioprine may be an effective maintenance therapy for those who are refractory to or intolerant of mesalazine or sulfasalazine; it may also be useful for patients who require repeated courses of corticosteroids.[5]

Continuation of azathioprine therapy beyond 4 years has had conflicting results in terms of relapse rates and flare incidence. A randomised study in patients with Crohn's disease and in clinical remission, having been treated with azathioprine for at least 42 months, found that relapse rates were higher in those patients continued on placebo compared with those continued on azathioprine.[6] In another study of patients with corticosteroid-dependent Crohn's disease, a breakthrough of symptoms during continuous therapy was common, particularly after 48 months on azathioprine.[7] In an analysis of 1176 patients with inflammatory bowel disease, the authors concluded that stopping azathioprine therapy may be considered after 3 to 4 years in Crohn's disease patients in complete remission and without corticosteroid requirements but that continuation appears beneficial in all other Crohn's disease patients and for patients with ulcerative colitis.[8]

The onset of benefit from oral azathioprine may be delayed for several months.[1] One study[9] reported that a more rapid response could be achieved with an intravenous loading dose but a later study failed to confirm this.[10]

1. Prefontaine E, *et al.* Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 6. Chichester: John Wiley; 2010 (accessed 14/07/10).
2. Prefontaine E, *et al.* Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 06/10/09).
3. Fraser AG, *et al.* The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut* 2002; **50:** 485–9.
4. Myrelid P, *et al.* Azathioprine as a postoperative prophylaxis reduces symptoms in aggressive Crohn's disease. *Scand J Gastroenterol* 2006; **41:** 1190–5.
5. Timmer A, *et al.* Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 15/01/08).
6. Lémann M, *et al.* A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 2005; **128:** 1812–18.
7. Chebli JM, *et al.* Long-term results with azathioprine therapy in patients with corticosteroid-dependent Crohn's disease: open-label prospective study. *J Gastroenterol Hepatol* 2007; **22:** 268–74.
8. Holtmann MH, *et al.* Long-term effectiveness of azathioprine in IBD beyond 4 years: a European multicenter study in 1176 patients. *Dig Dis Sci* 2006; **51:** 1516–24.
9. Sandborn WJ, *et al.* An intravenous loading dose of azathioprine decreases the time to response in patients with Crohn's disease. *Gastroenterology* 1995; **109:** 1808–17.
10. Sandborn WJ, *et al.* Lack of effect of intravenous administration on time to respond to azathioprine for steroid-treated Crohn's disease: North American Azathioprine Study Group. *Gastroenterology* 1999; **117:** 527–35.

Leprosy. For mention of the use of azathioprine as a corticosteroid-sparing agent in the management of type 1 lepra reactions, see p. 188.3.

Liver disorders. Azathioprine has been widely used with corticosteroids to produce and maintain remission of chronic active hepatitis (p. 1602.3); such combination therapy, which also permits a reduction in corticosteroid dosage, is generally thought to be more effective than azathioprine alone. Patients successfully maintained in remission for at least a year on azathioprine with a corticosteroid can subsequently be maintained on azathioprine (at a dose of 2 mg/kg daily) alone.[1] Results in patients with primary biliary cirrhosis (p. 2638.3) have been more equivocal, and initial studies did not indicate much benefit from azathioprine, although a later study did seem to indicate improved survival and disease retardation.[2]

1. Johnson PJ, *et al.* Azathioprine for long-term maintenance of remission in autoimmune hepatitis. *N Engl J Med* 1995; **333:** 958–63.
2. Christensen E, *et al.* Beneficial effect of azathioprine and prediction of prognosis in primary biliary cirrhosis: final results of an international trial. *Gastroenterology* 1985; **89:** 1084–91.

Lung disorders. Corticosteroids remain the mainstay of treatment for the various forms of interstitial lung disease (p. 1607.1). In idiopathic pulmonary fibrosis there is weak evidence that combined therapy with azathioprine has some benefits,[1] but expert collaborative guidelines have suggested[2] that although prednisolone with azathioprine (in a dose of 2 to 3 mg/kg daily, up to a maximum of 150 mg daily) was previously recommended, this regimen should now only be considered when combined with oral acetylcysteine, and the regimen should be regarded as experimental pending further evidence.

1. Raghu G, *et al.* Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective double-blind, randomized, placebo-controlled clinical trial. *Am Rev Respir Dis* 1991; **144:** 291–6.
2. Wells AU, *et al.* Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008; **63** (suppl 5): v1–v58. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/DPLD/Guidelines/Thorax%20Sept%2008.pdf (accessed 12/01/10)

Neuromuscular disorders. Azathioprine may be used for its corticosteroid-sparing properties in patients who require corticosteroid treatment for myasthenia gravis (p. 684.1). It may also be of use when corticosteroids are contra-indicated or when response to corticosteroids alone is insufficient. Azathioprine is not usually used alone because it may be several months before any beneficial effect is seen. Some studies have also indicated modest benefit from azathioprine in patients with multiple sclerosis (p. 996.3). It has been suggested that the benefits are too slight to justify the toxicity of the required doses, but it has also been pointed out that in terms of relapse reduction azathioprine appears as effective as newer treatments such as interferon beta. For a recommendation that the cumulative dose of azathioprine should not exceed 600 g, see under Carcinogenicity, p. 1942.1.

Ocular disorders. For mention of the use of azathioprine in various disorders characterised by ocular lesions such as scleritis or uveitis, see p. 1932.1.

Polymyalgia rheumatica. Azathioprine may be used for its corticosteroid-sparing properties in patients who require corticosteroid treatment for polymyalgia rheumatica (p. 1610.3) and in whom withdrawal is difficult.

Psoriatic arthritis. Azathioprine may be useful for severe or progressive cases of psoriatic arthritis (see under Spondyloarthropathies, p. 14.3) when the arthritis is not controlled by physical therapy and NSAIDs.

Retroperitoneal fibrosis. There are reports[1,2] of success with azathioprine and corticosteroids in the treatment of retroperitoneal fibrosis (p. 1612.1).

1. Moroni G, *et al.* Long-term outcome of idiopathic retroperitoneal fibrosis treated with surgical and/or medical approaches. *Nephrol Dial Transplant* 2006; **21:** 2485–90.
2. Kisiel B, *et al.* Idiopathic retroperitoneal fibrosis: case report. *Pol Arch Med Wewn* 2009; **119:** 677–8.

Rheumatoid arthritis. Although azathioprine may be beneficial in rheumatoid arthritis (p. 13.2) in the short-term, its toxicity is significantly more severe than other disease-modifying antirheumatic drugs (DMARDs).[1] It may, however, be useful in patients with severe disease unresponsive to other DMARDs especially in those with extra-articular manifestations such as vasculitis.[2]

1. Suarez-Almazor ME, *et al.* Azathioprine for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 15/01/08).
2. Heurkens AHM, *et al.* Prednisone plus azathioprine treatment in patients with rheumatoid arthritis complicated by vasculitis. *Arch Intern Med* 1991; **151:** 2249–54.

Sarcoidosis. Cytotoxic immunosuppressants such as azathioprine have been tried in patients with sarcoidosis (p. 1612.2) who do not respond to or cannot tolerate corticosteroids.

Skin disorders. Like other immunosuppressants, azathioprine has been tried in various refractory skin disorders, notably in pemphigus and pemphigoid[1,2] (see p. 1942.1). Other conditions in which it has been tried include atopic eczema,[3-5] nodular prurigo,[9] chronic actinic dermatitis,[3,6] pyoderma gangrenosum,[4] erythema multiforme,[4,10] pompholyx, and plaque psoriasis,[6] as well as in the skin manifestations of systemic disorders such as dermatomyositis and lupus erythematosus.[2] Guidelines for the use of azathioprine in dermatology have been developed.[1] The recommended dose for azathioprine in dermatological disorders is 1 to 3 mg/kg daily, adjusted according to response. Treatment should be withdrawn if no response is seen within 3 months. Azathioprine should not be used in dermatology patients with very low or absent thiopurine methyltransferase (TPMT) activity (see Therapeutic Drug Monitoring, p. 1943.2), due to the danger of prolonged and severe myelosuppression (see Effects on the Blood, p. 1942.2). If azathioprine is given to patients with low TPMT activity, doses of 0.5 to 1 mg/kg daily should be used, with monitoring for myelosuppression. Patients with normal to high TPMT activity should be started on doses at the higher end of the range of 1 to 3 mg/kg daily; in those who do not respond, and have not had adverse effects, doses above this range may be considered for a trial period.

1. Anstey AV, *et al.* British Association of Dermatologists Therapy, Guidelines and Audit Subcommittee. Guidelines for prescribing azathioprine in dermatology. *Br J Dermatol* 2004; **151:** 1123–32. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Azathioprine.pdf (accessed 15/01/08)
2. Patel AA, *et al.* Azathioprine in dermatology: the past, the present, and the future. *J Am Acad Dermatol* 2006; **55:** 369–89.
3. Younger IR, *et al.* Azathioprine in dermatology. *J Am Acad Dermatol* 1991; **25:** 281–6.
4. Tan BB, *et al.* Azathioprine in dermatology: a survey of current practice in the UK. *Br J Dermatol* 1997; **136:** 351–3.
5. Lear JT, *et al.* A retrospective review of the use of azathioprine in severe atopic dermatitis. *Br J Dermatol* 1996; **135** (suppl 47): 38.
6. Scerri L. Azathioprine in dermatological practice: an overview with special emphasis on its use in non-bullous inflammatory dermatoses. *Adv Exp Med Biol* 1999; **455:** 343–8.
7. Murphy L-A, Atherton D. A retrospective evaluation of azathioprine in severe childhood atopic eczema, using thiopurine methyltransferase levels to exclude patients at high risk of myelosuppression. *Br J Dermatol* 2002; **147:** 308–15.
8. Meggitt SJ, *et al.* Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. *Lancet* 2006; **367:** 839–46.
9. Lear JT, *et al.* Nodular prurigo responsive to azathioprine. *Br J Dermatol* 1996; **134:** 1151.
10. Schofield JK, *et al.* Recurrent erythema multiforme: clinical features and treatment in a large series of patients. *Br J Dermatol* 1993; **128:** 542–5.

PEMPHIGUS AND PEMPHIGOID. Corticosteroids are the main treatment for blistering in pemphigus and pemphigoid (p. 1687.1). Other immunosuppressants may be added to maintain disease control and allow a reduction in corticosteroid dosage, and azathioprine is commonly used in this way in pemphigus vulgaris.[1] There is limited evidence to suggest that azathioprine may also be effective as monotherapy to induce remission in mild pemphigus.[1] Azathioprine has been used similarly in bullous pemphigoid, but there is some disagreement about its efficacy,[2] and guidelines suggest that it should only be considered if the corticosteroid cannot be reduced to an acceptable dose.[3]

1. Harman KE, *et al.* British Association of Dermatologists. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol* 2003; 149: 926–37. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Pemphigus%20Vulgaris.pdf (accessed 15/01/08)
2. Walsh SRA, *et al.* Bullous pemphigoid: from bench to bedside. *Drugs* 2005; 65: 905–26.
3. Wojnarowska F, *et al.* British Association of Dermatologists. Guidelines for the management of bullous pemphigoid. *Br J Dermatol* 2002; 147: 214–21. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Bullous%20Pemphigoid.pdf (accessed 15/01/08)

Vasculitic syndromes. Azathioprine has been tried in vasculitic syndromes, including giant cell arteritis (p. 1604.2), microscopic polyangiitis (p. 1610.2), Churg-Strauss syndrome (p. 1603.1), Takayasu's arteritis (p. 1614.3), and Wegener's granulomatosis (p. 1615.2). In general it is most useful in maintenance for its corticosteroid-sparing effect. Cyclophosphamide tends to be preferred where a more aggressive regimen is required, as in some combinations for induction of remission.

Adverse Effects

Dose-related bone-marrow depression is common with use of azathioprine; this may be manifested as leucopenia or, less often, thrombocytopenia or anaemia, and rarely, as agranulocytosis, pancytopenia, or aplastic anaemia. Myelosuppression is generally reversible, and may occasionally be delayed. Macrocytic, including megaloblastic, anaemia has occurred. Patients with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) may be at increased risk of myelotoxicity. Azathioprine has also been associated with the development of liver damage; it has been suggested that cholestatic symptoms may be due to the mercaptopurine moiety. Rarely, delayed and potentially fatal veno-occlusive liver disease has occurred.

Other adverse effects associated with azathioprine include gastrointestinal disturbances, reversible alopecia, and symptoms including rashes, muscle and joint pains, fever, rigors, pneumonitis, pancreatitis, tachycardia, renal dysfunction, and hypotension, some or all of which may represent hypersensitivity reactions. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported rarely.

Solutions for injection are irritant.

References.

1. Lawson DH, *et al.* Adverse effects of azathioprine. *Adverse Drug React Acute Poisoning Rev* 1984; 3: 161–71.

Carcinogenicity. Immunosuppression, including that with azathioprine, may be associated with an increased risk of certain neoplasms such as lymphomas and skin cancers in transplant recipients,[1] in patients with inflammatory bowel disease,[2-4] and in patients with rheumatoid arthritis.[5-7] Partly because of lower doses of immunosuppressants used in inflammatory bowel disease, the risk of lymphoma in these patients appears to be less than that associated with transplant recipients.[8] The hazard ratio in patients with inflammatory bowel disease treated with a thiopurine such as azathioprine has been estimated at just over 5 times that in patients who did not receive thiopurines;[4] however, the absolute cumulative risk over 10 years in young patients remained below 1% and was not considered to alter the positive risk-benefit ratio of such treatment. Rheumatic diseases may themselves be associated with an increased risk of malignancy that is independent of treatment, but one study[4] concluded that there is a further risk related to the duration of exposure to immunosuppressive drugs, including azathioprine. A recent systematic review[9] of the use of azathioprine for multiple sclerosis concluded that, when the balance between the benefits and harms were considered, azathioprine was a reasonable alternative to interferon beta in patients who frequently relapse and require corticosteroids. Other evidence in the literature suggested that the long-term risk of malignancy may be related to use for longer than 10 years and a cumulative dose above 600 g and the reviewers recommended that this dose should not be exceeded. Others have suggested an increased risk at cumulative doses in excess of 140 g; it was also suggested that the development of unexpected cytopenias in patients stabilised on long-term therapy may be a sign of increased risk of myelodysplasia or leukaemia.[10]

Skin cancer may be a particular risk in immunosuppressed patients with a history of high sun exposure.[8] Azathioprine treatment has been reported to cause photosensitisation of skin to UVA light, which could contribute to the development of skin cancers;[11] limiting exposure to UV light and use of sunscreens is recommended during azathioprine treatment.

1. Kinlen LJ, *et al.* Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs. *BMJ* 1979; 2: 1461–6.
2. Kandiel A, *et al.* Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005; 54: 1121–5.
3. Kwon JH, Farrell RJ. The risk of lymphoma in the treatment of inflammatory bowel disease with immunosuppressive agents. *Crit Rev Oncol Hematol* 2005; 56: 169–78.
4. Beaugerie L, *et al.* CESAME Study Group. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009; 374: 1617–25.
5. Silman AJ, *et al.* Lymphoproliferative cancer and other malignancy in patients with rheumatoid arthritis treated with azathioprine: a 20 year follow up study. *Ann Rheum Dis* 1988; 47: 988–92.
6. Asten P, *et al.* Risk of developing certain malignancies is related to duration of immunosuppressive drug exposure in patients with rheumatic diseases. *J Rheumatol* 1999; 26: 1705–14.
7. Patel P, *et al.* Azathioprine induced Hodgkin lymphoma: a case report and review of literature. *Am J Clin Oncol* 2005; 28: 427–8.
8. Boyle J, *et al.* Cancer, warts, and sunshine in renal transplant patients: a case-control study. *Lancet* 1984; i: 702–5.
9. Casetta I, *et al.* Azathioprine for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 24/01/08).
10. Kwong Y-L. Azathioprine: association with therapy-related myelodysplastic syndrome and acute myeloid leukemia. *J Rheumatol* 2010; 37: 485–90.
11. Perrett CM, *et al.* Azathioprine treatment photosensitizes human skin to ultraviolet A radiation. *Br J Dermatol* 2008; 159: 198–204.

Effects on the blood. Neutropenia in patients receiving mercaptopurine has been reported to correlate negatively with the concentration of the metabolite tioguanine nucleotide in erythrocytes,[1] and it has been suggested that measurement of metabolite concentrations in erythrocytes,[2] or activity of the enzyme thiopurine methyltransferase (TPMT),[3-6] permits prediction of those individuals likely to develop severe bone-marrow toxicity with mercaptopurine and the related drugs tioguanine and azathioprine. However, not all studies have found such correlations,[7] and effects on the bone marrow with this class of drugs are probably multifactorial;[8,9] low activity of other enzymes such as lymphocyte 5-nucleotidase,[10] and other factors, may contribute to toxicity. A review[9] of studies investigating TPMT activity in patients with Crohn's disease concluded that measurement of TPMT activity on starting azathioprine has a role in identifying those at risk of severe myelosuppression. Lower TPMT activities correlate with low neutrophil counts in the initial 4 months of thiopurine therapy; identification of the heterozygote might allow for safer management (see Therapeutic Drug Monitoring, p. 1943.2). However, in those patients established on therapy, TPMT did not predict clinical response or toxicity. Life-threatening myelotoxicity developed in a patient with normal TPMT activity who was treated with azathioprine for atopic eczema; myelosuppression was initially undetected despite a profound decrease in blood counts within the first 2 weeks of treatment.[11]

For the suggestion that unexpected cytopenias may be a warning sign of future malignant transformation see Carcinogenicity, above.

Pure red cell aplasia occurs rarely with use of azathioprine; reported cases have all been in renal transplant recipients. In one such case,[12] reduction of the dose and use of erythropoietin was ineffective; however, the patient recovered within weeks of stopping azathioprine.

1. Lennard L, *et al.* Childhood leukaemia: a relationship between intracellular 6-mercaptopurine metabolites and neutropenia. *Br J Clin Pharmacol* 1983; 16: 359–63.
2. Maddocks JL, *et al.* Azathioprine and severe bone marrow depression. *Lancet* 1986; i: 156.
3. Schütz E, *et al.* Azathioprine-induced myelosuppression in thiopurine methyltransferase deficient heart transplant recipient. *Lancet* 1993; 341: 436.
4. Lennard L, *et al.* Congenital thiopurine methyltransferase deficiency and 6-mercaptopurine toxicity during treatment for acute lymphoblastic leukaemia. *Arch Dis Child* 1993; 69: 577–9.
5. Jackson AP, *et al.* Thiopurine methyltransferase levels should be measured before commencing patients on azathioprine. *Br J Dermatol* 1997; 136: 133–4.
6. Black AJ, *et al.* Thiopurine methyltransferase genotype predicts therapy-limiting severe toxicity from azathioprine. *Ann Intern Med* 1998; 129: 716–18.
7. Boulieu R, *et al.* Intracellular thiopurine nucleotides and azathioprine myelotoxicity in organ transplant patients. *Br J Clin Pharmacol* 1997; 43: 116–18.
8. Soria-Royer C, *et al.* Thiopurine-methyl-transferase activity to assess azathioprine myelotoxicity in renal transplant recipients. *Lancet* 1993; 341: 1593–4.
9. Lennard L. TPMT in the treatment of Crohn's disease with azathioprine. *Gut* 2002; 51: 143–6.
10. Kerstens PJSM, *et al.* 5-Nucleotidase and azathioprine-related bone-marrow toxicity. *Lancet* 1993; 342: 1245–6.
11. Wee JS, *et al.* Life threatening myelotoxicity secondary to azathioprine in a patient with atopic eczema and normal thiopurine methyltransferase activity. *BMJ* 2011; 342: d1417.
12. Agrawal A, *et al.* Azathioprine-induced pure red cell aplasia: case report and review. *Transplant Proc* 2004; 36: 2689–91.

Effects on the liver. A review[1] of drug-related hepatotoxicity noted that azathioprine has been associated with hepatocanalicular cholestasis, in which the interference with bile flow is combined with hepatocyte damage, and with several hepatic vascular disorders, including focal sinusoidal dilatation, peliosis, and veno-occlusive disease. A later review[2] grouped reported cases into three syndromes: hypersensitivity, idiosyncratic cholestatic reaction, and presumed endothelial cell injury, with the imidazole and 6-mercaptopurine components of azathioprine playing different roles in pathogenesis.

1. Sherlock S. The spectrum of hepatotoxicity due to drugs. *Lancet* 1986; ii: 440–4.
2. Romagnuolo J, *et al.* Cholestatic hepatocellular injury with azathioprine: a case report and review of the mechanisms of hepatotoxicity. *Can J Gastroenterol* 1998; 12: 479–83.

Hypersensitivity. In 2 of 5 renal transplant recipients with acute allergic reactions associated with azathioprine, the symptoms (interstitial nephritis) were initially mistaken for acute rejection episodes.[1] In another report,[2] shock, fever, and acute renal insufficiency in a patient led to an initial mistaken diagnosis of sepsis, and it was recommended that a hypersensitivity reaction be considered as a cause if any of these symptoms occurred within 4 weeks of azathioprine ingestion. Other reported features of hypersensitivity include malaise, gastrointestinal disturbances, myalgia, arthralgia, fever, headache and raised liver enzymes.[3,4] Skin lesions have been reported, with maculopapular erythema occurring most frequently; purpura, urticaria, and erythema nodosum-like lesions have also been described.[4,5] Skin biopsies often showed features of leucocytoclastic vasculitis.[4] Sweet syndrome (acute febrile neutrophilic dermatosis)[6,7] and Stevens-Johnson syndrome[5] have also been reported. In some cases, skin patch testing for azathioprine was negative;[3,5] a drug-induced lymphocyte stimulation test (which evaluates the antigen specific reactivity of lymphocytes by measuring the proliferation of peripheral blood lymphocytes exposed to the suspected drug) has been proposed as a sensitive and reliable test for azathioprine hypersensitivity.[5]

Indirect hypersensitivity has also been reported; allergic contact dermatitis occurred on the genitals of a man whose wife had been taking azathioprine. During her treatment, vaginal secretions were noted to be yellow, indicating secretion of the drug or its metabolites. The husband, but not the wife, reacted to azathioprine patch tests.[8]

1. Parnham AP, *et al.* Acute allergic reactions associated with azathioprine. *Lancet* 1996; 348: 542–3.
2. Fields CL, *et al.* Hypersensitivity reaction to azathioprine. *South Med J* 1998; 91: 471–4.
3. Hinrichs R, *et al.* Azathioprine hypersensitivity in a patient with peripheral demyelinating polyneuropathy. *Br J Dermatol* 2003; 148: 1076–7.
4. Sinico RA, *et al.* Azathioprine hypersensitivity: report of two cases and review of the literature. *J Nephrol* 2003; 16: 272–6.
5. Mori H, *et al.* Drug eruption caused by azathioprine: value of using the drug-induced lymphocytes stimulation test for diagnosis. *J Dermatol* 2004; 31: 731–6.
6. el-Azhary RA, *et al.* Sweet syndrome as a manifestation of azathioprine hypersensitivity. *Mayo Clin Proc* 2008; 83: 1026–30.
7. Ylasemides E, Thom G. Azathioprine hypersensitivity presenting as a neutrophilic dermatosis in a man with ulcerative colitis. *Australas J Dermatol* 2009; 50: 48–51.
8. Cooper HL, *et al.* A case of conjugal azathioprine-induced contact hypersensitivity. *N Engl J Med* 2008; 359: 1324–6.

Precautions

Regular monitoring of blood counts is required. Patients with renal or hepatic impairment require more frequent monitoring of blood counts and may need reduced doses; liver function tests should be performed in hepatic impairment. Consideration should be given to testing patients for thiopurine methyltransferase (TPMT) activity. Intra-uterine devices should be used with caution during immunosuppressive treatment as there is an increased risk of infection. Use of live vaccines should be avoided for the same reason. Azathioprine should generally be avoided in pregnancy (see p. 1943.1).

For a recommendation that the cumulative dose of azathioprine should not exceed 600 g in patients with multiple sclerosis, see under Carcinogenicity, above.

Breast feeding. Low concentrations of mercaptopurine have been found in human colostrum and breast milk of patients taking azathioprine.[1] Breast feeding by these patients has not been recommended because of the potential risk of immunosuppression in the infant.[1-3] However, there are reports[1,2] of 3 breast-fed infants, whose mothers had been taking doses of 75 or 100 mg of azathioprine daily, in whom no evidence of immunosuppression was found. All 3 had normal blood counts, no increase in infections, and above average growth rate. In one case, the levels of mercaptopurine were determined at 2 days and after 2 weeks of breast feeding,[1] and in the other 2 cases, no levels were determined.[2] In a third report, 31 breast-milk samples were collected from 10 breast-feeding

women (taking from 75 to 150 mg azathioprine daily);[3] low concentrations of mercaptopurine were only detected in one case. The neonates were followed for up to 28 days, and showed no signs of immunosuppression, nor were mercaptopurine and tioguanine nucleotides detectable in their red blood cells. The authors concluded that breast feeding should not be withheld in infants of mothers receiving azathioprine. However, they cautioned that there were no data on the effect of thiopurine methyltransferase (TPMT) activity (see Therapeutic Drug Monitoring, below) on metabolite concentrations in breast milk, and expressed concern as to whether a TPMT-deficient infant, unable to inactivate mercaptopurine absorbed into the breast milk, will be exposed to significant blood levels of the drug. In a study of 4 mothers and their infants,[4] all of whom had the wild-type TPMT genotype (with normal TPMT activity), infant exposure to azathioprine through breast milk was undetectable. The authors also cautioned that mothers taking higher doses or those with decreased TPMT activity might transfer more drug to the infant. It has been noted[5] that many breast-fed infants would have already been exposed to potentially much higher concentrations of mercaptopurine *in utero*.

A study[6] evaluating the long-term development of children exposed to thiopurines during pregnancy and breast feeding, found that none of the 9 children who were breast fed had any differences in development compared with 21 formula-fed children; no adverse effects on development or immune function were seen in any children due to *in utero* exposure.

1. Coulam CB, *et al.* Breast-feeding after renal transplantation. *Transplant Proc* 1982; 14: 605–9.
2. Grekas DM, *et al.* Immunosuppressive therapy and breast-feeding after renal transplantation. *Nephron* 1984; 37: 68.
3. Sau A, *et al.* Azathioprine and breastfeeding—is it safe? *Br J Obstet Gynaecol* 2007; 114: 498–501.
4. Gardiner SJ, *et al.* Exposure to thiopurine drugs through breast milk is low based on metabolite concentrations in mother-infant pairs. *Br J Clin Pharmacol* 2006; 62: 453–6.
5. Moretti ME, *et al.* Breast-feeding during maternal use of azathioprine. *Ann Pharmacother* 2006; 40: 2269–72.
6. de Meij TG, *et al.* The Dutch Initiative on Crohn and Colitis. Long-term follow-up of children exposed intrauterine to maternal thiopurine therapy during pregnancy in females with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; 38: 38–43.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies azathioprine 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 05/10/11)

Pregnancy. Azathioprine and/or its metabolites have been found in low concentrations in fetal blood after maternal use of azathioprine.[1] Azathioprine is teratogenic in *animals*, and congenital abnormalities, chromosomal aberrations,[2] fetal growth retardation,[3,4] low birth-weight, and spontaneous abortion have been reported in the offspring of pregnant women taking azathioprine. Neonatal leucopenia and thrombocytopenia have also been reported after maternal exposure.[5] Cohort studies have found an increased risk of congenital abnormalities, perinatal mortality, and preterm births after maternal or paternal exposure to azathioprine.[6,7] However, adverse birth outcomes may be related to the underlying disease rather than use of azathioprine or mercaptopurine,[8] and some consider its use in inflammatory bowel disease to be safe and not associated with an increased risk of congenital malformations.[9–11] There was no effect on long-term development or immune function in a 6 year follow-up of children exposed *in utero*.[11] A meta-analysis[12] of studies in inflammatory bowel disease also found no increase in congenital malformations with thiopurines, but noted a higher risk of preterm birth.

The UK Teratology Information Service[13] considers that the data suggests azathioprine and mercaptopurine are safe in pregnancy, with no overall increased risk of an adverse pregnancy outcome. Although premature delivery and intra-uterine growth abnormalities have been reported following thiopurine use in pregnancy, the severity of maternal conditions and frequent use of multiple medications makes it difficult to attribute these outcomes to maternal use of thiopurines. It also noted that there were theoretical concerns about the effect maternal immunosuppression with thiopurines might have on the development of the neonatal immune system.

1. de Boer NKH, *et al.* Azathioprine use during pregnancy: unexpected intrauterine exposure to metabolites. *Am J Gastroenterol* 2006; 101: 1390–2.
2. The Registration Committee of the European Dialysis and Transplant Association. Successful pregnancies in women treated by dialysis and kidney transplantation. *Br J Obstet Gynaecol* 1980; 87: 839–45.
3. Pirson Y, *et al.* Retardation of fetal growth in patients receiving immunosuppressive therapy. *N Engl J Med* 1985; 313: 328.
4. Hou S. Retardation of fetal growth in patients receiving immunosuppressive therapy. *N Engl J Med* 1985; 313: 328.
5. Davison JM, *et al.* Maternal azathioprine therapy and depressed haemopoiesis in the babies of renal allograft patients. *Br J Obstet Gynaecol* 1985; 92: 233–9.
6. Nørgård B, *et al.* Azathioprine, mercaptopurine and birth outcome: a population-based cohort study. *Aliment Pharmacol Ther* 2003; 17: 827–34.
7. Nørgård B, *et al.* The risk of congenital abnormalities in children fathered by men treated with azathioprine or mercaptopurine before conception. *Aliment Pharmacol Ther* 2004; 19: 679–85.
8. Langagergaard V, *et al.* Birth outcome in women treated with azathioprine or mercaptopurine during pregnancy: a Danish nationwide cohort study. *Aliment Pharmacol Ther* 2007; 25: 73–81.
9. Alstead EM, *et al.* Safety of azathioprine in pregnancy in inflammatory bowel disease. *Gastroenterology* 1990; 99: 443–6.
10. Coelho J, *et al.* Pregnancy outcome in patients with inflammatory bowel disease treated with thiopurines: cohort from the CESAME Study. *Gut* 2011; 60: 198–203.
11. de Meij TG, *et al.* The Dutch Initiative on Crohn and Colitis. Long-term follow-up of children exposed intrauterine to maternal thiopurine therapy during pregnancy in females with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; 38: 38–43.
12. Akbari M, *et al.* Systematic review and meta-analysis on the effects of thiopurines on birth outcomes from female and male patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013; 19: 15–22.
13. UK Teratology Information Service. Use of azathioprine/6-mercaptopurine in pregnancy (issued December 2010). Available at: http://www.toxbase.org/upload/Pregnancy%20pdfs/Azathioprine%202010.pdf (accessed 30/05/13)

Interactions

The effects of azathioprine are enhanced by allopurinol and the dose of azathioprine should be reduced to one-third to one-quarter of the usual dose when allopurinol is given. A further dose reduction or alternative therapy should be considered in those patients with low or absent thiopurine methyltransferase (TPMT) activity.

In addition to being affected by allopurinol, azathioprine may itself affect other drugs including the following:

- competitive neuromuscular blockers (antagonism, see under Immunosuppressants on p. 2033.1)
- vaccines (reduced response or generalised infection, see p. 2375.3)
- warfarin (inhibition, see Immunosuppressants p. 1534.2).

Gastrointestinal drugs. For mention of *5-aminosalicylates* inhibiting the metabolism of thiopurines such as azathioprine, and increasing their toxicity, see Mercaptopurine, p. 822.1.

Mercaptopurine. The Institute for Safe Medication Practices in the USA reported a case in which a patient with a history of Crohn's disease was prescribed azathioprine and mercaptopurine by separate practitioners. The patient developed profound myelosuppression, severe sepsis, and died. Many drug information software programs were found to not warn of this possible therapeutic duplication.[1]

1. Institute for Safe Medication Practices. Duplication with azathioprine and mercaptopurine (issued 29 June, 2006). Available at: http://www.ismp.org/Newsletters/acutecare/articles/20060629_3.asp?ptr=y (accessed 15/01/08)

Pharmacokinetics

Azathioprine is well absorbed from the gastrointestinal tract when given orally. After oral or intravenous doses it disappears rapidly from the circulation and is extensively metabolised to mercaptopurine (which is then further metabolised—see p. 822.1). Both azathioprine and mercaptopurine are about 30% bound to plasma proteins. About 10% of a dose of azathioprine is reported to be split between the sulfur and the purine ring to give 1-methyl-4-nitro-5-thioimidazole. The proportion of different metabolites is reported to vary between patients. Metabolites and small amounts of unchanged azathioprine and mercaptopurine are eliminated in the urine. Azathioprine is distributed into breast milk in low concentrations.

Therapeutic drug monitoring. Although plasma concentrations of 6-thiouric acid (the inactive product of mercaptopurine, and hence of azathioprine) can be readily measured in patients who have been receiving azathioprine, they are of little value in therapeutic drug monitoring.[1] The active moieties are the tioguanine nucleotides (6-TGN) formed intracellularly, which appear to have extremely long half-lives,[2] and mean erythrocyte concentrations of which appear to vary considerably between individuals.[2] The formation of other inactive metabolites is catalysed by thiopurine methyltransferase (TPMT) and its activity is genetically determined, with a trimodal distribution in the general population; 0.3% have low activity of TPMT, 11% have intermediate activity, and 89% have normal or high activity. Patients with low or intermediate activity appear to shift metabolism toward production of 6-TGN.

Because excess concentrations of 6-TGN have been associated with leucopenia, it has been suggested[3] that:

- patients with normal or high TPMT activity receive standard doses of azathioprine or mercaptopurine
- those with intermediate TPMT activity have reduced doses
- those with low activity not be treated with either drug

However, these recommendations remain controversial.[4] Haematological toxicity is not always explained by TPMT status, and other factors may be involved[5] (see also Effects on the Blood, p. 1942.2). Some consider that TPMT deficiency is not a contra-indication to thiopurine therapy; an initial dose reduction to 10 to 15% of the standard azathioprine dose has been used in TPMT-deficient patients with inflammatory bowel disease.[5] There are a proportion of patients in whom TPMT activity is very high; these patients appear to respond less well to standard doses, and higher-than-standard doses have been recommended.[6] While recommendations for pretreatment measurement of TPMT status remain controversial,[4,5] some consider the avoidance of potentially fatal toxicity a compelling argument for TPMT assessment before thiopurine therapy is started;[6] although becoming more common in the UK, there may be differences between medical specialties in the frequency with which testing is used.[7] However, TPMT units and normal ranges vary between laboratories depending on the methodology used,[6] and TPMT genotype or phenotype testing is not a surrogate for monitoring of complete blood counts.[4]

Because low concentrations of erythrocyte 6-TGN have been associated with disease relapse in lymphomas and leukaemias, a small study[8] of patients with inflammatory bowel disease attempted to define a therapeutic window of drug efficacy. Without monitoring TPMT genotype, treatment efficacy was found to correlate with erythrocyte 6-TGN levels. It was concluded that patients who remain symptomatic despite apparently therapeutic 6-TGN concentrations should be treated with adjunctive or alternative immunosuppression or surgery. However, a large study[9] did not confirm disease correlation with 6-TGN concentrations, and concluded that therapeutic drug monitoring of 6-TGN may be premature. It was noted that methodological differences, such as assay technique, existed between their study and others. As the role of routine monitoring of 6-TGN remains controversial,[4,10,11] it has been suggested that selective monitoring, such as in those with low or intermediate TPMT activity, be considered.[3] Some consider the measurement of 6-TGN useful to assess treatment compliance, or in cases of malabsorption.[4]

1. Chan GLC, *et al.* Pharmacokinetics of 6-thiouric acid and 6-mercaptopurine in renal allograft recipients after oral administration of azathioprine. *Eur J Clin Pharmacol* 1989; 36: 265–71.
2. Chan GLC, *et al.* Azathioprine metabolism: pharmacokinetics of 6-mercaptopurine, 6-thiouric acid and 6-thioguanine nucleotides in renal transplant patients. *J Clin Pharmacol* 1990; 30: 358–63.
3. Sandborn WJ. Rational dosing of azathioprine and 6-mercaptopurine. *Gut* 2001; 48: 591–2.
4. Lichtenstein GR. Use of laboratory testing to guide 6-mercaptopurine/azathioprine therapy. *Gastroenterology* 2004; 127: 1558–64.
5. Teml A, *et al.* Thiopurine treatment in inflammatory bowel disease: clinical pharmacology and implication of pharmacogenetically guided dosing. *Clin Pharmacokinet* 2007; 46: 187–208.
6. Sanderson J, *et al.* Thiopurine methyltransferase: should it be measured before commencing thiopurine drug therapy? *Ann Clin Biochem* 2004; 41: 294–302.
7. Anonymous. TPMT testing before azathioprine therapy?. *Drug Ther Bull* 2009; 47: 9–12.
8. Cuffari C, *et al.* Utilisation of erythrocyte 6-thioguanine metabolite levels to optimise azathioprine therapy in patients with inflammatory bowel disease. *Gut* 2001; 48: 642–6.
9. Lowry PW, *et al.* Measurement of thiopurine methyltransferase activity and azathioprine metabolites in patients with inflammatory bowel disease. *Gut* 2001; 49: 665–70.
10. Dubinsky MC. Monitoring of AZA/6-MP treatment in children with IBD is necessary. *Inflamm Bowel Dis* 2003; 9: 386–8.
11. Griffiths AM. Monitoring of azathioprine/6-mercaptopurine treatment in children with IBD is not necessary. *Inflamm Bowel Dis* 2003; 9: 389–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Imuran; *Austral.*: Azahexal†; Azamun; Azapin; Imuran; Thioprine; *Austria*: Azaglax†; Immunoprin; Imurek; *Belg.*: Imuran; *Braz.*: Imunen; Imuran; *Canad.*: Imuran; *Chile*: Imuran; *China*: Imuran (依木兰); *Cz.*: Azaprine; Immunoprin; Imuran; *Denm.*: Azathiodura; Azathioregio; Immunoprin; Imurel; *Fin.*: Azamun; Imurel; *Fr.*: Imurel; *Ger.*: Aza-Q†; Azafalk; Azaimun; Colinsan†; Imurek; Zytrim†; *Gr.*: Azapress; Imuran; *Hong Kong*: Imuprin; Imuran; *Hung.*: Imuran; *India*: Azap; Azimune; Azoprine; Azoran; Imuran; Imuzat; Transimune; *Indon.*: Imuran; *Irl.*: Imuger; Imuran; *Israel*: Azopi; Imuran; *Ital.*: Azafor; Immunoprin; *Malaysia*: Azamun; Imuran; *Mex.*: Azatilem; Imuran; *Neth.*: Azafalk; Immunoprin; Imuran; *Norw.*: Imurel; *NZ*: Azamun; Imuprine; Imuran; Thioprine†; *Philipp.*: Imuran; *Pol.*: Imuran; *Port.*: Imuran; *Rus.*: Imuran (Имуран); *S.Afr.*: Azamun; Azapress; Imuran; Zaprine; *Singapore*: Azafrine; Imuran; *Spain*: Imurel; *Swed.*: Immunoprin; Imurel; *Switz.*: Azaimun; Azarek; Imurek; *Thai.*: Azadus; Imuprin; Imuran; Zinothin; *Turk.*: Imuran; *UK*: Imuran; *USA*: Azasan; Imuran; *Venez.*: Azaprin.

Multi-ingredient Preparations. *Ger.*: Azamedac.

The symbol † denotes a preparation no longer actively marketed

Pharmacopoeial Preparations
BP 2014: Azathioprine Oral Suspension; Azathioprine Tablets; USP 36: Azathioprine Oral Suspension; Azathioprine Sodium for Injection; Azathioprine Tablets.

Basiliximab *(BAN, USAN, rINN)*

Basiliksimab; Basiliksimabi; Basiliximabum; chRFT5; SDZ-CHI-621; Базиликсимаб.
Immunoglobulin G1, anti-(human interleukin 2 receptor) (human-mouse monoclonal CHI621 γ1-chain), disulfide with human-mouse monoclonal CHI621 light chain, dimer.
CAS — 179045-86-4.
ATC — L04AC02.
ATC Vet — QL04AC02.
UNII — 9927MT646M.

Uses and Administration

Basiliximab is a chimeric murine/human monoclonal antibody similar to daclizumab (p. 1957.1) that functions as an interleukin-2 receptor antagonist by binding to the alpha chain (CD25 antigen) of the interleukin-2 receptor on the surface of activated T-lymphocytes. It is used in the prevention of acute graft rejection episodes in patients undergoing renal transplantation, and is given as part of an immunosuppressive regimen that includes ciclosporin and corticosteroids; azathioprine or mycophenolate mofetil may also be added to the regimen. Doses are given either as an intravenous bolus, or diluted to a usual concentration of 400 micrograms/mL in sodium chloride 0.9% or glucose 5%, for infusion over 20 to 30 minutes. The recommended dose for adults is 20 mg, given within 2 hours before transplant surgery and repeated once after 4 days. (For children's doses, see Administration in Children, below). The second dose should be withheld if graft loss or a severe hypersensitivity reaction occurs.

Administration in children. Licensed product information recommends the following intravenous doses of basiliximab in children over 1 year of age, for prophylaxis of acute rejection in allogeneic renal transplantation, as part of an immunosuppressive regimen containing ciclosporin and corticosteroids:

- body-weight under 35 kg: 10 mg within 2 hours before transplantation surgery; 10 mg 4 days after surgery
- body-weight 35 kg or more: 20 mg within 2 hours before transplantation surgery; 20 mg 4 days after surgery (same as adults, see Uses and Administration, above)

Doses may be given either as an intravenous bolus, or diluted to a usual concentration of 400 micrograms/mL in sodium chloride 0.9% or glucose 5%, for infusion over 20 to 30 minutes.

Organ and tissue transplantation. Basiliximab is used as induction therapy to reduce the incidence of acute rejection episodes after kidney transplantation (p. 1935.2), including paediatric renal transplant recipients; it is usually given as part of an immunosuppressive regimen that includes ciclosporin and corticosteroids. A small study found that basiliximab significantly reduced the occurrence of rejection episodes in those treated with dual therapy (calcineurin inhibitor and corticosteroids) but not in those given triple therapy (including mycophenolate).[1] In a study of paediatric renal transplant recipients, addition of basiliximab to a tacrolimus-based regimen was safe, but did not result in a lower incidence of rejection episodes.[2] There is some suggestion that antilymphocyte immunoglobulins may be more effective than basiliximab in reduction of acute rejection in adult renal transplant patients,[3,4] although some consider basiliximab to offer improved clinical efficacy over antilymphocyte immunoglobulin induction in paediatric patients,[5] and others have commented[6] that graft survival at 12 months has been similar with each drug. Reviews[7-9] have concluded that the use of basiliximab in renal transplantation is safe and effective, with reduced rates of acute rejection, but no long-term benefit in terms of graft survival; basiliximab appears to allow the safe withdrawal of corticosteroids or the use of corticosteroid-free immunosuppressive regimens.

There is a short report suggesting that the use of a single dose is as effective as the standard 2-dose regimen in renal transplantation in terms of the incidence of acute rejection.[10]

Basiliximab has also been investigated in liver transplantation (p. 1936.3). Given with dual therapy to adult patients, it was found to reduce the incidence of acute rejection episodes in the first year when compared with placebo, including patients positive for hepatitis C.[11] Basiliximab with dual therapy also reduced the incidence of acute graft rejection in small paediatric studies.[12,13] In paediatric liver transplantation, corticosteroid-free immunosuppressive regimens using basiliximab and tacrolimus have been associated with significantly lower rejection rates at 1 year than corticosteroid-based regimens.[14,15]

Basiliximab has been investigated for the prevention of rejection in heart,[16,17] lung,[18,19] and pancreatic transplantation (see p. 1934.2, p. 1937.3, and p. 1938.1, respectively). It has been reported to be effective[20] in the treatment of corticosteroid-refractory acute graft-versus-host disease (GVHD; see Haematopoietic Stem Cell Transplantation, p. 1933.1).

1. Lee BM, *et al.* Effect of basiliximab on renal allograft rejection within 1 year after transplantation. *Transplant Proc* 2006; 38: 2025–8.
2. Grenda R, *et al.* A prospective, randomized, multicenter trial of tacrolimus-based therapy with or without basiliximab in pediatric renal transplantation. *Am J Transplant* 2006; 6: 1666–72.
3. Heilman RL, *et al.* Acute rejection risk in kidney transplant recipients on steroid-avoidance immunosuppression receiving induction with either antithymocyte globulin or basiliximab. *Transplant Proc* 2006; 38: 1307–13.
4. Brennan DC, *et al.* Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 2006; 355: 1967–77.
5. Clark G, *et al.* Improved efficacy of basiliximab over antilymphocyte globulin induction therapy in paediatric renal transplantation. *Nephrol Dial Transplant* 2002; 17: 1304–9.
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18. Hachem RR, *et al.* A comparison of basiliximab and anti-thymocyte globulin as induction agents after lung transplantation. *J Heart Lung Transplant* 2005; 24: 1320–6.
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Skin disorders. There are a few case reports of successful treatment with basiliximab in psoriasis[1-4] (p. 1688.1), chronic atopic dermatitis[5] (see Eczema, p. 1684.1), lichen planus,[6] and epidermolysis bullosa acquisita[7] (p. 1684.3).

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Adverse Effects and Precautions

Severe acute hypersensitivity reactions have occurred rarely with basiliximab. These have included anaphylactoid-type reactions such as rash, urticaria, pruritus, sneezing, hypotension, tachycardia, cardiac failure, wheezing, dyspnoea, bronchospasm, pulmonary oedema, and respiratory failure. Capillary leak syndrome and cytokine release syndrome have been reported. Reactions have been seen both on initial exposure and with subsequent therapy. Patients in whom other immunosuppression was prematurely stopped, after initial therapy with basiliximab, appear to be at increased risk of hypersensitivity reactions. Therapy should be permanently stopped if a severe reaction occurs.

Giving basiliximab as a bolus may cause nausea, vomiting, and local reactions, including pain.

It is generally recommended that basiliximab is avoided during pregnancy or breast feeding; contraception is recommended before starting, during, and up to 4 months after treatment.

Effects on glucose tolerance. It has been suggested[1] that use of basiliximab in immunosuppressant regimens for kidney transplantation may be associated with the development of impaired glucose homoeostasis.

1. Assebo W, *et al.* Impaired glucose homeostasis in renal transplant recipients receiving basiliximab. *Nephrol Dial Transplant* 2010; 25: 1289–93.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies basiliximab 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 05/10/11)

Pharmacokinetics

Basiliximab has a terminal half-life of about 7 days in adults and about 9 days in children.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Simulect; *Austral.*: Simulect; *Belg.*: Simulect; *Braz.*: Simulect; *Canad.*: Simulect; *Chile*: Simulect; *China*: Simulect (舒莱); *Cz.*: Simulect; *Denm.*: Simulect; *Fin.*: Simulect; *Fr.*: Simulect; *Ger.*: Simulect; *Gr.*: Simulect; *Hong Kong*: Simulect; *Hung.*: Simulect; *Indon.*: Simulect; *Irl.*: Simulect; *Israel*: Simulect; *Ital.*: Simulect; *Malaysia*: Simulect; *Mex.*: Simulect; *Neth.*: Simulect; *Norw.*: Simulect; *NZ*: Simulect; *Philipp.*: Simulect; *Pol.*: Simulect; *Port.*: Simulect; *Rus.*: Simulect (Симулект); *S.Afr.*: Simulect; *Singapore*: Simulect; *Spain*: Simulect; *Swed.*: Simulect; *Switz.*: Simulect; *Thai.*: Simulect; *Turk.*: Simulect; *UK*: Simulect; *Ukr.*: Simulect (Симулект); *USA*: Simulect; *Venez.*: Simulect.

Belatacept *(USAN, rINN)*

Bélatacept; Belatacepte; Belataceptum; BMS-224818; LEA-29Y; Белатацепт.
CAS — 706808-37-9.
ATC — L04AA28.
ATC Vet — QL04AA28.
UNII — E3B2GI648A.

Uses and Administration

Belatacept is a derivative of abatacept (p. 15.2). It is a fusion protein and co-stimulation blocker that prevents T-cell activation. Belatacept is used for the prevention of organ rejection in adults undergoing kidney transplantation (p. 1935.2), and who are seropositive for the Epstein-Barr virus. It is used with basiliximab induction, mycophenolate mofetil, and corticosteroids.

Belatacept is reconstituted with a suitable diluent (sterile water for injection, sodium chloride 0.9%, or glucose 5%) using a silicone-free syringe. For intravenous infusion, it is further diluted in a suitable infusion fluid (sodium chloride 0.9% or glucose 5%) to a final concentration ranging from 2 mg/mL to 10 mg/mL (typically, 100 mL will be appropriate, although total infusion volumes range from 50 mL to 250 mL). Belatacept is infused over 30 minutes, via an infusion set with a non-pyrogenic, low-protein-binding filter (0.2 to 1.2 micrometres).

The total infusion dose of belatacept is based on the body-weight of the patient at the time of transplantation and should not be modified during the course of therapy, unless there is a change in body-weight of greater than 10%. The dosing for the *initial* phase is as follows:

- day 1 (day of transplantation, before implantation): 10 mg/kg
- day 5 (about 96 hours after day 1 dose): 10 mg/kg
- end of week 2 and week 4: 10 mg/kg
- end of week 8 and week 12: 10 mg/kg

Dosing in the *maintenance* phase is:

- end of week 16 and every 4 weeks (±3 days) thereafter: 5 mg/kg

The dose prescribed for the patient must be evenly divisible by 12.5 mg, in order for the dose to be prepared accurately using the reconstituted solution and the silicone-free syringe. *For example: if a patient weighs 64 kg, the dose at 10 mg/kg equals 640 mg; the closest dose divisible by 12.5 mg is 637.5 mg, which is then prescribed.*

References.

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5. Vincenti F, *et al.* Five-year safety and efficacy of belatacept in renal transplantation. *J Am Soc Nephrol* 2010; 21: 1587–96.

6. Larsen CP, *et al.* Belatacept-based regimens versus a cyclosporine A-based regimen in kidney transplant recipients: 2-year results from the BENEFIT and BENEFIT-EXT studies. *Transplantation* 2010; 90: 1528–35.
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8. Vanrenterghem Y, *et al.* Belatacept-based regimens are associated with improved cardiovascular and metabolic risk factors compared with cyclosporine in kidney transplant recipients (BENEFIT and BENEFIT-EXT studies). *Transplantation* 2011; 91: 976–83.

Adverse Effects, Treatment, and Precautions

The most common adverse effects associated with belatacept are anaemia, leucopenia, gastrointestinal disturbances, urinary-tract infections, peripheral oedema, hypertension, fever, cough, headache, and hypokalaemia or hyperkalaemia.

Patients taking immunosuppressants are at increased risk for the development of secondary malignancies. Post-transplant lymphoproliferative disorder (PTLD), mainly involving the CNS, has been reported; the risk of PTLD was higher in patients who were seronegative for the Epstein-Barr virus (EBV), and these patients, or those whose EBV serostatus is unknown, should not be given belatacept. Other risk factors for PTLD include CMV infection and T-cell depleting therapy; CMV prophylaxis is recommended for at least 3 months after transplantation, and T-cell depleting therapy to treat acute rejection should be used with caution. Non-melanoma skin cancer has also been reported, and exposure to sunlight or UV light should be limited; the use of protective clothing and sunscreen is advised.

Serious, and potentially fatal, infections can occur with immunosuppressants, and antibacterial prophylaxis is recommended after transplantation. Progressive multifocal leukoencephalopathy, caused by the JC virus, has been reported rarely, especially at higher cumulative doses or more frequent dosing of belatacept. Cases of polyoma virus-associated nephropathy have also been reported.

Other adverse effects include electrolyte disturbances, increased creatinine, dyslipidaemia, dyspnoea, hypotension, dizziness, tremor, anxiety, insomnia, acne, alopecia, hyperhidrosis, arthralgia, musculoskeletal pain, haematoma, and lymphocele. Atrial fibrillation may occur. Renal and urinary disorders include haematuria, proteinuria, dysuria, renal tubular necrosis, renal impairment (including acute renal failure), urinary incontinence, and hydronephrosis.

Live vaccines should not be given with belatacept.

Interactions

For precations about the use of live vaccines with belatacept, see Adverse Effects, Treatment, and Precautions, above.

Pharmacokinetics

Belatacept is reported to have linear pharmacokinetics at usual dosages. Steady-state concentrations occur by week 8 in the initial phase after transplantation and by month 6 during the maintenance phase (see Uses and Administration, p. 1944.3). After repeated intravenous doses of 10 mg/kg and 5 mg/kg belatacept in renal transplant patients, its mean terminal half-life is about 9.8 days and about 8.2 days, respectively. There is a trend towards higher clearance of belatacept with increasing body-weight.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Nulojix; ***Fr.***: Nulojix; ***Ger.***: Nulojix; ***Irl.***: Nulojix; ***Israel***: Nulojix; ***Ital.***: Nulojix; ***Neth.***: Nulojix; ***Norw.***: Nulojix; ***Swed.***: Nulojix; ***Switz.***: Nulojix; ***UK***: Nulojix; ***USA***: Nulojix.

Belimumab *(USAN, rINN)*

Bélimumab; Belimumabum; Белимумаб.

Immunoglobulin G1, anti-(human cytokine BAFF) (human monoclonal LymphoStat-B heavy chain), disulfide with human monoclonal LymphoStat-B λ-chain, dimer.

CAS — 356547-88-1.
ATC — L04AA26.
ATC Vet — QL04AA26.
UNII — 7380K5S26A.

NOTE. The name LymphoStat-B has been used as a trade mark for belimumab.

Uses and Administration

Belimumab is a human monoclonal antibody (p. 2561.1) that inhibits B-lymphocyte stimulator (BLyS; BAFF; TNFSF13B; a naturally occurring protein required for B lymphocyte development). Belimumab is used for the treatment of adults with active, autoantibody-positive SLE (p. 1613.3) who are receiving standard therapy. As experience is lacking, use is not recommended in patients with severe active lupus nephritis or severe active CNS disease. The recommended dose is 10 mg/kg intravenously every 2 weeks for the first 3 doses, and every 4 weeks thereafter. The dose is diluted in 250 mL of sodium chloride 0.9% and infused over 1 hour. Belimumab is under investigation for other auto-immune diseases such as rheumatoid arthritis.

References.
1. Ding C. Belimumab, an anti-BLyS human monoclonal antibody for potential treatment of inflammatory autoimmune diseases. *Expert Opin Biol Ther* 2008; 8: 1805–14.
2. Wallace DJ, *et al.* A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. *Arthritis Rheum* 2009; 61: 1168–78.
3. Jacobi AM, *et al.* Effect of long-term belimumab treatment on B cells in systemic lupus erythematosus: extension of a phase II, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum* 2010; 62: 201–10.
4. Navarra SV, *et al.* BLISS-52 Study Group. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011; 377: 721–31.
5. Thanou-Stavraki A, Sawalha AH. An update on belimumab for the treatment of lupus. *Biologics* 2011; 5: 33–43.
6. Sanz I, *et al.* Belimumab. *Nat Rev Drug Discov* 2011; 10: 335–6.

Adverse Effects, Treatment, and Precautions

The most common adverse effects with belimumab are nausea, diarrhoea, fever, insomnia, pain in extremities, and migraine. Depression is common, and can be serious, especially in those with a history of depressive or psychiatric disorders; suicide has been reported, although it is unknown whether belimumab therapy is associated with an increased risk for suicidal behaviour.

Serious and sometimes fatal infections, including pneumonia, urinary-tract infections, cellulitis, and bronchitis, have been reported in patients treated with belimumab, and treatment should not be started in those with chronic infections; belimumab should be stopped if a patient develops an infection. Other common infections include upper respiratory-tract infection, nasopharyngitis, sinusitis, and influenza.

The signs and symptoms of hypersensitivity reactions and infusion reactions are similar, and these are common on the day of belimumab infusion, despite premedication. Manifestations include rash, urticaria, pruritus, hypotension, dyspnoea, angioedema, bradycardia, myalgia, and headache. Anaphylaxis has also been reported.

Secondary malignancies can occur after immunosuppressive treatment and malignancies including non-melanoma skin cancer have been reported rarely after belimumab treatment. Live vaccines should not be given with belimumab, or for 30 days before treatment.

Interactions

For precautions about the use of live vaccines with belimumab, see Adverse Effects, Treatment, and Precautions, above.

Pharmacokinetics

After intravenous use, serum belimumab concentrations decline in a bi-exponential manner, with a distribution half-life of about 40 hours and a terminal half-life of about 19 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Benlysta; ***Canad.***: Benlysta; ***Denm.***: Benlysta; ***Ger.***: Benlysta; ***Israel***: Benlysta; ***Neth.***: Benlysta; ***Norw.***: Benlysta; ***Spain***: Benlysta; ***Swed.***: Benlysta; ***Switz.***: Benlysta; ***UK***: Benlysta; ***USA***: Benlysta.

Ciclosporin *(BAN, rINN)*

27-400; Ciclosporina; Ciclosporina A; Ciclosporine; Ciclosporinum; Ciklosporin; Ciklosporinas; Cyclosporin; Cyclosporin A; Cyclosporine (USAN); Cyklosporin; OL-27-400; Siklosporiini; Siklosporin; Циклоспорин.

Cyclo[-[4-(*E*)-but-2-enyl-*N*,4-dimethyl-L-threonyl]-L-homoalanyl-(*N*-methylglycyl)-(*N*-methyl-L-leucyl)-L-valyl-(*N*-methyl-L-leucyl)-L-alanyl-D-alanyl-(*N*-methyl-L-leucyl)-(*N*-methyl-L-leucyl)-(*N*-methyl-L-valyl)-].

$C_{62}H_{111}N_{11}O_{12}$=1202.6

CAS — 59865-13-3.
ATC — L04AD01; S01XA18.
ATC Vet — QL04AD01; QS01XA18.
UNII — 83HN0GTJ6D.

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

Ph. Eur. 8: (Ciclosporin). A substance produced by *Beauveria nivea* (=*Tolypocladium inflatum* Gams) or obtained by any other means. A white or almost white powder; practically insoluble in water; freely soluble in dehydrated alcohol and in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Cyclosporine). A white to almost white powder. Practically insoluble in water; soluble in alcohol, in acetone, in chloroform, in dichloromethane, in ether, and in methyl alcohol; slightly soluble in saturated hydrocarbons. Store in airtight containers. Protect from light.

Incompatibility. The plasticiser diethylhexyl phthalate, which is a possible carcinogen, was leached from PVC containers by ciclosporin preparations containing polyoxyl castor oil.[1] Such preparations should not be given through PVC tubing nor stored in PVC containers. Polysorbate 80, which is an excipient in other ciclosporin preparations, also leached plasticiser from PVC,[1] and similar precautions would apply to preparations so formulated. UK licensed product information further recommends that containers and stoppers be free of silicone oil and fatty substances.

For reported incompatibility between ciclosporin and mycophenolate, see Incompatibility, under Mycophenolate, p. 1961.2.

1. Pearson SD, Trissel LA. Leaching of diethylhexyl phthalate from polyvinyl chloride containers by selected drugs and formulation components. *Am J Hosp Pharm* 1993; 50: 1405–9.

Stability. Ciclosporin was stable over 72 hours after dilution in glucose 5% or glucose/amino-acid solutions and storage at room temperature in the dark; similar stability was seen after dilution in lipid emulsion, but dilutions in sodium chloride 0.9% were considered to be stable only for 8 hours.[1] In all cases miscibility in the diluent was poor and vigorous shaking was required after addition to produce even distribution of ciclosporin. An extemporaneously compounded paste produced from ciclosporin oral solution (*Sandimmun*) in an oral gel base was found to be stable[2] for at least 31 days in aluminium-lined ointment tubes stored at 2 degrees to 37 degrees.

1. McLeod RL, *et al.* Stability of cyclosporin in dextrose 5%, NaCl 0.9%, dextrose/amino acid solution, and lipid emulsion. *Ann Pharmacother* 1992; 26: 172–5.
2. Ghnassia LT, *et al.* Stability of cyclosporine in an extemporaneously compounded paste. *Am J Health-Syst Pharm* 1995; 52: 2204–7.

Uses and Administration

Ciclosporin is a powerful immunosuppressant that appears to act specifically on lymphocytes, mainly helper T-cells. It forms a complex with the receptor protein cyclophilin; this complex binds to and inhibits the activation of calcineurin, an important step in the production of lymphokines, including interleukin-2, and results in a depression of cell-mediated immune response. Unlike cytotoxic immunosuppressants such as cyclophospbamide it has little effect on bone marrow.

Ciclosporin is used, usually with corticosteroids (and often with other immunosuppressants), in organ and tissue transplantation for the prophylaxis of graft rejection, or in the management of graft rejection in patients previously treated with other immunosuppressants. It is also used in severe forms of atopic dermatitis, psoriasis, or rheumatoid arthritis, usually when conventional therapy is ineffective or inappropriate, and is used in nephrotic syndrome.

Ciclosporin has been tried in other diseases considered to have an auto-immune component, as indicated by the cross-references given below; they include aplastic anaemia, asthma, Behçet's syndrome, chronic active hepatitis, multiple sclerosis, myasthenia gravis, sarcoidosis, scleritis or uveitis, scleroderma, and various skin disorders.

Ciclosporin is given orally as liquid-filled capsules or as an oily solution, which may be diluted with milk or fruit juice (not grapefruit) immediately before use to improve palatability. Microemulsifying formulations with improved bioavailability are available in several countries. For advice on changing between oral formulations see Administration, Oral, p. 1946.2. The daily dose of ciclosporin is taken in 2 divided doses, although the conventional formulation is sometimes given as a single daily dose.

In **organ transplantation** the usual initial oral dose of ciclosporin is 10 to 15 mg/kg daily, beginning 4 to 12 hours before transplantation, and continued for 1 to 2 weeks; lower initial doses may be given with other immunosuppressants (e.g. with corticosteroids or as part of 'triple' or 'quadruple' therapy). Dosage may subsequently be reduced gradually to a daily maintenance dose of 2 to 6 mg/kg.

Kidney function and blood pressure should be monitored regularly, as well as blood concentrations of ciclosporin (see Therapeutic Drug Monitoring, p. 1956.1), and dosage should be adjusted as necessary. (For specific recommendations on adjustment when given with everolimus see Administration with Everolimus, p. 1946.3). Hepatic function should also be monitored.

Ciclosporin may also be given intravenously, at one-third of the oral dose, in patients in whom oral dosage is not feasible. It is given by slow intravenous infusion over 2 to 6 hours, the 5% concentrate being diluted 1:20 to 1:100 in sodium chloride 0.9% or glucose 5%, to give a 0.05 to

0.25% solution of ciclosporin. Because of the risk of anaphylactoid reactions, which have been attributed to the polyoxyl castor oil vehicle, patients should be transferred to oral therapy as soon as possible.

For the prevention of graft rejection in **bone marrow transplantation**, and prevention and treatment of graft-versus-host disease, an initial dose of 3 to 5 mg/kg daily by the intravenous route is recommended, starting the day before transplantation and continuing for up to 2 weeks until oral maintenance, in doses of 12.5 mg/kg daily can be instituted. If oral treatment is used to begin therapy the recommended dose is 12.5 to 15 mg/kg daily followed by 12.5 mg/kg daily for maintenance. The maintenance dose is continued for at least 3 to 6 months, then gradually reduced until ciclosporin is withdrawn altogether; this may take up to a year after transplantation.

Ciclosporin given by inhalation is under investigation for the prevention and treatment of graft rejection after lung transplantation in some countries.

A silicone matrix ocular implant that provides sustained release of ciclosporin (LX-201) is under investigation for the prevention of rejection in corneal transplantation.

In the treatment of **psoriasis**, ciclosporin may be given in usual initial oral doses of 2.5 mg/kg daily (a maximum of 5 mg/kg daily is recommended in the UK and 4 mg/kg daily in the USA), in 2 divided doses, reduced once remission is achieved to the lowest effective maintenance dose. Treatment should usually be stopped if there is insufficient response to the maximum dose within 6 weeks; overall, it has been recommended that ciclosporin should be given for about 3 months before being considered ineffective. A similar dosage range may be given for a maximum of 8 weeks in the treatment of severe **atopic dermatitis**.

In **rheumatoid arthritis** oral ciclosporin may be given in initial daily doses of 2.5 mg/kg, divided into two doses, for a period of 6 or 8 weeks. If the clinical effect is insufficient dosage may then be gradually increased to a maximum of 4 mg/kg daily; if there is no response after 3 to 4 months, treatment should be stopped.

For **nephrotic syndrome** secondary to glomerular kidney disease (minimal change nephropathy, focal glomerulosclerosis, or membranous nephropathy) dosage of ciclosporin depends on age and renal function. To induce remission in patients with normal renal function 5 mg/kg daily may be given to adults, in 2 divided doses orally. In patients with renal impairment the initial dose should not exceed 2.5 mg/kg daily. Treatment may be stopped if there is no response after 3 months (or 6 months in patients with membranous nephropathy). In patients who do respond, maintenance doses should be gradually reduced to the minimum effective value.

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

Eye drops containing ciclosporin 0.05% are used in the management of **dry eye** associated with ocular inflammation. A topical emulsion of ciclosporin is under investigation for the treatment of vernal keratoconjunctivitis, a severe form of chronic allergic conjunctivitis.

Ciclosporin can inhibit the P-glycoprotein cellular pump responsible for multidrug resistance, and has been given with antineoplastics to raise their intracellular concentrations. Nonimmunosuppressive ciclosporin analogues such as valspodar (p. 2641.3) are also being investigated for their ability to reverse multidrug resistance.

Administration. It has been suggested that calculating doses in mg/kg may not be the best way to achieve the desired blood concentrations of ciclosporin.[1] (See also Therapeutic Drug Monitoring, p. 1956.1) Retrospective study of 1071 renal transplant recipients indicated that blood ciclosporin concentrations were not significantly correlated with patient weight, the best prediction of trough blood concentration being given by the formula:

$$\text{Blood concentration (nanograms/mL)} = \frac{\text{dose in mg/day}}{X}$$

$$X = (1.34 + 0.00011 \times \text{days after transplant} - 0.0049 \times \text{height in cm})$$

This formula appeared useful in predicting blood concentrations in prospective studies; from the seventh day after transplantation target trough concentrations could be expected to be about 0.3 times the daily ciclosporin dose in mg.

1. Bock HA, *et al.* Weight-independent dosing of cyclosporine—an alternative to the mg/kg doctrine. *Transplantation* 1994; 57: 1484–9.

INHALATION. Aerosolised ciclosporin given by inhalation has proved effective[1,2] in the management of acute graft rejection in lung transplantation (p. 1937.3). Doses were up to 300 mg daily via a nebuliser, in either propylene glycol or ethanol solvents.[3] Pulmonary delivery of ciclosporin has been reviewed.[3,4] A positive association between deposited aerosolised ciclosporin dose and improvement in lung function was found in 15 subjects treated over 2 years postoperatively.[5] In a case-control study,[6] aerosolised ciclosporin improved survival among lung transplant recipients with bronchiolitis obliterans. In a randomised controlled study, inhaled ciclosporin given prophylactically did not improve the rate of acute rejection, but it did improve chronic rejection-free survival and overall survival.[7]

A dry powder formulation of ciclosporin for inhalation use has been developed in order to overcome problems of local irritation with propylene glycol; feasibility and efficacy studies with this new formulation are needed.[8]

1. Keenan RJ, *et al.* Efficacy of inhaled cyclosporine in lung transplant recipients with refractory rejection: correlation of intragraft cytokine gene expression with pulmonary function and histologic characteristics. *Surgery* 1995; 118: 385–91.
2. Iacono AT, *et al.* Dose-related reversal of acute lung rejection by aerosolized cyclosporine. *Am J Respir Crit Care Med* 1997; 155: 1690–8.
3. Klyashchitsky BA, Owen AJ. Nebulizer-compatible liquid formulations for aerosol pulmonary delivery of hydrophobic drugs: glucocorticoids and cyclosporine. *J Drug Target* 1999; 7: 79–99.
4. Corcoran TE. Inhaled delivery of aerosolized cyclosporine. *Adv Drug Deliv Rev* 2006; 58: 1119–27.
5. Corcoran TE, *et al.* Preservation of post-transplant lung function with aerosol cyclosporin. *Eur Respir J* 2004; 23: 378–83.
6. Iacono AT, *et al.* Aerosol cyclosporin therapy in lung transplant recipients with bronchiolitis obliterans. *Eur Respir J* 2004; 23: 384–90.
7. Iacono AT, *et al.* A randomized trial of inhaled cyclosporine in lung-transplant recipients. *N Engl J Med* 2006; 354: 141–50.
8. Zijlstra GS, *et al.* Characterization of a cyclosporine solid dispersion for inhalation. *AAPS J* 2007; 9: E190–E199.

OCULAR. Topical ciclosporin, in strengths ranging from 0.05 to 2% has been shown to be effective[1,2] in the treatment of various ocular surface disorders, particularly dry eye (see p. 1947.1) and atopic keratoconjunctivitis. It has also been used for corneal ulcers, glaucoma (see p. 1947.1 and p. 1947.2, respectively), as adjunctive therapy in corneal allograft rejection, and for the ocular manifestations of graft-versus-host disease.

A silicone matrix ocular implant that provides sustained release of ciclosporin (LX-201) is under investigation for the prevention of rejection in corneal transplantation.

1. Tatlipinar S, Akpek EK. Topical ciclosporin in the treatment of ocular surface disorders. *Br J Ophthalmol* 2005; 89: 1363–7.
2. Poulis GN. Topical cyclosporine for treatment of ocular surface disease. *Int Ophthalmol Clin* 2006; 46: 105–22.

ORAL. The microemulsifying formulation of ciclosporin has been reviewed.[1,2] Different oral formulations of ciclosporin are not considered interchangeable without careful monitoring, to avoid changes in bioavailability. When switching to a different formulation, ciclosporin blood concentration and graft function should be measured and the patient monitored for adverse effects.[3] The *BNF* recommends prescribing by trade name to avoid unintended changes.

After development of the oral microemulsifying formulation of ciclosporin patients were switched from the old formulation on a 1:1 basis by weight initially, with monitoring of resultant ciclosporin concentrations and subsequent dosage adjustment. Results were generally good, despite some reports of nephrotoxicity or rejection in previously stable grafts,[4-7] and a meta-analysis[8] concluded that of *de novo* transplant recipients, those receiving the microemulsifying formulation had significantly fewer instances of rejection, and, in liver transplant recipients, significantly fewer adverse events. Licensed product information for the original microemulsifying formulation (*Neoral*) recommends transfer on this 1:1 basis by dose for patients stabilised on the conventional formulation, with monitoring of blood-ciclosporin concentrations, serum creatinine, and blood pressure, and subsequent dose adjustment as appropriate.

1. Noble S, Markham A. Cyclosporin: a review of the pharmacokinetic properties, clinical efficacy and tolerability of a microemulsion-based formulation (Neoral). *Drugs* 1995; 50: 924–41.
2. Dunn CJ, *et al.* Cyclosporin: an updated review of the pharmacokinetic properties, clinical efficacy and tolerability of a microemulsion-based formulation (Neoral) in organ transplantation. *Drugs* 2001; 61: 1957–2016.
3. MHRA/CHM. Drug safety advice. Ciclosporin: must be prescribed and dispensed by brand name. *Drug Safety Update* 2009; 3 (5): 2–3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON065445&RevisionSelectionMethod=LatestReleased (accessed 11/06/10)
4. Bennett WM, *et al.* Which cyclosporin formulation? *Lancet* 1996; 348: 205.
5. Olyaei AJ, *et al.* Switching between cyclosporin formulations: what are the risks? *Drug Safety* 1997; 16: 366–73.
6. Piller G, Ehrich J. Which cyclosporin formulation? *Lancet* 1996; 348: 1176–7.
7. Gennery A, *et al.* Which cyclosporin formulation? *Lancet* 1996; 348: 1177.
8. Shah MB, *et al.* A meta-analysis to assess the safety and tolerability of two formulations of cyclosporine: Sandimmune and Neoral. *Transplant Proc* 1998; 30: 4048–53.

Administration in children. UK licensed product information states that, while experience with ciclosporin in children is limited, transplant patients from 3 months of age have received the drug at the same doses recommended for adults (see Uses and Administration, p. 1945.3). However, at doses above the recommended range, children seem to be more susceptible to fluid retention, convulsions, and hypertension. These effects respond to dose reduction.

In contrast, US licensed product information states that, while data in children are lacking, transplant recipients as young as 6 months and 1 year have received the standard formulation and microemulsifying formulation, respectively, with no unusual adverse effects, and that children have generally required and tolerated higher doses of the standard formulation than those used in adults.

The *BNFC* advises to consult local treatment protocols for details of use in organ transplantation.

For the treatment of **psoriasis** and **atopic dermatitis** doses recommended by the *BNFC* for children from 1 month of age are the same as for adults (see Uses and Administration, p. 1945.3).

In the treatment of **nephrotic syndrome** UK licensed product information states that children may be given 6 mg/kg daily orally, in 2 divided doses, if renal function is normal. The dose should not exceed 2.5 mg/kg daily in patients with impaired renal function. The *BNFC* specifies use from 1 month of age.

Although ciclosporin is not licensed in the UK for use in **ulcerative colitis**, the *BNFC* recommends the following initial doses in refractory disease in children, which are then adjusted according to ciclosporin blood concentrations and response:

- orally in those aged 2 to 18 years: 2 mg/kg twice daily (maximum 5 mg/kg twice daily)
- by intravenous infusion in those aged 3 to 18 years: 0.5 to 1 mg/kg twice daily

A dose regimen with an initial fixed dose and further adjustment depending on the area under the concentration-time curve has also been suggested, see Children, under Pharmacokinetics, p. 1955.3.

Administration with everolimus. Everolimus is given with ciclosporin and corticosteroids to prevent graft rejection in renal or cardiac transplantation. Exposure to ciclosporin should be reduced from 1 month after transplantation. Because ciclosporin interacts with everolimus, and the dose adjustments of ciclosporin will affect exposure to everolimus, licensed product information for everolimus recommends that concentrations of *both* drugs be monitored to minimise the risk of graft rejection. Before dose reduction of ciclosporin, everolimus whole blood concentrations should be at least 3 nanograms/mL (see Therapeutic Drug Monitoring, p. 1956.1, and under Everolimus, p. 1959.2).

In renal transplantation, ciclosporin doses may be adjusted according to either ciclosporin concentrations taken 2 hours after a dose (C_2) or trough concentrations (C_0). The following ciclosporin C_2 target ranges have been suggested:

- weeks 0 to 4: 1000 to 1400 nanograms/mL
- weeks 5 to 8: 700 to 900 nanograms/mL
- weeks 9 to 12: 550 to 650 nanograms/mL
- weeks 13 to 52: 350 to 450 nanograms/mL

Alternatively, the following ciclosporin target trough concentrations (C_0) have been suggested:

- month 1: 100 to 200 nanograms/mL
- months 2 to 3: 75 to 150 nanograms/mL
- months 4 to 5: 50 to 100 nanograms/mL
- months 6 to 12: 25 to 50 nanograms/mL

In cardiac transplantation the following ciclosporin target trough concentrations have been suggested:

- month 1: 200 to 350 nanograms/mL
- month 2: 150 to 250 nanograms/mL
- months 3 to 4: 100 to 200 nanograms/mL
- months 5 to 6: 75 to 150 nanograms/mL
- months 7 to 12: 50 to 100 nanograms/mL

Asthma. Ciclosporin is being considered as a potential treatment for some cases of refractory asthma (p. 1195.2). A controlled study[1] in patients with chronic severe asthma requiring long-standing oral corticosteroid treatment found that addition of ciclosporin in an initial dose of 5 mg/kg daily to their regimen resulted in significant improvement in lung function and a reduced frequency of disease exacerbation, compared with placebo. The results were interesting because of the improvement in what had been considered 'irreversible' airflow obstruction. A subsequent study[2] from the same centre involving 39 patients with severe corticosteroid-dependent asthma found that low-dose oral ciclosporin (an initial dose of 5 mg/kg daily) permitted a reduction in the daily dosage of prednisolone, from a median of 10 to 3.5 mg daily. However, a systematic review[3] considered that, given the adverse effects of ciclosporin, any clinical benefit was debatable.

1. Alexander AG, *et al.* Trial of cyclosporin in corticosteroid-dependent chronic severe asthma. *Lancet* 1992; 339: 324–8.
2. Lock SH, *et al.* Double-blind, placebo-controlled study of cyclosporin A as a corticosteroid-sparing agent in corticosteroid-dependent asthma. *Am J Respir Crit Care Med* 1996; 153: 509–14.
3. Evans DJ, *et al.* Cyclosporin as an oral corticosteroid sparing agent in stable asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 15/01/08).

Behçet's syndrome. Ciclosporin has been tried in Behçet's syndrome, see p. 1601.1.

Blood disorders. In primary acquired red cell aplasia (see Normocytic-normochromic Anaemia, p. 1123.1), ciclosporin is considered as effective at inducing remission as corticosteroid monotherapy, or corticosteroids plus cyclophosphamide, and some consider it first-line treatment for relapsed disease.[1]

Ciclosporin, usually combined with antilymphocyte immunoglobulin, is used in patients with aplastic anaemia when bone marrow transplantation is unsuitable (see p. 1121.3).

1. Sawada K, *et al.* Acquired pure red cell aplasia: updated review of treatment. *Br J Haematol* 2008; 142: 505–14.

Cogan's syndrome. Ciclosporin has been used with corticosteroids for severe Cogan's syndrome with large-vessel vasculitis (see p. 1603.2).

Corneal ulcer. Ciclosporin 1% eye drops, with lamellar keratoplasty, proved effective in treating Mooren's ulcer, a possibly auto-immune corneal disease that is difficult to manage and can lead to blindness.[1] Treatment with topical ciclosporin alone may also be useful[2] in patients with sterile corneal ulcers associated with rheumatoid disease.

1. Chen J, *et al.* Mooren's ulcer in China: a study of clinical characteristics and treatment. *Br J Ophthalmol* 2000; 84: 1244–9.
2. Gottsch JD, Akpek EK. Topical cyclosporin stimulates neovascularization in resolving sterile rheumatoid central corneal ulcers. *Trans Am Ophthalmol Soc* 2000; 98: 81–90.

Dermatomyositis. See Polymyositis and Dermatomyositis, p. 1948.1.

Diabetes mellitus. Immunosuppressants have been used in attempts to prolong the so called 'honeymoon period' in recently diagnosed diabetics (p. 460.3). Ciclosporin has apparently produced modest benefits in such a context,[1-3] but its use is limited by concerns about toxicity.[4]

1. Bougneres PF, *et al.* Factors associated with early remission of type 1 diabetes in children treated with cyclosporine. *N Engl J Med* 1988; 318: 663–70.
2. The Canadian-European Randomized Control Trial Group. Cyclosporin-induced remission of IDDM after early intervention: association of 1 yr of cyclosporin treatment with enhanced insulin secretion. *Diabetes* 1988; 37: 1574–82.
3. Carel JC, *et al.* Cyclosporine delays but does not prevent clinical onset in glucose intolerant pre-type 1 diabetic children. *J Autoimmun* 1996; 9: 739–45.
4. Parving H-H, *et al.* Cyclosporine nephrotoxicity in type 1 diabetic patients: a 7-year follow-up study. *Diabetes Care* 1999; 22: 478–83.

Dry eye. Topical ciclosporin has been used,[1-3] with apparent benefit, for keratoconjunctivitis sicca (dry eye—see p. 2190.1). Studies[4,5] found ciclosporin 0.05% and 0.1% to be the most appropriate formulations since no additional benefit was found with higher concentrations[4] and both were significantly better than placebo.[5]

Topical ciclosporin has also been reported to be beneficial for patients with dry eyes secondary to graft-versus-host disease.[6]

1. Laibovitz RA, *et al.* Pilot trial of cyclosporine 1% ophthalmic ointment in the treatment of keratoconjunctivitis sicca. *Cornea* 1993; 12: 315–23.
2. Wilson SE, Perry HD. Long-term resolution of chronic dry eye symptoms and signs after topical cyclosporine treatment. *Ophthalmology* 2007; 114: 76–9.
3. Ridder WH. Ciclosporin use in dry eye disease patients. *Expert Opin Pharmacother* 2008; 9: 3121–8.
4. Stevenson D, *et al.* Efficacy and safety of cyclosporin A ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomized trial. *Ophthalmology* 2000; 107: 967–74.
5. Sall K, *et al.* Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. *Ophthalmology* 2000; 107: 631–9.
6. Lelli GJ, *et al.* Ophthalmic cyclosporine use in ocular GVHD. *Cornea* 2006; 25: 635–8.

Eczema. Ciclosporin is effective in atopic eczema (atopic dermatitis),[1-3] where it is used as adjunctive therapy (see p. 1684.1). It is generally reserved for short-term treatment (up to 8 weeks) in patients with severe disease unresponsive to all conventional therapies, although reports have described long-term use in adult patients.[4] It has also been suggested[5] that long-term remission is possible, even in those treated with short courses. Ciclosporin has been used for both short courses[6,7] and continuous therapy in children.[8] A systematic review and meta-analysis[9] that incorporated most of these studies concluded that the mean clinical improvement in disease severity after 6 to 8 weeks of ciclosporin treatment is about 55%; however, the true benefit may be somewhat lower due to publication bias. Higher initial doses of 4 to 5 mg/kg led to a more rapid response, and the mean benefit after 2 weeks at this dose was about 40%. In a small, open, crossover study,[10] the microemulsifying form was considered equivalent or superior in tolerability and efficacy when compared with the conventional formulation. Responses have also been reported in severe eczematisation associated with Darier's disease[11] (p. 1683.2).

1. van Joost T, *et al.* Cyclosporin in atopic dermatitis: a multicentre placebo-controlled study. *Br J Dermatol* 1994; 130: 634–40.
2. Munro CS, *et al.* Maintenance treatment with cyclosporin in atopic eczema. *Br J Dermatol* 1994; 130: 376–80.
3. Granlund H, *et al.* Cyclosporin in atopic dermatitis: time to relapse and effect of intermittent therapy. *Br J Dermatol* 1995; 132: 106–12.
4. Berth-Jones J, *et al.* Long-term efficacy and safety of cyclosporin in severe adult atopic dermatitis. *Br J Dermatol* 1997; 136: 76–81.
5. Granlund H, *et al.* Long-term follow-up of eczema patients treated with cyclosporine. *Acta Derm Venereol (Stockh)* 1998; 78: 40–3.
6. Zaki I, *et al.* Treatment of severe atopic dermatitis in childhood with cyclosporin. *Br J Dermatol* 1996; 135 (suppl 48): 21–4.
7. Berth-Jones J, *et al.* Cyclosporine in severe childhood atopic dermatitis: a multicenter study. *J Am Acad Dermatol* 1996; 34: 1016–21.
8. Harper JI, *et al.* Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. *Br J Dermatol* 2000; 142: 52–8.
9. Schmitt J, *et al.* Cyclosporin in the treatment of patients with atopic eczema—a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2007; 21: 606–19.
10. Chawla M, *et al.* Comparison of the steady state pharmacokinetics of two formulations of cyclosporin in patients with atopic dermatitis. *Br J Dermatol* 1996; 135 (suppl 48): 9–14.
11. Shahidullah H, *et al.* Darier's disease: severe eczematization successfully treated with cyclosporin. *Br J Dermatol* 1994; 131: 713–16.

Glaucoma. Topical ciclosporin has produced some encouraging results[1] when used as an adjunct to reduce formation of scar tissue and improve outcome of glaucoma filtering surgery. It has been suggested[2] that topical ciclosporin 0.5% may be substituted for topical corticosteroids in the treatment of postkeratoplasty glaucoma.

1. Turaçli E, *et al.* A comparative clinical trial of mitomycin C and cyclosporin A in trabeculectomy. *Eur J Ophthalmol* 1996; 6: 398–401.
2. Perry HD, *et al.* Topical cyclosporin A in the management of postkeratoplasty glaucoma. *Cornea* 1997; 16: 284–8.

Glomerular kidney disease. Ciclosporin has been tried in various forms of glomerular kidney disease (p. 1604.3) but use has been cautious because of fears about nephrotoxicity. Nonetheless, responses have been seen in patients with corticosteroid-resistant minimal change nephropathy,[1,2] focal glomerulosclerosis,[1-3] and membranous nephropathy.[4-6] An international workshop[7] considered that ciclosporin therapy was effective at inducing a sustained remission from proteinuria, and preserved renal function long-term in corticosteroid-dependent or -resistant minimal change nephropathy and corticosteroid-resistant focal glomerulosclerosis in both adults and children. There was evidence to support its use as a first-line option in membranous nephropathy and focal glomerulosclerosis, and after a 12-week course of cytotoxic therapy has failed in minimal change nephropathy.

1. Nyrop M, Olgaard K. Cyclosporin A treatment of severe steroid resistant nephrotic syndrome in adults. *J Intern Med* 1990; 227: 65–8.
2. Niaudet P, *et al.* Steroid-resistant idiopathic nephrotic syndrome and ciclosporin. *Nephron* 1991; 57: 481.
3. Chishti AS, *et al.* Long-term treatment of focal segmental glomerulosclerosis in children with cyclosporine given as a single daily dose. *Am J Kidney Dis* 2001; 38: 754–60.
4. Cattran DC, *et al.* A controlled trial of cyclosporine in patients with progressive membranous nephropathy. *Kidney Int* 1995; 47: 1130–5.
5. Cattran DC, *et al.* Cyclosporine in patients with steroid-resistant membranous nephropathy: a randomized trial. *Kidney Int* 2001; 59: 1484–90.
6. Goumenos DS. What have we learned from the use of ciclosporin A in the treatment of nephrotic patients with idiopathic membranous nephropathy? *Expert Opin Pharmacother* 2008; 9: 1695–1704.
7. Cattran DC, *et al.* Cyclosporin in idiopathic glomerular disease associated with the nephrotic syndrome: workshop recommendations. *Kidney Int* 2007; 72: 1429–47.

Hepatitis. In chronic active hepatitis (p. 1602.3), some evidence suggests that ciclosporin may offer an alternative therapy in patients with severe auto-immune (non-viral) disease where corticosteroids alone or with azathioprine do not suffice.

Histiocytic syndromes. Ciclosporin has been tried in patients with advanced Langerhans-cell histiocytosis (p. 692.1).

Inflammatory bowel disease. Ciclosporin has been tried with variable success as a second-line drug in inflammatory bowel disease (p. 1808.3). Intravenous high-dose ciclosporin has shown some efficacy in refractory ulcerative colitis,[1] and a review[2] concluded that intravenous ciclosporin should be offered to selected patients as an alternative to surgery. Treatment should be started at 2 mg/kg daily, as it appears to be as effective as 4 mg/kg daily. A systematic review,[3] which included only 2 studies, concluded that short-term ciclosporin may be used where surgery is the only option, but that this is not based on strong evidence.

Benefit from ciclosporin in Crohn's disease is less clear. A systematic review[4] concluded that low dose (5 mg/kg daily) oral ciclosporin is not effective for induction of remission in Crohn's disease. While some studies suggest that higher oral doses or intravenous ciclosporin might be beneficial, these are not considered to be useful alternatives for long-term management due to the risk of nephrotoxicity and the availability of other proven therapy.

1. Loftus CG, *et al.* Cyclosporin for refractory ulcerative colitis. *Gut* 2003; 52: 172–3.
2. Pham CQD, *et al.* Cyclosporine for severe ulcerative colitis. *Ann Pharmacother* 2006; 40: 96–101.
3. Shibolet O, *et al.* Cyclosporine A for induction of remission in severe ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 15/01/08).
4. McDonald JWD, *et al.* Cyclosporine for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 15/01/08).

Interstitial lung disease. There are reports of benefit from the use of ciclosporin in idiopathic pulmonary fibrosis (see Interstitial Lung Disease, p. 1607.1), although data are too limited to support its use.

Leprosy. For mention of the use of ciclosporin in the management of type 1 lepra reactions in patients with leprosy, see p. 188.3.

Lichen planus. Lichen planus is a skin disorder generally controlled with corticosteroids (see p. 1685.2), although ciclosporin has also been used. Ciclosporin has been given successfully in relatively low doses (3 to 5 mg/kg orally) to produce remission of severe lichen planus,[1] but such therapy may be associated with the development of hypertension and impairment of renal function. Use of topical ciclosporin for oral lichen planus has been tried, but results have been variable.[2-8] One such study failed to note any benefit long-term from either ciclosporin mouthwash or corticosteroid oral paste.[7]

1. Pigatto PD, *et al.* Cyclosporin A for treatment of severe lichen planus. *Br J Dermatol* 1990; 123: 121–3.
2. Eisen D, *et al.* Cyclosporin wash for oral lichen planus. *Lancet* 1990; 335: 535–6.
3. Eisen D, *et al.* Effect of topical cyclosporine rinse on oral lichen planus: a double-blind analysis. *N Engl J Med* 1990; 323: 290–4.
4. Levell NJ, *et al.* Lack of effect of cyclosporin mouthwash in oral lichen planus. *Lancet* 1991; 337: 796–7.
5. Ho VC, Conklin RJ. Effect of topical cyclosporine rinse on oral lichen planus. *N Engl J Med* 1991; 325: 435.
6. Porter SR, *et al.* The efficacy of topical cyclosporin in the management of desquamative gingivitis due to lichen planus. *Br J Dermatol* 1993; 129: 753–5.
7. Sieg P, *et al.* Topical cyclosporin in oral lichen planus: a controlled, randomized prospective trial. *Br J Dermatol* 1995; 132: 790–4.
8. Conrotto D, *et al.* Ciclosporin vs. clobetasol in the topical management of atrophic and erosive oral lichen planus: a double-blind, randomized controlled trial. *Br J Dermatol* 2006; 154: 139–45.

Lupus nephritis. Ciclosporin has been investigated for SLE (p. 1613.3), particularly lupus nephritis. Significant reductions in proteinuria have been reported,[1-6] although controlled studies are needed.

1. Pu LW, *et al.* Clinical efficacy of cyclosporin A Neoral in the treatment of paediatric lupus nephritis with heavy proteinuria. *Br J Rheumatol* 1998; 37: 217–21.
2. Tam LS, *et al.* Long-term treatment of lupus nephritis with cyclosporin A. *Q J Med* 1998; 91: 373–80.
3. Hallegua D, *et al.* Cyclosporine for lupus membranous nephritis: experience with ten patients and review of the literature. *Lupus* 2000; 9: 241–51.
4. Pujinaga S, *et al.* Treatment of steroid-resistant membranous lupus nephritis with plasmapheresis and low-dose cyclosporine. *Pediatr Nephrol* 2007; 22: 616–17.
5. Rihova Z, *et al.* Treatment of lupus nephritis with cyclosporine—an outcome analysis. *Kidney Blood Press Res* 2007; 30: 124–8.
6. Ogawa H, *et al.* Prospective study of low-dose cyclosporine A in patients with refractory lupus nephritis. *Mod Rheumatol* 2007; 17: 92–7.

Multiple sclerosis. As noted on p. 996.3, immunosuppressants, including ciclosporin, have produced modest benefit in patients with multiple sclerosis. However, it has been concluded that the scanty benefits of therapy are outweighed by the toxicity of the doses required.

Muscular dystrophies. A study in 15 boys with Duchenne muscular dystrophy (p. 1608.1) given oral ciclosporin 5 mg/kg daily in divided doses, adjusted according to trough serum concentrations of ciclosporin, found that muscular force generation was improved during treatment, but declined again once treatment ceased.[1] The clinical significance, if any, is unknown.

1. Sharma KR, *et al.* Cyclosporine increases muscular force generation in Duchenne muscular dystrophy. *Neurology* 1993; 43: 527–32.

Myasthenia gravis. Ciclosporin may be of use as an alternative to azathioprine in the management of myasthenia gravis (p. 684.1) for its corticosteroid-sparing effect[1] or when patients are intolerant of or unresponsive to corticosteroids and azathioprine.[2-4] It appears to be of similar efficacy to azathioprine[3] with a more rapid effect but serious adverse effects such as nephrotoxicity may limit its use.

1. Tindall RSA, *et al.* A clinical therapeutic trial of cyclosporine in myasthenia gravis. *Ann N Y Acad Sci* 1993; 681: 539–51.
2. Bonifati DM, Angelini C. Long-term cyclosporine treatment in a group of severe myasthenia gravis patients. *J Neurol* 1997; 244: 542–7.
3. Ciafaloni E, *et al.* Retrospective analysis of the use of cyclosporine in myasthenia gravis. *Neurology* 2000; 55: 448–50.
4. Lavrnic D, *et al.* Cyclosporine in the treatment of myasthenia gravis. *Acta Neurol Scand* 2005; 111: 247–52.
5. Schalke BCG, *et al.* Ciclosporin A vs azathioprine in the treatment of myasthenia gravis: final results of a randomized, controlled double-blind clinical trial. *Neurology* 1988; 38 (suppl 1): 135.

Organ and tissue transplantation. Ciclosporin has greatly improved the prospects for successful organ and tissue transplantation, and is a mainstay of regimens used to prevent rejection of solid organ grafts as well as being used for the prevention of graft-versus-host disease in bone

marrow transplantation. For more detailed discussion of organ and tissue transplantation and the role of ciclosporin, see p. 1932.2. Ciclosporin has also occasionally been used for corneal graft rejection (p. 1603.3) in high-risk patients, where corticosteroids alone are insufficient. An ocular implant that provides sustained release of ciclosporin (LX-201) is under investigation for the prevention of rejection in corneal transplantation. Inhaled ciclosporin is under investigation in lung transplantation, see p. 1937.3 and under Administration, p. 1946.1.

A few selected references to the use of ciclosporin in transplantation are given below.

1. Frei UA, *et al.* Randomized, double-blind, one-year study of the safety and tolerability of cyclosporine microemulsion compared with conventional cyclosporine in renal transplant patients. *Transplantation* 1998; 65: 1455–60.
2. Eisen HJ, *et al.* Safety, tolerability, and efficacy of cyclosporine microemulsion in heart transplant recipients: a randomized, multicenter, double-blind comparison with the oil-based formulation of cyclosporine—results at 24 months after transplantation. *Transplantation* 2001; 71: 70–78.
3. Thervet E, *et al.* Benefit-risk assessment of ciclosporin withdrawal in renal transplant recipients. *Drug Safety* 2004; 27: 457–76.
4. Hesselink DA, *et al.* The use of cyclosporine in renal transplantation. *Transplant Proc* 2004; 36 (suppl): 99S–106S.
5. Pape L, *et al.* Cyclosporine in pediatric kidney transplantation. *Transplant Proc* 2004; 36 (suppl): 203S–207S.
6. Banner NR, Yacoub MH. Cyclosporine in thoracic organ transplantation. *Transplant Proc* 2004; 36 (suppl): 302S–308S.
7. Patel JK, Kobashigawa JA. Cardiac transplant experience with cyclosporine. *Transplant Proc* 2004; 36 (suppl): 323S–330S.
8. Johnston A, *et al.* Potential clinical implications of substitution of generic cyclosporine formulations for cyclosporine microemulsion (Neoral) in transplant recipients. *Eur J Clin Pharmacol* 2004; 60: 389–95.
9. Schrem H, *et al.* Update on liver transplantation using cyclosporine. *Transplant Proc* 2004; 36: 2525–31.
10. Duncan N, Craddock C. Optimizing the use of cyclosporin in allogeneic stem cell transplantation. *Bone Marrow Transplant* 2006; 38: 169–74.

Pemphigus. Although pemphigus is usually treated with corticosteroids (see p. 1687.1), ciclosporin has also been tried in a few patients with pemphigus vulgaris, with variable results.[1–4] A small, randomised study[5] found that use of corticosteroids with ciclosporin had no advantage over corticosteroids alone.

1. Luist AF, Stoukides CA. Cyclosporine for the treatment of pemphigus vulgaris. *Ann Pharmacother* 1994; 28: 1183–5.
2. Vardy DA, Cohen AD. Cyclosporine therapy should be considered for maintenance of remission in patients with pemphigus. *Arch Dermatol* 2001; 137: 505.
3. Gooptu C, Staughton RCD. Use of topical cyclosporin in oral pemphigus. *J Am Acad Dermatol* 1998; 38: 860–1.
4. Olszewska M, *et al.* Efficacy and safety of cyclophosphamide, azathioprine, and cyclosporine (ciclosporin) as adjuvant drugs in pemphigus vulgaris. *Am J Clin Dermatol* 2007; 8: 85–92.
5. Ioannides D, *et al.* Ineffectiveness of cyclosporine as an adjuvant to corticosteroids in the treatment of pemphigus. *Arch Dermatol* 2000; 136: 868–72.

Polymyositis and dermatomyositis. Ciclosporin may be of benefit[1,2] in refractory polymyositis and dermatomyositis (see p. 1611.1).

1. Qushmaq KA, *et al.* Cyclosporin A in the treatment of refractory adult polymyositis/dermatomyositis: population based experience in 6 patients and literature review. *J Rheumatol* 2000; 27: 2855–9.
2. Kim H-J, *et al.* Dermatomyositis, complicated with pneumomediastinum, successfully treated with cyclosporine A: a case report and review of literature. *Rheumatol Int* 2009; 29: 1101–4.

Primary biliary cirrhosis. In primary biliary cirrhosis (p. 2638.3) some benefit has been reported with ciclosporin, but there are problems with toxicity. A systematic review[1] concluded that, despite improvements in pruritus and liver biochemical variables, ciclosporin did not delay the progression of the disease, and that its use outside of clinical studies could not be recommended.

1. Gong Y, *et al.* Cyclosporin A for primary biliary cirrhosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 15/01/08).

Psoriasis. Ciclosporin is used to induce remission or prevent relapse in severe refractory psoriasis (p. 1688.1). Response to ciclosporin has been reported for virtually all the clinical manifestations of the disease,[1] including pustular psoriasis of pregnancy.[2–4] Benefit has also been reported in children with severe refractory psoriasis,[1,5] although exposure should be limited in view of the potential for cumulative toxicity.

Doses of 2.5 to 5 mg/kg daily given for up to 12 weeks produced marked improvement in the majority of patients with severe plaque psoriasis.[6] This intermittent therapy allows for a lower cumulative dose of ciclosporin and in turn decreases the risk of nephrotoxicity or hypertension.[7] Recommendations have been made in the UK for the use of ciclosporin in the management of psoriasis:[8] for those with severe stable disease, an initial starting dose of 2.5 mg/kg daily is suggested, with dose increases of 0.5 to 1 mg/kg daily made at intervals of 2 to 4 weeks, according to clinical response, and up to a maximum of 5 mg/kg daily. Treatment is given for about 12 weeks, and use of adjunctive topical therapy is recommended. Ciclosporin should be stopped once remission is achieved, and restarted at the previous effective dose if the patient relapses. In acute flares of the disease, ciclosporin may be started at higher doses (maximum 5 mg/kg daily) and titrated down as symptoms improve. The patient's renal function and blood pressure should be monitored before and during treatment. In a minority of patients requiring long-term continuous therapy, the duration of treatment should be limited to a maximum of 2 years, and an annual assessment of the patient's glomerular filtration rate is recommended. In most studies, maintenance doses were less than 3.5 mg/kg daily.

Reviews[1,9] have concluded that patients on short-term ciclosporin therapy for psoriasis do not require routine therapeutic drug monitoring (see under Pharmacokinetics, p. 1956.1). However, some consider that monitoring of trough concentrations is necessary in those treated with greater than 3 mg/kg daily, or in those at risk of renal impairment.[9] Monitoring may also be useful when compliance is questionable, or drug interactions are suspected.[1]

1. Berth-Jones J. The use of ciclosporin in psoriasis. *J Dermatol Treat* 2005; 16: 258–77.
2. Edmonds EVJ, *et al.* Pustular psoriasis of pregnancy treated with ciclosporin and high-dose prednisolone. *Clin Exp Dermatol* 2005; 30: 709–10.
3. Kura MM, Surjushe AU. Generalized pustular psoriasis of pregnancy treated with oral cyclosporin. *Indian J Dermatol Venereol Leprol* 2006; 72: 458–9.
4. Kapoor R, Kapoor JR. Cyclosporine resolves generalized pustular psoriasis of pregnancy. *Arch Dermatol* 2006; 142: 1373–5.
5. Pereira TM, *et al.* Cyclosporin A treatment in severe childhood psoriasis. *J Eur Acad Dermatol Venereol* 2006; 20: 651–6.
6. Faerber L, *et al.* Cyclosporine in severe psoriasis: results of a meta-analysis in 579 patients. *Am J Clin Dermatol* 2001; 2: 41–7.
7. Ho VC. The use of ciclosporin in psoriasis: a clinical review. *Br J Dermatol* 2004; 150 (suppl. 67): 1–10.
8. Griffiths CEM, *et al.* Ciclosporin in psoriasis clinical practice: an international consensus statement. *Br J Dermatol* 2004; 150 (suppl. 67): 11–23.
9. Heydendael VMR, *et al.* Cyclosporin trough levels: is monitoring necessary during short-term treatment in psoriasis? A systematic review and clinical data on trough levels. *Br J Dermatol* 2002; 147: 122–9.

Psoriatic arthritis. One study[1] has shown that low-dose ciclosporin effectively improves joint complaints in psoriatic arthritis (see under Spondyloarthropathies, p. 14.3), and another[2] found ciclosporin to be more effective than sulfasalazine. Its use in psoriatic arthritis has been reviewed.[3]

1. Mahrle G, *et al.* Anti-inflammatory efficacy of low-dose cyclosporin A in psoriatic arthritis: a prospective multicentre study. *Br J Dermatol* 1996; 135: 752–7.
2. Salvarani C, *et al.* A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis. *J Rheumatol* 2001; 28: 2274–82.
3. Salvarani C, *et al.* Multidisciplinary focus on cyclosporin A. *J Rheumatol Suppl* 2009; 83: 52–5.

Pyoderma gangrenosum. There have been reports[1–6] of responses to ciclosporin in patients with pyoderma gangrenosum (p. 1688.3).

1. Sassolas B, *et al.* Pyoderma gangrenosum with pathergic phenomenon in pregnancy. *Br J Dermatol* 2000; 142: 827–8.
2. Vena GA, Cassano N. Can we still suggest the topical cyclosporin treatment in cutaneous disorders? *J Eur Acad Dermatol Venereol* 2001; 15: 18–19.
3. Schöfer H, Baur S. Successful treatment of postoperative pyoderma gangrenosum with cyclosporin. *J Eur Acad Dermatol Venereol* 2002; 16: 148–51.
4. Patrone P, *et al.* Pyoderma gangrenosum of the scalp treated with cyclosporine A. *Int J Dermatol* 2002; 41: 916–18.
5. Park H-J, *et al.* Recalcitrant oral pyoderma gangrenosum in a child responsive to cyclosporine. *J Dermatol* 2003; 30: 612–16.
6. Hasselmann DO, *et al.* Pyoderma gangrenosum: clinical presentation and outcome in 18 cases and review of the literature. *J Dtsch Dermatol Ges* 2007; 5: 560–4.

Reperfusion and revascularisation procedures. Ciclosporin has been investigated as an adjunct to limit reperfusion injury (p. 1259.2) in acute myocardial infarction. A controlled pilot study[1] in which patients received ciclosporin before undergoing percutaneous coronary intervention, reported a reduced infarct size as measured by creatine kinase release and magnetic resonance imaging; troponin release was not affected.

1. Piot C, *et al.* Effect of cyclosporine on reperfusion injury in acute myocardial infarction. *N Engl J Med* 2008; 359: 473–81.

Retroperitoneal fibrosis. There is a report[1] of response to ciclosporin in a patient with retroperitoneal fibrosis (p. 1612.1).

1. Marzano A, *et al.* Treatment of idiopathic retroperitoneal fibrosis using cyclosporin. *Ann Rheum Dis* 2001; 60: 427–8.

Rheumatoid arthritis. Various disease-modifying antirheumatic drugs (DMARDs) are used in rheumatoid arthritis (p. 13.2) in an attempt to modify the disease process. Ciclosporin has produced responses in active disease,[1–4] and there is some evidence that it can slow radiological progression of disease[4] as well as providing symptomatic relief; a systematic review[5] has concluded it has an important clinical benefit in the short-term (up to one year) treatment of progressive disease. There has been some concern about associated nephrotoxicity,[1] but the use of low-dose regimens may help to minimise this.

Ciclosporin has also been combined with other DMARDs. Use with methotrexate has reportedly produced responses in patients unresponsive to methotrexate alone,[6] but some investigators found that a combination of methotrexate, ciclosporin and intra-articular corticosteroids was no more effective than standard DMARD therapy.[7] Others consider that ciclosporin monotherapy is of limited benefit, but that combination therapy with methotrexate is one of the best options to control aggressive disease.[8]

International consensus recommendations for the use of ciclosporin in rheumatoid arthritis[9] suggested that it might be considered in patients who are candidates for DMARDs and who did not have risk factors such as malignancy, uncontrolled hypertension, renal dysfunction, cytopenias, or marked disorder of liver function. They recommended a starting dose of between 2.5 and 3 mg/kg daily, increased if necessary after 4 to 8 weeks, in increments of 0.5 or 1 mg/kg at 1 to 2 month intervals, up to a maximum of 5 mg/kg daily, particular care being taken at doses over 4 mg/kg daily. Once the patient's disease had been stable for at least 3 months the daily dose should be decreased monthly or bimonthly in decrements of 500 micrograms/kg to the lowest effective dose. If it was only partially effective after 3 months at the maximum tolerable dose another medication should be considered instead or in addition; if there was no response to the maximum tolerable dose after 3 months, ciclosporin should be stopped. Patients should be carefully monitored before and during therapy.

Ciclosporin has been shown to have a corticosteroid-sparing effect and control the fever of juvenile idiopathic arthritis.[10] In patients with refractory juvenile idiopathic arthritis, adding ciclosporin to methotrexate therapy has been reported to elicit significant clinical improvement.[11]

1. Yocum DE, *et al.* Cyclosporin A in severe, treatment-refractory rheumatoid arthritis: a randomized study. *Ann Intern Med* 1988; 109: 863–9.
2. Tugwell P, *et al.* Low-dose cyclosporin versus placebo in patients with rheumatoid arthritis. *Lancet* 1990; 335: 1051–5.
3. Landewé RBM, *et al.* A randomized, double-blind, 24-week controlled study of low-dose cyclosporine versus chloroquine for early rheumatoid arthritis. *Arthritis Rheum* 1994; 37: 637–43.
4. Forre Ø, *et al.* Radiologic evidence of disease modification in rheumatoid arthritis patients treated with cyclosporine: results of a 48-week multicenter study comparing low-dose cyclosporine with placebo. *Arthritis Rheum* 1994; 37: 1506–12.
5. Wells GA, *et al.* Cyclosporine for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 1998 (accessed 15/01/08).
6. Tugwell P, *et al.* Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. *N Engl J Med* 1995; 333: 137–41.
7. Proudman SM, *et al.* Treatment of poor-prognosis early rheumatoid arthritis. *Arthritis Rheum* 2000; 43: 1809–19.
8. Gremese E, Ferraccioli GF. Benefit/risk of cyclosporine in rheumatoid arthritis. *Clin Exp Rheumatol* 2004; 22 (suppl 35): S101–S107.
9. Panayi GS, Tugwell P. The use of cyclosporin A microemulsion in rheumatoid arthritis: conclusions of an international review. *Br J Rheumatol* 1997; 36: 808–11.
10. Gerloni V, *et al.* Efficacy and safety profile of cyclosporin A in the treatment of juvenile chronic (idiopathic) arthritis: results of a 10-year prospective study. *Rheumatology (Oxford)* 2001; 40: 907–13.
11. Ravelli A, *et al.* Combination therapy with methotrexate and cyclosporine A in juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2002; 20: 569–72.

Sarcoidosis. Corticosteroids are the usual therapy for symptomatic sarcoidosis (p. 1612.2), and other agents are very much second-line; ciclosporin is one of several immunosuppressants that have been tried with variable results.

Scleritis. Ciclosporin is used alone or with corticosteroids in the treatment of scleritis (see p. 1612.3).

Scleroderma. There are a few reports of responses to ciclosporin in patients with scleroderma (p. 1938.3).

Toxic epidermal necrolysis. Ciclosporin has been reported to be of benefit in toxic epidermal necrolysis;[1–4] it has been given both enterally[1] and intravenously,[2] often combined with corticosteroids.[3,4]

1. Arévalo JM, *et al.* Treatment of toxic epidermal necrolysis with cyclosporin A. *J Trauma* 2000; 48: 473–8.
2. Hashim N, *et al.* Early cyclosporine treatment of incipient toxic epidermal necrolysis induced by concomitant use of lamotrigine and sodium valproate. *Acta Derm Venereol* 2004; 84: 90–1.
3. Aihara Y, *et al.* Toxic epidermal necrolysis in a child successfully treated with cyclosporin A and methylprednisolone. *Pediatr Int* 2007; 49: 659–62.
4. Rai R, Srinivas CR. Supraphamacologic doses of intravenous dexamethasone followed by cyclosporine in the treatment of toxic epidermal necrolysis. *Indian J Dermatol Venereol Leprol* 2008; 74: 263–5.

Uveitis. Ciclosporin is used in uveitis, see p. 1615.1.

Vasculitic syndromes. For the use of ciclosporin in Takayasu's arteritis and Wegener's granulomatosis, see p. 1614.3 and p. 1615.2, respectively.

Adverse Effects and Treatment

Nephrotoxicity, manifesting as raised serum creatinine and urea, is the major adverse effect of ciclosporin. It is related to drug-plasma concentrations and is usually reversible on reduction of the dose. In renal graft recipients episodes of nephrotoxicity may be difficult to distinguish from graft

rejection. Interstitial fibrosis may develop during long-term therapy.

Other frequent adverse effects include hypertension, gastrointestinal disturbances, fatigue, hepatotoxicity, hypertrichosis, gum hyperplasia, tremor, headaches, hyperlipidaemias, hyperkalaemia, hypomagnesaemia, hyperuricaemia, paraesthesia, and muscle cramps and myalgia. Less commonly, anaemia, thrombocytopenia, rashes, weight increase, oedema, pancreatitis, myopathy, neuropathy, and hyperglycaemia have been reported. Glomerular capillary thrombosis has occurred, and may progress to graft failure. Encephalopathy, manifest as convulsions, confusion, visual disturbances including blindness, movement disorders, or psychiatric disturbances, has been reported. Optic disc oedema, including papilloedema with possible visual impairment secondary to benign intracranial hypertension, has occurred rarely.

Anaphylactoid reactions have occurred after intravenous use; it has been suggested that these represent a reaction to the polyoxyl castor oil vehicle of the intravenous preparation.

Immunosuppression, including ciclosporin treatment, is associated with an increased incidence of lymphoma and other malignancies, particularly those of the skin, and excess exposure to UV light should be avoided during treatment. There is also an increased risk of infection, including activation of latent viral infections. These include BK virus-associated nephropathy that can lead to renal graft loss.

Alopecia. Although ciclosporin is more often associated with reports of hypertrichosis, there have been cases of alopecia areata developing in patients given ciclosporin,[1] sometimes with complete hair loss (alopecia universalis).[2,3]

1. Davies MG, Bowers PW. Alopecia areata arising in patients receiving cyclosporin immunosuppression. *Br J Dermatol* 1995; 132: 835–6.
2. Monti M, *et al.* Alopecia universalis in liver transplant patients treated with cyclosporin. *Br J Dermatol* 1995; 133: 663–4.
3. Parodi A, *et al.* Alopecia universalis and cyclosporin A. *Br J Dermatol* 1996; 135: 657.

Calcineurin inhibitor-induced pain syndrome. Calcineurin inhibitor-induced pain syndrome is reported rarely after organ or tissue transplantation and is associated with the use of ciclosporin, and less frequently tacrolimus. Symptoms vary from deep, aching rest pain to the sudden onset of severe, periarticular bone pain.[1] In some cases the pain resembled an electric shock, and was accompanied or preceded by intense pruritus;[2,3] progression to allodynia has been reported in one patient. Weight-bearing areas are commonly affected, particularly the lower limbs and pain is generally bilateral and symmetrical. Onset has been associated with high trough concentrations of calcineurin inhibitors. The mechanism of the syndrome is unclear, but it has been suggested that calcineurin inhibitors cause vascular changes that disturb bone perfusion and permeability, leading to vasoconstriction and bone marrow oedema.[1,4] Elevation of the feet, and dose reduction or withdrawal of calcineurin-inhibitor treatment are reported to relieve pain;[1] switching from one calcineurin inhibitor to another has had variable results.[4] Response to usual analgesia is often poor, but calcium-channel blockers such as nifedipine have been used with some success.[1,4]

1. Elder GJ. Prom marrow oedema to osteonecrosis: common paths in the development of post-transplant bone pain. *Nephrology (Carlton)* 2006; 11: 560–7.
2. Noda Y, *et al.* Calcineurin-inhibitor-induced pain syndrome after bone marrow transplantation. *J Anesth* 2008; 22: 61–3.
3. Kida A, *et al.* Incapacitating lower limb pain syndrome in cord blood stem cell transplant recipients with calcineurin inhibitor. *Pathol Oncol Res* 2004; 10: 204–6.
4. Lavoratore SR, *et al.* Cyclosporine-induced pain syndrome in a child undergoing hematopoietic stem cell transplant. *Ann Pharmacother* 2009; 43: 767–71.

Carcinogenicity. The use of ciclosporin in **organ transplant** recipients is associated with an increased incidence of malignancy, notably lymphoma,[1] and also skin cancer and Kaposi's sarcoma. The manufacturers have stated that of an estimated 5550 transplant patients who had been treated with ciclosporin by February 1984, lymphoproliferative disorders had been reported in 40; this represented an overall incidence of 0.7%, varying from 0.2 to 8% in different series.[2] In 1991, a report of 12 cases of lymphoproliferative disorders among 132 paediatric liver graft recipients estimated the incidence at about 2.8% per year for the first 6 years after transplantation, giving a cumulative risk of nearly 20% after 7 years.[3] There is evidence that the incidence of malignancy is related to dose,[2,4] and is greater when ciclosporin is used with other potent immunosuppressants.[2] In addition, the incidence of malignancy varies geographically, possibly reflecting environmental triggers and genetic susceptibility.[5]

It has been suggested that these lymphomas represent proliferation of B-cells under the influence of Epstein-Barr virus, a process normally prevented by the T-cells which are specifically inhibited by ciclosporin.[3] The resultant, usually polyclonal, lymphoproliferative tumours appear to regress on prompt excision of the affected tissue and reduction or withdrawal of the immunosuppressant regimen, in most cases without graft loss.[6] However, the need for vigilance and rapid response to these conditions has been stressed, since the responsive polyclonal disorder may evolve into a monoclonal, frankly malignant form; where the presentation is indistinguishable from a classic non-Hodgkins lymphoma the prognosis is much less good.[3] Interestingly, use of lower dose ciclosporin regimens appears to maintain normal elimination of Epstein-Barr virus-infected B-cells by specific T-cells,[7] and may lead to a reduced incidence of malignancy compared with earlier results.[4,7]

The risk of skin cancers in ciclosporin recipients is further increased by the exposure to sunlight.[8] Prophylactic retinoid therapy may prevent skin cancer in patients with renal transplants.[9]

There is no clear evidence that ciclosporin is associated with an increased incidence of malignancy compared with other immunosuppressants, although in one study dysplastic skin lesions were found in 14 of 64 transplant patients receiving ciclosporin compared with 3 of 33 previous similar patients who had received azathioprine.[10] However, such comparisons are difficult, not least because many transplant patients tend to have received multiple immunosuppressant agents. The safety of ciclosporin in **dermatology** patients has been reviewed.[11] Despite reports of lymphomas and other malignancies in dermatology patients treated with ciclosporin, a 5-year cohort study showed no increased risk of lymphoma or internal malignancies. While there was an increased risk of non-melanoma skin cancers, especially squamous cell carcinoma, many patients had been previously exposed to PUVA, methotrexate, or other immunosuppressants. Adjusting for these variables, more than 2 years of cumulative treatment with ciclosporin was estimated to increase the risk of non-melanoma skin cancer by a factor of 3.3 when compared with less than 2 years of cumulative treatment.

1. Penn I. Cancers following cyclosporine therapy. *Transplantation* 1987; 43: 32–5.
2. Beveridge T, *et al.* Lymphomas and lymphoproliferative lesions developing under cyclosporin therapy. *Lancet* 1984; i: 788.
3. Malatack JJ, *et al.* Orthotopic liver transplantation, Epstein-Barr virus, cyclosporine, and lymphoproliferative disease: a growing concern. *J Pediatr* 1991; 118: 667–75.
4. Dantal J, *et al.* Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. *Lancet* 1998; 351: 623–8.
5. Newstead CG. Assessment of risk of cancer after renal transplantation. *Lancet* 1998; 351: 610–11.
6. Starzl TE, *et al.* Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporin-steroid therapy. *Lancet* 1984; i: 583–7.
7. Crawford DH, Edwards JMB. Immunity to Epstein-Barr virus in cyclosporin A-treated renal allograft recipients. *Lancet* 1982; i: 1469–70.
8. Stockfleth E, *et al.* Epithelial malignancies in organ transplant patients: clinical presentation and new methods of treatment. *Recent Results Cancer Res* 2002; 160: 251–8.
9. Bavinck JN, *et al.* Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. *J Clin Oncol* 1995; 13: 1933–8.
10. Shuttleworth D, *et al.* Epidermal dysplasia and cyclosporine therapy in renal transplant patients: a comparison with azathioprine. *Br J Dermatol* 1989; 120: 551–4.
11. Behnam SM, *et al.* Review of cyclosporine immunosuppressive safety data in dermatology patients after two decades of use. *J Drugs Dermatol* 2005; 4: 189–94.

Dysmorphic changes. There was pronounced coarsening of facial features in 11 children who were treated with prednisone and ciclosporin for renal transplantation and followed up for more than 6 months.[1] The changes resembled those seen with phenytoin therapy. In a 13-year-old patient given ciclosporin as part of an immunosuppressive regimen after lung transplantation, facial dysmorphism, which developed along with follicular disturbances, later improved upon conversion to tacrolimus.[2] Similarly, lip hypertrophy associated with ciclosporin use in 2 paediatric patients resolved after therapy was changed to tacrolimus.[3] A 58-year-old renal transplant recipient on long-term ciclosporin therapy developed progressive facial changes, including swelling and distortion of the nose (rhinophyma);[4] surgery or physical ablation of excess tissue may provide cosmetic improvement.

1. Reznik VM, *et al.* Changes in facial appearance during cyclosporin treatment. *Lancet* 1987; i: 1405–7.
2. Chastain MA, Millikan LE. Pilomatrix dysplasia in an immunosuppressed patient. *J Am Acad Dermatol* 2000; 43: 118–22.
3. Cansick JC, Hulton S-A. Lip hypertrophy secondary to cyclosporin treatment. *Pediatr Nephrol* 2003; 18: 710–11.
4. Brown S, *et al.* Minerva picture]. *BMJ* 2005; 330: 1218.

Effects on the blood. Erythraemia[1,2] and thrombocytosis[3] have both been reported with ciclosporin treatment, both of which may contribute to **thromboembolic complications.** One retrospective study reported 17 thromboembolic events (pulmonary embolism, renal-vein or deep-vein thrombosis, or haemorrhoidal thrombosis) in 13 of 90 renal allograft recipients treated with ciclosporin and corticosteroids, compared with only 1 episode of superficial thrombophlebitis in 90 similar patients treated with an azathioprine-based regimen.[4] However, other authors dispute that the incidence of thromboembolic events is any greater after ciclosporin than azathioprine,[5-7] and one group found the reverse.[8]

Other effects that have been associated with ciclosporin therapy include cases of the haemolytic-uraemic syndrome,[9] and thrombocytopenia,[10] or leucopenia.[11] Post-transplant thrombotic microangiopathy has also been reported.[12,13] This syndrome can include haemolytic anaemia and thrombocytopenia, and must be distinguished from rejection in renal transplant recipients. In those patients with a history of thrombotic microangiopathy, the risk of recurrence is high, irrespective of ciclosporin treatment.

1. Tatman AJ, *et al.* Erythraemia in renal transplant recipients treated with cyclosporin. *Lancet* 1988; i: 1279.
2. Innes A, *et al.* Cyclosporin and erythraemia. *Lancet* 1988; ii: 285.
3. Itami N, *et al.* Thrombocytosis after cyclosporin therapy in child with nephrotic syndrome. *Lancet* 1988; ii: 1018.
4. Vanrenterghem Y, *et al.* Thromboembolic complications and haemostatic changes in cyclosporin-treated cadaveric kidney allograft recipients. *Lancet* 1985; i: 999–1002.
5. Bergentz S-E, *et al.* Venous thrombosis and cyclosporin. *Lancet* 1985; ii: 101–2.
6. Zazgornik J, *et al.* Venous thrombosis and cyclosporin. *Lancet* 1985; ii: 102.
7. Choudhury N, *et al.* Thromboembolic complications in cyclosporin-treated kidney allograft recipients. *Lancet* 1985; ii: 606.
8. Allen RD, *et al.* Venous thrombosis and cyclosporin. *Lancet* 1985; ii: 1004.
9. Bonsef RS, *et al.* Cyclosporin-induced haemolytic uraemic syndrome in liver allograft recipient. *Lancet* 1984; ii: 1337.
10. Dejong DJ, Sayler DJ. Possible cyclosporine-associated thrombocytopenia. *DICP Ann Pharmacother* 1990; 24: 1007.
11. Michel P, *et al.* Bone marrow toxicity of cyclosporin in a kidney transplant patient. *Lancet* 1986; ii: 394.
12. Pisoni R, *et al.* Drug-induced thrombotic microangiopathy: incidence, prevention and management. *Drug Safety* 2001; 24: 491–501.
13. Bren A, *et al.* Follow-up of kidney graft recipients with cyclosporine-associated hemolytic-uremic syndrome and thrombotic microangiopathy. *Transplant Proc* 2005; 37: 1889–91.

Effects on the cardiovascular system. The principal cardiovascular adverse effect of ciclosporin is **hypertension.** This may be severe,[1,2] appears to be dose-related,[1-3] and is particularly common in recipients of cardiac or heart-lung grafts.[4,5] There may be an association with low serum-magnesium concentrations.[6] Mechanisms that may contribute to ciclosporin-induced hypertension include impaired sodium excretion,[7] enhanced sympathetic nervous activity,[4,8] effects on renal prostaglandin metabolism,[3] and direct damage to endothelial cells[9] with release of the potent vasoconstrictor endothelin,[10] all of which may be due to calcineurin inhibition.[11] Thus hypertension may occur independently of nephrotoxicity,[3,8] and may be difficult to treat with conventional antihypertensive regimens.[7] Calcium-channel blockers are the preferred class of antihypertensives for hypertension that develops after transplantation.[1,12] It is important to choose one that does not interact with ciclosporin (see Cardiovascular Drugs under Interactions, p. 1953.3).[1] Beta blockers may also be used. Diuretics are usually avoided.[12] For mention of the ability of calcium-channel blockers to ameliorate the nephrotoxic effects of ciclosporin, see Transplantation, under Diltiazem, p. 1360.1, Nifedipine, p. 1450.2, and Verapamil, p. 1523.3 Occasionally, hypertension may be irreversible.[3,13]

Raynaud's syndrome has been reported with ciclosporin.[14] Conversely, use of ciclosporin has also reportedly caused erythromelalgia, with painful inflammatory vasodilatation of the extremities.[15] For a discussion of possible thromboembolic complications, see Effects on the Blood, above.

1. Textor SC, *et al.* Cyclosporine-induced hypertension after transplantation. *Mayo Clin Proc* 1994; 69: 1182–93.
2. Robert N, *et al.* Effect of cyclosporine on blood pressure. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 15/07/10).
3. Porter GA, *et al.* Cyclosporine-associated hypertension. *Arch Intern Med* 1990; 150: 280–3.
4. Scherrer U, *et al.* Cyclosporine-induced sympathetic activation and hypertension after heart transplantation. *N Engl J Med* 1990; 323: 693–9.
5. Weidle PJ, Vlasses PH. Systemic hypertension associated with cyclosporine: a review. *Drug Intell Clin Pharm* 1988; 22: 443–51.
6. June CH, *et al.* Correlation of hypomagnesemia with the onset of cyclosporine-associated hypertension in marrow transplant patients. *Transplantation* 1986; 41: 47–51.
7. Weinman EJ. Cyclosporine-associated hypertension. *Am J Med* 1989; 86: 256–7.
8. Mark AL. Cyclosporine, sympathetic activity, and hypertension. *N Engl J Med* 1990; 323: 748–50.
9. Zaal MJW, *et al.* Is cyclosporin toxic to endothelial cells? *Lancet* 1988; ii: 956–7.
10. Deray G, *et al.* Increased endothelin level after cyclosporine therapy. *Ann Intern Med* 1991; 114: 809.
11. Koomans HA, Ligtenberg G. Mechanisms and consequences of arterial hypertension after renal transplantation. *Transplantation* 2001; 72: S9–12.
12. Taler SJ, *et al.* Cyclosporin-induced hypertension: incidence, pathogenesis and management. *Drug Safety* 1999; 20: 437–49.
13. Senneseal JJ, *et al.* Hypertension and cyclosporine. *Ann Intern Med* 1986; 104: 729.
14. Deray G, *et al.* Cyclosporin and Raynaud phenomenon. *Lancet* 1986; ii: 1092–3.
15. Thami GP, Bhalla M. Erythromelalgia induced by possible calcium channel blockade by ciclosporin. *BMJ* 2003; 326: 910.

Effects on the gastrointestinal tract. There have been reports[1,2] of severe non-specific colitis associated with both elevated[1] and therapeutic[2] blood or serum concentrations of ciclosporin.

1. Innes A, *et al.* Cyclosporin toxicity and colitis. *Lancet* 1988; ii: 957. Correction. *Ibid.*: 1094.
2. Bowen JRC, Sahi S. Cyclosporin induced colitis. *BMJ* 1993; 307: 484.

Effects on glucose tolerance. Ciclosporin, particularly in high doses, may be associated with reduced insulin production,[1] impaired glucose tolerance,[2] and occasional overt diabetes mellitus,[3,4] although ciclosporin has also been tried, with some apparent benefit, in the treatment of recent-onset diabetes mellitus (see under Uses and Administration, p. 1947.1). The incidence of fasting hyperglycaemia has been estimated at about 8% in ciclosporin-treated renal transplant recipients, compared with about 5% in those given an azathioprine-based regimen.[4]

1. Scott JP, Hilgenbottam TW. Adverse reactions and interactions of cyclosporin. *Med Toxicol* 1983; 3: 107–27.
2. Gunnarsson R, *et al.* Deterioration in glucose metabolism in pancreatic transplant recipients given cyclosporin. *Lancet* 1983; ii: 571–2.
3. Bending JJ, *et al.* Diabetogenic effect of cyclosporin. *BMJ* 1987; 294: 401–2.
4. Yagisawa T, *et al.* Deterioration in glucose metabolism in cyclosporine-treated kidney transplant recipients and rats. *Transplant Proc* 1986; 18: 1548–51.

Effects on the kidneys. Ciclosporin nephrotoxicity comprises 2 distinct forms of renal injury.[1,2]

Acute nephrotoxicity is dose-related, and reversible.[1–4] It occurs shortly after starting ciclosporin and often presents as an asymptomatic increase in serum creatinine, which improves quickly on dosage adjustment or drug withdrawal.[2,5] It may be difficult to distinguish ciclosporin nephrotoxicity from acute graft rejection after kidney transplantation.[5] Extremely high intravenous doses of ciclosporin (21 mg/kg per 24 hours for 60 hours) have been associated with fatal acute tubular necrosis;[6] in another patient given an overdose of 30 mg/kg per 24 hours, the error was detected after 18 hours, and the necrosis deemed to be partially reversible.[7]

Acute ciclosporin nephrotoxicity appears to be related to a renal imbalance of vasoconstrictor and vasodilator mediators, leading to intense vasoconstriction within the kidney.[1,2] Stimulation of the renin-angiotensin system,[5] free radical damage,[1,2] and activation of the sympathetic nervous system[1,5] have been suggested to play a role; numerous vasoactive mediators, including prostaglandins, thromboxanes, nitric oxide, and endothelin-1, may be implicated.[2,3] However, studies with therapies affecting vasoactive factors have produced equivocal results.[1–3]

Chronic nephrotoxicity is related to long-term exposure to ciclosporin.[2] It may be difficult to distinguish between chronic ciclosporin nephrotoxicity and chronic allograft rejection or nephropathy.[4,5] There is a decline in glomerular filtration rate, which may be irreversible or only partially reversible in transplant patients;[3] Some cardiac transplant patients given higher doses than those used in renal transplantation have developed end-stage renal failure.[3] One study[8] in paediatric heart transplant patients found that the decline in renal function correlated with early exposure to ciclosporin. However, in non-transplant patients, renal function impairment has been reported to be reversible after stopping ciclosporin.[3,9] Long-term follow-up has not shown progressive loss of renal function in these patients.[3] Chronic nephrotoxicity is also associated with typical irreversible histological changes, such as interstitial fibrosis.[1–3] which may occur as a result of ischaemic damage secondary to the prolonged alterations in intrarenal haemodynamics.[3] The mechanism is not completely understood, and chronic nephrotoxicity can occur independently of acute renal dysfunction, dosage, or ciclosporin blood concentrations.[4]

Acquired cystic kidney disease developed in 24 of 89 paediatric liver transplant patients treated with ciclosporin compared with 2 of 146 patients treated with tacrolimus in a retrospective study; this difference became evident after 5 to 10 years of follow-up. Those with renal impairment were also found to be at increased risk. However, factors such as renal injury during transplantation, hypertension, or exposure to other nephrotoxic drugs could have contributed to the difference in cyst formation between ciclosporin and tacrolimus. Patients taking ciclosporin were also followed for more than twice as many years as those taking tacrolimus, allowing more time for cysts to develop. Ciclosporin-induced interstitial fibrosis was suggested as a possible mechanism for the effect.[10]

Drugs tried to *ameliorate* the nephrotoxic effects of ciclosporin in patients who have undergone transplantation include calcium-channel blockers (see Transplantation, under Diltiazem, p. 1360.1, Nifedipine, p. 1450.2, and Verapamil, p. 1523.3), clonidine, codergocrine,[11–13] omega-3 triglycerides,[14] misoprostol and other prostaglandin analogues,[15,16] and cilastatin.[17] Although benefits have been reported with some of these, hydration, careful monitoring of ciclosporin concentrations, and the use where possible of low-dose or intermittent regimens of ciclosporin appear to remain the major means of minimising nephrotoxicity. Calcium-channel blockers are used if hypertension occurs (see Effects on the Cardiovascular System, p. 1949.3).

1. Burdmann EA, *et al.* Cyclosporine nephrotoxicity. *Semin Nephrol* 2003; 23: 465–76.
2. Cattaneo D, *et al.* Nephrotoxic aspects of cyclosporine. *Transplant Proc* 2004; 36 (suppl): 234S–239S.
3. Leaker B, Cairns HS. Clinical aspects of cyclosporin nephrotoxicity. *Br J Hosp Med* 1994; 52: 529–34.
4. Vítko Š, Viklický O. Cyclosporine renal dysfunction. *Transplant Proc* 2004; 36 (suppl): 243S–247S.
5. Busauschina A, *et al.* Cyclosporine nephrotoxicity. *Transplant Proc* 2004; 36 (suppl): 229S–233S.
6. Shechter P. Acute tubular necrosis following high-dose cyclosporine A therapy. *Eur J Clin Pharmacol* 1996; 49: 521–3.
7. Dussol B, *et al.* Acute tubular necrosis induced by high level of cyclosporine A in a lung transplant. *Transplantation* 2000; 70: 1234–6.
8. Hornung TS, *et al.* Renal function after pediatric cardiac transplantation: the effect of early cyclosporin dosage. *Pediatrics* 2001; 107: 1346–50.
9. Powles AV, *et al.* Renal function after 10 years' treatment with cyclosporin for psoriasis. *Br J Dermatol* 1998; 138: 443–9.
10. Calvo-Garcia MA, *et al.* Acquired renal cysts after pediatric liver transplantation: association with cyclosporine and renal dysfunction. *Pediatr Transplant* 2008; 12: 666–71.
11. Heinrichs DA, *et al.* The effects of co-dergocrine on cyclosporin A pharmacokinetics and pharmacodynamics. *Br J Clin Pharmacol* 1987; 24: 117–18.
12. Nussenblatt RB, *et al.* Hydergine and cyclosporin nephrotoxicity. *Lancet* 1986; i: 1220–1.
13. Kho TL, *et al.* Hydergine and reversibility of cyclosporin nephrotoxicity. *Lancet* 1986; ii: 394–5.
14. Stoof TJ, *et al.* Does fish oil protect renal function in cyclosporin-treated psoriasis patients? *Br J Dermatol* 1990; 123: 535.
15. Moran M, *et al.* Prevention of acute graft rejection by the prostaglandin E_1 analogue misoprostol in renal-transplant recipients treated with cyclosporine and prednisone. *N Engl J Med* 1990; 322: 1183–8.
16. Di Palo PQ, *et al.* Role of a prostaglandin E_1 analogue in the prevention of acute graft rejection by cyclosporine. *N Engl J Med* 1990; 323: 832.
17. Tejedor A, *et al.* Cilastatin protection against cyclosporin A-induced nephrotoxicity: clinical evidence. *Curr Med Res Opin* 2007; 23: 505–13.

Effects on lipids. Marked hyperlipidaemia has been associated with ciclosporin therapy, with notable increases reported in low-density lipoprotein cholesterol,[1,2] and triglycerides. An increase in lipoprotein(a) has been reported,[3] but this was disputed.[4–6] Ciclosporin has been reported to have greater effects on lipids than azathioprine[7] or tacrolimus[8] post-transplantation. The use of corticosteroids with ciclosporin appears to have an additive adverse effect on lipids.[9] Lipid regulating drugs are used to decrease hypercholesterolaemia in transplant patients.

1. Luke DR, *et al.* Longitudinal study of cyclosporine and lipids in patients undergoing bone marrow transplantation. *J Clin Pharmacol* 1990; 30: 163–9.
2. Ballantyne CM, *et al.* Effects of cyclosporine therapy on plasma lipoprotein levels. *JAMA* 1989; 262: 53–6.
3. Webb AT, *et al.* Does cyclosporin increase lipoprotein(a) concentrations in renal transplant recipients? *Lancet* 1993; 341: 268–70.
4. Kronenberg F, *et al.* Cyclosporin and serum lipids in renal transplant recipients. *Lancet* 1993; 341: 765.
5. Segarra A, *et al.* Cyclosporin and serum lipids in renal transplant recipients. *Lancet* 1993; 341: 766.
6. Hunt BJ, *et al.* Does cyclosporin affect lipoprotein(a) concentrations? *Lancet* 1994; 343: 119–20.
7. Van den Dorpel MA, *et al.* Conversion from cyclosporine A to azathioprine treatment improves LDL oxidation in kidney transplant recipients. *Kidney Int* 1997; 51: 1608–12.
8. Taylor DO, *et al.* A randomized, multicenter comparison of tacrolimus and cyclosporine immunosuppressive regimens in cardiac transplantation: decreased hyperlipidemia and hypertension with tacrolimus. *J Heart Lung Transplant* 1999; 18: 336–45.
9. Moore R, *et al.* Calcineurin inhibitors and post-transplant hyperlipidaemias. *Drug Safety* 2001; 24: 755–66.

Effects on the nervous system. Adverse effects of ciclosporin on the CNS include tremor,[1–4] ataxia,[1–3] confusion[1,2,5] or agitation,[2] mental depression,[3] headache,[2,5] sleep disturbances,[2] lethargy,[1,2,6,7] or coma[2,5–7] (in one case coma persisted for 44 days),[8] convulsions,[2,3,5,9–13] leukoencephalopathy,[2,6,9,13] cortical blindness,[2,9] diplopia,[14] and spasticity or paralysis of the limbs.[1,2] Opsoclonus (an involuntary eye movement disorder) has also been reported.[13] In one reported case of posterior leukoencephalopathy, the patient developed irreversible abulia (impairment of ability to perform voluntary actions or make decisions; reduction in speech, movement, thought, and emotional reaction);[15] the patient initially presented with subtle symptoms of decreased appetite and reduced activity. Convulsions have sometimes been associated with hypertension and fluid retention,[11] but this is by no means always the case.[9,10]

Although neurotoxicity usually manifests within a month of beginning treatment, it may be delayed, and in one case occurred only after 3 years of ciclosporin therapy.[16] Severe CNS toxicity has been stated to vary in incidence from 0.1% in renal transplant patients to about 1.6% in bone marrow transplant recipients.[12] There is some evidence for an association of serious neurological effects with low total serum-cholesterol concentrations,[2] and the use of the intravenous formulation.[2] Neurotoxicity may also be associated with the use of lipid solutions.[17] An association with hypomagnesaemia has also been proposed[3] but may just represent concomitant nephrotoxicity.[18] Convulsions may be more likely or more severe in patients with a familial history of epilepsy,[19] subclinical aluminium overload,[20] or in those also given high-dose corticosteroids.[5,21,22]

The mechanism of toxicity is unknown but may be associated with disturbance of the blood-brain barrier;[10,12,23] it has been suggested that the metabolite M-17, or possibly other metabolites, are responsible for neurotoxicity.[6] Ciclosporin may be selectively toxic for glial cells, and alteration of sympathetic outflow by calcineurin inhibition may also mediate neurotoxicity.[24]

For reports of calcineurin inhibitor-induced pain syndrome which has sometimes been associated with use of ciclosporin, see p. 1949.1.

1. Atkinson K, *et al.* Cyclosporine-associated central-nervous-system toxicity after allogeneic bone-marrow transplantation. *N Engl J Med* 1984; 310: 527.
2. de Groen PC, *et al.* Central nervous system toxicity after liver transplantation: the role of cyclosporine and cholesterol. *N Engl J Med* 1987; 317: 861–6.
3. Thompson CB, *et al.* Association between cyclosporin neurotoxicity and hypomagnesaemia. *Lancet* 1984; ii: 1116–20.
4. Munhoz RP, *et al.* Movement disorders secondary to long-term treatment with cyclosporine A. *Arq Neuropsiquiatr* 2005; 63: 592–6.
5. Taque S, *et al.* Central neurotoxicity of cyclosporine in two children with nephrotic syndrome. *Pediatr Nephrol* 2004; 19: 276–80.
6. Kunzendorf U, *et al.* Cyclosporin metabolites and central-nervous-system toxicity. *Lancet* 1988; i: 1223.
7. Lischke R, *et al.* Cyclosporine-related neurotoxicity in a patient after bilateral lung transplantation for cystic fibrosis. *Transplant Proc* 2004; 36: 2837–9.
8. Berden JHM, *et al.* Severe central-nervous-system toxicity associated with cyclosporin. *Lancet* 1985; i: 219–20.
9. Hughes RL. Cyclosporine-related central nervous system toxicity in cardiac transplantation. *N Engl J Med* 1990; 323: 420–1.
10. Gertrand F, *et al.* Cyclosporine neurotoxicity. *N Engl J Med* 1991; 324: 1744–5.
11. Joss DV, *et al.* Hypertension and convulsions in children receiving cyclosporin A. *Lancet* 1982; i: 906.
12. Krupp P, *et al.* Encephalopathy associated with fat embolism induced by solvent for cyclosporin. *Lancet* 1989; i: 168–9.
13. Marchiori PE, *et al.* Cyclosporine A-induced ocular opsoclonus and reversible leukoencephalopathy after orthotopic liver transplantation: brief report. *Clin Neuropharmacol* 2004; 27: 195–7.
14. Openshaw H. Eye movement abnormality associated with cyclosporin. *J Neurol Neurosurg Psychiatry* 2001; 70: 809.
15. Nishie M, *et al.* Posterior encephalopathy subsequent to cyclosporin A presenting as irreversible abulia. *Intern Med* 2003; 42: 750–5.
16. Welge-Lüssen UC, Gerhartz HH. Late onset of neurotoxicity with cyclosporin. *Lancet* 1994; 343: 293.
17. De Klippel N. Cyclosporin leukoencephalopathy induced by intravenous lipid solution. *Lancet* 1992; 339: 1114.
18. Allen RD, *et al.* Cyclosporin and magnesium. *Lancet* 1985; i: 1283–4.
19. Velu T, *et al.* Cyclosporin-associated fatal convulsions. *Lancet* 1985; i: 219.
20. Nordal KP, *et al.* Aluminium overload, a predisposing condition for epileptic seizures in renal-transplant patients treated with cyclosporin. *Lancet* 1985; ii: 153–4.
21. Durrant S, *et al.* Cyclosporin A, methylprednisolone, and convulsions. *Lancet* 1982; ii: 829–30.
22. Boogaerts MA, *et al.* Cyclosporin, methylprednisolone, and convulsions. *Lancet* 1982; ii: 1216–17.
23. Sloane JP, *et al.* Disturbance of blood-brain barrier after bone-marrow transplantation. *Lancet* 1985; ii: 280–1.
24. Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. *Transpl Int* 2000; 13: 313–26.

Effects on skeletal muscle. Ciclosporin has occasionally been associated with myopathy.[1–6] The manufacturer noted that 29 cases had been reported by December 1990, which appeared to be divided into cases of toxic or non-specific myopathy or mild sensory motor neuropathy, which were generally dose-related; and rhabdomyolysis, often, but not always, when used with lovastatin or colchicine.[7] Rhabdomyolysis has also been reported when other statins were used with ciclosporin, see Lipid Regulating Drugs, under Interactions, p. 1954.1.

1. Noppen M, *et al.* Cyclosporine and myopathy. *Ann Intern Med* 1987; 107: 945–6.
2. Goy J-J. Myopathy as possible side-effect of cyclosporin. *Lancet* 1989; i: 1446–7.
3. Grezard O, *et al.* Cyclosporin-induced muscular toxicity. *Lancet* 1990; 335: 177.
4. Fernandez-Sola J, *et al.* Reversible cyclosporin myopathy. *Lancet* 1990; 335: 362–3.
5. Wahie S, Meggitt SJ. Myotoxicity occurring with ciclosporin in a patient with atopic dermatitis. *Br J Dermatol* 2005; 153: 1238.
6. Khan S, *et al.* Musculoskeletal and myotoxic side-effects in a patient treated for psoriasis. *Br J Dermatol* 2006; 155: 481.
7. Arellano F, Krupp P. Muscular disorders associated with cyclosporin. *Lancet* 1991; 337: 915.

Hyperplasia. Ciclosporin is well known to be associated with the development of gingival hyperplasia or gingival overgrowth: one review[1] has estimated the incidence at about 30% in transplant patients, while noting that reported values in the literature range from about 7 to 70%. A large study[2] found dosage and serum concentration of ciclosporin to be the most significant risk factors in the development of gingival hyperplasia. The presence of dental plaque may exacerbate the response, and good oral hygiene is important in preventing or minimising of gingival overgrowth.[1] Use with nifedipine (which can itself produce hyperplasia) may exacerbate overgrowth;[3] a cohort study[4] of renal transplant recipients found that amlodipine was associated with a greater prevalence of overgrowth than nifedipine. Overgrowth is generally reversible after dosage reduction or withdrawal of ciclosporin; where this is not feasible, surgical excision is recommended.[1] However, improvement or resolution of the overgrowth may

also be produced by a course of azithromycin.[3-7] Similar benefit has been reported for metronidazole in some[8,9] but not all patients.[10] There are reports[11,12] of marked improvement in hyperplasia after changing treatment from ciclosporin to tacrolimus, including a case apparently resistant to azithromycin.[13]

Enlargement of the papillae of the tongue[14] and sebaceous gland hyperplasia[15] have also occurred in association with ciclosporin.

1. Brunet L, *et al.* Gingival enlargement induced by drugs. *Drug Safety* 1996; 15: 219–31.
2. Thomas DW, *et al.* Risk factors in the development of cyclosporine-induced gingival overgrowth. *Transplantation* 2000; 69: 522–6.
3. Slavin J, Taylor J. Cyclosporin, nifedipine, and gingival hyperplasia. *Lancet* 1987; ii: 739.
4. James JA, *et al.* The calcium channel blocker used with cyclosporin has an effect on gingival overgrowth. *J Clin Periodontol* 2000; 27: 109–15.
5. Jucglà A, *et al.* The use of azithromycin for cyclosporin-induced gingival overgrowth. *Br J Dermatol* 1998; 138: 198–9.
6. Nash MM, Zaltzman JS. Efficacy of azithromycin in the treatment of cyclosporine-induced gingival hyperplasia in renal transplant recipients. *Transplantation* 1998; 65: 1611–15.
7. Citterio F, *et al.* Azithromycin treatment of gingival hyperplasia in kidney transplant recipients is effective and safe. *Transplant Proc* 2001; 33: 2134–5.
8. Wong W, *et al.* Resolution of cyclosporin-induced gingival hypertrophy with metronidazole. *Lancet* 1994; 343: 986.
9. Cecchin E, *et al.* Treatment of cyclosporine-induced gingival hypertrophy. *Ann Intern Med* 1997; 126: 409–10.
10. Aufricht C, *et al.* Oral metronidazole does not improve cyclosporine A-induced gingival hyperplasia. *Pediatr Nephrol* 1997; 11: 552–5.
11. Thorp M, *et al.* The effect of conversion from cyclosporine to tacrolimus on gingival hyperplasia, hirsutism and cholesterol. *Transplantation* 2000; 69: 1218–20.
12. James JA, *et al.* Reduction in gingival overgrowth associated with conversion from cyclosporin A to tacrolimus. *J Clin Periodontol* 2000; 27: 144–8.
13. Vallejo C, *et al.* Resolution of cyclosporine-induced gingival hyperplasia resistant to azithromycin by switching to tacrolimus. *Haematologica* 2001; 86: 110.
14. Silverberg NB, *et al.* Lingual fungiform papillae hypertrophy with cyclosporin A. *Lancet* 1996; 348: 967.
15. Boschnakow A, *et al.* Ciclosporin A-induced sebaceous gland hyperplasia. *Br J Dermatol* 2003; 149: 198–200.

Hypersensitivity. Anaphylactoid reactions in 5 of 21 patients given intravenous ciclosporin infusions were found to be associated with improper mixing of the ciclosporin concentrate, which had a polyoxyl castor oil vehicle, with the infusion solution.[1] It was concluded that this had led to an initial bolus of polyoxyl castor oil that had triggered the anaphylactic reactions. Subsequent study indicated that peak concentrations of up to 9 times the intended concentration of ciclosporin and polyoxyl castor oil were present in the first 10 minutes of a poorly mixed infusion.[2] Anaphylactic shock after ingestion of ciclosporin capsules has been reported. The microemulsifying base containing corn oil and polyoxyl 40 hydrogenated castor oil, which is related to the polyoxyl castor oil vehicle used in the intravenous formulation, was considered to be the likely cause.[3]

1. Liau M, *et al.* High incidence of anaphylactoid reactions to iv cyclosporin A caused by improper dissolution of Cremophor EL. *Clin Pharmacol Ther* 1995; 57: 209.
2. Liau-Chu M, *et al.* Mechanism of anaphylactoid reactions: improper preparation of high-dose intravenous cyclosporine leads to bolus infusion of Cremophor EL and cyclosporine. *Ann Pharmacother* 1997; 31: 1287–91.
3. Kuiper RAJ, *et al.* Cyclosporine-induced anaphylaxis. *Ann Pharmacother* 2000; 34: 858–61.

Hyperuricaemia. Ciclosporin therapy may be associated with marked hyperuricaemia,[1-3] which may lead (mainly in male patients[1]) to episodes of severe gouty arthritis.[1-3] It has been suggested that ciclosporin specifically reduces urate clearance by the kidney independently of its effects on glomerular filtration,[4,5] but this has been disputed.[6] Treatment of ciclosporin-induced gout can be difficult since interactions with NSAIDs may lead to enhanced renal toxicity[5] and patients who are also receiving azathioprine may have increased bone-marrow toxicity if given allopurinol.[7] Benzbromarone appears to be an alternative[8] for treating hyperuricaemia in renal transplant recipients with a creatinine clearance greater than 25 mL/minute.

1. Lin H-Y, *et al.* Cyclosporine-induced hyperuricemia and gout. *N Engl J Med* 1989; 321: 287–92.
2. Kahl LE, *et al.* Gout in the heart transplant recipient: physiologic puzzle and therapeutic challenge. *Am J Med* 1989; 87: 289–94.
3. Burack DA, *et al.* Hyperuricemia and gout among heart transplant recipients receiving cyclosporine. *Am J Med* 1992; 92: 141–6.
4. Noordzij TC, *et al.* Cyclosporine-induced hyperuricemia and gout. *N Engl J Med* 1990; 322: 335.
5. Parge D, *et al.* Hyperuricemia and gouty arthritis in heart transplant recipients. *Am J Med* 1990; 88: 553.
6. Zürcher RM, *et al.* Hyperuricaemia in cyclosporin-treated patients: a GFR-related effect. *Nephrol Dial Transplant* 1996; 11: 153–8.
7. Pigg WD. Cyclosporine-induced hyperuricemia and gout. *N Engl J Med* 1990; 332: 334–5.
8. Zürcher RM, *et al.* Excellent uricosuric efficacy of benzbromarone in cyclosporin-A-treated renal transplant patients: a prospective study. *Nephrol Dial Transplant* 1994; 9: 548–51.

Overdosage. Anxiety, diarrhoea, vomiting, and perspiration, with weak and irregular pulse, occurred in a patient accidentally injected with 250 mg (estimated 6.25 mg/kg) of ciclosporin.[1] The patient subsequently developed atrial fibrillation, which was treated with digoxin, and in the next 36 hours showed signs of slight renal insufficiency. Two days later no adverse effects were apparent. Atrial fibrillation also developed in another patient accidentally given 1 g of microemulsifying oral ciclosporin.[2] No adverse renal, hepatic, or neurological effects were seen in a third patient[3] who took 25 g of ciclosporin over 8 days. There was a mild increase in blood pressure and other symptoms included burning sensations in the mouth and the extremities, dysgeusia, facial flushing, and gastrointestinal disturbances. Symptoms resolved within 2 weeks of stopping ciclosporin.

A patient accidentally given intravenous ciclosporin at 30 mg/hour for 13 hours, developed massive intracerebral oedema and brainstem compression and died despite stopping the infusion.[4]

Although ciclosporin is only minimally dialysable, whole blood exchange (therapeutic erythrocytapheresis followed by plasma exchange) has been used in the management of a patient inadvertently given 3.5 g of ciclosporin orally; the overdose was discovered too late for the use of activated charcoal or gastric lavage, and plasma exchange alone was considered unsuitable because of the partitioning of ciclosporin between plasma and erythrocytes. The patient, who had signs of nephrotoxicity and hepatotoxicity, recovered without long-term sequelae.[5]

For reference to tubular necrosis after extremely high intravenous doses of ciclosporin, see under Effects on the Kidneys, p. 1950.1.

1. Wallemacq PE, Lesne ML. Accidental massive IV administration of cyclosporine in man. *Drug Intell Clin Pharm* 1985; 19: 29–30.
2. LoVecchio FA, Goltz HR. Atrial fibrillation following acute overdose with oral cyclosporine. *Ann Pharmacother* 2000; 34: 405.
3. Baumhefner RW, *et al.* Huge cyclosporin overdose with favourable outcome. *Lancet* 1987; ii: 332.
4. de Perrot M, *et al.* Massive cerebral edema after i.v. cyclosporin overdose. *Transplantation* 2000; 70: 1259–60.
5. Kwon SU, *et al.* Successful whole blood exchange by apheresis in a patient with acute cyclosporine intoxication without long-term sequelae. *J Heart Lung Transplant* 2006; 25: 483–5.

Precautions

Regular monitoring of renal and hepatic function, blood pressure, and serum electrolytes (chiefly potassium and magnesium) is required in patients receiving ciclosporin. Serum lipids should also be monitored. Monitoring of plasma ciclosporin concentrations is mandatory in transplant patients. Dosage adjustment is often necessary in patients with renal impairment or other factors affecting plasma ciclosporin concentrations. Care is required in patients with hyperuricaemia, and intravenous formulations should be given cautiously to those who have previously received parenteral drugs formulated in polyoxyl castor oil, or to those with a history of allergic reactions.

Ciclosporin should not be used to treat atopic dermatitis, psoriasis, or rheumatoid arthritis in patients with persistently raised creatinine, uncontrolled hypertension, uncontrolled infections, or malignancy. An exception is patients with treated malignant or pre-malignant lesions of the skin who may receive ciclosporin as a last resort for psoriasis. Psoriatic patients should not be given concomitant ultraviolet irradiation and should avoid excessive sun exposure. Ciclosporin may increase the risk of benign intracranial hypertension.

The commercially available oral formulations of ciclosporin differ in their bioavailability, and patients should not be transferred from one to another without appropriate monitoring (see Administration, Oral, p. 1946.2). Intra-uterine contraceptive devices should be used with caution during immunosuppressive treatment as there is an increased risk of infection. Immunosuppressants may reduce the response to vaccines and use with live vaccines should generally be avoided as there is a possibility of generalised infection, see Vaccines, p. 1955.1.

Breast feeding. The American Academy of Pediatrics considers that ciclosporin may possibly suppress the immune system in a nursing infant.[1] However, a study[2] in the breast-fed infants of 7 women given ciclosporin found that the amounts ingested by the infant produced undetectable blood concentrations. In another case it was estimated that a breast-fed infant received less than 100 micrograms/kg of ciclosporin daily.[3]

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 15/01/08)
2. Nyberg G, *et al.* Breast feeding during treatment with cyclosporine. *Transplantation* 1998; 65: 253–5.
3. Thiru Y, *et al.* Successful breast feeding while mother was taking cyclosporin. *BMJ* 1997; 315: 463.

Porphyria. There have been reports of patients with acute intermittent porphyria given ciclosporin pre- and post-transplant with no exacerbation of symptoms.[1,2] The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ciclosporin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[3]

1. Barone GW, *et al.* The tolerability of newer immunosuppressive medications in a patient with acute intermittent porphyria. *J Clin Pharmacol* 2001; 41: 113–15.
2. Warholm C, Wilczek H. Renal transplantation in a case of acute intermittent porphyria. *J Clin Pharmacol* 2003; 43: 1158–60.
3. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Pregnancy. Ciclosporin has been used successfully in pregnant women. However, in common with other immunosuppressants, fetal growth retardation may be a significant problem.[1-4] Patients with hypertension or graft dysfunction are more likely to have adverse outcomes, so patients should have stable graft function and be on maintenance therapy before considering pregnancy.[1,2] Serum ciclosporin concentrations may fall during pregnancy,[2,3,5] but although frequent monitoring is necessary, the altered immune state of pregnancy may protect against rejection episodes.[5] Ciclosporin should be used at the lowest possible dose to maintain efficacy, and one review[3] has recommended that the daily dose should be kept below 5 mg/kg.

One case of osseous malformation, resulting in hypoplasia of the right leg has been reported in an infant born to a ciclosporin-treated mother.[6]

1. Armenti VT, *et al.* Variables affecting birthweight and graft survival in 197 pregnancies in cyclosporine-treated female kidney transplant recipients. *Transplantation* 1995; 59: 476–9.
2. Armenti VT, *et al.* National Transplantation Pregnancy Registry (NTPR): cyclosporine dosing and pregnancy outcome in female renal transplant recipients. *Transplant Proc* 1996; 28: 2111–12.
3. Huynh LA, Min DI. Outcomes of pregnancy and the management of immunosuppressive agents to minimize fetal risks in organ transplant patients. *Ann Pharmacother* 1994; 28: 1355–6.
4. Lamarque V, *et al.* Analysis of 629 pregnancy outcomes in transplant recipients treated with Sandimmun. *Transplant Proc* 1997; 29: 2480.
5. Thomas AG, *et al.* The effect of pregnancy on cyclosporine levels in renal allograft patients. *Obstet Gynecol* 1997; 90: 916–19.
6. Pujals JM, *et al.* Osseous malformation in baby born to woman on cyclosporin. *Lancet* 1989; i: 667.

Interactions

Ciclosporin is extensively metabolised in the liver and plasma-ciclosporin concentrations may be affected by inducers or competitive inhibitors of hepatic enzymes, particularly cytochrome P450 isoenzyme CYP3A4. For example, use of carbamazepine, nevirapine, phenytoin, phenobarbital, rifampicin, St John's wort, and other inducers of hepatic enzymes may lead to lower plasma concentrations of ciclosporin, and increased plasma concentrations have been reported with some antifungals, macrolide antibacterials, HIV-protease inhibitors, the NNRTI delavirdine, some calcium-channel blockers, sex hormones, corticosteroids and grapefruit juice. In transplant patients frequent measurement of plasma ciclosporin and, if necessary, ciclosporin dosage adjustment is required, particularly during the introduction or withdrawal of other drugs.

Concurrent use of statins may increase the risk of myopathy and rhabdomyolysis. Potassium-sparing diuretics should be avoided because of the risk of hyperkalaemia, and patients taking ciclosporin should avoid a high dietary intake of potassium. The risk of gingival hyperplasia may be increased by amlodipine or nifedipine.

During treatment with ciclosporin, vaccination may be less effective, and the use of live vaccines should generally be avoided.

Care should be taken when ciclosporin is given with other nephrotoxic drugs.

Reviews of the interactions of ciclosporin.

1. Yee GC, McGuire TR. Pharmacokinetic drug interactions with cyclosporin. *Clin Pharmacokinet* 1990; 19: 319–32 and 400–15.
2. Lake KD, Canalax DM. Important interactions of drugs with immunosuppressive agents used in transplant recipients. *J Antimicrob Chemother* 1995; 36 (suppl B): 11–22.
3. Campana C, *et al.* Clinically significant drug interactions with cyclosporin: an update. *Clin Pharmacokinet* 1996; 30: 141–79.
4. Chan L-N. Drug-nutrient interactions in transplant recipients. *J Parenter Enteral Nutr* 2001; 25: 132–41.

Antibacterials. *AMINOGLYCOSIDES.* Increased nephrotoxicity has been reported after the use of aminoglycosides with ciclosporin.[1,2] However, a retrospective analysis in 21 patients given ciclosporin for allogeneic bone marrow transplant, in whom aminoglycosides were used if fever and neutropenia developed, showed no greater incidence of nephrotoxicity than in 20 autologous bone marrow recipients who did not receive ciclosporin, suggesting that these drugs can be given together provided careful monitoring is maintained.[3]

1. Termeer A, *et al.* Severe nephrotoxicity cause by the combined use of gentamicin and cyclosporine in renal allograft recipients. *Transplantation* 1986; 42: 220–1.
2. Morales JM, *et al.* Reversible acute renal toxicity by toxic sinergic effect between gentamicin and cyclosporine. *Clin Nephrol* 1988; 29: 272.
3. Chandrasekar PH, Cronin SM. Nephrotoxicity in bone marrow transplant recipients receiving aminoglycoside plus cyclosporine or aminoglycoside alone. *J Antimicrob Chemother* 1991; 27: 845–9.

CHLORAMPHENICOL. Marked rises in plasma-ciclosporin concentrations have been reported when chloramphenicol was given.[1-3] Ciclosporin trough concentrations should be monitored if these drugs are used together.[3]

1. Steinfort CL, McConachy KA. Cyclosporin-chloramphenicol drug interaction in a heart-lung transplant recipient. *Med J Aust* 1994; 161: 455.
2. Bui LL, Huang DD. Possible interaction between cyclosporine and chloramphenicol. *Ann Pharmacother* 1999; 33: 252–3.
3. Mathis AS, *et al.* Interaction of chloramphenicol and the calcineurin inhibitors in renal transplant recipients. *Transpl Infect Dis* 2002; 4: 169–74.

FLUOROQUINOLONES. Several reports have indicated that the quinolone *ciprofloxacin* has no effect on the pharmacokinetics of ciclosporin.[1-3] However, there is a report of enhanced nephrotoxicity without a change in ciclosporin concentrations in a patient given ciprofloxacin,[4] and another report showing both enhanced nephrotoxicity and increased ciclosporin concentrations.[5] Furthermore, a small case-control study suggested an increase in transplant rejection with ciprofloxacin.[6] *Norfloxacin* has been reported to decrease clearance and increase blood concentrations of ciclosporin in paediatric patients,[7] probably by inhibition of ciclosporin metabolism. *Levofloxacin* did not alter ciclosporin pharmacokinetics in healthy subjects,[8] but a study in renal transplant patients found that levofloxacin partially inhibited the metabolism of ciclosporin;[9] no adverse effects and no supratherapeutic concentrations of ciclosporin were seen.

1. Hooper TL, *et al.* Ciprofloxacin: a preferred treatment for legionella infections in patients receiving cyclosporin A. *J Antimicrob Chemother* 1988; 22: 952–3.
2. Tan KKC, *et al.* Co-administration of ciprofloxacin and cyclosporin: lack of evidence for a pharmacokinetic interaction. *Br J Clin Pharmacol* 1989; 28: 185–7.
3. Krüger HU, *et al.* Investigation of potential interaction of ciprofloxacin with cyclosporine in bone marrow transplant recipients. *Antimicrob Agents Chemother* 1990; 34: 1048–52.
4. Elston RA, Taylor J. Possible interaction of ciprofloxacin with cyclosporin A. *J Antimicrob Chemother* 1988; 21: 679–80.
5. Nasir M, *et al.* Interaction between ciclosporin and ciprofloxacin. *Nephron* 1991; 57: 245–6.
6. Wrishko RE, *et al.* Investigation of a possible interaction between ciprofloxacin and cyclosporine in renal transplant patients. *Transplantation* 1997; 64: 996–9.
7. McLellan RA, *et al.* Norfloxacin interferes with cyclosporine disposition in pediatric patients undergoing renal transplantation. *Clin Pharmacol Ther* 1995; 58: 322–7.
8. Doose DR, *et al.* Levofloxacin does not alter cyclosporine disposition. *J Clin Pharmacol* 1998; 38: 90–93.
9. Federico S, *et al.* Pharmacokinetic interaction between levofloxacin and ciclosporin or tacrolimus in kidney transplant recipients: ciclosporin, tacrolimus and levofloxacin in renal transplantation. *Clin Pharmacokinet* 2006; 45: 169–75.

LINCOSAMIDES. Decreased plasma-ciclosporin concentrations, requiring increases in the daily dose, were seen in 2 lung transplant patients given oral *clindamycin* for lung infection. In both cases, the original doses of ciclosporin were resumed once clindamycin had been stopped. The authors suggested close monitoring of plasma-ciclosporin levels if this combination were used.[1]

1. Thumbeer R, *et al.* Possible interaction between clindamycin and cyclosporin. *BMJ* 1999; 319: 163.

MACROLIDES. Markedly raised blood concentrations of ciclosporin have been reported in patients also given *erythromycin.*[1-4] The mechanism involved appears to be a combination of decreased hepatic metabolism of ciclosporin and increased gastrointestinal absorption.[5] Similar elevations of ciclosporin concentrations have been noted after use with other macrolide antibacterials, including *clarithromycin,*[6-8] *josamycin,*[9,10] *midecamycin,*[11] *midecamycin acetate,*[12] and the structurally-related streptogramins, *pristinamycin*[13] and *quinupristin/dalfopristin.*[14] Small increases in ciclosporin concentrations have been seen with *roxithromycin.*[15] Increases in ciclosporin concentrations were attributed to *azithromycin* in 2 patients,[16,17] but a study in 6 patients found no effect.[18] *Spiramycin* does not appear to affect the pharmacokinetics of ciclosporin.[19,20]

1. Ptachcinski RJ, *et al.* Effect of erythromycin on cyclosporine levels. *N Engl J Med* 1985; 313: 1416–17.
2. Martell R, *et al.* The effects of erythromycin in patients treated with cyclosporine. *Ann Intern Med* 1986; 104: 660–1.
3. Wadhwa NK, *et al.* Interaction between erythromycin and cyclosporine in a kidney and pancreas allograft recipient. *Ther Drug Monit* 1987; 9: 123–5.
4. Gupta SK, *et al.* Cyclosporin-erythromycin interaction in renal transplant patients. *Br J Clin Pharmacol* 1989; 27: 475–81.
5. Ignoffo RJ, Kim LB. Erythromycin and cyclosporine drug interaction. *DICP Ann Pharmacother* 1991; 25: 30–1.
6. Ferrari SL, *et al.* The interaction between clarithromycin and cyclosporine in kidney transplant recipients. *Transplantation* 1994; 58: 725–7.
7. Treille S, *et al.* Kidney graft dysfunction after drug interaction between clarithromycin and cyclosporin. *Nephrol Dial Transplant* 1996; 11: 1192–3.
8. Sádaba B, *et al.* Concurrent clarithromycin and cyclosporin A treatment. *J Antimicrob Chemother* 1998; 42: 393–5.
9. Kreft-Jais C, *et al.* Effect of josamycin on plasma cyclosporine levels. *Eur J Clin Pharmacol* 1987; 32: 327–8.
10. Azanza JR, *et al.* Possible interaction between cyclosporine and josamycin: a description of three cases. *Clin Pharmacol Ther* 1992; 51: 572–5.
11. Alfonso I, *et al.* Interaction between cyclosporine A and midecamycin. *Eur J Clin Pharmacol* 1997; 52: 79–80.
12. Couet W, *et al.* Effect of ponsinomycin on cyclosporin pharmacokinetics. *Eur J Clin Pharmacol* 1990; 39: 165–7.
13. Garraffo R, *et al.* Pristinamycin increases cyclosporin blood levels. *Med Sci Res* 1987; 15: 461.
14. Stamatakis MK, Richards JG. Interaction between quinupristin/dalfopristin and cyclosporine. *Ann Pharmacother* 1997; 31: 576–8.
15. Billaud EM, *et al.* Interaction between roxithromycin and cyclosporin in heart transplant patients. *Clin Pharmacokinet* 1990; 19: 499–502.
16. Ljutic D, Rumboldt Z. Possible interaction between azithromycin and cyclosporin: a case report. *Nephron* 1995; 70: 130.
17. Page RL, *et al.* Possible interaction between intravenous azithromycin and oral cyclosporine. *Pharmacotherapy* 2001; 21: 1436–43.
18. Gómez B, *et al.* Interaction between azithromycin and cyclosporin? *Nephron* 1996; 73: 724.
19. Vernillet L, *et al.* Lack of effect of spiramycin on cyclosporin pharmacokinetics. *Br J Clin Pharmacol* 1989; 27: 789–94.
20. Kessler M, *et al.* Lack of effect of spiramycin on cyclosporin pharmacokinetics. *Br J Clin Pharmacol* 1990; 29: 370–1.

PENICILLINS. Decreased plasma-ciclosporin concentrations and effect were seen in a patient given *nafcillin.*[1] Conversely, another study reported increased nephrotoxicity from the use of ciclosporin with nafcillin but no apparent increase in ciclosporin concentrations.[2] Raised plasma-ciclosporin concentrations have been reported in a patient after receiving treatment with *ticarcillin.*[3]

1. Veremis SA, *et al.* Subtherapeutic cyclosporine concentrations during nafcillin therapy. *Transplantation* 1987; 43: 913–15.
2. Jahansouz F, *et al.* Potentiation of cyclosporine nephrotoxicity by nafcillin in lung transplant recipients. *Transplantation* 1993; 55: 1045–8.
3. Lambert C, *et al.* Interaction ciclosporine-ticarcilline chez un transplanté rénal. *Presse Med* 1989; 18: 230.

RIFAMYCINS. Use with *rifampicin* has been associated with marked decreases in blood-ciclosporin concentrations,[1-5] and has resulted in graft rejection.[1,3] Although it has been assumed that this effect represents induction of the hepatic metabolism of ciclosporin by rifampicin, there is some suggestion that rifampicin may decrease the absorption of ciclosporin or induce intestinal metabolism, resulting in reduced bioavailability.[6] Topical application of *rifamycin* has also been associated with a decrease in blood-ciclosporin concentrations in another patient;[7] ciclosporin concentrations rose immediately after withdrawal of rifamycin, suggesting that the effect was not due to enzyme induction.

1. Langhoff E, Madsen S. Rapid metabolism of cyclosporin and prednisone in kidney transplant patient receiving tuberculostatic treatment. *Lancet* 1983; ii: 1031.
2. Daniels NJ, *et al.* Interaction between cyclosporin and rifampicin. *Lancet* 1984; ii: 639.
3. Allen RDM, *et al.* Cyclosporin and rifampicin in renal transplantation. *Lancet* 1985; i: 980.
4. Freitag VL, *et al.* Effect of short-term rifampin on stable cyclosporine concentrations. *Ann Pharmacother* 1999; 33: 871–2.
5. Zelunka EJ. Intravenous cyclosporine-rifampin interaction in a pediatric bone marrow transplant recipient. *Pharmacotherapy* 2002; 22: 387–90.
6. Hebert MF, *et al.* Bioavailability of cyclosporine with concomitant rifampin administration is markedly less than predicted by hepatic enzyme induction. *Clin Pharmacol Ther* 1992; 52: 453–7.
7. Renoult E, *et al.* Effect of topical rifamycin SV treatment on cyclosporin A blood levels in a renal transplant recipient. *Eur J Clin Pharmacol* 1991; 40: 433–4.

STREPTOGRAMINS. Increased plasma concentrations of ciclosporin have occurred after therapy with *pristinamycin* and *quinupristin/dalfopristin* (see Macrolides, above).

SULFONAMIDES. Intravenous, but not oral, therapy with *sulfadimidine* and *trimethoprim* has been associated with falls in ciclosporin concentrations to subtherapeutic values.[1,2] Oral *sulfadiazine* has had a similar effect.[3] Conversely, *trimethoprim* and *co-trimoxazole* can cause rises in serum creatinine, and therefore may contribute to ciclosporin-induced nephrotoxicity.[4,5]

1. Wallwork J, *et al.* Cyclosporin and intravenous sulphadimidine and trimethoprim therapy. *Lancet* 1983; i: 366–7.
2. Jones DK, *et al.* Serious interaction between cyclosporin A and sulphadimidine. *BMJ* 1986; 292: 728–9.
3. Spes CH, *et al.* Sulfadiazine therapy for toxoplasmosis in heart transplant recipients decreases cyclosporine concentration. *Clin Investig* 1992; 70: 752–4.
4. Thompson JF, *et al.* Nephrotoxicity of trimethoprim and cotrimoxazole in renal allograft recipients treated with cyclosporine. *Transplantation* 1983; 36: 204–6.
5. Ringden O, *et al.* Nephrotoxicity by co-trimoxazole and cyclosporin in transplanted patients. *Lancet* 1984; i: 1016.

TIGECYCLINE. Marked increases in the serum concentration of ciclosporin occurred in a renal transplant patient during antibacterial treatment with tigecycline;[1] the patient developed signs of nephrotoxicity and the ciclosporin dose had to be reduced by 50% and omitted for one day. Three days after antibacterial therapy was complete, ciclosporin had to be increased again to the previous dose in order to maintain therapeutic concentrations.

1. Stumpf AN, *et al.* High serum concentrations of ciclosporin related to administration of tigecycline. *Eur J Clin Pharmacol* 2009; 65: 101–3.

Antidepressants. Giving *fluoxetine* to a patient receiving ciclosporin as part of an immunosuppressant regimen after cardiac transplantation was associated with a subsequent marked increase in ciclosporin trough blood concentrations to about twice their original value, necessitating a reduction in ciclosporin dosage.[1] After withdrawal of fluoxetine, ciclosporin concentrations fell, and dosage had to be increased. However, a study in 13 other patients given ciclosporin with fluoxetine failed to find any evidence of altered ciclosporin concentrations.[2] A nearly tenfold increase in ciclosporin concentration was seen in a cardiac transplant patient after use of *nefazodone,*[3] and there are 2 case reports[4] of ciclosporin toxicity due to interactions with nefazodone and *fluvoxamine* in renal transplant recipients. Ciclosporin concentrations decreased in a 10-year-old African American heart transplant recipient 22 days after starting *bupropion.* Despite an increase in ciclosporin dosage, ciclosporin concentrations decreased even further, necessitating another increase in ciclosporin dose, and withdrawal of bupropion.[5]

1. Horton RC, Bonser RS. Interaction between cyclosporin and fluoxetine. *BMJ* 1995; 311: 422.
2. Strouse TB, *et al.* Fluoxetine and cyclosporine in organ transplantation: failure to detect significant drug interactions or adverse clinical events in depressed organ recipients. *Psychosomatics* 1996; 37: 23–30.
3. Wright DH, *et al.* Nefazodone and cyclosporine drug-drug interaction. *J Heart Lung Transplant* 1999; 18: 913–15.
4. Velle JP, Sayegh MH. Interactions between cyclosporine and newer antidepressant medications. *Am J Kidney Dis* 1998; 31: 320–3.
5. Lewis BR, *et al.* Pharmacokinetic interactions between cyclosporine and bupropion or methylphenidate. *J Child Adolesc Psychopharmacol* 2001; 11: 193–8.

ST JOHN'S WORT. Ciclosporin plasma levels are reduced by St John's wort.[1] This has led to acute rejection episodes in transplant patients,[2] and the two drugs should not be used together.[3]

1. Bauer S, *et al.* Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients. *Br J Clin Pharmacol* 2003; 55: 203–11.
2. Ernst E. St John's wort supplements endanger the success of organ transplantation. *Arch Surg* 2002; 137: 316–19.
3. CSM/MCA Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; 26: 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE5dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 15/01/08)

Antidiabetics. Use of *glibenclamide* with ciclosporin in 6 patients was associated with a mean 57% increase in the steady-state plasma concentration of ciclosporin, suggesting that dosage adjustment may be necessary when both drugs are given.[1]

For the effect of ciclosporin on *repaglinide,* see under Interactions of Repaglinide, p. 496.1.

1. Islam SI, *et al.* Possible interaction between cyclosporine and glibenclamide in posttransplant diabetic patients. *Ther Drug Monit* 1996; 18: 624–6.

Antiepileptics. Use with the antiepileptics *carbamazepine,*[1-3] *phenobarbital,*[4] and *phenytoin,*[5] which are all inducers of hepatic cytochrome P450, has been associated with a reduction in blood-ciclosporin concentrations. *Oxcarbazepine* also decreased ciclosporin trough concentrations in a kidney transplant recipient with epilepsy; concentrations were corrected by an increase in ciclosporin dose. The dose of oxcarbazepine also had to be reduced due to hyponatraemia, and ciclosporin concentrations remained stable thereafter.[6] *Valproate* has been successfully used in ciclosporin-treated patients without apparent interaction.[1,2]

1. Hillebrand G, *et al.* Valproate for epilepsy in renal transplant recipients receiving cyclosporine. *Transplantation* 1987; 43: 915–16.
2. Schofield OMV, *et al.* Cyclosporin A in psoriasis: interaction with carbamazepine. *Br J Dermatol* 1990; 122: 425–6.
3. Cooney GF, *et al.* Effects of carbamazepine on cyclosporine metabolism in pediatric renal transplant recipients. *Pharmacotherapy* 1995; 15: 353–6.
4. Carstensen H, *et al.* Interaction between cyclosporin A and phenobarbitone. *Br J Clin Pharmacol* 1986; 21: 550–1.
5. Freeman DJ, *et al.* Evaluation of cyclosporin-phenytoin interaction with observations on cyclosporin metabolites. *Br J Clin Pharmacol* 1984; 18: 887–93.
6. Rösche J, *et al.* Possible oxcarbazepine interaction with cyclosporine serum levels: a single case study. *Clin Neuropharmacol* 2001; 24: 113–16.

Antifungals. The imidazole *ketoconazole* is a potent inhibitor of hepatic cytochrome P450 and markedly increased blood-ciclosporin concentrations have resulted when conventional formulations of the latter were given with the antifungal.[1-4] The interaction has been used, similarly to the calcium-channel blockers (see p. 1953.3), to permit therapeutic blood concentrations of ciclosporin to be achieved at lower doses;[5-8] however, this method may result in considerable variations in ciclosporin pharmacokinetics, and has been criticised on several grounds.[9] It was noted[10] that this improved bioavailability of ciclosporin was not seen when the microemulsifying formulation (see Absorption under Pharmacokinetics, p. 1955.2) was given with ketoconazole, suggesting that bioavailability was already maximal. Increased ciclosporin concentrations have also been reported with *itraconazole,*[11,12] and it has also been suggested[13] that use be made of this interaction, similarly to ketoconazole, to allow for decreased ciclosporin doses. *Voriconazole* also increases exposure to ciclosporin, and ciclosporin concentrations should be closely monitored.[14,15] There is a single report of increased ciclosporin plasma concentrations with use of *miconazole.*[16] However, although such an interaction has also been reported with *fluconazole,*[17,18] a small study has failed to note any significant interaction;[19,20] it has been suggested that an interaction may take place only at high doses of fluconazole,[21] or that sex and ethnicity may play a role.[18]

Increased nephrotoxicity may occur if ciclosporin is used with *amphotericin B,*[22,23] while liposomal amphotericin B has

been reported possibly to exacerbate ciclosporin neurotoxicity.[24] There is a report of decreased ciclosporin concentrations in a patient after addition of *griseofulvin* to therapy.[25] Modest decreases have also been seen in ciclosporin concentrations when *terbinafine* was given.[26] *Micafungin* modestly inhibits ciclosporin metabolism; however, in a minority of patients it may cause a significant increase in ciclosporin concentrations.[27]

1. Ferguson RM, *et al.* Ketoconazole, cyclosporin metabolism, and renal transplantation. *Lancet* 1982; ii: 882–3.
2. Dieperink H, Møller J. Ketoconazole and cyclosporin. *Lancet* 1982; ii: 1217.
3. Shepard JH, *et al.* Cyclosporine-ketoconazole: a potentially dangerous drug-drug interaction. *Clin Pharm* 1986; 5: 468.
4. Gomez DY, *et al.* The effects of ketoconazole on the intestinal metabolism and bioavailability of cyclosporine. *Clin Pharmacol Ther* 1995; 58: 15–19.
5. First MR, *et al.* Concomitant administration of cyclosporin and ketoconazole in renal transplant recipients. *Lancet* 1989; ii: 1198–1201.
6. Keogh A, *et al.* Ketoconazole to reduce the need for cyclosporine after cardiac transplantation. *N Engl J Med* 1995; 333: 628–33.
7. El-Husseini A, *et al.* Concomitant administration of cyclosporine and ketoconazole in idiopathic nephrotic syndrome. *Nephrol Dial Transplant* 2004; 19: 2266–71.
8. El-Husseini A, *et al.* Co-administration of cyclosporine and ketoconazole in idiopathic childhood nephrosis. *Pediatr Nephrol* 2004; 19: 976–81.
9. Prey FJ. Concomitant cyclosporin and ketoconazole. *Lancet* 1990; 335: 109–10.
10. Akhlaghi F, *et al.* Pharmacokinetics of cyclosporine in heart transplant recipients receiving metabolic inhibitors. *J Heart Lung Transplant* 2001; 20: 431–8.
11. Kramer MR, *et al.* Cyclosporine and itraconazole interaction in heart and lung transplant recipients. *Ann Intern Med* 1990; 113: 327–9.
12. Leather H, *et al.* Pharmacokinetic evaluation of the drug interaction between intravenous itraconazole and intravenous tacrolimus or intravenous cyclosporin A in allogeneic hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant* 2006; 12: 325–34.
13. Florea NR, *et al.* Beneficial pharmacokinetic interaction between cyclosporine and itraconazole in renal transplant recipients. *Transplant Proc* 2003; 35: 2873–7.
14. Romero AJ, *et al.* Effect of voriconazole on the pharmacokinetics of cyclosporine in renal transplant patients. *Clin Pharmacol Ther* 2002; 71: 226–34.
15. Groll AH, *et al.* Pharmacokinetic interaction between voriconazole and ciclosporin A following allogeneic bone marrow transplantation. *J Antimicrob Chemother* 2004; 53: 113–14.
16. Horton CM, *et al.* Cyclosporine interactions with miconazole and other azole-antimycotics: a case report and review of the literature. *J Heart Lung Transplant* 1992; 11: 1127–32.
17. Collignon P, *et al.* Interaction of fluconazole with cyclosporin. *Lancet* 1989; i: 1262.
18. Mathis AS, *et al.* Sex and ethnicity may chiefly influence the interaction of fluconazole with calcineurin inhibitors. *Transplantation* 2001; 71: 1069–75.
19. Krüger HU, *et al.* Absence of significant interaction of fluconazole with cyclosporin. *J Antimicrob Chemother* 1989; 24: 781–6.
20. Ihninger G, *et al.* Interaction of fluconazole with cyclosporin. *Lancet* 1989; ii: 104–5.
21. López-Gil JA. Fluconazole-cyclosporine interaction: a dose-dependent effect? *Ann Pharmacother* 1993; 27: 427–30.
22. Kennedy MS, *et al.* Acute renal toxicity with combined use of amphotericin B and cyclosporine after marrow transplantation. *Transplantation* 1983; 35: 211–15.
23. Purrer K, *et al.* Nephrotoxicity of cyclosporine A and amphotericin B-deoxycholate as continuous infusion in allogenic stem cell transplantation. *Swiss Med Wkly* 2002; 132: 316–20.
24. Ellis ME, *et al.* Is cyclosporin neurotoxicity enhanced in the presence of liposomal amphotericin B? *J Infect* 1994; 29: 106–7.
25. Abu-Romeh SH, *et al.* Ciclosporin A and griseofulvin: another drug interaction. *Nephron* 1991; 58: 237.
26. Lo ACY, *et al.* The interaction of terbinafine and cyclosporine A in renal transplant patients. *Br J Clin Pharmacol* 1997; 43: 340–1.
27. Hebert MF, *et al.* Concomitant cyclosporine and micafungin pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2005; 45: 954–60.

Antigout drugs. A patient who had been receiving maintenance doses of ciclosporin for some years, with consistent whole-blood trough concentrations of around 130 nanograms/mL at doses of 175 mg twice daily had a rise in ciclosporin concentrations to 410 nanograms/mL after 2 months of treatment with *allopurinol* 200 mg daily.[1] Ciclosporin concentrations returned to their previous levels over several weeks after stopping allopurinol, and rose again on rechallenge. Dosage of ciclosporin was then reduced. For a report of a low dose of allopurinol being added to a ciclosporin-containing immunosuppressive regimen, see Organ and Tissue Transplantation, p. 601.2.

UK licensed product information states that *colchicine* may increase ciclosporin concentrations.

In a report of 120 heart transplant recipients with hyperuricaemia, *sulfinpyrazone* reduced ciclosporin concentrations, and 2 patients needed treatment for acute rejection.[2]

1. Gorrie M, *et al.* Allopurinol interaction with cyclosporin. *BMJ* 1994; 308: 113.
2. Caforio ALP, *et al.* Sulfinpyrazone reduces cyclosporine levels: a new drug interaction in heart transplant recipients. *J Heart Lung Transplant* 2000; 19: 1205–8.

Antimalarials. A large rise in serum-ciclosporin concentration was seen on 2 occasions in a renal graft recipient when *chloroquine* was added to his medication for malaria prophylaxis.[1] *Quinine* has been reported to reduce ciclosporin concentrations.[2]

1. Finielz P, *et al.* Interaction between cyclosporin and chloroquine. *Nephron* 1993; 63: 333.
2. Tan HW, Ch'ng SL. Drug interaction between cyclosporine A and quinine in a renal transplant patient with malaria. *Singapore Med J* 1991; 32: 189–90.

Antineoplastics. Elevated plasma-ciclosporin concentrations and an increased incidence of nephrotoxic effects and hypertension have been reported in patients receiving ciclosporin for psoriasis who had been previously,[1] or concurrently,[2] treated with *methotrexate*. Conversely, methotrexate has been used effectively with reduced-dose ciclosporin in graft-versus-host disease.[3] Severe renal failure has been reported when standard oral doses of ciclosporin were given after high-dose intravenous *melphalan* (used as a bone marrow conditioning agent before allogeneic bone marrow transplantation).[4] A retrospective analysis of allogeneic haematopoietic stem cell transplant patients taking ciclosporin found that, in those given a conditioning regimen containing *cyclophosphamide*, mean serum-ciclosporin concentrations were reduced; no effect on the incidence of graft-versus-host disease could be established.[5]

UK licensed product information states that *imatinib* may increase ciclosporin concentrations.

Ciclosporin increases plasma-*doxorubicin* concentrations and toxicity (see p. 785.3), and has been used to increase oral absorption of *paclitaxel* (see p. 842.2). For the effects of ciclosporin on the pharmacokinetics of *teniposide* and *etoposide*, see p. 867.2 and p. 792.1, respectively.

Ciclosporin and its analogues have been given with antineoplastics for their ability to inhibit the P-glycoprotein cellular pump responsible for multidrug resistance, thus resulting in raised intracellular concentrations of the other drug.

1. Powles AV, *et al.* Cyclosporin toxicity. *Lancet* 1990; i: 610.
2. Korstanje MJ, *et al.* Cyclosporine and methotrexate: a dangerous combination. *J Am Acad Dermatol* 1990; 23: 320–1.
3. Stockschlaeder M, *et al.* A pilot study of low-dose cyclosporin for graft-versus-host prophylaxis in marrow transplantation. *Br J Haematol* 1992; 80: 49–54.
4. Morgenstern GR, *et al.* Cyclosporin interaction with ketoconazole and melphalan. *Lancet* 1982; ii: 1342.
5. Nagamura F, *et al.* Effect of cyclophosphamide on serum cyclosporine levels at the conditioning of hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2003; 32: 1051–8.

Antiobesity drugs. A reduction in ciclosporin concentrations to subtherapeutic levels has been reported[1-3] in transplant recipients given *orlistat*. It was postulated[2] that the interaction was a result of reduced absorption of ciclosporin in the presence of orlistat and that at least 2 hours should elapse between doses of these two drugs. However, despite this dosing interval, there has been a further report[3] of subtherapeutic plasma levels of ciclosporin. The patient had had severe diarrhoea, and the subsequent decreased absorption of fats was thought to have decreased the absorption of ciclosporin.

An increase in ciclosporin trough concentrations occurred when a renal transplant patient was given *sibutramine*;[4] both drugs are metabolised by cytochrome P450 isoenzyme 3A4.

1. Nägele H, *et al.* Effect of orlistat on blood cyclosporin concentration in an obese heart transplant patient. *Eur J Clin Pharmacol* 1999; 55: 667–9.
2. Colman E, Fossler M. Reduction in blood cyclosporine concentrations by orlistat. *N Engl J Med* 2000; 342: 1141–2.
3. Barbaro D, *et al.* Obesity in transplant patients: case report showing interference of orlistat with absorption of cyclosporine and review of literature. *Endocr Pract* 2002; 8: 124–6.
4. Clerbaux G, *et al.* Interaction between sibutramine and cyclosporine. *Am J Transplant* 2003; 3: 906.

Antivirals. For a report of mutual elevations in the area under the plasma concentration-time curves for ciclosporin and the HIV-protease inhibitor *saquinavir*, see Indinavir, p. 988.2.

Bifendate. In 2 patients given maintenance doses of ciclosporin, trough whole-blood concentrations decreased from 97.7 nanograms/mL to 49.0 nanograms/mL and from 127.5 nanograms/mL to 45.0 nanograms/mL respectively when bifendate was given. Ciclosporin concentrations returned to pre-treatment levels over several weeks once bifendate was stopped.[1]

1. Kim YS, *et al.* The effect of diphenyl-dimethyl-dicarboxylate on cyclosporine-A blood level in kidney transplants with chronic hepatitis. *Korean J Intern Med* 1997; 12: 67–9.

Cardiovascular drugs. *ACE INHIBITORS.* There may be an increased risk of hyperkalaemia when ACE inhibitors are used with ciclosporin. Acute renal failure, associated with use of *enalapril*, has been reported in 2 patients given ciclosporin after renal transplantation.[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.

ANTIARRHYTHMICS. Marked rises in serum-ciclosporin concentrations despite reductions in dose have been noted in recipients of organ transplants after treatment with *amiodarone*.[1-3] A rise in serum ciclosporin has similarly been seen in a patient given both ciclosporin and *propafenone*.[4]

1. Mamprin F, *et al.* Amiodarone-cyclosporine interaction in cardiac transplantation. *Am Heart J* 1992; 123: 1725–6.
2. Egami J, *et al.* Increase in cyclosporine levels due to amiodarone therapy after heart and heart-lung transplantation. *J Am Coll Cardiol* 1993; 21: 141A.
3. Chitwood KK, *et al.* Cyclosporine-amiodarone interaction. *Ann Pharmacother* 1993; 27: 569–71.
4. Spes CH, *et al.* Ciclosporin-propafenone interaction. *Klin Wochenschr* 1990; 68: 872.

ANTICOAGULANTS. Treatment with *warfarin* for deep-vein thrombosis in a patient maintained on ciclosporin for pure red cell aplasia resulted in a relapse of the latter and a significant fall in ciclosporin blood concentrations.[1] Increase in the ciclosporin dose restored control of the aplasia but resulted in a marked increase in prothrombin activity requiring an increase in warfarin dosage. The results suggest that each drug interferes with the activity of the other. The influence of the patient's other medications (including phenobarbital and folic acid), if any, is unknown, although it has been suggested[2,3] that the phenobarbital had enhanced the metabolism of both drugs. In another report,[2] a patient on long-term warfarin for deep-vein thrombosis was started on ciclosporin for lymphoma relapse, and subsequently required larger doses of warfarin. During use of *acenocoumarol* with ciclosporin, the dose of ciclosporin had to be increased[3] in one patient and both drugs decreased[4] in another. It appears that the interaction between ciclosporin and anticoagulants is unpredictable[3] and dependent on the anticoagulant used.[2]

1. Snyder DS. Interaction between cyclosporine and warfarin. *Ann Intern Med* 1988; 108: 311.
2. Turri D, *et al.* Oral anticoagulants and cyclosporin A. *Haematologica* 2000; 85: 893–4.
3. Borrás-Blasco J, *et al.* Interaction between cyclosporine and acenocoumarol in a patient with nephrotic syndrome. *Clin Nephrol* 2001; 55: 338–40.
4. Campistol JM, *et al.* Interaction between ciclosporin A and Sinirom. *Nephron* 1989; 53: 291–2.

ANTIPLATELET DRUGS. Ticlopidine decreased serum-ciclosporin concentrations in isolated cases,[1-3] but a study in 20 heart transplant patients failed to show any interaction between ciclosporin and low-dose ticlopidine.[4] For reports of rhabdomyolysis occurring in patients stabilised on ciclosporin and a statin when *clopidogrel* was added to their treatment, see Statins, p. 1344.3.

1. Birmelé B, *et al.* Interaction of cyclosporin and ticlopidine. *Nephrol Dial Transplant* 1991; 6: 150–1.
2. Verdejo A, *et al.* Probable interaction between cyclosporin A and low dose ticlopidine. *BMJ* 2000; 320: 1037.
3. Feriozzi S, *et al.* Treatment with ticlopidine is associated with reduction of cyclosporin A blood levels. *Nephron* 2002; 92: 249–50.
4. Boissonnat P, *et al.* A drug interaction study between ticlopidine and cyclosporin in heart transplant recipients. *Eur J Clin Pharmacol* 1997; 53: 39–45.

BETA BLOCKERS. Ciclosporin plasma concentrations increased when *carvedilol* was added to treatment regimens of renal[1] and cardiac[2] transplant patients. Considerable interindividual variation was seen in one study,[1] so it is recommended that ciclosporin concentrations should be monitored carefully if the drugs are used together.

1. Kaljser M, *et al.* Elevation of cyclosporin A blood levels during carvedilol treatment in renal transplant patients. *Clin Transplant* 1997; 11: 577–81.
2. Bader FM, *et al.* The effect of β-blocker use on cyclosporine level in cardiac transplant recipients. *J Heart Lung Transplant* 2005; 24: 2144–7.

ENDOTHELIN RECEPTOR ANTAGONISTS. There is a complex interaction between ciclosporin and bosentan. If the drugs are given together reduced ciclosporin concentrations and increased bosentan concentrations may occur; further details are given on p. 1328.1. For information on ciclosporin increasing exposure to ambrisentan, see p. 1298.3.

CALCIUM-CHANNEL BLOCKERS. The calcium-channel blockers *diltiazem*,[1-3] *lercanidipine*, *nicardipine*,[4,5] and *verapamil*[6,7] have all been associated with increases in ciclosporin blood concentrations. It has been suggested that such an interaction can be used to obtain effective ciclosporin concentrations with lower doses.[8] In addition, there is some evidence of mitigation of ciclosporin-induced nephrotoxicity when calcium-channel blockers are given (see Effects on the Kidneys, p. 1950.1), and they are useful for ciclosporin-induced hypertension (see Effects on the Cardiovascular System, p. 1949.3). However, some caution is required: one report has pointed out that diltiazem does not increase ciclosporin concentrations in all cases,[9] while others have found that use together alters the pattern of ciclosporin metabolites, and that pharmacokinetic changes are greater in female than in male patients.[10] Therefore, some prefer a calcium-channel blocker that does not alter ciclosporin pharmacokinetics for hypertension and renal protection. *Nifedipine* has not been shown to increase blood-ciclosporin concentrations.[6] For a report of increased nifedipine toxicity with ciclosporin see Immunosuppressants, p. 1454.1. Other calcium-channel blockers that do not appear to affect ciclosporin pharmacokinetics include *felodipine*[7,11] and *isradipine*.[7,12] Ciclosporin concentrations have been reported to increase or to remain unchanged with *amlodipine*.[13] Use of amlodipine or nifedipine with ciclosporin may exacerbate the problem of gingival hyperplasia—see Hyperplasia under Adverse Effects, p. 1950.3.

1. Brockmöller J, *et al.* Pharmacokinetic interaction between cyclosporin and diltiazem. *Eur J Clin Pharmacol* 1990; 38: 237–42.
2. 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.

3. Åsberg A, *et al.* Pharmacokinetic interactions between microemulsion formulated cyclosporine A and diltiazem in renal transplant recipients. *Eur J Clin Pharmacol* 1999; 55: 383–7.
4. Todd P, *et al.* Nicardipine interacts with cyclosporin. *Br J Dermatol* 1989; 121: 820.
5. 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.
6. Tortorice KL, *et al.* The effects of calcium channel blockers on cyclosporine and its metabolites in renal transplant patients. *Ther Drug Monit* 1990; 12: 321–8.
7. Yildiz A, *et al.* Interaction between cyclosporine A and verapamil, felodipine, and isradipine. *Nephron* 1999; 81: 117–18.
8. Skeuris IS, *et al.* Effect of calcium-channel blockers on cyclosporine clearance and use in renal transplant patients. *Ann Pharmacother* 1994; 28: 1227–31.
9. Jones TE, Morris RG. Diltiazem does not always increase blood cyclosporin concentration. *Br J Clin Pharmacol* 1996; 42: 642–4.
10. Bleck JS, *et al.* Diltiazem increases blood concentrations of cyclized cyclosporine metabolites resulting in different cyclosporine metabolite patterns in stable male and female renal allograft recipients. *Br J Clin Pharmacol* 1996; 41: 551–6.
11. Cohen DJ, *et al.* Influence of oral felodipine on serum cyclosporine concentrations. *Clin Transplant* 1994; 8: 541–5.
12. Endresen L, *et al.* Lack of effect of the calcium antagonist isradipine on cyclosporine pharmacokinetics in renal transplant patients. *Ther Drug Monit* 1991; 13: 490–5.
13. Schrama YC, Koomans HA. Interactions of cyclosporin A and amlodipine: blood cyclosporin A levels, hypertension and kidney function. *J Hypertens* 1998; 16 (suppl): S33–S38.

CARDIAC GLYCOSIDES. For reference to the effect of ciclosporin on serum-digoxin concentrations, see Immunosuppressants, under Interactions of Digoxin, p. 1357.3.

CLONIDINE. Addition of clonidine to the regimen of a 3-year-old child who had developed hypertension after a renal transplant resulted in a marked increase in whole blood ciclosporin concentrations, despite a reduction in ciclosporin dose.[1] Ciclosporin concentrations fell rapidly on withdrawal of clonidine.

1. Gilbert RD, *et al.* Interaction between clonidine and cyclosporine A. *Nephron* 1995; 71: 105.

DIURETICS. Enhanced nephrotoxicity, without apparent change in ciclosporin blood concentrations, has been seen in individual patients after addition of *metolazone*[1] or *amiloride* with *chlorothiazide*[2] to their regimen. Severe nephrotoxicity, resulting in loss of graft function, has been seen in a renal transplant patient given *mannitol* with ciclosporin;[3] graft function recovered on withdrawal of the diuretic.

1. Christensen P, Leski M. Nephrotoxic drug interaction between metolazone and cyclosporin. *BMJ* 1987; 294: 578.
2. Deray G, *et al.* Enhancement of cyclosporin nephrotoxicity by diuretic therapy. *Clin Nephrol* 1989; 32: 47.
3. Brunner FP, *et al.* Mannitol potentiates cyclosporine nephrotoxicity. *Clin Nephrol* 1986; 25 (suppl 1): S130–6.

LIPID REGULATING DRUGS. A study in 10 renal transplant recipients indicated that use of ciclosporin with *probucol* markedly reduced the whole blood and plasma concentrations of the former in 9 of them, compared with use of ciclosporin alone.[1] *Bezafibrate* has been reported to increase blood concentrations of ciclosporin, with resultant nephrotoxicity.[2] However, other studies with bezafibrate have found a small decrease in ciclosporin concentrations,[3] or no effect,[4,5] despite an increase in serum creatinine in each study. Conflicting effects have also been reported with other fibrates: decreased[6] and unchanged[7] ciclosporin concentrations have occurred with *fenofibrate*, and both a decrease[8] and lack of effect[9] have also occurred with *gemfibrozil*.

In 1 study, *simvastatin* increased the unbound fraction of ciclosporin in the blood, resulting in a modest increase in apparent ciclosporin clearance.[10] In renal transplant recipients, *atorvastatin* increased ciclosporin blood concentrations in 4 out of 10 patients in one study[11] but was deemed to have minimal clinical effect in others.[12,13] Ciclosporin concentrations were unaffected by *cerivastatin*,[11,14] *fluvastatin*,[15] *lovastatin*,[16] and *pravastatin*.[16,17] A literature review concluded that the statins do not interact with ciclosporin to a clinically relevant degree. However, given the narrow therapeutic range of ciclosporin, the increase in systemic exposure to statins, and reports of rhabdomyolysis when used together, the authors advise that ciclosporin levels be monitored when starting statin therapy, and that lower doses of statins be used.[18] For the effects of ciclosporin on plasma levels of statins and reports of rhabdomyolysis, see Immunosuppressants, under Interactions of Simvastatin, p. 1495.3.

1. Gallego C, *et al.* Interaction between probucol and cyclosporine in renal transplant patients. *Ann Pharmacother* 1994; 28: 940–3.
2. Hirai M, *et al.* Elevated blood concentrations of cyclosporine and kidney failure after bezafibrate in renal graft recipient. *Ann Pharmacother* 1996; 30: 883–4.
3. Barbir M, *et al.* Maxepa versus bezafibrate in hyperlipidemic cardiac transplant recipients. *Am J Cardiol* 1992; 70: 1596–1601.
4. Lipkin GW, Tomson CRV. Severe reversible renal failure with bezafibrate. *Lancet* 1993; 341: 371.
5. Jespersen B, Tvedegaard E. Bezafibrate induced reduction of renal function in a renal transplant recipient. *Nephrol Dial Transplant* 1995; 10: 702–3.
6. Boissonnat P, *et al.* The long-term effects of the lipid-lowering agent fenofibrate in hypertipidemic heart transplant recipients. *Transplantation* 1994; 58: 245–7.
7. de Lorgeril M, *et al.* Pharmacokinetics of cyclosporine in hyperlipidaemic long-term survivors of heart transplantation: lack of interaction with the lipid-lowering agent, fenofibrate. *Eur J Clin Pharmacol* 1992; 43: 161–5.
8. Pehrman-Ekholm I, *et al.* Decreased cyclosporine levels during gemfibrozil treatment of hyperlipidemia after kidney transplantation. *Nephron* 1996; 72: 483.
9. Pisani N, *et al.* Lack of effect of gemfibrozil on cyclosporine blood concentrations in kidney-transplanted patients. *Am J Nephrol* 1998; 18: 199–203.
10. Akhlaghi F, *et al.* Effect of simvastatin on cyclosporine unbound fraction and apparent blood clearance in heart transplant recipients. *Br J Clin Pharmacol* 1997; 44: 537–42.
11. Renders L, *et al.* Efficacy and drug interactions of the new HMG-CoA reductase inhibitors cerivastatin and atorvastatin in CsA-treated renal transplant recipients. *Nephrol Dial Transplant* 2001; 16: 141–6.
12. Åsberg A, *et al.* Bilateral pharmacokinetic interaction between cyclosporine A and atorvastatin in renal transplant recipients. *Am J Transplant* 2001; 1: 382–6.
13. Taylor PJ, *et al.* Effect of atorvastatin on cyclosporine pharmacokinetics in liver transplant recipients. *Ann Pharmacother* 2004; 38: 205–8.
14. Mück W, *et al.* Increase in cerivastatin systemic exposure after single and multiple dosing in cyclosporine-treated kidney transplant recipients. *Clin Pharmacol Ther* 1999; 65: 251–61.
15. Goldberg R, Roth D. Evaluation of fluvastatin in the treatment of hypercholesterolemia in renal transplant recipients taking cyclosporine. *Transplantation* 1996; 62: 1559–64.
16. Olbricht C, *et al.* Accumulation of lovastatin, but not pravastatin, in the blood of cyclosporine-treated kidney graft patients after multiple doses. *Clin Pharmacol Ther* 1997; 62: 311–21.
17. Regazzi MB, *et al.* Altered disposition of pravastatin following concomitant drug therapy with cyclosporin A in transplant recipients. *Transplant Proc* 1993; 25: 2732–4.
18. Åsberg A. Interactions between cyclosporin and lipid-lowering drugs: implications for organ transplant recipients. *Drugs* 2003; 63: 367–78.

Colchicine. Use of ciclosporin with colchicine may result in myopathy or rhabdomyolysis—see Effects on Skeletal Muscle, under Adverse Effects, p. 1950.3. For reports of adverse effects and increased serum-ciclosporin concentrations when given with colchicine, see also p. 606.3.

Corticosteroids. It has been suggested that use of ciclosporin with corticosteroids increases plasma concentrations of both drugs, but not all studies support this—see Immunosuppressants, p. 1620.2.

Gastrointestinal drugs. Giving *cisapride*[1] or *metoclopramide*[2] to renal transplant recipients receiving ciclosporin has been reported to increase peak ciclosporin concentrations and increase the speed of absorption. *Cimetidine*,[3,4] *ranitidine*,[3] or *famotidine*,[4] do not appear to affect ciclosporin pharmacokinetics. A literature review[5] noted that although there are reports of cimetidine influencing peak concentrations of ciclosporin, there is no support for a pharmacokinetic interaction. A pharmacodynamic interaction between ciclosporin and histamine H_2-receptor antagonists, resulting in a potentiation of nephrotoxicity, is also unlikely.

1. Finet L, *et al.* Effects of cisapride on the intestinal absorption of cyclosporine in renal transplant recipients. *Gastroenterology* 1991; 100: A209.
2. Wadhwa NK, *et al.* The effect of oral metoclopramide on the absorption of cyclosporine. *Transplant Proc* 1987; 19: 1730–3.
3. Barri YM, *et al.* Cimetidine or ranitidine in renal transplant patients receiving cyclosporine. *Clin Transplant* 1996; 10: 34–8.
4. Shaefer MS, *et al.* Evaluation of the pharmacokinetic interaction between cimetidine or famotidine and cyclosporine in healthy men. *Ann Pharmacother* 1995; 29: 1088–91.
5. Lewis SM, McCloskey WW. Potentiation of nephrotoxicity by H_2-antagonists in patients receiving cyclosporine. *Ann Pharmacother* 1997; 31: 363–5.

Grapefruit juice. Grapefruit juice increases the bioavailability of oral ciclosporin,[1-4] including the microemulsion formulation,[5] leading to marked increases in blood-ciclosporin concentrations; intravenous ciclosporin is unaffected. The effect appears to be due to inhibition of cytochrome P450 enzymes in the gut wall by substances present in grapefruit juice,[3] resulting in transiently reduced ciclosporin metabolism. Although it has been suggested that the effect might be used similarly to that of calcium-channel blockers or ketoconazole in reducing the required dose of ciclosporin,[2] others have pointed out that grapefruit juice is not standardised and its effects are variable.[6]

Pomelo juice has also reportedly increased ciclosporin bioavailability; pomelo is a citrus fruit closely related to grapefruit.[7]

1. Proppe DG, *et al.* Influence of chronic ingestion of grapefruit juice on steady-state blood concentrations of cyclosporine A in renal transplant patients with stable graft function. *Br J Clin Pharmacol* 1995; 39: 337–8.
2. Yee GC, *et al.* Effect of grapefruit juice on blood cyclosporin concentration. *Lancet* 1995; 345: 955–6.
3. Hollander AAMJ, *et al.* The effect of grapefruit juice on cyclosporine and prednisone metabolism in transplant patients. *Clin Pharmacol Ther* 1995; 57: 318–24.
4. Ducharme MP, *et al.* Disposition of intravenous and oral cyclosporine after administration with grapefruit juice. *Clin Pharmacol Ther* 1995; 57: 485–91.
5. Ku Y-M, *et al.* Effect of grapefruit juice on the pharmacokinetics of microemulsion cyclosporine and its metabolite in healthy volunteers: does the formulation difference matter? *J Clin Pharmacol* 1998; 38: 959–65.
6. Johnston A, Holt DW. Effect of grapefruit juice on blood cyclosporin concentration. *Lancet* 1995; 346: 122–3.
7. Grenier J, *et al.* Pomelo juice, but not cranberry juice, affects the pharmacokinetics of cyclosporine in humans. *Clin Pharmacol Ther* 2006; 79: 255–62.

Immunosuppressants. There has been a report of altered ciclosporin requirements in paediatric renal graft patients treated with *basiliximab*,[1] but others have failed to note such an effect,[2] and whether an interaction exists is unclear.

Treatment of acute rejection of kidney grafts in 10 patients using *muromonab-CD3* resulted in increases in mean trough ciclosporin concentrations, despite a reduction in ciclosporin dosage.[3] Once muromonab-CD3 was withdrawn the dosage of ciclosporin had to be increased again to provide adequate concentrations. In a retrospective study[4] of renal transplant recipients given ciclosporin and either muromonab-CD3 or antilymphocyte immunoglobulin, ciclosporin trough concentrations were found to be raised on day 5 postoperatively in the patients receiving muromonab-CD3. Although no differences were found in trough concentrations on days 7 and 10, the doses of ciclosporin had by then been adjusted based on the levels obtained on day 5.

For the effects of ciclosporin on the pharmacokinetics of *everolimus*, *mycophenolate mofetil*, and *sirolimus*, see p. 1959.1, p. 1964.2, and p. 1968.1 respectively.

Tacrolimus inhibits ciclosporin metabolism *in vitro*[5] but did not alter the pharmacokinetics of intravenous ciclosporin in 7 liver transplant patients.[6] However, there is a possibility of increased nephrotoxicity when the drugs are used together, so licensed product information contra-indicates such use.

1. Strehlau J, *et al.* Interleukin-2 receptor antibody-induced alterations of ciclosporin dose requirements in paediatric transplant recipients. *Lancet* 2000; 356: 1327–8.
2. Vester U, *et al.* Basiliximab in paediatric liver-transplant recipients. *Lancet* 2001; 357: 388–9.
3. Vrahnos D, *et al.* Cyclosporin levels during OKT3 treatment of acute renal allograft rejection. *Pharmacotherapy* 1991; 11: 278.
4. Vasquez EM, Pollak R. OKT3 therapy increases cyclosporine blood levels. *Clin Transplant* 1997; 11: 38–41.
5. Venkataramanan R, *et al.* Pharmacokinetics of FK 506 in transplant patients. *Transplant Proc* 1991; 23: 2736–40.
6. Jain AB, *et al.* Pharmacokinetics of cyclosporine and nephrotoxicity in orthotopic liver transplant patients rescued with FK 506. *Transplant Proc* 1991; 23: 2777–9.

Methoxsalen. In a pharmacokinetic study, a single oral dose of methoxsalen significantly increased the oral bioavailability of ciclosporin.[1]

1. Rheeders M, *et al.* Drug-drug interaction after single oral doses of the furanocoumarin methoxsalen and cyclosporine. *J Clin Pharmacol* 2006; 46: 768–75.

Methylphenidate. Methylphenidate led to an increase in ciclosporin concentrations in a 10-year-old African American boy, necessitating reduction of the ciclosporin dose.[1] The patient had previously had to stop bupropion because of decreased ciclosporin concentrations.

1. Lewis BR, *et al.* Pharmacokinetic interactions between cyclosporine and bupropion or methylphenidate. *J Child Adolesc Psychopharmacol* 2001; 11: 193–8.

NSAIDs. Raised serum-ciclosporin trough concentrations and small increases in serum creatinine and BUN concentrations, followed the use of *sulindac* in a previously-stabilised renal graft recipient taking an immunosuppressive regimen including ciclosporin.[1] Increased renal impairment was seen when sulindac or *naproxen* were added to ciclosporin therapy in patients with rheumatoid arthritis.[2] Nephrotoxicity, in the absence of significantly raised blood-ciclosporin concentrations, has been reported in other patients given *diclofenac* with ciclosporin.[3] Ciclosporin may also increase plasma-diclofenac concentrations, see p. 50.2. In general, because of the known potential of NSAIDs to adversely affect renal function, careful monitoring of renal function is advised if these drugs are added to ciclosporin therapy or their dosages altered.

1. Sesin GP, *et al.* Sulindac-induced elevation of serum cyclosporine concentration. *Clin Pharm* 1989; 8: 445–6.
2. Altman RD, *et al.* Interaction of cyclosporine A and nonsteroidal anti-inflammatory drugs on renal function in patients with rheumatoid arthritis. *Am J Med* 1992; 93: 396–402.
3. Branthwaite JP, Nicholls A. Cyclosporin and diclofenac interaction in rheumatoid arthritis. *Lancet* 1991; 337: 252.

Octreotide. A marked reduction in ciclosporin serum concentrations was seen in 10 diabetic patients with pancreatic transplants when octreotide was also given;[1] it was suggested that if these 2 drugs are used together the oral dosage of ciclosporin needs to be increased on average by 50%.

1. Landgraf R, *et al.* Effect of somatostatin analogue (SMS 201-995) on cyclosporine levels. *Transplantation* 1987; 44: 724–5.

Quercetin. In a small study in healthy males, pre-treatment with the flavonoid quercetin significantly increased the peak concentration and bioavailability of ciclosporin.[1]

1. Choi JS, *et al.* Effect of quercetin on the pharmacokinetics of oral cyclosporine. *Am J Health-Syst Pharm* 2004; 61: 2406–9.

Retinoids. After a report of increased whole-blood ciclosporin concentrations and nephrotoxicity in a patient given *etretinate* with ciclosporin, *in-vitro* results indicated that

etretinate inhibited hepatic microsomal metabolism of ciclosporin, as did *acitretin* and *isotretinoin*.[1] However, a study failed to find evidence of such an interaction *in vitro*.[2]

1. Shah IA, *et al.* The effects of retinoids and terbinafine on the human hepatic microsomal metabolism of cyclosporin. *Br J Dermatol* 1993; 129: 395–8.
2. Webber IR, Back DJ. Effect of etretinate on cyclosporin metabolism in vitro. *Br J Dermatol* 1993; 128: 42–4.

Sevelamer. Although sevelamer did not appear to affect ciclosporin concentrations in one study,[1] a case report[2] described a reduction in ciclosporin trough concentrations after sevelamer was started, an effect that was seen again upon rechallenge. It was suggested that sevelamer may bind with bile acids in the gut, affecting ciclosporin absorption,[2] or bind to ciclosporin, thereby reducing ciclosporin absorption directly.[3] Licensed product information for sevelamer suggests that it should be given at least 3 hours before or 1 hour after drugs for which a reduction in bioavailability could be clinically significant.

1. Pieper A-K, *et al.* The effect of sevelamer on the pharmacokinetics of cyclosporin A and mycophenolate mofetil after renal transplantation. *Nephrol Dial Transplant* 2004; 19: 2630–3.
2. Guillen-Anaya M-A, Jadoul M. Drug interaction between sevelamer and cyclosporin. *Nephrol Dial Transplant* 2004; 19: 515.
3. Wauters J-P, *et al.* Drug interaction between sevelamer and cyclosporin. *Nephrol Dial Transplant* 2005; 20: 660–1.

Sex hormones. Raised ciclosporin concentrations in blood have been seen when therapy with *danazol*,[1] *methyltestosterone*,[2] or *norethisterone*[1] was given with ciclosporin, and clinical evidence of both nephrotoxicity[1,2] and hepatotoxicity[2] has been seen. Severe hepatotoxicity and raised plasma-ciclosporin trough values also resulted when an oral contraceptive containing *levonorgestrel* and *ethinylestradiol* was taken by a woman receiving ciclosporin;[3] she had taken the same contraceptive before beginning ciclosporin without ill-effects.

1. Ross WB, *et al.* Cyclosporin interaction with danazol and norethisterone. *Lancet* 1986; i: 330.
2. Møller BB, Ekelund B. Toxicity of cyclosporine during treatment with androgens. *N Engl J Med* 1985; 313: 1416.
3. Deray G, *et al.* Oral contraceptive interaction with cyclosporin. *Lancet* 1987; i: 158.

Tolvaptan. For the effect of ciclosporin on tolvaptan concentrations, see p. 2633.1.

Ursodeoxycholic acid. In a heart transplant patient with short bowel syndrome, ursodeoxycholic acid increased the trough concentrations of ciclosporin by enhancing its absorption.[1] In an attempt to determine whether this interaction would aid the attainment of therapeutic ciclosporin concentrations after heart transplantation, a patient with a jejunoileal bypass was given ciclosporin both with and without ursodeoxycholic acid; no difference was noted in the bioavailability of ciclosporin.[2] Small studies in liver transplant recipients found no alteration in ciclosporin pharmacokinetics when given single doses of ursodeoxycholic acid,[3] nor any difference in ciclosporin requirements between patients given ursodeoxycholic acid and those given placebo.[4] Another study in 12 liver transplant patients, 6 of whom had cholestatic liver dysfunction, found that ursodeoxycholic acid increased the rate of absorption of ciclosporin, but that peak concentrations and bioavailability did not change significantly.[5] In a study using microemulsifying ciclosporin in liver transplant recipients, ursodeoxycholic acid reduced the absorption rate and bioavailability of ciclosporin in 9 patients without cholestasis, but increased absorption rate and bioavailability in 3 cholestatic patients.[6] UK licensed product information for the microemulsifying formulation states that ursodeoxycholic acid increases ciclosporin concentrations.

1. Gutzler F, *et al.* Ursodeoxycholic acid enhances the absorption of cyclosporine in a heart transplant patient with short bowel syndrome. *Transplant Proc* 1992; 24: 2620–1.
2. Kino KJ, Wittkowsky AK. Influence of bile acid replacement on cyclosporine absorption in a patient with jejunoileal bypass. *Pharmacotherapy* 1995; 15: 350–2.
3. Maboudou CW, *et al.* A single dose of ursodiol does not affect cyclosporine absorption in liver transplant patients. *Eur J Clin Pharmacol* 1996; 50: 335–7.
4. Söderdahl G, *et al.* Ursodeoxycholic acid increased bile flow and affects bile composition in the early postoperative phase following liver transplantation. *Transpl Int* 1998; 11 (suppl): S231–S238.
5. Al-Quaiz MN, *et al.* Variable effect of ursodeoxycholic acid on cyclosporin absorption after orthotopic liver transplantation. *Transpl Int* 1994; 7: 190–4.
6. Caroli-Bosc F-X, *et al.* Ursodeoxycholic acid modulates cyclosporin A oral absorption in liver transplant recipients. *Fundam Clin Pharmacol* 2000; 14: 601–9.

Vaccines. Efficacy of immunoprophylaxis may be expected to be reduced during ciclosporin therapy, and use of live virus vaccines, in particular, is contra-indicated in immunocompromised patients;[1] there has also been concern that vaccine antigens given during ciclosporin therapy might induce tolerance and result in increased rather than decreased susceptibility to diseases.

1. Grabenstein JD, Baker JR. Comment: cyclosporine and vaccination. *Drug Intell Clin Pharm* 1985; 19: 679–80.

Vitamins. For reference to increased absorption of ciclosporin when given with a water-soluble macrogol derivative of *vitamin E*, see Absorption, under Pharmacokinetics, below.

Pharmacokinetics

The pharmacokinetics of ciclosporin are variable and difficult to determine. Results vary depending on the assay used, and values obtained by different methods are not strictly comparable.

Absorption of conventional formulations of ciclosporin from the gastrointestinal tract is variable and incomplete. An oral microemulsifying formulation with improved absorption characteristics is available and is more rapidly and completely absorbed, with peak concentrations achieved about 1.5 to 2 hours after a dose.

Ciclosporin is widely distributed throughout the body. Distribution in the blood is concentration-dependent, with between 41 and 58% in erythrocytes and 10 to 20% in leucocytes; the remainder is found in plasma, about 90% protein-bound, mostly to lipoprotein. Because of distribution into blood cells whole blood concentrations are higher than, and not comparable with, plasma concentrations; where peak plasma concentrations are reported to be about 1 nanogram/mL (by specific HPLC assay) for each mg of oral ciclosporin, whole blood concentrations for each mg range from about 1.4 to 2.7 nanograms/mL. Ciclosporin is reported to cross the placenta, and to be distributed into breast milk.

Clearance from the blood is biphasic. The terminal elimination half-life of an oral dose is reported to range from about 5 to 20 hours; clearance in children is more rapid.

Ciclosporin is extensively metabolised in the liver and mainly excreted in faeces via the bile. About 6% of a dose is reported to be excreted in urine, less than 0.1% unchanged.

References.

1. Mendonza AE, *et al.* Blood and plasma pharmacokinetics of ciclosporin in diabetic kidney transplant recipients. *Clin Pharmacokinet* 2008; 47: 733–42.
2. Xiaoli D, Qiang F. Population pharmacokinetic study of cyclosporine in patients with nephrotic syndrome. *J Clin Pharmacol* 2009; 49: 782–8.

Absorption. Ingestion of conventional *oral* formulations of ciclosporin with food may increase its bioavailability, although the effect only appears to be significant when the meal is high in fat;[1] ingestion with food and added bile acids may also increase absorption moderately.[2] A micelle-forming macrogol derivative of vitamin E (tocofersolan) has also been reported to markedly increase ciclosporin absorption.[3,4]

Because of the problems of variable oral absorption, an oral microemulsifying formulation has been developed that offers greatly improved and more predictable bioavailability,[5–8] particularly in liver transplant patients with impaired bile flow.[5] It should be noted that the formulation of this product in fact includes a vitamin E compound.

However, a study[9] has suggested that contrary to previous assumptions, conventional formulations of ciclosporin are quite well absorbed, and that the low bioavailability is due to extensive cytochrome-mediated metabolism in the gut wall (see also Metabolism, p. 1956.1). If this were the case, the improved bioavailability seen with the microemulsifying formulation is presumably less to do with improved absorption than with protection from such metabolism.

Very little drug is absorbed after application to the *eye*; ciclosporin accumulates on the ocular surface and cornea, achieving concentrations considered suitable for local immunomodulation. Corneal concentrations are affected by the choice of vehicle, but intra-ocular penetration is low. Little or no ocular metabolism is considered to occur in humans.[10]

1. Gupta SK, *et al.* Effect of food on the pharmacokinetics of cyclosporine in healthy subjects following oral and intravenous administration. *J Clin Pharmacol* 1990; 30: 643–53.
2. Lindholm A, *et al.* The effect of food and bile acid administration on the relative bioavailability of cyclosporin. *Br J Clin Pharmacol* 1990; 29: 541–8.
3. Sokol RJ, *et al.* Improvement of cyclosporin absorption in children after liver transplantation by means of water-soluble vitamin E. *Lancet* 1991; 338: 212–15.
4. Chang T, *et al.* The effect of water-soluble vitamin E on cyclosporine pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther* 1996; 59: 297–303.
5. Trull AK, *et al.* Absorption of cyclosporin from conventional and new microemulsion oral formulations in liver transplant recipients with external biliary diversion. *Br J Clin Pharmacol* 1995; 39: 627–31.
6. van den Borne BEEM, *et al.* Relative bioavailability of a new oral form of cyclosporin A in patients with rheumatoid arthritis. *Br J Clin Pharmacol* 1995; 39: 172–5.
7. Friman S, Bäckman L. A new microemulsion formulation of cyclosporin: pharmacokinetic and clinical features. *Clin Pharmacokinet* 1996; 30: 181–93.
8. Schädeli F, *et al.* Population pharmacokinetic model to predict steady-state exposure to once-daily cyclosporin microemulsion in renal transplant recipients. *Clin Pharmacokinet* 2002; 41: 59–69.
9. Wu C-Y, *et al.* Differentiation of absorption and first-pass gut and hepatic metabolism in humans: studies with cyclosporine. *Clin Pharmacol Ther* 1995; 58: 492–7.
10. Tang-Liu DD-S, Acheampong A. Ocular pharmacokinetics and safety of ciclosporin, a novel topical treatment for dry eye. *Clin Pharmacokinet* 2005; 44: 247–61.

Children. A pharmacokinetic study in paediatric renal transplant recipients found that clearance of ciclosporin (when adjusted for body weight) was about 25% higher in children 8 years old or less than in older children or adults; clearance was highest in children between 4 months and 2 years of age and declined steadily thereafter, reaching adult values by about 12 years. As bioavailability and the volume of distribution (as adjusted for body weight) was similar in all age groups, the half-life was estimated to be 20% shorter in younger patients. The authors suggested that children up to 8 years of age may need a higher dose of ciclosporin per body weight and a shorter dosage interval to achieve similar exposure to older patients.[1]

In a study[2] in paediatric haematopoietic stem cell transplant recipients, however, no relationship was found between body weight, length, age, or glomerular filtration rate and clearance or volume of distribution. This led the authors to question commonly-used dosing strategies using an initial dose based on body weight and then adjusted according to trough ciclosporin concentrations (see also Administration in Children, p. 1946.2). They suggested initial intravenous doses (ciclosporin 40 mg daily for children weighing between 10 and 20 kg, 60 mg daily for those weighing 20 to 35 kg, and 80 mg daily for those weighing 35 to 60 kg), should then be adjusted according to the calculated area under the concentration-time curve (AUC) using 2 blood ciclosporin concentrations (a trough concentration and another 2 to 3 hours later). Although an optimum AUC for prophylaxis of graft-versus-host disease has not been determined, a target AUC of about 3.5 hours/mg per litre was thought to be appropriate.[2] For further discussion of strategies for monitoring ciclosporin concentrations, see p. 1956.1.

1. Fanta S, *et al.* Developmental pharmacokinetics of ciclosporin—a population pharmacokinetic study in paediatric renal transplant candidates. *Br J Clin Pharmacol* 2007; 64: 772–84. Correction. *ibid.* 2008; 65: 973.
2. Willemze AJ, *et al.* Ciclosporin kinetics in children after stem cell transplantation. *Br J Clin Pharmacol* 2008; 66: 539–45.

Distribution. The distribution characteristics of ciclosporin are clinically important; binding in blood and plasma is of importance in determining immunosuppressive activity after organ transplantation.[1] The unbound concentration of ciclosporin may have a closer association with both renal and cardiac allograft rejection than the total (bound plus unbound) concentration.

1. Akhlaghi F, Trull AK. Distribution of cyclosporin in organ transplant recipients. *Clin Pharmacokinet* 2002; 41: 615–37.

Ethnicity and sex. Gender-dependent racial differences in the pharmacokinetics of ciclosporin have been suggested.[1] African American women showed larger clearances of intravenous and oral ciclosporin (microemulsifying formulation) than African American men, and white women. There were no significant differences in clearance between men of different ethnic origin, or between white men and women. Overall bioavailability was also lower in African Americans compared with white subjects. However, other studies[2,3] found no differences in relative bioavailability between races.

Differences in hepatic cytochrome P450 isoenzyme CYP3A and intestinal P-glycoprotein activity may account for interindividual variability in ciclosporin disposition, and it has been speculated that polymorphic CYP3A5 expression might contribute to interracial differences.[4] However, most studies[5,6] have found little or no association between CYP3A4 or CYP3A5 genotype and ciclosporin pharmacokinetics, although one study found that patients with a CYP3A4 variant allele had a small but significantly higher oral clearance of ciclosporin.[7] However, black and Asian transplant recipients were found to have a reduced oral clearance in this study, independent of their CYP3A genotype, and in apparent contradiction to the literature. The authors commented that most of the studies had been conducted with the older oil-based products, and use of the microemulsifying formulation had not been associated with significant differences in ciclosporin pharmacokinetics between ethnic groups.[7] Genotyping of transplant recipients was considered unlikely to be of use in optimising ciclosporin dosage in clinical practice.[6,7]

1. Min DI, *et al.* Gender-dependent racial difference in disposition of cyclosporine among healthy African American and white volunteers. *Clin Pharmacol Ther* 2000; 68: 478–86.
2. Stein CM, *et al.* Cyclosporine pharmacokinetics and pharmacodynamics in African American and white subjects. *Clin Pharmacol Ther* 2001; 69: 317–23.
3. Pollak R, *et al.* Cyclosporine bioavailability of Neoral and Sandimmune in white and black de novo renal transplant recipients. *Ther Drug Monit* 1999; 21: 661–3.
4. Yates CR, *et al.* The effect of CYP3A5 and MDR1 polymorphic expression on cyclosporine oral disposition in renal transplant patients. *J Clin Pharmacol* 2003; 43: 555–64.

5. Hesselink DA, *et al.* Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. *Clin Pharmacol Ther* 2003; 74: 245–54.
6. Anglicheau D, *et al.* CYP3A5 and MDR1 genetic polymorphisms and cyclosporine pharmacokinetics after renal transplantation. *Clin Pharmacol Ther* 2004; 75: 422–33.
7. Hesselink DA, *et al.* Population pharmacokinetics of cyclosporine in kidney and heart transplant recipients and the influence of ethnicity and genetic polymorphisms in the MDR-1, CYP3A4, and CYP3A5 genes. *Clin Pharmacol Ther* 2004; 76: 545–56.

Metabolism. *In vitro*[1] and *in vivo*[2-4] evidence indicates that the low oral bioavailability of ciclosporin is due to first-pass metabolism in the gastrointestinal tract rather than the liver.

1. Tjia JF, *et al.* Cyclosporin metabolism by the gastrointestinal mucosa. *Br J Clin Pharmacol* 1991; 31: 344–6.
2. Kolars JC, *et al.* First-pass metabolism of cyclosporin by the gut. *Lancet* 1991; 338: 1488–90.
3. Hoppu K, *et al.* Evidence for pre-hepatic metabolism of oral cyclosporine in children. *Br J Clin Pharmacol* 1991; 32: 477–81.
4. Wu C-Y, *et al.* Differentiation of absorption and first-pass gut and hepatic metabolism in humans: studies with cyclosporine. *Clin Pharmacol Ther* 1995; 58: 492–7.

Therapeutic drug monitoring. Considerable debate has attended the necessity for therapeutic monitoring of ciclosporin concentrations and also on the questions of which assay methods to use and whether to measure drug concentrations in whole blood or plasma.

Before the introduction of specific monoclonal radioimmunoassay the high performance liquid chromatography (HPLC) assay for ciclosporin had the advantage of being specific for the parent compound, and some suggested it to be the method of choice.[1,2] However, it is a more complex procedure, is not universally available, and is slower to perform than radio-immunoassay.[1,3-5] Specific monoclonal radio-immunoassays are now widely available; a comparative study of specific and non-specific radio-immunoassays, HPLC, and polyclonal fluorescence polarisation immunoassay (FPIA) found that the specific assays, used on whole blood samples, gave the best correlation with clinical events.[6]

Because the distribution of ciclosporin between blood cells and plasma is temperature-dependent,[7] plasma concentrations may be twice as high at 37 degrees as at 21 degrees. The temperature at which samples are stored and processed may therefore considerably influence results. In consequence, measurement of drug concentrations in whole blood is to be preferred.[1,3,4,8] However, many, particularly early, clinical studies have given plasma or serum concentrations, which makes comparison of literature data difficult. This problem is compounded by a considerable degree of variation between laboratories,[9,10] even when the same technique is used,[10] and by circadian variations in ciclosporin metabolism which mean that samples should be taken at the same time of day.[11] Since ciclosporin concentrations appear to be generally higher in the morning than the evening, some have suggested that the morning might be the best time for therapeutic drug monitoring.[12]

Because of the variability in results caused by difficulties in monitoring it has proved difficult to determine precisely the ciclosporin concentrations associated with therapeutic benefit and toxicity,[1,3-5] and it has been suggested that measurement of the therapeutic concentrations is unnecessary (provided the patient's clinical condition and renal function are monitored) when low-dose ciclosporin is being given (for example, in psoriasis).[13] However, others consider that it is always critical that ciclosporin blood trough concentrations are regularly measured,[14] in addition to other monitoring. A study in paediatric haematopoietic stem cell transplant recipients found a significant relationship between ciclosporin blood trough concentrations and the severity of acute graft-versus-host disease (GVHD); with lower trough concentrations, GVHD was more severe during the early post-transplantation period.[15] It has been suggested[16] that trough ciclosporin concentrations (C_0), measured by a specific method in whole blood, should not be less than 150 nanograms/mL during the first month after renal transplantation, although lower concentrations are subsequently acceptable; trough concentrations of 250 to 300 nanograms/mL are recommended in the 3 months after liver transplantation.

Other methods of monitoring ciclosporin therapy include monitoring the area under the concentration-time curve (AUC), limited sampling strategies, and Bayesian forecasting.[14,17-22] However, these methods also have limitations, often requiring several samples at inconvenient times for the patient, and can involve complex calculations.

Maximum calcineurin inhibition occurs in the first 1 to 2 hours after ciclosporin dosing, and it was hypothesised that AUC in the first 4 hours after a dose, or the blood concentration at 2 hours after a dose (C_2) might better predict immunosuppressive efficacy than trough concentrations (C_0) or AUC over 12 hours.[23] A large study[24] in liver transplant recipients found that measuring C_2 was superior to C_0 monitoring, resulting in a reduction of the incidence and severity of rejection. It was pointed out that these results could not necessarily be extrapolated to different transplant groups and that analysis when sampling high ciclosporin concentrations needed to be extremely accurate.[25] Data from lung transplant recipients found measurements of C_0 but not C_2 or C_4 to be associated with the risk of acute lung allograft rejection.[26] However, there was some suggestion that C_2 predicted rejection better than C_0 in renal[27] and heart[28] transplant recipients also. In paediatric renal transplant recipients,[23] C_2 monitoring was found to be a better predictor of ciclosporin exposure during the absorption phase than C_0.

C_2 is widely considered to be the best time-point predictor of exposure to ciclosporin during the first 4 hours postdose. This was based on data from studies in adult renal, liver, heart, and lung transplant recipients, as well as in paediatric renal and liver transplant patients; patients had received microemulsifying ciclosporin.[29-31] C_2 monitoring was also able to identify high, intermediate, or low absorbers of ciclosporin. Additional monitoring beyond the C_2 time point was considered necessary in low absorbers to identify true low absorbers from slow absorbers.[29,30] Target C_2 concentrations at various times post-transplantation were recommended by an international consensus group for adult renal and liver transplant patients receiving ciclosporin microemulsion.[29]

For adult renal transplant recipients:

- 1 month post-transplant: C_2 1.5 to 2 micrograms/mL (this should be achieved by days 3 to 5 after transplantation to maximise clinical benefit);
- 2 months post-transplant: C_2 1.5 micrograms/mL;
- 3 months post-transplant: C_2 1.3 micrograms/mL;
- 4 to 6 months post-transplant: C_2 1.1 micrograms/mL;
- 7 to 12 months post-transplant: C_2 900 nanograms/mL;
- 12 months post-transplant or more: C_2 800 nanograms/mL

For adult liver transplant recipients:

- 0 to 6 months post-transplant: C_2 1 microgram/mL (initially achieved by days 3 to 5 after transplantation to maximise clinical benefit);
- 6 to 12 months post-transplant: C_2 800 nanograms/mL;
- more than 12 months post-transplant: C_2 600 nanograms/mL

Data on long-term clinical benefit of monitoring in terms of rejection prophylaxis and overall safety profile were lacking, and target levels were not established for other transplant groups. A 15-minute 'window of opportunity' before and after the 2-hour time point was considered to provide an acceptable (10%) margin of error, during which time the C_2 sample could be taken.[29] Findings from a 3-year prospective study of C_2 monitoring in stable renal transplant recipients suggested that this method offered clinical benefits in terms of control of hypertension and dyslipidaemia, and protection against chronic renal allograft dysfunction.[32] A subsequent study of C_2 monitoring in heart transplant patients[33] found that higher C_2 concentrations were associated with less episodes of acute cellular rejection. However, in renal transplant patients,[34,35] C_2 concentrations did not predict rejection. A multicentre, retrospective French study[36] determined that, in renal transplant patients monitored on C_0, most patients had C_2 concentrations below the target ranges recommended by the international consensus group; the authors suggested that lower C_2 ranges might be targeted in the early- and long-term post-transplantation periods for those given interleukin-2 receptor antibodies, and that optimal therapeutic windows for ciclosporin monitoring based on C_2 needed more definition. A review of limited sampling strategies in liver transplant patients[37] concluded that, while C_2 monitoring might be better than C_0 monitoring to improve acute rejection rate in the early post-transplantation period, the evidence was not strong, and that further well-designed studies were needed. A review of ciclosporin monitoring after allogeneic stem cell transplantation[38] acknowledged that C_2 monitoring might be preferable to trough concentration monitoring in these patients, but also stated that optimal strategies remained to be defined and that randomised studies were needed.

There has been concern that differences in blood ciclosporin results from various assay systems would necessitate assay-specific target ranges for monitoring. Most transplant centres have developed target ciclosporin ranges that reflect the methodology in use. A study[39] of 5 different assay methods, including radio-immunoassay, HPLC, and FPIA, found that when measuring C_0, this would indeed be the case, but that with C_2 monitoring, differences in the results from the various assay methods were not statistically significant, and were unlikely to be of clinical significance. Different proportions of parent ciclosporin and metabolites were thought to be the reason for this disparity at the two time points. The authors considered that a single target therapeutic range could be adopted when monitoring C_2 concentrations, regardless of the assay method used.

For suggested C_0 and C_2 values used to adjust ciclosporin dosage when given with everolimus, see Administration with Everolimus, p. 1946.3.

1. Ptachcinski RJ, *et al.* Cyclosporine concentration determinations for monitoring and pharmacokinetic studies. *J Clin Pharmacol* 1986; 26: 358–66.
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4. Burkle WS. Cyclosporine pharmacokinetics and blood level monitoring. *Drug Intell Clin Pharm* 1985; 19: 101–5.
5. Rodighiero V. Therapeutic drug monitoring of cyclosporin: practical applications and limitations. *Clin Pharmacokinet* 1989; 16: 27–37.
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13. Heydendael VMR, *et al.* Cyclosporin trough levels: is monitoring necessary during short-term treatment in psoriasis? A systematic review and clinical data on trough levels. *Br J Dermatol* 2002; 147: 122–9.
14. Dumont RJ, Ensom MHH. Methods for clinical monitoring of cyclosporin in transplant patients. *Clin Pharmacokinet* 2000; 38: 427–4
15. Martin P, *et al.* Relationship between CsA trough blood concentration and severity of acute graft-versus-host disease after paediatric stem cell transplantation from matched-sibling or unrelated donors. *Bone Marrow Transplant* 2003; 32: 777–84.
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17. David O, Johnston A. Limited sampling strategies. *Clin Pharmacokinet* 2000; 39: 311–13.
18. Leger F, *et al.* Maximum A Posteriori Bayesian estimation of oral cyclosporin pharmacokinetics in patients with stable renal transplant. *Clin Pharmacokinet* 2002; 41: 71–80.
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22. Willemze AJ, *et al.* Ciclosporin kinetics in children after stem cell transplantation. *Br J Clin Pharmacol* 2008; 66: 539–45.
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30. Nashan B, *et al.* Use of Neoral C_2 monitoring: a European consensus. *Transpl Int* 2005; 18: 768–78.
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36. Loichot C, *et al.* Cyclosporine monitoring in renal transplant recipient with induction therapy: C_2 levels in patients monitored on C_0. *Pundan Clin Pharmacol* 2006; 20: 93–6.
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38. Duncan N, Craddock C. Optimizing the use of cyclosporin in allogeneic stem cell transplantation. *Bone Marrow Transplant* 2006; 38: 169–74.
39. Johnston A, *et al.* Monitoring cyclosporin in blood: between-assay differences at trough and 2 hours post-dose (C2). *Ther Drug Monit* 2003; 25: 167–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cermox; Lacrinmune Restasis; Sandimmun; Sigmasporin; *Austral.*: Cicloral; Cysporin†; Neoral; Sandimmun; *Austria*: Cicloralhexal; Neoimmun Sandimmun; *Belg.*: Neoral-Sandimmun; Sandimmun; *Braz.* Gengraf; Restasis; Sandimmun; Sigmasporin; *Canad.*: Neoral Restasis; Sandimmune; *Chile*: Equoral; Gengraf†; Modusik-A Restasis; Sandimmun; *China*: Gengraf (金格福); Implanta (因普兰他); Lizhu Huanming (丽珠环明); Neoral (新山地明); Saisip

ing (赛斯平); Tianke (田可); Xin Sai Si Ping (新赛斯平); Cz.: Cyclaid; Equoral; Sandimmun; Sigmasporon; *Denm.*: Dexi-mune; Sandimmun; *Fin.*: Sandimmun; *Fr.*: Neoral; Sandimmun; *Ger.*: Ciclorai†; Deximune; Immunosporin; Sandimmun; *Gr.*: Imunofar; Neoral; Restasis; Sandimmun; *Hong Kong*: Gengraf†; Restasis; Sandimmun; *Hung.*: Sandimmun; *India*: Cyclomune; Cyclophil ME; Cyrin; Graftin; Immusol; Imusporin; Panimun Bioral; Sandimmun; *Indon.*: Sandimmun; *Irl.*: Deximune; Neoral; Sandimmun; *Israel*: Dexi-mune; Restasis; Sandimmun; Sangcya†; *Ital.*: Sandimmun; *Jpn*: Papilock; *Malaysia*: Gengraf†; Restasis; Sandimmun; *Mex.*: Immulem†; Modusik-A; Restasis; Sandimmun; Supremunn; *Neth.*: Neoral; Sandimmune; *Norw.*: Sandimmun; *NZ*: Gen-graf†; Neoral; Sandimmun; *Philipp.*: Arpimune; Cyrin; Ospor-in; Restasis; Sandimmun; *Pol.*: Cyclaid; Equoral; Sandimmun; *Port.*: Ciclostar; Sandimmun; *Rus.*: Ciclopren (Циклопрен); Consupren (Консупрен)†; Cycloral (Циклорал); Equoral (Экорал); Imusporin (Имуспорин); Orgasporin (Оргаспорин); Panimun Bioral (Панимун Биорал); Sandimmun (Сандиммун); *S.Afr.*: Cidohexal†; Sandimmun; *Singapore*: Gengraf; Sandimmun; *Spain*: Sandimmun; *Swed.*: Sandimmun; *Switz.*: Ciclosol†; Sandimmun; *Thai.*: Consupren†; Equoral; Gengraf†; Kasporin; Panimun Bioral†; Restasis; Sanda; Sandimmun; *Turk.*: Gengraf; Restasis; Sandimmun; *UAE*: Sigmasporin; *UK*: Capimune; Capsorin; Deximune; Neoral; Sandimmun; *Ukr.*: Equoral (Экорал); Restasis (Рестасис); Sandimmun (Сандиммун Неорал); *USA*: Gengraf; Neoral; Restasis; Sandim-mune; *Venez.*: Imusporin; Restasis; Sandimmun.

Pharmacopoeial Preparations
BP 2014: Ciclosporin Eye Drops;
USP 36: Cyclosporine Capsules; Cyclosporine Injection; Cyclosporine Oral Solution.

Daclizumab *(BAN, USAN, rINN)*

Daclixmab; Daclizumabum; Daklitsumabi; Daklizumab; Humanised Anti-Tac Antibody; Ro-24-7375; Даклизумаб. Immunoglobulin G 1, (human-mouse monoclonal 1H4 γ-chain, anti-human interleukin 2 receptor), disulfide with human-mouse monoclonal clone 1H4 light chain, dimer.
CAS — 152923-56-3.
ATC — L04AC01.
ATC Vet — QL04AC01.
UNII — CUJ2MVI71Y.

Uses and Administration

Daclizumab is a humanised monoclonal murine antibody that functions as an interleukin-2 receptor antagonist by binding to the alpha chain (CD25 antigen, Tac subunit) of the interleukin-2 receptor on the surface of activated T-lymphocytes. It is used in the prevention of acute graft rejection after kidney transplantation as part of an immunosuppressive regimen that includes ciclosporin and corticosteroids. It is given in a dose of 1 mg/kg intravenously over 15 minutes within 24 hours before surgery and repeated at intervals of 2 weeks for a total of 5 doses. The required dose is diluted in 50 mL of sodium chloride 0.9%, and may be infused either centrally or peripherally. Daclizumab is also under investigation for its immunosup-pressant properties in other forms of transplantation (see below) and in various diseases with an auto-immune component.

Administration in children. The dose for daclizumab in children aged 1 year and over is the same as in adults (see Uses and Administration, above).

Multiple sclerosis. Daclizumab has been tried[1-8] (alone or with interferon beta) in patients with relapsing-remitting or secondary progressive multiple sclerosis; clinical benefit and a reduction in new lesions on MRI has been reported.

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4. Martin R. Humanized anti-CD25 antibody treatment with daclizumab in multiple sclerosis. *Neurodegener Dis* 2008; 5: 23–6.
5. Ali EN, *et al.* Daclizumab in treatment of multiple sclerosis patients. *Multiple Sclerosis* 2009; 15: 272–4.
6. Kim SE. Daclizumab treatment for multiple sclerosis. *Pharmacotherapy* 2009; 29: 227–35.
7. Bielekova B, *et al.* Effect of anti-CD25 antibody daclizumab in the inhibition of inflammation and stabilization of disease progression in multiple sclerosis. *Arch Neurol* 2009; 66: 483–9.
8. Wynn D, *et al.* CHOICE investigators. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. *Lancet Neurol* 2010; 9: 381–90.

Ocular disorders. There have been reports of benefit with daclizumab in ocular inflammatory disorders[1] including scleritis, ocular cicatricial pemphigoid, and uveitis, all of which had been resistant to conventional therapy.

1. Papaliodis GN, *et al.* Treatment of ocular inflammatory disorders with daclizumab. *Ophthalmology* 2003; 110: 786–9.

Organ and tissue transplantation. Daclizumab is used as induction therapy to reduce the incidence of acute rejec-tion episodes after kidney transplantation (p. 1935.2);[1-4] it is usually given as part of an immunosuppressive regimen that includes a calcineurin inhibitor and corticosteroids.

There are reports of successful corticosteroid withdrawal and corticosteroid-free regimens using daclizumab.[5] An attempt at using daclizumab to avoid use of ciclosporin after renal transplantation was unsuccessful, with a high rate of overall acute rejection in the daclizumab group.[6] However, prolonged monotherapy with daclizumab has been used to avoid rejection in patients non-adherent to standard maintenance regimens.[7]

Daclizumab has also been investigated for the prevention of acute rejection after heart,[8] liver,[9,10] and lung[11] transplantation (see p. 1934.2, p. 1936.3, and p. 1937.3, respectively) but increased mortality has followed its use in patients receiving heart grafts[12] (see also Effects on Mortality, below).

Daclizumab has also been tried in the management of acute graft-versus-host disease (GVHD; see Haematopoietic Stem Cell Transplantation, p. 1933.1). While some consider it a viable alternative for corticosteroid-refractory acute GVHD,[13] others found that when daclizumab was used with corticosteroids to treat acute GVHD, this combination had a significantly deleterious effect on patient survival.[14]

Controlled studies that directly compare 2 doses of daclizumab with the standard 5-dose regimen in kidney transplantation are lacking; despite this, many centres use a 2-dose regimen.[15] In a small, retrospective analysis[16] of simultaneous kidney-pancreas transplant recipients (see Pancreatic Transplantation, p. 1938.1), patients given 1 to 3 doses of daclizumab in addition to triple therapy had a significantly higher incidence of rejection than those given 4 to 5 doses. There was no difference in patient or graft survival. A larger multicentre study[17,18] found that simultaneous kidney-pancreas recipients given daclizumab 2 mg/kg every 14 days for 2 doses had a similar incidence of rejection to those given the standard 5-dose regimen; mean time to onset of rejection was delayed in the 2-dose regimen but there was no beneficial effect of daclizumab on graft survival at 3 years. A small comparative study[19] in heart transplant recipients found 2 doses of daclizumab to be at least as effective as the 5-dose regimen; no significant differences were seen for mortality. A novel 3-dose regimen has been investigated in liver transplantation.[20]

1. Vincenti F, *et al.* Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. *N Engl J Med* 1998; 338: 161–5.
2. Nashan B, *et al.* Reduction of acute renal allograft rejection by daclizumab. *Transplantation* 1999; 67: 110–15.
3. Bumgardner GL, *et al.* Results of 3-year phase III clinical trials with daclizumab prophylaxis for prevention of acute rejection after renal transplantation. *Transplantation* 2001; 72: 839–45.
4. Ciancio G, *et al.* Daclizumab induction, tacrolimus, mycophenolate mofetil and steroids as an immunosuppression regimen for primary kidney transplant recipients. *Transplantation* 2002; 73: 1100–6.
5. ter Meulen CG, *et al.* Steroid-withdrawal at 3 days after renal transplamation with anti-IL-2 receptor α therapy: a prospective, randomized, multicenter study. *Am J Transplant* 2004; 4: 803–10.
6. Åsberg A, *et al.* Calcineurin inhibitor avoidance with daclizumab, mycophenolate mofetil, and prednisolone in DR-matched de novo kidney transplant recipients. *Transplantation* 2006; 82: 62–8.
7. Chaudhuri A, *et al.* Extended daclizumab monotherapy for rejection-free survival in non-adherent adolescent recipients of renal allografts. *Pediatr Transplant* 2009; 13: 927–32.
8. Beniaminovitz A, *et al.* Prevention of rejection in cardiac transplantation by blockade of the interleukin-2 receptor with a monoclonal antibody. *N Engl J Med* 2000; 342: 613–19.
9. Niemeyer G, *et al.* Long-term safety, tolerability and efficacy of daclizumab (Zenapax) in a two-dose regimen in liver transplant recipients. *Am J Transplant* 2002; 2: 454–60.
10. Figueras J, *et al.* Daclizumab induction and maintenance steroid-free immunosuppression with mycophenolate mofetil and tacrolimus to prevent acute rejection of hepatic allografts. *Transpl Int* 2006; 19: 641–8.
11. Garrity ER, *et al.* Low rate of acute lung allograft rejection after the use of daclizumab, an interleukin 2 receptor antibody. *Transplantation* 2001; 71: 773–7.
12. Hershberger RE, *et al.* Daclizumab to prevent rejection after cardiac transplantation. *N Engl J Med* 2005; 352: 2705–13.
13. Bordigoni P, *et al.* Daclizumab, an efficient treatment for steroid-refractory acute graft-versus-host disease. *Br J Haematol* 2006; 135: 382–5.
14. Lee SJ, *et al.* Effect of up-front daclizumab when combined with steroids for the treatment of acute graft-versus-host disease: results of a randomized trial. *Blood* 2004; 104: 1559–64.
15. van Gelder T, *et al.* Anti-interleukin-2 receptor antibodies in transplantation: what is the basis for choice? *Drugs* 2004; 64: 1737–41.
16. Bruce DS, *et al.* Multicenter survey of daclizumab induction in simultaneous kidney-pancreas transplant recipients. *Transplantation* 2001; 72: 1637–43.
17. Stratta RJ, *et al.* One-year outcomes in simultaneous kidney-pancreas transplant recipients receiving an alternative dosing regimen of daclizumab. *Transplant Proc* 2004; 36: 1080–1.
18. Stratta RJ, *et al.* A prospective, randomized, multicenter study evaluating the safety and efficacy of two dosing regimens of daclizumab compared to no antibody induction in simultaneous kidney-pancreas transplantation: results at 3 years. *Transplant Proc* 2005; 37: 3531–4.
19. Ortiz V, *et al.* Induction therapy with daclizumab in heart transplantation—how many doses? *Transplant Proc* 2006; 38: 2541–3.
20. Washburn WK, *et al.* A novel three-dose regimen of daclizumab in liver transplant recipients with hepatitis C: a pharmacokinetic and pharmacodynamic study. *Liver Transpl* 2006; 12: 585–91.

Skin disorders. There are reports of successful treatment with daclizumab in psoriasis (p. 1688.1),[1,2] pemphigus vulgaris,[3] bullous pemphigoid[4] (see Pemphigus and Pemphigoid, p. 1687.1), and epidermolysis bullosa acquisita[5] (p. 1684.3). Cutaneous manifestations of adult T-cell leukaemia/lymphoma have also been reported to respond to daclizumab.[6]

1. Wohlrab J, *et al.* Treatment of recalcitrant psoriasis with daclizumab. *Br J Dermatol* 2001; 144: 209–10.
2. Dichmann S, *et al.* Humanized monoclonal anti-CD25 antibody as a novel therapeutic option in HIV-associated psoriatic erythroderma. *J Am Acad Dermatol* 2002; 47: 635–6.
3. Renki A, *et al.* A novel therapeutic option in pemphigus vulgaris: humanized monoclonal anti-CD25 antibody. *Br J Dermatol* 2004; 150: 1220–2.
4. Mockenhaupt M, *et al.* Daclizumab: a novel therapeutic option in severe bullous pemphigoid. *Acta Derm Venereol* 2005; 85: 65–6.
5. Egan CA, *et al.* Treatment of epidermolysis bullosa acquisita with the humanised anti-Tac mAb daclizumab. *Clin Immunol* 2001; 101: 146–51.
6. Osborne GBN, *et al.* Novel treatment of Sézary-like syndrome due to adult T-cell leukaemia/lymphoma with daclizumab (humanized anti-interleukin-2 receptor α antibody). *Br J Dermatol* 2006; 155: 617–20.

Adverse Effects and Precautions

Severe acute hypersensitivity reactions have occurred rarely with daclizumab. These have included anaphylactoid-type reactions such as rash, urticaria, pruritus, hypotension, hypoxia, tachycardia, cardiac arrest, wheezing, dyspnoea, bronchospasm, pulmonary oedema, peripheral oedema, laryngeal oedema, and respiratory failure. Injection site reactions have also been reported. Reactions have been seen both on initial exposure and with subsequent therapy. Therapy should be permanently stopped if a severe reaction occurs.

Effects on the heart. A report of sinus bradycardia[1] associated with the use of daclizumab.

1. Bassily-Marcus A, *et al.* Sinus bradycardia associated with daclizumab in liver transplant recipients: report of 3 cases. *Exp Clin Transplant* 2008; 6: 80–3.

Effects on mortality. Increased mortality was reported in cardiac transplant recipients given an immunosuppressive regimen of daclizumab with ciclosporin, mycophenolate mofetil, and corticosteroids. Some deaths were associated with severe infection and use with antilymphocyte immu-noglobulins.[1,2]

1. Roche, USA. Zenapax (daclizumab) (issued August 2003). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm168401.htm (accessed 05/08/10)
2. Hershberger RE, *et al.* Daclizumab to prevent rejection after cardiac transplantation. *N Engl J Med* 2005; 352: 2705–13.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies daclizumab 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 05/10/11)

Pharmacokinetics

The recommended regimen of daclizumab (see above) should result in serum concentrations sufficient to saturate interleukin-2 receptors for about 90 days post-transplanta-tion in adult patients, and 120 days in paediatric patients. The terminal elimination half-life of daclizumab has ranged from 11 to 38 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Zenapax; *Austral.*: Zena-pax†; *Austria*: Zenapax†; *Belg.*: Zenapax; *Braz.*: Zenapax; *Canad.*: Zenapax†; *Chile*: Zenapax; *China*: Zenapax (赛尼哌); *Cz.*: Zenapax†; *Denm.*: Zenapax†; *Fin.*: Zenapax†; *Fr.*: Zena-pax†; *Ger.*: Zenapax†; *Gr.*: Zenapax; *Hong Kong*: Zenapax†; *Hung.*: Zenapax; *Irl.*: Zenapax†; *Israel*: Zenapax†; *Ital.*: Zena-pax†; *Mex.*: Zenapax; *Neth.*: Zenapax†; *NZ*: Zenapax†; *Philipp.*: Zenapax; *Pol.*: Zenapax†; *Rus.*: Zenapax (Зенапакс); *S.Afr.*: Zenapax†; *Singapore*: Zenapax; *Spain*: Zenapax†; *Swed.*: Zena-pax†; *Switz.*: Zenapax†; *Thai.*: Zenapax†; *Turk.*: Zenapax; *UK*: Zenapax†; *USA*: Zenapax†; *Venez.*: Zenapax.

Everolimus *(BAN, USAN, rINN)*

Everolimo; Everolimus; Everolimusum; Eweroli-mus; NVP-RAD-001; RAD-001; SDZ-RAD; SDZ-RAD-666; Эверолимус.
(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahy-dro-9,27-dihydroxy-3-[(1*R*)-2-[(1*S*,3*R*,4*R*)-4-(2-hydro-xyethoxy)-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyri-do[2,1-*c*][1,4]oxaazacyclohentriacontine-1,5,11,28,29 (4*H*,6*H*,31*H*)-pentone.
$C_{53}H_{83}NO_{14}$=958.2
CAS — 159351-69-6.

The symbol † denotes a preparation no longer actively marketed

ATC — L01XE10; L04AA18.
ATC Vet — QL01XE10; QL04AA18.
UNII — 9HW64Q8G6G.

Uses and Administration

Everolimus is a derivative of sirolimus (p. 1966.2). It is used as a proliferation signal inhibitor in the prevention of graft rejection episodes in patients undergoing heart or kidney transplantation as part of an immunosuppressive regimen that includes ciclosporin (microemulsifying) and corticosteroids, or in patients undergoing liver transplantation as part of a regimen that includes tacrolimus and corticosteroids. It is also used for the treatment of advanced renal cell carcinoma (p. 708.3) after failure of therapies such as sunitinib or sorafenib that target vascular endothelial growth factor. In postmenopausal women with advanced hormone-receptor positive HER2-negative breast cancer (p. 702.1), everolimus is used with exemestane after treatment with a nonsteroidal aromatase inhibitor such as letrozole or anastrozole has failed. Everolimus is also used for the treatment of progressive neuroendocrine tumours of pancreatic origin (p. 716.3) in patients with unresectable, locally advanced, or metastatic disease. Everolimus is used in the treatment of subependymal giant-cell astrocytoma (see Malignant Neoplasms of the Brain, p. 701.2) associated with tuberous sclerosis in patients who are unable to have surgery. Patients with renal angiomyolipoma associated with tuberous sclerosis who are at risk of complications but not needing immediate surgery may also be treated with everolimus.

For immunosuppression in patients undergoing **heart or kidney transplantation**, the recommended oral dose is everolimus 750 micrograms twice daily, begun as soon as possible after transplantation, and given at the same time as ciclosporin. Whole blood concentrations of both everolimus and ciclosporin should be monitored, see Administration with Everolimus, p. 1946.3. In **liver transplantation** the recommended oral dose of everolimus is 1 mg twice daily, begun about 4 weeks after transplantation, and given at the same time of day as tacrolimus.

In advanced **renal cell carcinoma**, advanced **breast cancer**, advanced **neuroendocrine tumours**, and **renal angiomyolipoma**, the recommended oral dose is everolimus 10 mg once daily. If toxicity occurs, the dose may be reduced to 5 mg once daily, or withheld and restarted at 5 mg once daily. Dose adjustments are required when everolimus is given with some other drugs, see Administration with Other Drugs, below.

In subependymal **giant-cell astrocytoma** the initial oral dose of everolimus, given once daily, is based on body-surface. US licensed product information recommends a dose of 4.5 mg/m^2 for adults and children aged 1 year and older. UK information provides a more specific regimen licensed for use in adults and children aged 3 years and older:

- up to 1.2 m^2: 2.5 mg
- 1.3 to 2.1 m^2: 5 mg
- 2.2 m^2 or over: 7.5 mg

Everolimus whole blood trough concentrations should be measured about 2 weeks after starting treatment and doses adjusted to attain a concentration of 5 to 15 nanograms/mL. In patients whose trough concentrations are below 5 nanograms/mL or above 15 nanograms/mL, dose adjustments may be made in steps of 2.5 mg (or 2 mg for dispersible tablets) every 2 weeks to achieve the target range. If a dose reduction is required in a patient taking 2.5 mg daily, alternate day dosing should be used. Treatment may be withheld and/or the dose temporarily reduced for severe adverse effects. Trough concentrations should be measured about 2 weeks after adjusting the dose of everolimus or starting/adjusting the dose of other drugs that may affect everolimus concentrations (see Administration with Other Drugs, below).

Dose adjustments may be required when everolimus is used in patients with hepatic impairment, see below.

Everolimus-releasing stents have been developed to reduce restenosis after coronary artery stent placement.

Administration in children. For doses of everolimus used in children with subependymal giant-cell astrocytoma associated with tuberous sclerosis, see Uses and Administration, above.

Administration in hepatic impairment. The clearance of everolimus was significantly reduced in patients with moderate hepatic impairment.[1] When used orally for immunosuppression in patients undergoing **heart, kidney, or liver transplantation**, licensed product information for everolimus suggests the following reductions to the usual initial daily dose:

- mild impairment (Child Pugh class A): reduce by one-third
- moderate impairment (Child Pugh class B): reduce by one-half
- severe impairment (Child Pugh class C): reduce by at least one-half

Further titration of the dose is based on therapeutic drug monitoring (see Therapeutic Drug Monitoring, under Pharmacokinetics, p. 1959.2).

In some countries where everolimus is licensed for heart and kidney transplantation, the dose should be reduced to about one-half of the usual recommended dose if 2 of the following parameters occur in patients with mild or moderate hepatic impairment:

- bilirubin > 34 micromoles/litre
- albumin < 35 g/litre
- INR > 1.3

When used for **renal cell carcinoma, breast cancer, neuroendocrine tumours** of pancreatic origin, or **renal angiomyolipoma** associated with tuberous sclerosis, the recommended oral dose of everolimus is 7.5 mg daily in patients with mild hepatic impairment and 5 mg once daily in moderate impairment. In those with severe hepatic impairment, everolimus may be used to a maximum dose of 2.5 mg daily.

In the treatment of subependymal **giant-cell astrocytoma** associated with tuberous sclerosis, US licensed product information suggests that no dose adjustment is needed in patients with mild or moderate hepatic impairment, but that in severe impairment the starting dose of everolimus should be reduced by one-half. UK licensed product information does not recommend the use of everolimus in patients younger than 18 years old who have hepatic impairment. In those aged 18 and older, it recommends that 75% of the usual starting dose should be given to patients with mild impairment, 25% of the usual dose in moderate impairment, and that it should be avoided in severe impairment. It also recommends whole blood trough concentrations for everolimus of 3 to 15 nanograms/mL. For usual doses, see Uses and Administration, above.

1. Kovarik JM, *et al.* Influence of hepatic impairment on everolimus pharmacokinetics: implications for dose adjustment. *Clin Pharmacol Ther* 2001; 70: 425–30.

Administration with other drugs. Exposure to everolimus may be affected by inducers or inhibitors of the cytochrome P450 isoenzyme CYP3A4 or P-glycoprotein. The oral dose of everolimus may need to be modified if given with such drugs and whole blood everolimus concentrations should be monitored (see Therapeutic Drug Monitoring, p. 1959.2). Strong CYP3A4 inhibitors should not be given with everolimus.

In **heart, kidney, or liver transplantation** use of strong CYP3A4 inducers or inhibitors with everolimus is not recommended. For guidance on adjusting *ciclosporin* doses when the two drugs are given together for transplantation see Administration with Everolimus, under Ciclosporin, p. 1946.3.

Strong CYP3A4 inducers should also be avoided if possible in **renal cell carcinoma, breast cancer, neuroendocrine tumours**, and **renal angiomyolipoma**, but if they must be used, the dose of everolimus may be increased up to 20 mg once daily in 5 mg increments, (usually four and eight days after starting the inducer). Once the inducer is stopped everolimus should be reduced to the original dose. When moderate CYP3A4 inhibitors or P-glycoprotein inhibitors are to be used, the dose of everolimus may be reduced to 2.5 to 5 mg once daily (or 5 mg every other day) with close monitoring for adverse effects. About 2 or 3 days after the inhibitor is stopped, everolimus should be increased to the original dose.

If strong CYP3A4 inducers need to be used in **giant-cell astrocytoma** UK licensed product information recommends titrating the dose to ensure everolimus concentrations remain in the target range (see Uses and Administration, above); US information suggests doubling the dose initially, and then making further adjustments as necessary. Once the inducer is stopped everolimus should be reduced to the original dose. When moderate CYP3A4 inhibitors or P-glycoprotein inhibitors are to be used, the everolimus dose should initially be reduced by about 50% and then adjusted further as necessary. Once the inhibitor is stopped everolimus should be increased to the original dose 2 or 3 days later.

Malignant neoplasms. References.

1. Motzer RJ, *et al.* RECORD-1 Study Group. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008; 372: 449–56.
2. Oudard S, *et al.* Everolimus (RAD001): an mTOR inhibitor for the treatment of metastatic renal cell carcinoma. *Expert Rev Anticancer Ther* 2009; 9: 705–17.
3. Garnock-Jones KP, Keating GM. Everolimus: in advanced renal cell carcinoma. *Drugs* 2009; 69: 2115–24.
4. Yao JC, *et al.* Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *J Clin Oncol* 2010; 28: 69–76.
5. Grgic T, *et al.* Everolimus: a new mammalian target of rapamycin inhibitor for the treatment of advanced renal cell carcinoma. *Ann Pharmacother* 2011; 45: 78–83.
6. Yao JC, *et al.* RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011; 364: 514–23.
7. Pavel ME, *et al.* Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* 2011; 378: 2005–12.
8. Baselga J, *et al.* Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012; 366: 520–9.
9. Thompson LA, *et al.* Everolimus: a new treatment option for advanced pancreatic neuroendocrine tumors. *Ann Pharmacother* 2012; 46: 121–19.
10. Dhillon S. Everolimus in combination with exemestane: a review of its use in the treatment of patients with postmenopausal hormone receptor-positive, HER2-negative advanced breast cancer. *Drugs* 2013; 73: 475–85.

Organ and tissue transplantation. References.

1. Eisen HJ, *et al.* Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med* 2003; 349: 847–58.
2. Vitko S, *et al.* Everolimus with optimized cyclosporine dosing in renal transplant recipients: 6-month safety and efficacy results of two randomized studies. *Am J Transplant* 2004; 4: 626–35.
3. Nashan B, *et al.* Everolimus and reduced-exposure cyclosporine in de novo renal-transplant recipients: a three-year phase II, randomized, multicenter, open-label study. *Transplantation* 2004; 78: 1332–40.
4. Lorber MI, *et al.* Everolimus versus mycophenolate mofetil in the prevention of rejection in de novo renal transplant recipients: a 3-year randomized, multicenter, phase III study. *Transplantation* 2005; 80: 244–52.
5. Vitko S, *et al.* Three-year efficacy and safety results from a study of everolimus versus mycophenolate mofetil in de novo renal transplant patients. *Am J Transplant* 2005; 5: 2521–30. Correction. *ibid.* 2006; 6: 243.
6. Pascual J. Everolimus in clinical practice—renal transplantation. *Nephr Dial Transplant* 2006; 21 (suppl 3): iii18–iii23.
7. Webster AC, *et al.* Target of rapamycin inhibitors (TOR-I; sirolimus and everolimus) for primary immunosuppression in kidney transplant recipients. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 18/02/08).
8. Dunn C, Croom KF. Everolimus: a review of its use in renal and cardiac transplantation. *Drugs* 2006; 66: 547–70.
9. Snell GI, *et al.* Everolimus versus azathioprine in maintenance lung transplant recipients: an international, randomized, double-blind clinical trial. *Am J Transplant* 2006; 6: 169–77.
10. Levy G, *et al.* Safety, tolerability, and efficacy of everolimus in de novo liver transplant recipients: 12- and 36-month results. *Liver Transpl* 2006; 12: 1640–8.
11. Chapman JR, *et al.* Proliferation signal inhibitors in transplantation: questions at the cutting edge of everolimus therapy. *Transplant Proc* 2007; 39: 2937–50.
12. Vigano M, *et al.* RAD B253 Study Group. Prevention of acute rejection and allograft vasculopathy by everolimus in cardiac transplant recipients: a 24-month analysis. *J Heart Lung Transplant* 2007; 26: 584–92.
13. Hill JA, *et al.* A lower incidence of cytomegalovirus infection in de novo heart transplant recipients randomized to everolimus. *Transplantation* 2007; 84: 1436–42.
14. Chan L, *et al.* CRADUS09 Study Group. Multicenter, randomized study of the use of everolimus with tacrolimus after renal transplantation demonstrates its effectiveness. *Transplantation* 2008; 85: 821–6.
15. Salvadori M, *et al.* Everolimus with very low-exposure cyclosporine a in de novo kidney transplantation: a multicenter, randomized, controlled trial. *Transplantation* 2009; 88: 1194–1202.
16. Koch M. Everolimus in liver and lung transplantation. *Drugs Today* 2009; 45: 11–20.

Polycystic kidney disease. Autosomal dominant polycystic kidney disease is a slowly progressive hereditary disorder in which renal cysts develop, usually leading to end-stage renal disease. In a controlled 2-year study, everolimus slowed the increase in total kidney volume over the first year, but did not slow the progression of renal impairment.[1]

1. Walz G, *et al.* Everolimus in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2010; 363: 830–40. Correction. *ibid.*; 1190 and 1977.

Psoriasis. A patient with psoriasis and a poor response to conventional therapy was treated with everolimus and ciclosporin. All manifestations improved after 4 weeks of therapy, but treatment had to be stopped after the patient developed leucopenia.[1]

1. Frigerio E, *et al.* Severe psoriasis treated with a new macrolide: everolimus. *Br J Dermatol* 2007; 156: 372–4.

Reperfusion and revascularisation procedures. References to the use of everolimus-eluting stents.

1. Zhang F, *et al.* Clinical safety and efficacy of everolimus-eluting stents compared to paclitaxel-eluting stents in patients with coronary artery disease. *Ann Med* 2011; 43: 75–9.
2. de Waha A, *et al.* Everolimus-eluting versus sirolimus-eluting stents: an updated meta-analysis of randomized trials. *Clin Res Cardiol* 2012; 101: 461–7.
3. Palmerini T, *et al.* Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 2012; 379: 1393–1402.
4. Palmerini T, *et al.* Stent thrombosis with everolimus-eluting stents: meta-analysis of comparative randomized controlled trials. *Circ Cardiovasc Interv* 2012; 5: 357–64.
5. Townsend JC, *et al.* Everolimus-eluting stents in interventional cardiology. *Vasc Health Risk Manag* 2012; 8: 393–404.
6. Park KW, *et al.* Safety and efficacy of second-generation everolimus-eluting Xience V stents versus zotarolimus-eluting resolute stents in real-world practice: patient-related and stent-related outcomes from the multicenter prospective EXCELLENT and RESOLUTE-Korea registries. *J Am Coll Cardiol* 2013; 61: 536–44.

Tuberous sclerosis complex. References.

1. Krueger DA, *et al.* Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. *N Engl J Med* 2010; 363: 1801–11.

2. Curran MP. Everolimus: in patients with subependymal giant cell astrocytoma associated with tuberous sclerosis complex. *Paediatr Drugs* 2012; 14: 51–60.
3. Franz DN, *et al.* Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet* 2013; 381: 125–32.
4. Bissler JJ, *et al.* Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2013; 381: 817–24.

Adverse Effects and Precautions

As for Sirolimus, see p. 1967.2.

Other adverse effects that have been reported with everolimus include dehydration, fatigue, diabetes mellitus, chest pain, heart failure, dysgeusia, insomnia, conjunctivitis, nail disorders, haemoptysis, dyspnoea, and skin disorders such as pruritus, palmar-plantar erythrodysesthesia syndrome, and acneform dermatitis.

Renal function, fasting glucose concentrations, and full blood count should be measured at baseline and periodically during treatment.

Effects on the lungs. Pulmonary toxicity is a well-known adverse effect in patients given sirolimus (p. 1967.3) and similar toxicity has occurred[1-4] in patients given everolimus.

1. Expósito V, *et al.* Everolimus-related pulmonary toxicity in heart transplant recipients. *J Heart Lung Transplant* 2008; 27: 797–800.
2. Otton J, *et al.* Everolimus-associated pneumonitis in 3 heart transplant recipients. *J Heart Lung Transplant* 2009; 28: 104–6.
3. Vandewiele B, *et al.* Diffuse alveolar hemorrhage induced by everolimus. *Chest* 2010; 137: 456–9.
4. Depuydt P, *et al.* Fatal acute pulmonary injury associated with everolimus. *Ann Pharmacother* 2012; 46: e7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies everolimus 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 05/10/11)

Interactions

Everolimus is a substrate of cytochrome P450 isoenzyme CYP3A4 and a substrate and moderate inhibitor of P-glycoprotein. Plasma concentrations of everolimus may be affected by inducers or competitive inhibitors of CYP3A4 or P-glycoprotein. Exposure to everolimus is increased when given with the CYP3A4/P-glycoprotein inhibitors ciclosporin, ketoconazole, erythromycin, and verapamil. Licensed product information advises avoiding the use of everolimus with CYP3A4 or P-glycoprotein inhibitors; dosage reductions have been suggested if use with a moderate CYP3A4 inhibitor is necessary. Substances that are potent inducers of CYP3A4 or P-glycoprotein may decrease exposure to everolimus; dosage increases have been suggested if use together cannot be avoided. For dose adjustments, see Uses and Administration, p. 1958.1.

In vitro results suggest that systemic concentrations of everolimus after usual oral doses are unlikely to inhibit P-glycoprotein, CYP3A4, or CYP2D6, but theoretically, everolimus may affect the bioavailability of CYP3A4 or P-glycoprotein substrates when given together.

Use with live vaccines should be avoided.

References.

1. Kovarik JM, *et al.* Everolimus drug interactions: application of a classification system for clinical decision making. *Biopharm Drug Dispos* 2006; 27: 421–6.

Immunosuppressants. The bioavailability of everolimus was significantly increased when given with *ciclosporin*,[1] and dose adjustment of everolimus may be necessary if the ciclosporin dose is altered (see Administration with Everolimus, p. 1946.3).

In contrast, results from a small study implied that *tacrolimus* appeared to have a minimal effect on everolimus blood concentrations, and the dose of everolimus, when used with tacrolimus, may need to be higher than that given with ciclosporin in order to achieve therapeutic everolimus blood concentrations.[2]

1. Kovarik JM, *et al.* Differential influence of two cyclosporine formulations on everolimus pharmacokinetics: a clinically relevant pharmacokinetic interaction. *J Clin Pharmacol* 2002; 42: 95–9.
2. Kovarik JM, *et al.* Differential pharmacokinetic interaction of tacrolimus and cyclosporine on everolimus. *Transplant Proc* 2006; 38: 3456–8.

Ketoconazole. In a pharmacokinetic study in 12 healthy subjects,[1] ketoconazole increased the maximum concentration of everolimus by an average of 3.9-fold; area under the concentration-time curve was also increased by about 15-fold. The half-life of everolimus was significantly prolonged, and its clearance reduced. Since ketoconazole inhibits both cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein, the authors supposed that both pathways might have contributed to this interaction. The interaction was deemed to be clinically relevant and they advised against use of these 2 drugs together.

1. Kovarik JM, *et al.* Blood concentrations of everolimus are markedly increased by ketoconazole. *J Clin Pharmacol* 2005; 45: 514–18.

Rifampicin. In a pharmacokinetic study,[1] rifampicin increased the clearance of everolimus, decreasing exposure to everolimus by about 63%.

1. Kovarik JM, *et al.* Effect of rifampin on apparent clearance of everolimus. *Ann Pharmacother* 2002; 36: 981–5.

Verapamil. Verapamil increased the bioavailability of everolimus; the half-life of everolimus was essentially unchanged. The dose of everolimus should be reduced when these two drugs are given together, but the amount should be determined by blood concentrations and clinical monitoring. Verapamil concentrations may also be affected by everolimus, but the mechanism is unclear; any dose adjustment of verapamil should be guided by blood pressure monitoring.[1]

1. Kovarik JM, *et al.* Pharmacokinetic interaction between verapamil and everolimus in healthy subjects. *Br J Clin Pharmacol* 2005; 60: 434–7.

Pharmacokinetics

Peak plasma concentrations of everolimus occur about 1 to 2 hours after an oral dose. Plasma protein binding is about 74%. Everolimus is metabolised in the liver and to some extent in the gastrointestinal wall, and is a substrate of P-glycoprotein and the cytochrome P450 isoenzyme CYP3A4. Most metabolites are excreted in the faeces with small amounts found in urine. The mean elimination half-life of everolimus is about 30 hours.

References.

1. Kovarik JM, *et al.* Clinical development of an everolimus pediatric formulation: relative bioavailability, food effect, and steady-state pharmacokinetics. *J Clin Pharmacol* 2003; 43: 141–7.
2. Kirchner GI, *et al.* Clinical pharmacokinetics of everolimus. *Clin Pharmacokinet* 2004; 43: 83–95.
3. Moes DJAR, *et al.* Population pharmacokinetics and pharmacogenetics of everolimus in renal transplant patients. *Clin Pharmacokinet* 2012; 51: 467–80.

Therapeutic drug monitoring. Licensed product information recommends routine monitoring of whole blood everolimus concentrations when used as an immunosuppressant for transplantation, or for giant-cell astrocytoma.

In heart, kidney, and liver **transplantation** patients with everolimus trough levels of 3 nanograms/mL or greater have been found to have a lower incidence of acute rejection; an upper limit of 8 nanograms/mL is recommended. Monitoring is considered especially important in those with hepatic impairment (see under Uses and Administration, p. 1958.1) and if ciclosporin formulation or dosage is changed (see Administration with Everolimus, under Ciclosporin, p. 1946.3).

In **giant-cell astrocytoma** doses should be adjusted to attain everolimus trough concentrations of 5 to 15 nanograms/mL (see under Uses and Administration, p. 1958.1).

Use of everolimus with some other drugs may affect trough concentrations, see Administration with Other Drugs, p. 1958.2.

Further references.

1. Kovarik JM, *et al.* Exposure-response relationships for everolimus in de novo kidney transplantation: defining a therapeutic range. *Transplantation* 2002; 73: 920–5.
2. Kovarik JM, *et al.* Everolimus therapeutic concentration range defined from a prospective trial with reduced-exposure cyclosporine in de novo kidney transplantation. *Ther Drug Monit* 2004; 26: 499–505.
3. Starling RC, *et al.* Therapeutic drug monitoring for everolimus in heart transplant recipients based on exposure-effect modeling. *Am J Transplant* 2004; 4: 2126–31.
4. Lorber MI, *et al.* Therapeutic drug monitoring for everolimus in kidney transplantation using 12-month exposure, efficacy, and safety data. *Clin Transplant* 2005; 19: 145–52.
5. Mabasa VH, Ensom MH. The role of therapeutic monitoring of everolimus in solid organ transplantation. *Ther Drug Monit* 2005; 27: 666–76.
6. Kovarik JM, *et al.* Everolimus in pulmonary transplantation: pharmacokinetics and exposure-response relationships. *J Heart Lung Transplant* 2006; 25: 440–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Certican; *Austral.*: Afinitor; Certican; *Austria*: Afinitor; Certican; *Belg.*: Afinitor; Certican; *Braz.*: Afinitor; Certican; *Canad.*: Afinitor; *Chile*: Certican; *Cz.*: Afinitor; Certican; *Denm.*: Afinitor; Certican; Votubia; *Fin.*: Certican; *Fr.*: Afinitor; Certican; Votubia; *Ger.*: Afinitor; Certican; Votubia; *Gr.*: Afinitor; Certican; *Hong Kong*: Afinitor; Certican; *Hung.*: Certican; *India*: Certican; *Indon.*: Certican; *Irl.*: Afinitor; Votubia; *Israel*: Afinitor; Certican; *Ital.*: Certican; *Jpn*: Afinitor; Certican; *Malaysia*: Afinitor; Certican; *Mex.*: Certican; *Neth.*: Afinitor; Certican; Votubia; *Norw.*: Afinitor; Certican; Votubia; *NZ*: Afinitor; *Philipp.*: Afinitor; Certican; *Pol.*: Afinitor; Certican; *Port.*: Afinitor; Certican; *Rus.*: Afinitor (Афинитор); Certican (Сертикан); *S.Afr.*: Certican; *Singapore*: Afinitor; Certican; *Spain*: Afinitor; Certican; Votubia; *Swed.*: Afinitor; Certican; Votubia; *Switz.*: Afinitor; Certican; Votubia; *Thai.*: Afinitor; Certican; *Turk.*: Afinitor; Certican; *UK*: Afinitor; Votubia; *Ukr.*: Afinitor (Афинитор); Certican (Сертикан); Sertikan (Сертикан)†; *USA*: Afinitor; Zortress; *Venez.*: Certican.

Gusperimus Hydrochloride *(rINNM)*

BMS-181173; BMY-42215-1; 15-Deoxyspergualin Hydrochloride; Deoxyspergualin Hydrochloride; Guspérimus, Chlorhydrate de; Gusperimús, hidrocloruro de; Gusperimus Trihydrochloride (USAN); Gusperimusi Hydrochloridum; Hidrocloruro de gusperimús; NKT-01; NSC-356894; Гуспериmуса Гидрохлорид.

(±)-*N*-[[[4-[(3-Aminopropyl)amino]butyl]carbamoyl]hydroxymethyl]-7-guanidinoheptanamide trihydrochloride.

$C_{17}H_{37}N_7O_3,3HCl=496.9$

CAS — 104317-84-2 (gusperimus); 89149-10-0 (gusperimus); 85468-01-5 (gusperimus hydrochloride).

ATC — L04AA19.

ATC Vet — QL04AA19.

UNII — QZS4144I00.

Profile

Gusperimus is a guanidine derivative that inhibits both cell-mediated and antibody-mediated immunity. It is used in the treatment of renal graft rejection, and has been investigated in the management of graft-versus-host disease and Wegener's granulomatosis. For mention of its role in reversing acute graft rejection in kidney transplantation, see p. 1935.2.

Gusperimus is used as the hydrochloride. A dose of 3 to 5 mg/kg of gusperimus hydrochloride given daily for 7 days, by intravenous infusion over 3 hours, has been suggested in the treatment of acute renal graft rejection. Treatment may be continued for a further 3 days if required.

Adverse effects reported with gusperimus include bone-marrow depression, numbness of face and extremities, headache, gastrointestinal disturbances, alterations in liver enzyme values, and facial flushing. Rapid injection should be avoided as an acute increase in plasma concentration may produce respiratory depression.

References.

1. Ramos EL, *et al.* Deoxyspergualin: mechanism of action and pharmacokinetics. *Transplant Proc* 1996; 28: 873–5.
2. Tanabe K, *et al.* Effect of deoxyspergualin on the long-term outcome of renal transplantation. *Transplant Proc* 2000; 32: 1745–6.
3. Amada N, *et al.* Prophylactic use of deoxyspergualin improves long-term graft survival in living related renal transplant recipients transfused with donor-specific blood. *Transplant Proc* 2001; 33: 2256–7.
4. Birck R, *et al.* 15-Deoxyspergualin in patients with refractory ANCA-associated systemic vasculitis: a six-month open-label trial to evaluate safety and efficacy. *J Am Soc Nephrol* 2003; 14: 440–7.
5. Schmitt WH, *et al.* Prolonged treatment of refractory Wegener's granulomatosis with 15-deoxyspergualin: an open study in seven patients. *Nephrol Dial Transplant* 2005; 20: 1083–92.
6. Amada N, *et al.* Deoxyspergualin prophylaxis with tacrolimus further improves long-term graft survival in living-related renal-transplant recipients transfused with donor-specific blood. *Transplant Proc* 2005; 37: 927–9.
7. Nojima M, *et al.* Combined therapy of deoxyspergualin and plasmapheresis: a useful treatment for antibody-mediated acute rejection after kidney transplantation. *Transplant Proc* 2005; 37: 930–3.
8. Kawagishi N, *et al.* Usage of deoxyspergualin on steroid-resistant acute rejection in living donor liver transplantation. *Tohoku J Exp Med* 2006; 208: 225–33.
9. Flossmann O, *et al.* Deoxyspergualin in relapsing and refractory Wegener's granulomatosis. *Ann Rheum Dis* 2009; 68: 1125–30.
10. Flossmann O, Jayne DRW. Long-term treatment of relapsing Wegener's granulomatosis with 15-deoxyspergualin. *Rheumatology (Oxford)* 2010; 49: 556–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. Cz.: Spanidin; *Jpn*: Spanidin.

Inolimomab *(rINN)*

BT-563; Inolimomabum; Инолимомаб.

Immunoglobulin G1, anti-(human interleukin 2 receptor α-chain) (mouse monoclonal B-B10 γ1-chain), disulfide with mouse monoclonal B-B10 κ-chain, dimer.

CAS — 152981-31-2.

Profile

Inolimomab is a murine/human monoclonal antibody similar to daclizumab (p. 1957.1) that acts as an interleukin-2 receptor antagonist at the alpha chain (CD25) of the interleukin-2 receptor on the surface of activated T-lymphocytes. It is under investigation for the treatment of graft-versus-host disease after organ transplantation.

References.

1. Winkler M. Inolimomab (OPI). *Curr Opin Investig Drugs* 2002; 3: 1464–7.
2. Wabbijn M, *et al.* Ten-year follow-up of recipients of a kidney or heart transplant who received induction therapy with a monoclonal antibody against the interleukin-2 receptor. *Exp Clin Transplant* 2004; 2: 201–7.
3. Bay JO, *et al.* Inolimomab in steroid-refractory acute graft-versus-host disease following allogeneic hematopoietic stem cell transplantation: retrospective analysis and comparison with other interleukin-2 receptor antibodies. *Transplantation* 2005; 80: 782–8.

4. Bonaros N, *et al.* Ten-year follow-up of a prospective, randomized trial of BT563/bb10 versus anti-thymocyte globulin as induction therapy after heart transplantation. *J Heart Lung Transplant* 2006; 25: 1154–63.
5. Piñana JL, *et al.* Encouraging results with inolimomab (anti-IL-2 receptor) as treatment for refractory acute graft-versus-host disease. *Biol Blood Marrow Transplant* 2006; 12: 1135–41.
6. Dartois C, *et al.* Exposure-effect population model of inolimomab, a monoclonal antibody administered in first-line treatment for acute graft-versus-host disease. *Clin Pharmacokinet* 2007; 46: 417–32.

Mizoribine *(rINN)*

HE-69; Mizoribina; Mizoribinum; Мизорибин.
5-Hydroxy-1-β-D-ribofuranosylimidazole-4-carboxamide.
$C_9H_{13}N_3O_6$=259.2
CAS — 50924-49-7
UNII — 4JR41A10VP

Pharmacopoeias. In *Jpn*.

Profile

Mizoribine is an oral immunosuppressant that is used for the management of rejection in kidney transplantation, for nephrotic syndrome associated with primary glomerular disease, for lupus nephritis, and for rheumatoid arthritis.

Adverse effects include myelosuppression, hyperuricaemia, gastrointestinal disturbances, and hypersensitivity reactions. Stevens-Johnson syndrome has also been reported.

Administration. Although oral doses of mizoribine of 1 to 3 mg/kg daily have been recommended in renal transplantation, higher doses (above 5 mg/kg daily) have been widely used. Similarly, an oral dose of 50 mg three times daily has been recommended for patients with nephrotic syndrome associated with primary glomerular disease or lupus nephritis, and in rheumatoid arthritis, but high-dose regimens have been investigated.

Further references.

1. Tanabe K, *et al.* Long-term results in mizoribine-treated renal transplant recipients: a prospective, randomized trial of mizoribine and azathioprine under cyclosporine-based immunosuppression. *Transplant Proc* 1999; 31: 2877–9.
2. Yoshioka K, *et al.* A multicenter trial of mizoribine compared with placebo in children with frequently relapsing nephrotic syndrome. *Kidney Int* 2000; 58: 317–24.
3. Yokota S. Mizoribine: mode of action and effects in clinical use. *Pediatr Int* 2002; 44: 196–8.
4. Takei S. Mizoribine in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. *Pediatr Int* 2002; 44: 205–9.
5. Honda M. Nephrotic syndrome and mizoribine in children. *Pediatr Int* 2002; 44: 210–6.
6. Nagaoka R, *et al.* Mizoribine treatment for childhood IgA nephropathy. *Pediatr Int* 2002; 44: 217–23.
7. Tsuzuki K. Role of mizoribine in renal transplantation. *Pediatr Int* 2002; 44: 224–31.
8. Shibasaki T, *et al.* A randomized open-label comparative study of conventional therapy versus mizoribine onlay therapy in patients with steroid-resistant nephrotic syndrome (postmarketing survey). *Clin Exp Nephrol* 2004; 8: 117–26.
9. Akiyama T, *et al.* Mizoribine in combination therapy with tacrolimus for living donor renal transplantation: analysis of a nationwide study in Japan. *Transplant Proc* 2005; 37: 843–5.
10. Tanaka H, *et al.* Long-term mizoribine intermittent pulse therapy for young patients with flare of lupus nephritis. *Pediatr Nephrol* 2006; 21: 962–6.
11. Tanaka E, *et al.* Acceptability and usefulness of mizoribine in the management of rheumatoid arthritis in methotrexate-refractory patients and elderly patients, based on analysis of data from a large-scale observational cohort study. *Mod Rheumatol* 2006; 16: 214–19.
12. Sugitani A, *et al.* Revival of effective and safe high-dose mizoribine for the kidney transplantation. *Clin Transplant* 2006; 20: 590–5.
13. Kawasaki Y, *et al.* Efficacy of single dose of oral mizoribine pulse therapy two times per week for frequently relapsing nephrotic syndrome. *J Nephrol* 2007; 20: 52–6.
14. Stypinski D, *et al.* Safety, tolerability and pharmacokinetics of higher-dose mizoribine in healthy male volunteers. *Br J Clin Pharmacol* 2007; 63: 459–68.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Bredinin (布累迪宁); *Jpn*: Bredinin.

Muromonab-CD3 *(USAN, rINN)*

Muromonabum-CD3; OKT3; Муромонаб-CD3.
ATC — L04AA02
ATC Vet — QL04AA02
UNII — 7GA39ICE2V

Description. A murine monoclonal antibody comprising a purified IgG_{2a} immunoglobulin with a heavy chain having a molecular weight of about 50 000 daltons and a light chain with a molecular weight of about 25 000 daltons.

Pharmacopoeias. In *Chin*.

Uses and Administration

Muromonab-CD3 is a murine monoclonal antibody to the T3 (CD3) antigen of human T-lymphocytes, which is essential to antigen recognition and response; the antibody thus specifically blocks T-cell generation and function, to exert an immunosuppressant effect without affecting the bone marrow.

It is used in the treatment of acute allograft rejection in organ transplant recipients, in doses of 5 mg daily by intravenous injection for 10 to 14 days. For children's doses, see Administration in Children, below. The dose of any other immunosuppressant therapy may need to be reduced. Patients should be monitored closely after the first few doses of muromonab-CD3 because of the risk of cytokine release syndrome and hypersensitivity reactions. The first dose may be preceded by intravenous methylprednisolone sodium succinate, in a dose of 8 mg/kg, 1 to 4 hours before muromonab-CD3. Paracetamol and antihistamines may also be given with muromonab-CD3 to reduce early reactions.

Muromonab-CD3 has also been given experimentally as part of regimens for the prophylaxis of graft rejection. For further details of the use of muromonab-CD3 in the treatment and prophylaxis of graft rejection see Organ and Tissue Transplantation, p. 1932.2, *et seq*.

References.

1. ten Berge IJM, *et al.* Guidelines for optimal use of muromonab CD3 in transplantation. *BioDrugs* 1999; 11: 277–84.
2. Flechner SM. A randomized prospective trial of low-dose OKT3 induction therapy to prevent rejection and minimize side effects in recipients of kidney transplants. *Transplantation* 2000; 69: 2374–81.
3. Henry ML, *et al.* A randomized prospective trial of OKT3 induction in the current immunosuppression era. *Clin Transplant* 2001; 15: 410–14.
4. Benfield MR, *et al.* A randomized multicenter trial of OKT3 mAbs induction compared with intravenous cyclosporine in pediatric renal transplantation. *Pediatr Transplant* 2005; 9: 282–92.
5. Knop S, *et al.* OKT3 muromonab as second-line and subsequent treatment in recipients of stem cell allografts with steroid-resistant acute graft-versus-host disease. *Bone Marrow Transplant* 2005; 36: 831–7.
6. Sevmis S, *et al.* OKT3 treatment for steroid-resistant acute rejection in kidney transplantation. *Transplant Proc* 2005; 37: 3016–18.
7. Wilmot L, *et al.* OKT3 treatment in refractory pediatric heart transplant rejection. *J Heart Lung Transplant* 2005; 24: 1793–7.
8. Knop S, *et al.* Treatment of steroid-resistant acute GVHD with OKT3 and high-dose steroids results in better disease control and lower incidence of infectious complications when compared to high-dose steroids alone: a randomized multicenter trial by the EBMT Chronic Leukemia Working Party. *Leukemia* 2007; 21: 1830–3.

Administration. *ORAL* Oral muromonab-CD3 has been investigated in doses of 0.2 to 5 mg daily (with or without the glycolipid beta-glucosylceramide), and appears to have some activity.[1]

1. Ilan Y, *et al.* Oral administration of OKT3 monoclonal antibody to human subjects induces a dose-dependent immunologic effect in T cells and dendritic cells. *J Clin Immunol* 2010; 30: 167–77.

Administration in children. The initial recommended doses in children given muromonab-CD3 for acute allograft rejection are as follows:

- those weighing 30 kg or less: 2.5 mg daily
- those weighing more than 30 kg: 5 mg daily

Doses are given by intravenous injection for 10 to 14 days.

Paediatric patients are known to have higher CD3 lymphocyte counts than adults, and often require doses to be titrated upwards. The initial dose may be subsequently adjusted in 2.5 mg increments to achieve T-cell clearance (CD3-positive cells less than 25 cells/mm³) and ensure therapeutic serum concentrations of muromonab-CD3 (of 800 nanograms/mL or greater, see Therapeutic Drug Monitoring, p. 1961.1).

Adverse Effects, Treatment, and Precautions

An acute cytokine release syndrome occurs in most patients, typically 30 to 60 minutes after the first few doses of muromonab-CD3 (although it may occur later). Frequency and severity tend to decrease with successive doses, while prophylactic corticosteroids may reduce initial adverse reactions (see Uses and Administration, above). The syndrome ranges from a more frequently reported, mild, self-limiting, flu-like illness to a less common, severe, and life-threatening, shock-like reaction, which may include serious cardiovascular and CNS manifestations. Typical clinical manifestations of the cytokine release syndrome include high fever, chills or rigors, headache, tremor, gastrointestinal disturbances, myalgia, and generalised weakness. Rash and pruritus may also occur. Cardiorespiratory findings may include apnoea, dyspnoea, bronchospasm or wheezing, tachypnoea, respiratory arrest or failure, acute respiratory distress syndrome, angina, myocardial infarction, chest pain or tightness, tachycardia, hypertension, hypotension, cardiac failure, pulmonary oedema, hypoxaemia, and arrhythmias. Reversible impairment of renal function may also be associated with the syndrome.

Other reported effects of muromonab-CD3 include encephalopathy, cerebral oedema, and a syndrome resembling aseptic meningitis, with headache, fever, stiff neck, and photophobia; seizures have also occurred. Hypersensitivity reactions, including fatal anaphylaxis, have been reported and may be difficult to distinguish from the cytokine release syndrome.

As with other potent immunosuppressants, treatment with muromonab-CD3 may increase the risk of serious infections and the development of certain malignancies. Intra-uterine devices should be used with caution during immunosuppressive therapy as there is an increased risk of infection. Use of live vaccines should be avoided for the same reason.

Muromonab-CD3 should not be given to patients with uncontrolled hypertension, or in patients hypersensitive to products of murine origin. It should be avoided in patients with a history of seizures. Because fluid overload is associated with an increased risk of pulmonary oedema due to the cytokine release syndrome, muromonab-CD3 is contra-indicated in patients who have undergone a more than 3% weight gain in the week preceding therapy, or who have radiographic evidence of fluid overloading. Repeated courses of muromonab-CD3 may be less effective because of the development of antibodies to the drug. Paediatric patients may be at increased risk of serious adverse effects following muromonab-CD3 therapy.

Effects on the blood. *THROMBOEMBOLISM.* Intragraft thromboses developed in 9 of 93 consecutive kidney transplant recipients given high-dose muromonab-CD3 (10 mg daily) as part of their immunosuppressive regimen.[1] In one patient the thrombosis was in the renal artery, and in 3 in the renal vein; the remainder had thromboses in the glomerular capillaries and thrombotic microangiopathy similar to that of haemolytic-uraemic syndrome. The authors suggested that muromonab-CD3 has procoagulant effects, perhaps mediated by released tumour necrosis factor; these effects had also been seen in 3 patients receiving muromonab-CD3 at conventional doses (5 mg daily). Another group[2] has also reported an apparently increased incidence of acute vascular thrombosis in patients given muromonab-CD3 at conventional doses, but in the experience of others,[3] despite evidence of activation of coagulation by the drug, treatment of acute rejection with 5 mg daily was not associated with thromboembolic complications. US licensed product information states that the relationship to dose remains unclear, but that the relative risk appears to be greater with doses above the recommended dose.

1. Abramowicz D, *et al.* Induction of thromboses within renal grafts by high-dose prophylactic OKT3. *Lancet* 1992; 339: 777–8.
2. Gomez E, *et al.* Main graft vessels thromboses due to conventional-dose OKT3 in renal transplantation. *Lancet* 1992; 339: 1612–13.
3. Raasveld MHM, *et al.* Thromboembolic complications and dose of monoclonal OKT3 antibody. *Lancet* 1992; 339: 1363–4.

Effects on the ears. Bilateral sensorineural hearing loss has occurred after muromonab-CD3 therapy. In one case series, 5 out of 7 patients were affected, showing a mean hearing loss of 18 decibels.[1] Tinnitus may also occur.[1,2] Although symptoms are generally reversible,[1,2] one patient still showed a deficit in hearing after 6 months.[3]

1. Hartnick CJ, *et al.* Reversible sensorineural hearing loss following administration of muromonab-CD3 (OKT3) for cadaveric renal transplant immunosuppression. *Ann Otol Rhinol Laryngol* 2000; 109: 45–7.
2. Hartnick CJ, *et al.* Reversible sensorineural hearing loss after renal transplant immunosuppression with OKT3 (muromonab-CD3). *Ann Otol Rhinol Laryngol* 1997; 106: 640–2.
3. Michals M, *et al.* Hearing loss associated with muromonab-CD3 therapy. *Clin Pharm* 1988; 7: 867–8.

Effects on the nervous system. Generalised seizures were reported in 2 uraemic kidney-graft recipients given muromonab-CD3.[1] Delayed graft function may result in the accumulation of uraemic toxins which combine with cytokines released by the immunosuppressant to produce the effects on the CNS. Seizures and encephalopathy were reported in siblings given muromonab-CD3 after renal transplantation, and appeared to predispose one of them to develop ciclosporin neurotoxicity.[2] A neurological syndrome characterised by akinetic mutism, blepharospasm, anomic aphasia, and delirium, occurred in a heart transplant patient given muromonab-CD3; symptoms resolved after stopping therapy.[3]

The manufacturers have warned that children treated with muromonab-CD3 may be at increased risk of nervous system complications, notably cerebral oedema that may result in fatal cerebral herniation. Since 1986, and as of May 2004, 9 cases of cerebral oedema had been reported worldwide in children, resulting in 6 deaths. Cerebral herniation had occurred within a few hours to 1 day after injection. Signs include the sudden appearance of severe headache, seizures, impaired mental function, drowsiness and lethargy, and coma.[4]

1. Seifeldin RA, *et al.* Generalized seizures associated with the use of muromonab-CD3 in two patients after kidney transplantation. *Ann Pharmacother* 1997; 31: 586–9.
2. Thaisenthawatkul P, *et al.* Muromonab-CD3-induced neurotoxicity: report of two siblings, one of whom had subsequent cyclosporin-induced neurotoxicity. *J Child Neurol* 2001; 16: 825–31.
3. Pittock SJ, *et al.* OKT3 neurotoxicity presenting as akinetic mutism. *Transplantation* 2003; 75: 1058–60.

4. Janssen-Ortho, Canada. Important new safety information on Orthoclone OKT*3 (muromonab-CD3) (issued 17 May 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/orthoclone_okt3_pa-ap-eng.pdf (accessed 18/02/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies muromonab-CD3 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 05/10/11)

Pharmacokinetics

Therapeutic drug monitoring. US licensed product information states that serum concentrations of muromonab-CD3 are measurable using an enzyme-linked immunosorbent assay (ELISA). Studies in organ transplant recipients found that patients less than 10 years of age had higher concentrations than patients aged 10 to 50 years. Subsequent clinical experience has shown that serum concentrations of muromonab-CD3 greater than or equal to 800 nanograms/mL block the function of T-cells. Reduced T-cell clearance or low plasma concentrations of muromonab-CD3 provide a basis for adjusting muromonab dosage or stopping therapy.

In adults, periodic monitoring to ensure plasma muromonab-CD3 concentrations of 800 nanograms/mL or greater, or CD3-positive cells less than 25 cells/mm³ is recommended. Paediatric patients are known to have higher CD3 lymphocyte counts than adults, and often require increased doses of muromonab-CD3 to achieve similar depletion of CD3-positive cells and therapeutic serum concentrations; both T-cell clearance and plasma muromonab-CD3 should be monitored daily in children.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Orthoclone OKT3†; ***Belg.***: Orthoclone OKT3; ***Braz.***: Orthoclone OKT3; ***China***: Ior T3 (爱获山); ***Fin.***: Orthoclone OKT3†; ***Fr.***: Orthoclone OKT3†; ***Ger.***: Orthoclone OKT3†; ***Gr.***: Orthoclone; ***Israel***: Orthoclone OKT3; ***Ital.***: Orthoclone OKT3; ***Mex.***: Ior-T3†; Orthoclone OKT3; ***Neth.***: Orthoclone OKT3†; ***Norw.***: Orthoclone OKT3†; ***NZ***: Orthoclone OKT3; ***Port.***: Orthoclone OKT3; ***S.Afr.***: Orthoclone†; ***Singapore***: Orthoclone OKT3; ***Swed.***: Orthoclone OKT3†; ***Switz.***: Orthoclone OKT3†; ***Turk.***: Orthoclone OKT3†; ***USA***: Orthoclone OKT3†; ***Venez.***: OKT3.

Mycophenolate

ATC — L04AA06.
ATC Vet — QL04AA06.

Mycophenolic Acid *(BAN, USAN, rINN)*

Acide Mycophénolique; Ácido micofenólico; Acidum Mycophenolicum; Lilly-68618; MPA; NSC-129185; Микофеноловая Кислота.

(*E*)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-5-phthalanyl)-4-methyl-4-hexenoic acid.

$C_{17}H_{20}O_6$=320.3

CAS — 24280-93-1.
ATC — L04AA06.
ATC Vet — QL04AA06.
UNII — HU9DX48N0T.

Mycophenolate Mofetil *(BANM, USAN, rINNM)*

Micofenolato de mofetilo; Mikofenolat Mofetil; Mikofenolato mofetilis; Mofetilis Mycophenolas; Mofetil-mykofenolát; Mofetilo micofenolato de; Mycophenolas Mofetil; Mycophenolas Mofetilum; Mycophenolas-mofetil; Mycophénolate mofétil; Mycophénolate; Mofétil de; Mycophenolate Morpholinoethyl; Mycophenolatmofetil; Mykofenolaattimofetiili; Mykofenolatmofetil; RS-61443; Микофеноловаая Мофетил.

2-Morpholinoethyl (*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-5-phthalanyl)-4-methyl-4-hexenoate.

$C_{23}H_{31}NO_7$=433.5

CAS — 115007-34-6; 128794-94-5.
ATC — L04AA06.
ATC Vet — QL04AA06.
UNII — 9242ECW6R0.

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

Ph. Eur. 8: (Mycophenolate Mofetil). A white or almost white, crystalline powder. M.p. about 96 degrees. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone. Protect from light.

USP 36: (Mycophenolate Mofetil). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol; soluble in methyl alcohol; freely soluble in acetone. Store in airtight containers.

Mycophenolate Mofetil Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro del micofenolato de mofetilo; Mycophénolate, Mofétil Chlorhydrate de; Mycophenolati Mofetili Hydrochloridum; RS-61443-190; Микофеноловой Мофетила Гидрохлорид.

2-Morpholinoethyl (*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-5-phthalanyl)-4-methyl-4-hexenoate hydrochloride.

$C_{23}H_{31}NO_7$,HCl=470.0

CAS — 116680-01-4.
ATC — L04AA06.
ATC Vet — QL04AA06.
UNII — UXH81S8ZVB.

Incompatibility. Solutions of mycophenolate mofetil hydrochloride were found to be physically compatible and chemically stable with solutions containing clinically relevant concentrations of cefepime, dopamine, noradrenaline, tacrolimus, and vancomycin, for up to 4 hours of simulated Y-site administration. However, combining ciclosporin and mycophenolate resulted in effervescence and chemical instability.[1]

1. Cochran BG, *et al.* Physical compatibility and chemical stability of mycophenolate mofetil during simulated Y-site administration with commonly coadministered drugs. *Am J Health-Syst Pharm* 2007; 64: 1410–14.

Stability. UK and US licensed product information states that, after reconstitution of *mycophenolate mofetil oral suspension*, it may be stored at room temperature (15 degrees to 30 degrees) or in a refrigerator (2 degrees to 8 degrees) for up to 60 days; it should not be frozen.

UK licensed product information for *mycophenolate mofetil hydrochloride solution for infusion* states that the infusion should be started within 3 hours of reconstitution and dilution; solutions may be kept at room temperature (15 degrees to 30 degrees). A study found that solutions of mycophenolate mofetil hydrochloride in concentrations equivalent to mycophenolate mofetil 1, 5, or 10 mg/mL were stable for 7 days when stored at 4 degrees or 25 degrees in PVC infusion bags.[1] However, it was noted that a progressive discoloration occurred in bags unprotected from light and stored at 25 degrees; further study was required to determine the source of the discoloration.

1. Certain E, *et al.* Stability of i.v. mycophenolate mofetil in 5% dextrose injection in polyvinyl chloride infusion bags. *Am J Health-Syst Pharm* 2002; 59: 2434–9.

Mycophenolate Sodium *(BANM, USAN, rINNM)*

ERL-080; Micofenolato sódico; Mycophénolate de Sodium; Natril Mycophenolas; Натрий Микофеноловая.

Sodium 4(*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate.

$C_{17}H_{19}NaO_6$=342.3

CAS — 37415-62-6.
ATC — L04AA06.
ATC Vet — QL04AA06.
UNII — WX877SQI1G.

Uses and Administration

Mycophenolic acid is an immunosuppressant derived from *Penicillium stoloniferum*. It is a reversible inhibitor of inosine monophosphate dehydrogenase and thus inhibits purine synthesis, with potent cytostatic effects on both T- and B-lymphocytes. It is given with other immunosuppressants, for the prevention of graft rejection, and has also been tried in diseases with an auto-immune or immune-mediated inflammatory component.

It has been used mainly as the morpholinoethyl derivative, mycophenolate mofetil, or its hydrochloride salt; doses of both are expressed as mycophenolate mofetil. 1.08 g of mycophenolate mofetil hydrochloride is equivalent to about 1 g of mycophenolate mofetil. An enteric-coated formulation of mycophenolate sodium (the sodium salt of mycophenolic acid) is also available in some countries. Doses are expressed in terms of the acid; mycophenolate sodium 769 mg is equivalent to about 720 mg of mycophenolic acid.

In patients to whom oral therapy cannot initially be given, mycophenolate mofetil may be given for up to 14 days by intravenous infusion. Infusions are given as the hydrochloride salt. It is dissolved in glucose 5% to a final concentration equivalent to mycophenolate mofetil 6 mg/mL, and given over 2 hours through either a central or peripheral vein.

In the prophylaxis of acute **renal** graft rejection in adults, the conventional formulation of mycophenolate mofetil is given orally in doses of 1 g twice daily, usually within 72 hours of transplantation; the equivalent dose may be given by intravenous infusion, but is usually started within 24 hours after transplantation.

The enteric-coated formulation of mycophenolate sodium is also given for the prophylaxis of acute renal graft rejection to adults in a dose equivalent to mycophenolic acid 720 mg twice daily; the two formulations cannot be indiscriminately interchanged or substituted.

In the prophylaxis of **cardiac** graft rejection in adults, mycophenolate mofetil 1.5 g twice daily is given orally, within 5 days after transplantation, or by intravenous infusion at an equivalent dose.

For use in the prophylaxis of rejection in **hepatic** transplantation in adults, the equivalent of mycophenolate mofetil 1 g twice daily is given by intravenous infusion for the first 4 days after transplantation, with subsequent conversion to 1.5 g twice daily orally as soon as it can be tolerated.

For doses of mycophenolate used for organ transplantation in children see Administration in Children, below.

Patients should undergo regular blood counts; if neutropenia develops consideration should be given to interrupting mycophenolate treatment, reducing the dose, or stopping therapy.

Administration in children. Oral mycophenolate mofetil is licensed from the age of 2 years in the UK, and from 3 months of age in the USA. For prevention of renal graft rejection in patients up to 18 years of age, the recommended oral dose of mycophenolate mofetil is 600 mg/m² twice daily, up to a maximum of 1 g twice daily. Patients with a body-surface of 1.25 to 1.5 m² may be given 750 mg twice daily, whereas those with a body-surface of greater than 1.5 m² may be given the same dose as adults (see Uses and Administration, above). In the UK, the *BNFC* allows for use from 1 month to 18 years at 600 mg/m² twice daily orally or by intravenous infusion when used with ciclosporin and corticosteroids, but recommends 300 mg/m² twice daily when used with tacrolimus and corticosteroids; the maximum in both cases is 2 g daily.

UK licensed product information states that no data are available for paediatric cardiac and hepatic transplant patients. However, for prophylaxis of rejection in **hepatic** transplantation, the *BNFC* recommends mycophenolate mofetil 10 mg/kg twice daily, orally or by intravenous infusion, for children aged from 1 month to 18 years. This may be increased to 20 mg/kg twice daily, to a maximum of 2 g daily. The dose is the same whether used with either ciclosporin and corticosteroids, or tacrolimus and corticosteroids.

Mycophenolate mofetil is used in paediatric **haematopoietic stem cell** transplant (HSCT) recipients, often with a calcineurin inhibitor such as ciclosporin. Dosing guidelines for paediatric HSCT patients are lacking, but exposure to mycophenolic acid has been found to differ compared with other transplant recipients, see under Pharmacokinetics, p. 1965.2.

Mycophenolate mofetil is also used for severe refractory eczema in children, see p. 1962.1.

Administration in hepatic impairment. Licensed product information in the UK and USA states that no dose adjustments of *mycophenolate mofetil* are needed for renal transplant recipients with severe hepatic parenchymal disease. However, it is not known whether dose adjustments are necessary for those with hepatic disease of differing aetiology. No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

UK licensed product information states that no dose adjustments are needed for *mycophenolate sodium* in renal transplant patients with hepatic impairment.

Administration in renal impairment. US licensed product information states that exposure to mycophenolic acid (MPA) is increased in patients with severe chronic renal impairment. Although mean MPA concentrations in patients with delayed renal graft function were comparable to those transplant patients without delayed renal graft function, there is a potential for a transient increase in MPA concentrations if renal graft function is delayed. However, dose adjustment does not appear to be necessary in these patients. Both US and UK licensed product information state that in renal transplant patients with severe chronic renal impairment (GFR less than 25 mL/minute per 1.73 m²), oral or intravenous doses of *mycophenolate mofetil* above 1 g twice daily should be avoided; UK product information recommends that the daily dose of *mycophenolate sodium* in these patients should not exceed 1.44 g. No dose adjustments of mycophenolate are needed in those with delayed renal graft function. No data are available for cardiac or hepatic transplant recipients with severe chronic renal impairment.

Chronic active hepatitis. Mycophenolate mofetil may be of benefit in patients with auto-immune hepatitis

(p. 1602.3) who are intolerant of or unresponsive to azathioprine or other standard therapy.[1-5]

1. Richardson PD, *et al.* Mycophenolate mofetil for maintenance of remission in autoimmune hepatitis in patients resistant to or intolerant of azathioprine. *J Hepatol* 2000; 33: 371–5.
2. Devlin SM, *et al.* Mycophenolate mofetil for the treatment of autoimmune hepatitis in patients refractory to standard therapy. *Can J Gastroenterol* 2004; 18: 321–6.
3. Inductivo-Yu I, *et al.* Mycophenolate mofetil in autoimmune hepatitis patients not responsive or intolerant to standard immunosuppressive therapy. *Clin Gastroenterol Hepatol* 2007; 5: 799–802.
4. Hennes EM, *et al.* Mycophenolate mofetil as second line therapy in autoimmune hepatitis? *Am J Gastroenterol* 2008; 103: 3063–70.
5. Aw MM, *et al.* Mycophenolate mofetil as rescue treatment for autoimmune liver disease in children: a 5-year follow-up. *J Hepatol* 2009; 51: 156–60.

Eczema. Mycophenolate mofetil has been reported to be safe and effective in the treatment of moderate-to-severe, refractory eczema (p. 1684.1). Typical oral doses are 1 to 2 g daily in adults, and 30 to 50 mg/kg (or 1.2 g/m^2) daily in children.[1-3]

1. Neuber K, *et al.* Treatment of atopic eczema with oral mycophenolate mofetil. *Br J Dermatol* 2000; 143: 385–91.
2. Grundmann-Kollmann M, *et al.* Mycophenolate mofetil is effective in the treatment of atopic dermatitis. *Arch Dermatol* 2001; 137: 870–3.
3. Heller M, *et al.* Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. *Br J Dermatol* 2007; 157: 127–32.

Eye disorders. Retrospective evaluations of treatment outcomes in patients with chronic inflammatory eye disease treated with mycophenolate mofetil found that it was effective in controlling inflammation and had a useful corticosteroid-sparing effect.[1,2] Mycophenolate mofetil, used either alone or adjunctively, has been reported[3-8] to be of benefit in refractory uveitis (p. 1615.1). Oral doses of 600 mg/m^2 twice daily or 1 g twice daily have been used in children; the latter dose has also been used in adults with uveitis. There was some suggestion mycophenolate might be less effective in those patients initially unresponsive to azathioprine.[5] For mention of its use in uveitis associated with sarcoidosis see p. 1963.1.

1. Baltatzis S, *et al.* Mycophenolate mofetil as an immunomodulatory agent in the treatment of chronic ocular inflammatory disorders. *Ophthalmology* 2003; 110: 1061–5.
2. Thorne JE, *et al.* Mycophenolate mofetil therapy for inflammatory eye disease. *Ophthalmology* 2005; 112: 1472–7.
3. Zierhut M, *et al.* Immunsuppressive Therapie mit Mycophenolat Mofetil (CellCept) in der Behandlung der Uveitis. *Ophthalmologe* 2001; 98: 647–51.
4. Greiner K, *et al.* Effizienz von Mycophenolat-Mofetil bei der Therapie der intermediären und posterioren Uveitis. *Ophthalmologe* 2002; 99: 691–4.
5. Lau CH, *et al.* Long-term efficacy of mycophenolate mofetil in the control of severe intraocular inflammation. *Clin Experiment Ophthalmol* 2003; 31: 487–91.
6. Siepmann K, *et al.* Mycophenolate mofetil is a highly effective and safe immunosuppressive agent for the treatment of uveitis: a retrospective analysis of 106 patients. *Graefes Arch Clin Exp Ophthalmol* 2006; 244: 788–94.
7. Doycheva D, *et al.* Mycophenolate mofetil in the treatment of uveitis in children. *Br J Ophthalmol* 2007; 91: 180–4.
8. Teoh SC, *et al.* Mycophenolate mofetil for the treatment of uveitis. *Am J Ophthalmol* 2008; 146: 752–60.

Glomerular kidney disease. Mycophenolate mofetil, in usual adult oral doses of 1 to 2 g daily, has been reported[1-10] to be of benefit in various forms of glomerular kidney disease (p. 1604.3); in childhood nephrotic syndrome, it was reported to have a significant corticosteroid-sparing effect, reduce relapse rates,[5,11] and benefit renal function.[8,12]

1. Choi MJ, *et al.* Mycophenolate mofetil treatment for primary glomerular diseases. *Kidney Int* 2002; 61: 1098–1114.
2. Karim MY, Abbs IC. Mycophenolate mofetil in nonlupus glomerulonephropathy. *Lupus* 2005; 14 (suppl): s39–s41.
3. Segarra A, *et al.* Efficacy and safety of 'rescue therapy' with mycophenolate mofetil in resistant primary glomerulonephritis—a multicenter study. *Nephrol Dial Transplant* 2007; 22: 1351–60.
4. Moudgil A, *et al.* Mycophenolate mofetil therapy in frequently relapsing steroid-dependent and steroid-resistant nephrotic syndrome of childhood: current status and future directions. *Pediatr Nephrol* 2005; 20: 1376–81.
5. Hogg RJ, *et al.* Mycophenolate mofetil in children with frequently relapsing nephrotic syndrome: a report from the Southwest Pediatric Nephrology Study Group. *Clin J Am Soc Nephrol* 2006; 1: 1173–8.
6. Afzal K, *et al.* Treatment with mycophenolate mofetil and prednisolone for steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 2007; 22: 2059–65.
7. Okada M, *et al.* Mycophenolate mofetil therapy for children with intractable nephrotic syndrome. *Pediatr Int* 2007; 49: 933–7.
8. Caillez M, *et al.* Le mycophénolate mofétil améliore la fonction rénale et l'imprégnation cortisonique au cours du syndrome néphrotique corticodépendant de l'enfant. Une étude de cohorte. *Nephrol Ther* 2008; 4: 15–20.
9. Dorresteijn EM, *et al.* Mycophenolate mofetil versus cyclosporine for remission maintenance in nephrotic syndrome. *Pediatr Nephrol* 2008; 23: 2013–20.
10. Fujinaga S, *et al.* Mycophenolate mofetil therapy for childhood-onset steroid dependent nephrotic syndrome after long-term cyclosporine: extended experience in a single center. *Clin Nephrol* 2009; 72: 268–73.
11. Bagga A, *et al.* Mycophenolate mofetil and prednisolone therapy in children with steroid-dependent nephrotic syndrome. *Am J Kidney Dis* 2003; 42: 1114–20.
12. Gellermann J, Querfeld U. Frequently relapsing nephrotic syndrome: treatment with mycophenolate mofetil. *Pediatr Nephrol* 2004; 19: 101–4.

Immune thrombocytopenia. Mycophenolate mofetil has been reported[1-4] to be of benefit in small numbers of patients with refractory immune thrombocytopenia (p. 1606.1).

1. Howard J, *et al.* Mycophenolate mofetil for the treatment of refractory auto-immune haemolytic anaemia and auto-immune thrombocytopenia purpura. *Br J Haematol* 2002; 117: 712–15.
2. Hou M, *et al.* Mycophenolate mofetil (MMF) for the treatment of steroid-resistant idiopathic thrombocytopenic purpura. *Eur J Haematol* 2003; 70: 353–7.
3. Kotb R, *et al.* Efficacy of mycophenolate mofetil in adult refractory autoimmune cytopenias: a single center preliminary study. *Eur J Haematol* 2005; 75: 60–64.
4. Provan D, *et al.* Efficacy of mycophenolate mofetil as single-agent therapy for refractory immune thrombocytopenic purpura. *Am J Hematol* 2006; 81: 19–25.

Inflammatory bowel disease. Mycophenolate mofetil has been investigated as an alternative to azathioprine in Crohn's disease (see Inflammatory Bowel Disease, p. 1808.3). A randomised study in 70 patients compared therapy with corticosteroids plus mycophenolate mofetil or azathioprine in patients with moderate or severe Crohn's disease. The authors concluded that the mycophenolate regimen produced a clinical response earlier than the azathioprine regimen, and that mycophenolate should be considered in patients allergic or unresponsive to azathioprine or mercaptopurine.[1] However, it has been suggested[2] that the study may have been too short to draw definite conclusions, given the known delayed therapeutic effect of azathioprine. A beneficial effect for 5 out of 6 patients with severe Crohn's disease was reported[3] after 3 months of therapy with oral mycophenolate mofetil 1 g twice daily, but this effect was not sustained beyond 6 months.[4] Others have also noted relapse or lack of response to be relatively common;[5,6] while mycophenolate may have a role in those who cannot tolerate, or are refractory to, azathioprine,[7,8] the latter remains the immunosuppressant of choice due to its greater ability to prevent flare-ups.[2]

1. Neurath MF, *et al.* Randomised trial of mycophenolate mofetil versus azathioprine for treatment of chronic active Crohn's disease. *Gut* 1999; 44: 625–8.
2. Michsler W, *et al.* Is mycophenolate mofetil an effective alternative in azathioprine-intolerant patients with chronic active Crohn's disease? *Am J Gastroenterol* 2001; 96: 782–7.
3. Florin THJ, *et al.* Treatment of steroid refractory inflammatory bowel disease (IBD) with mycophenolate mofetil (MMF). *Aust N Z J Med* 1998; 28: 344–5.
4. Radford-Smith GL, *et al.* Mycophenolate mofetil in IBD patients. *Lancet* 1999; 354: 1386–7.
5. Ford AC, *et al.* Mycophenolate mofetil in refractory inflammatory bowel disease. *Aliment Pharmacol Ther* 2003; 17: 1365–9.
6. Wenzl HH, *et al.* Mycophenolate mofetil for Crohn's disease: short-term efficacy and long-term outcome. *Aliment Pharmacol Ther* 2004; 19: 427–34.
7. Palaniappan S, *et al.* Mycophenolate mofetil therapy for refractory inflammatory bowel disease. *Inflamm Bowel Dis* 2007; 13: 1488–92.
8. Tan T, Lawrance IC. Use of mycophenolate mofetil in inflammatory bowel disease. *World J Gastroenterol* 2009; 15: 1594–9.

Multiple sclerosis. In a small open-label study, 5 out of 7 patients with multiple sclerosis (p. 996.3) benefited from mycophenolate mofetil; 3 of these patients reported improved movement.[1] A retrospective review[2] of mycophenolate mofetil treatment (given either adjunctively or as monotherapy) in 79 patients, reported subjective improvements in 12 patients given adjunctive therapy. It has been tried as combination therapy with interferon beta-1a.[3]

1. Ahrens N, *et al.* Mycophenolate-mofetil in the treatment of refractory multiple sclerosis. *J Neurol* 2001; 248: 713–14.
2. Prohman EM, *et al.* Mycophenolate mofetil in multiple sclerosis. *Clin Neuropharmacol* 2004; 27: 80–83.
3. Vermersch P, *et al.* G-SEP (Groupe septentrional d'études et de prise en charge de la sclérose en plaques). Combination of IFN β-1a (Avonex) and mycophenolate mofetil (Cellcept) in multiple sclerosis. *Eur J Neurol* 2007; 14: 85–9.

Myasthenia gravis. Mycophenolate mofetil has been investigated in the treatment of myasthenia gravis (p. 684.1) but did not appear to be of benefit in controlled studies.[1,2]

1. Sanders DB, *et al.* An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. *Neurology* 2008; 71: 400–6.
2. Muscle Study Group. A trial of mycophenolate mofetil with prednisone as initial immunotherapy in myasthenia gravis. *Neurology* 2008; 71: 394–9.

Organ and tissue transplantation. Mycophenolate mofetil is used for the prophylaxis of graft rejection in kidney (p. 1935.2), heart (p. 1934.2), and liver transplantation (p. 1936.3), and has also been used after transplantation of the lung (p. 1937.3), pancreas (p. 1938.1), and intestines (p. 1935.1). It has been used as an alternative to, or replacement for, azathioprine, and may result in fewer rejections. However, in a small study of heart transplant recipients switched from standard immunosuppressive therapy with a calcineurin inhibitor, mycophenolate mofetil, and corticosteroids, to sirolimus with mycophenolate mofetil, there was an increased incidence of acute rejection; target sirolimus and mycophenolate concentrations may have been insufficient to maintain adequate immunosuppression. It has also been tried for the prophylaxis of graft-versus-host disease after bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p. 1933.1).

A few selected references to the use of mycophenolate mofetil in transplantation are given below.

1. European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet* 1995; 345: 1321–5.
2. Halloran P, *et al.* Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. *Transplantation* 1997; 63: 39–47. Correction. *ibid.*: 618.
3. Mathew TH. A blinded, long-term, randomized multicenter study of mycophenolate mofetil in cadaveric renal transplantation: results at three years. *Transplantation* 1998; 65: 1450–4. Correction. *ibid.*: 66: 817.
4. Oh JM, *et al.* Comparison of azathioprine and mycophenolate mofetil for the prevention of acute rejection in recipients of pancreas transplantation. *J Clin Pharmacol* 2001; 41: 861–9.
5. Salvadori M, *et al.* Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in de novo renal transplant patients. *Am J Transplant* 2003; 4: 231–6.
6. Sollinger HW. Mycophenolates in transplantation. *Clin Transplant* 2004; 18: 485–92.
7. Remuzzi G, *et al.* Mycophenolate mofetil versus azathioprine for prevention of acute rejection in renal transplantation (MYSS): a randomised trial. *Lancet* 2004; 364: 503–12.
8. Budde K, *et al.* Safety and efficacy after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium: results of a 1-year extension study. *Transplant Proc* 2005; 37: 912–15.
9. Curran MP, Keating GM. Mycophenolate sodium delayed release: prevention of renal transplant rejection. *Drugs* 2005; 65: 799–805.
10. Manzia TM, *et al.* Use of mycophenolate mofetil in liver transplantation: a literature review. *Transplant Proc* 2005; 37: 2616–17.
11. Ciancio G, *et al.* Review of major clinical trials with mycophenolate mofetil in renal transplantation. *Transplantation* 2005; 80 (suppl 2): S191–S200.
12. Srinivas TR, *et al.* The impact of mycophenolate mofetil on long-term outcomes in kidney transplantation. *Transplantation* 2005; 80 (suppl 2): S211–S220.
13. Kobashigawa JA, Meiser BM. Review of major clinical trials with mycophenolate mofetil in cardiac transplantation. *Transplantation* 2005; 80 (suppl 2): S235–S243.
14. Kaplan B. Enteric-coated mycophenolate sodium (Myfortic): an overview of current and future use in transplantation. *Drugs* 2006; 66 (suppl 2): 1–8.
15. Kobashigawa JA, *et al.* Similar efficacy and safety of enteric-coated mycophenolate sodium (EC-MPS, Myfortic) compared with mycophenolate mofetil (MMF) in de novo heart transplant recipients: results of a 12-month, single-blind, randomized, parallel-group, multicenter study. *J Heart Lung Transplant* 2006; 25: 935–41.
16. Zimmerhackl LB, *et al.* Mycophenolate mofetil (Cellcept) in pediatric renal transplantation. *Transplant Proc* 2006; 38: 2038–40.
17. Schmeding M, *et al.* Mycophenolate mofetil in liver transplantation—monotherapy safe? *Clin Transplant* 2006; 20 (suppl 17): 75–9.
18. Sanford M, Keating GM. Enteric-coated mycophenolate sodium: review of its use in the prevention of renal transplant rejection. *Drugs* 2008; 68: 2505–33.

Pemphigus and pemphigoid. Mycophenolate mofetil has been used successfully in the treatment of pemphigus and pemphigoid (p. 1687.1), both with prednisolone[1-3] and alone.[4] In randomised, non-blinded studies, adjuvant mycophenolate mofetil was found to be as effective as adjuvant azathioprine in pemphigus (vulgaris and foliaceus)[5] and pemphigoid;[6] corticosteroid-sparing effects were similar and there was a trend towards fewer adverse effects with mycophenolate.

1. Enk AH, Knop J. Mycophenolate is effective in the treatment of pemphigus vulgaris. *Arch Dermatol* 1999; 135: 54–6.
2. Williams JV, *et al.* Use of mycophenolate mofetil in the treatment of paraneoplastic pemphigus. *Br J Dermatol* 2000; 142: 506–8.
3. Powell AM, *et al.* An evaluation of the usefulness of mycophenolate mofetil in pemphigus. *Br J Dermatol* 2003; 149: 138–45.
4. Bredlich R-O, *et al.* Mycophenolate mofetil monotherapy for pemphigus vulgaris. *Br J Dermatol* 1999; 141: 934.
5. Beissert S, *et al.* A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of pemphigus. *Arch Dermatol* 2006; 142: 1447–54.
6. Beissert S, *et al.* A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of bullous pemphigoid. *Arch Dermatol* 2007; 143: 1536–42.

Polymyositis and dermatomyositis. Mycophenolate mofetil has been reported to be of benefit in refractory cases of polymyositis and dermatomyositis (p. 1611.1), allowing for tapering of corticosteroid doses.[1-3] Despite benefit in 6 out of 10 patients in another study,[4] 3 patients developed opportunistic infection, which was fatal in 1 case. While acknowledging that other factors may have had a role in this, the authors advised caution in the use of mycophenolate in dermatomyositis.

1. Gelber AC, *et al.* Mycophenolate mofetil in the treatment of severe skin manifestations of dermatomyositis: a series of 4 cases. *J Rheumatol* 2000; 27: 1542–5.
2. Majithia V, Harisdangkul V. Mycophenolate mofetil (CellCept): an alternative therapy for autoimmune inflammatory myopathy. *Rheumatology (Oxford)* 2005; 44: 386–9.
3. Edge JC, *et al.* Mycophenolate mofetil as an effective corticosteroid-sparing therapy for recalcitrant dermatomyositis. *Arch Dermatol* 2006; 142: 65–9.
4. Rowin J, *et al.* Mycophenolate mofetil in dermatomyositis: is it safe? *Neurology* 2006; 66: 1245–7.

Primary biliary cirrhosis. Despite initial reports[1] of benefit with mycophenolate mofetil in the treatment of primary biliary cirrhosis (p. 2638.3), a small study found no clinical benefit when it was given to patients with incomplete responses to ursodeoxycholic acid.[2]

1. Jones EA. Rationale for trials of long-term mycophenolate mofetil therapy for primary biliary cirrhosis. *Hepatology* 2002; 35: 258–62.

2. Talwalkar JA, *et al.* Mycophenolate mofetil for the treatment of primary biliary cirrhosis in patients with an incomplete response to ursodeoxycholic acid. *J Clin Gastroenterol* 2005; 39: 168–71.

Psoriasis. Mycophenolate mofetil has proved successful in some cases of psoriasis (p. 1688.1) refractory to conventional therapies,[1-3] although a comparative study found it to be less effective than ciclosporin.[4] Topical application (as a 2% cream) has been investigated.[5]

1. Grundmann-Kollmann M, *et al.* Treatment of chronic plaque-stage psoriasis and psoriatic arthritis with mycophenolate mofetil. *J Am Acad Dermatol* 2000; 42: 835–7.
2. Gellen CC, *et al.* Mycophenolate mofetil as a systemic antipsoriatic agent: positive experience in 11 patients. *Br J Dermatol* 2001; 144: 583–6.
3. Zhou Y, *et al.* Mycophenolate mofetil (CellCept) for psoriasis: a two-center, prospective, open-label clinical trial. *J Cutan Med Surg* 2003; 7: 193–7.
4. Beissert S, *et al.* A comparison of mycophenolate mofetil with ciclosporine for the treatment of chronic plaque-type psoriasis. *Dermatology* 2009; 219: 126–32.
5. Wohlrab J, *et al.* Topical application of mycophenolate mofetil in plaque-type psoriasis. *Br J Dermatol* 2001; 144: 1263–4.

Retroperitoneal fibrosis. There are several reports[1-5] of success with mycophenolate mofetil and corticosteroids in the treatment of retroperitoneal fibrosis (p. 1612.1).

1. Jois RN, *et al.* Mycophenolate mofetil for maintenance of remission in idiopathic retroperitoneal fibrosis. *Rheumatology (Oxford)* 2007; 46: 717–18.
2. Adler S, *et al.* Successful mycophenolate mofetil therapy in nine patients with idiopathic retroperitoneal fibrosis. *Rheumatology (Oxford)* 2008; 47: 1535–8.
3. Swartz RD, *et al.* Idiopathic retroperitoneal fibrosis: a role for mycophenolate mofetil. *Clin Nephrol* 2008; 69: 260–8.
4. Witschi M, *et al.* Treatment of mediastinal fibrosis with mycophenolate mofetil. *Respiration* 2009; 78: 330–3.
5. Scheel PJ, *et al.* Combined prednisone and mycophenolate mofetil treatment for retroperitoneal fibrosis: a case series. *Ann Intern Med* 2011; 154: 31–6.

Rheumatoid arthritis. Mycophenolate mofetil has been tried in rheumatoid arthritis (p. 13.2); reports suggest it may effectively suppress synovial inflammation.[1]

1. McMurray RW, Harisdangkul V. Mycophenolate mofetil: selective T cell inhibition. *Am J Med Sci* 2002; 323: 194–6.

Sarcoidosis. Mycophenolate mofetil has been used as an adjunct in the successful treatment of patients with mucocutaneous sarcoidosis (p. 1612.2)[1] and neurosarcoidosis.[2,3] It was reported to have a significant corticosteroid-sparing effect in an adolescent with renal involvement,[4] and was effective in a case of severe, relapsing, corticosteroid-dependent gastrointestinal sarcoidosis.[5] It has also been used in sarcoidosis-associated uveitis.[6]

1. Kouba DJ, *et al.* Mycophenolate mofetil may serve as a steroid-sparing agent for sarcoidosis. *Br J Dermatol* 2003; 148: 147–8.
2. Chaussenot A, *et al.* Neurosarcoïdose et mycophénolate mofétil. *Rev Neurol (Paris)* 2007; 163: 471–5.
3. Moravan M, Segal BM. Treatment of CNS sarcoidosis with infliximab and mycophenolate mofetil. *Neurology* 2009; 72: 337–40.
4. Moudgil A, *et al.* Successful steroid-sparing treatment of renal limited sarcoidosis with mycophenolate mofetil. *Pediatr Nephrol* 2006; 21: 281–5.
5. O'Connor AS, *et al.* Pancreatitis and duodenitis from sarcoidosis: successful therapy with mycophenolate mofetil. *Dig Dis Sci* 2003; 48: 2191–5.
6. Bhat P, *et al.* Mycophenolate mofetil therapy for sarcoidosis-associated uveitis. *Ocul Immunol Inflamm* 2009; 17: 185–90.

Scleroderma. There are reports of response to mycophenolate in patients with scleroderma (p. 1938.3).

References.

1. Nihtyanova SI, *et al.* Mycophenolate mofetil in diffuse cutaneous systemic sclerosis—a retrospective analysis. *Rheumatology (Oxford)* 2007; 46: 442–5.
2. Vanthuyne M, *et al.* A pilot study of mycophenolate mofetil combined to intravenous methylprednisolone pulses and oral low-dose glucocorticoids in severe early systemic sclerosis. *Clin Exp Rheumatol* 2007; 25: 287–92.
3. Shenin M, *et al.* The use of mycophenolate mofetil for the treatment of systemic sclerosis. *Endocr Metab Immune Disord Drug Targets* 2008; 8: 11–14.

Systemic lupus erythematosus. Oral mycophenolate mofetil plus prednisolone, given for 12 months, was found to be as effective as oral cyclophosphamide plus prednisolone, for 6 months, followed by azathioprine plus prednisolone for 6 months,[1] in the treatment of Chinese patients with diffuse proliferative *lupus nephritis* (see Systemic Lupus Erythematosus, p. 1613.3). However, some[2,3] have cautioned about generalising these findings to other patients since mycophenolate was compared with oral and not intravenous pulsed cyclophosphamide, which is considered the standard of care in those with diffuse proliferative disease. Patients with poorer prognoses were also considered to have been excluded or underrepresented in the study, and follow-up was short. However, in a 24-week unblinded study[4] oral mycophenolate mofetil was more effective in inducing complete remission than intermittent intravenous cyclophosphamide when used as induction therapy for active lupus nephritis and appeared to be better tolerated. Also, there have been reports of benefit with mycophenolate mofetil in patients with various forms of refractory lupus nephritis, including proliferative disease and membranous nephropathy,[5-7] and some consider it a good therapeutic alternative.[8,9] A review[10] concluded that limited data support induction with cyclophosphamide followed by maintenance with azathioprine or mycophenolate; in selected patients induction with mycophenolate is a reasonable alternative. Meta-analyses concluded that daily oral mycophenolate mofetil, in average or median doses of 1 to 2 g, was more effective than pulsed intravenous or oral cyclophosphamide,[11] and that mycophenolate reduced the risk of failure to induce remission during induction therapy when compared with cyclophosphamide.[12] However, the role of racial and ethnic differences in lupus remain poorly understood, and enrolment of varying ethnic populations in studies can significantly affect results of therapy.[13] Furthermore, it has been pointed out that subjects in studies included in one meta-analysis had relatively preserved renal function, and results cannot be generalised to patients with moderate to severe renal impairment and rapidly progressive glomerulonephritis.[14] While acknowledging data of mycophenolate use in children are limited, another review[15] concluded that from data in adults, mycophenolate is an acceptable alternative to intravenous cyclophosphamide in the induction phase for newly diagnosed patients with mild to moderate nephritis and intact renal function; it may also be suitable if there is concern about a patient's future fertility. However, the optimal dose and length of induction treatment with mycophenolate are still unknown.

Mycophenolate mofetil has been used to control extrarenal manifestations of SLE,[16,17] although it was ineffective in a small number of patients with severe refractory cutaneous disease.[18] Oral mycophenolate sodium 1.44 g daily has been reported to be effective in the treatment of patients with subacute cutaneous lupus erythematosus resistant to standard therapy.[19]

1. Chan TM, *et al.* Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med* 2000; 343: 1156–62.
2. Falk RJ. Treatment of lupus nephritis—a work in progress. *N Engl J Med* 2000; 343: 1182–3.
3. Karassa FB, Isenberg DA. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med* 2001; 344: 382–3. Correction, *ibid.*: 1176.
4. Ginzler EM, *et al.* Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005; 353: 2219–28.
5. Kingdon EJ, *et al.* The safety and efficacy of MMF in lupus nephritis: a pilot study. *Lupus* 2001; 10: 606–11.
6. Kapitsinou PP, *et al.* Lupus nephritis: treatment with mycophenolate mofetil. *Rheumatology (Oxford)* 2004; 43: 377–80.
7. Speeti DN, *et al.* Mycophenolate therapy of SLE membranous nephropathy. *Kidney Int* 2004; 66: 2411–15.
8. Ginzler EM, Aranow C. Mycophenolate mofetil in lupus nephritis. *Lupus* 2005; 14: 59–64.
9. Pisoni CN, *et al.* Mycophenolate mofetil in systemic lupus erythematosus: efficacy and tolerability in 86 patients. *J Rheumatol* 2005; 32: 1047–52.
10. Lenz O, *et al.* Defining the role of mycophenolate mofetil in the treatment of proliferative lupus nephritis. *Drugs* 2005; 65: 2429–36.
11. Moore RA, Derry S. Systematic review and meta-analysis of randomised trials and cohort studies of mycophenolate mofetil in lupus nephritis. *Arthritis Res Ther* 2006; 8: R182.
12. Walsh M, *et al.* Mycophenolate mofetil for induction therapy of lupus nephritis: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2007; 2: 968–75.
13. Dooley MA. Mycophenylate [sic] mofetil: what role in the treatment of lupus? *Lupus* 2006; 15: 179–82.
14. Contreras G, Sosnov J. Role of mycophenolate mofetil in the treatment of lupus nephritis. *Clin J Am Soc Nephrol* 2007; 2: 879–82.
15. Paredes A. Can mycophenolate mofetil substitute cyclophosphamide treatment of pediatric lupus nephritis? *Pediatr Nephrol* 2007; 22: 1077–82.
16. Karim MY, *et al.* Mycophenolate mofetil for systemic lupus erythematosus refractory to other immunosuppressive agents. *Rheumatology (Oxford)* 2002; 41: 876–82.
17. Pisoni CN, *et al.* Mycophenolate mofetil and systemic lupus erythematosus: an overview. *Lupus* 2005; 14 (suppl): s9–s11.
18. Pisoni CN, *et al.* Skin manifestations of systemic lupus erythematosus refractory to multiple treatment modalities: poor results with mycophenolate mofetil. *Clin Exp Rheumatol* 2005; 23: 393–6.
19. Kreuter A, *et al.* Mycophenolate sodium for subacute cutaneous lupus erythematosus resistant to standard therapy. *Br J Dermatol* 2007; 156: 1321–7.

Vasculitic syndromes. Mycophenolate mofetil has been tried in various vasculitic syndromes, including Churg-Strauss syndrome (p. 1603.1), polyarteritis nodosa and microscopic polyangiitis (p. 1610.2), Takayasu's arteritis (p. 1614.3), and Wegener's granulomatosis (p. 1615.2).

Adverse Effects, Treatment, and Precautions

Mycophenolate is associated with gastrointestinal disturbances, particularly diarrhoea and vomiting; gastrointestinal ulceration, haemorrhage, and perforation have occurred. Immunosuppression, including mycophenolate treatment, is associated with an increased incidence of lymphoma and other malignancies, particularly those of the skin, and excess exposure to UV light should be avoided during treatment. There is also an increased risk of infection, including activation of latent viral infections. These include JC virus-associated progressive multifocal leukoencephalopathy (fatalities have been reported), and BK virus-associated nephropathy which can lead to renal graft loss. Leucopenia, thrombocytopenia, and anaemia are common and there have been reports of aplastic anaemia and bone-marrow depression, sometimes fatal. Pure red cell aplasia has also occurred. Regular full blood counts are recommended during therapy, and treatment may need to be stopped if severe neutropenia develops. Isolated cases of abnormal neutrophil morphology without impaired function, including acquired Pelger-Huët anomaly, have been reported. Other reported adverse effects include asthenia, fever, pain, headache, renal impairment, hypertension or hypotension, hyperglycaemia, disturbances of electrolytes and blood lipids, peripheral oedema, pleural effusion, dyspnoea, cough, acne, rash, alopecia, dizziness, insomnia or somnolence, paraesthesia, and tremor. Agitation, depression, anxiety, tachycardia, and arthralgia are also common. Abnormal hepatic function tests have also been reported. Hypersensitivity reactions, including angioedema and anaphylaxis, have occurred. Pancreatitis, hepatitis, colitis, and gingival hyperplasia have been reported. There are rare reports of interstitial lung disorders, including fatal pulmonary fibrosis. Mycophenolate is teratogenic in *animals*; malformations, especially of the external ear, and other facial abnormalities, have been reported in infants after maternal exposure to mycophenolate (see p. 1964.1).

Mycophenolate should be given with care to patients with severe renal impairment or active disorders of the gastrointestinal tract. Intra-uterine devices should be used with caution in those given immunosuppressive treatment as there is an increased risk of infection. Live vaccines should be avoided in these patients for the same reason.

Mycophenolate mofetil and mycophenolate sodium should not be indiscriminately interchanged or substituted because of their differing pharmacokinetic profiles.

Effects on the blood. Mycophenolate mofetil has been associated with pure red cell aplasia; as of April 2009, 41 cases had been reported worldwide.[1] Some patients were also taking other medicines that could have contributed to the development of pure red cell aplasia. The condition resolved in 16 patients when the dose of mycophenolate mofetil was reduced or withdrawn.

1. MHRA/CHM. Mycophenolate mofetil: pure red cell aplasia. *Drug Safety Update* 2009; 2 (12): 8. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON051771&RevisionSelectionMethod=LatestReleased (accessed 14/10/09)

Effects on the gastrointestinal tract. The adverse effects of mycophenolate mofetil on the gastrointestinal tract appeared to be mostly of an irritative nature and included diarrhoea, abdominal pain, nausea and vomiting, anorexia, dyspepsia, and occasionally gastrointestinal haemorrhage or perforation.[1] Paediatric patients tended to have a higher incidence of adverse gastrointestinal events than adults. There was some evidence that adverse effects were related to peak plasma concentrations of the drug.

A review comparing the adverse effect profile of enteric-coated mycophenolate sodium with that of mycophenolate mofetil found a similar incidence of gastrointestinal adverse effects with the two formulations. It was noted that the pathophysiology of the gastrointestinal disturbances seen with mycophenolate is complex and not fully understood. An increased incidence of diarrhoea has been seen with higher mycophenolic acid (MPA) concentrations, possibly due to a direct effect of MPA on intestinal enterocytes, caused by its inhibitory effect on inosine monophosphate dehydrogenase. While exposure to MPA may be higher with the enteric-coated formulation, studies have not shown an appreciable increase in gastrointestinal adverse effects with mycophenolate sodium; the enteric coating might have diminished the direct effect of MPA on enterocytes in the upper gastrointestinal tract.[2] Two studies found that gastrointestinal adverse effects decreased after patients were switched from mycophenolate mofetil to enteric-coated mycophenolate sodium.[3,4]

1. Behrend M. Adverse gastrointestinal effects of mycophenolate mofetil: aetiology, incidence and management. *Drug Safety* 2001; 24: 645–63.
2. Behrend M. Braun F. Enteric-coated mycophenolate sodium: tolerability profile compared with mycophenolate mofetil. *Drugs* 2005; 65: 1037–50.
3. Calvo N, *et al.* Renal transplant patients with gastrointestinal intolerability to mycophenolate mofetil: conversion to enteric-coated mycophenolate sodium. *Transplant Proc* 2006; 38: 2396–7.
4. Boswell A, *et al.* Conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in patients with gastrointestinal side effects: case studies. *Prog Transplant* 2006; 16: 138–40.

Handling. The UK licensed product information for film-coated gastro-resistant tablets of mycophenolate sodium (*Myfortic, Novartis*) warns that if it is necessary to crush the tablets, inhalation of the powder or direct contact of the powder with the skin or mucous membranes should be avoided.

Infection. The use of mycophenolate mofetil was not found to increase the risk of CMV infection in 2 small studies.[1,2] However, it did appear to be associated with an increased frequency[1] and severity[2] of CMV disease (defined as CMV infection plus evidence of viral syndrome). The number of organs affected in patients with CMV disease was also higher in those treated with mycophenolate mofetil.[2]

A retrospective study[3] found that the use of a protocol containing mycophenolate mofetil and tacrolimus was an independent risk factor for the development of CMV disease, but that the dose of mycophenolate mofetil was not. The authors interpreted this to mean that either the combination of mycophenolate mofetil and tacrolimus had an overall stronger immunosuppressive effect than other regimens, or that this protocol bore a specific risk for the development of CMV disease. The pharmacokinetics of mycophenolic acid (MPA), a metabolite of mycophenolate mofetil, and its interaction with tacrolimus, must be considered, with further studies taking MPA levels into account (see Immunosuppressants, under Interactions, below).

In contrast to these findings, another retrospective study[4] found that, although no patient developed CMV disease, the use of mycophenolate mofetil was an independent risk factor for the development of CMV infection in those patients initially seropositive for the CMV antigen.

In a study comparing the adverse effects of mycophenolate mofetil and enteric-coated mycophenolate sodium in renal transplant patients, the overall incidence of infections was similar. However, patients receiving mycophenolate sodium had significantly fewer serious infections. The incidence of CMV infection was very low and similar in both groups.[5]

In February 2008 the manufacturer in agreement with the EMEA warned[6] that isolated cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, had been reported in patients receiving mycophenolate mofetil (*CellCept, Roche*) for transplant rejection or SLE; a diagnosis of PML should be considered in patients who develop neurological symptoms while receiving mycophenolate mofetil. It was also recommended that consideration should be given to reducing the total immunosuppression in patients who develop PML but with a reminder that such a reduction may place the graft at risk in transplant patients.

Regimens containing mycophenolate, particularly with tacrolimus, have been associated with an increased risk of BK-virus nephropathy,[7] although the association may be with intensive immunosuppression rather than mycophenolate itself.[8,9]

1. ter Meulen CG, *et al.* The influence of mycophenolate mofetil on the incidence and severity of primary cytomegalovirus infections and disease after renal transplantation. *Nephrol Dial Transplant* 2000; 15: 711–14.
2. Sarmiento JM, *et al.* Mycophenolate mofetil increases cytomegalovirus invasive organ disease in renal transplant patients. *Clin Transplant* 2000; 14: 136–8.
3. Kuypers DRJ, *et al.* Role of immunosuppressive drugs in the development of tissue-invasive cytomegalovirus infection in renal transplant recipients. *Transplant Proc* 2002; 34: 1164–70.
4. Hambach L, *et al.* Increased risk of complicated CMV infection with the use of mycophenolate mofetil in allogeneic stem cell transplantation. *Bone Marrow Transplant* 2002; 29: 903–6.
5. Budde K, *et al.* Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: results of a 1-year study. *Am J Transplant* 2003; 4: 237–43.
6. Roche, UK. Reports of progressive multifocal leukoencephalopathy (PML) in CellCept (mycophenolate mofetil) treated patients (issued 18th February 2008). Available at: http://www.mhra.gov.uk/home/idcplg?idcService=GET_FILE&dDocName=CON0141066&RevisionSelectionMethod=Latest (accessed 19/05/08)
7. Ritter ML, Pirofski L. Mycophenolate mofetil: effects on cellular immune subsets, infectious complications, and antimicrobial activity. *Transpl Infect Dis* 2009; 11: 290–7.
8. Hirsch HH, *et al.* Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. *Transplantation* 2005; 79: 1277–86.
9. Manitpisitkul W, *et al.* Maintenance immunosuppressive agents as risk factors for BK virus nephropathy: a case-control study. *Transplantation* 2009; 88: 83–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mycophenolate 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 05/10/11)

Pregnancy. There have been reports of spontaneous abortions and structural malformations in infants born to women taking mycophenolate.[1-3] The manufacturers of mycophenolate mofetil (*Roche, USA*) have warned that use of the drug during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, oesophagus, and kidney.[1] Women of child-bearing potential should have a negative pregnancy test within 1 week of starting mycophenolate therapy. Women taking mycophenolate should use effective contraception, from at least 4 weeks before starting therapy, and until 6 weeks after stopping mycophenolate.

1. Roche, USA. Important changes in the CellCept (mycophenolate mofetil) prescribing information—use of CellCept is associated with increased pregnancy loss and congenital malformations/change from pregnancy category C to pregnancy category D (issued October 2007). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM154077.pdf (accessed 05/08/10)
2. Anderka MT, *et al.* Reviewing the evidence for mycophenolate mofetil as a new teratogen: case report and review of the literature. *Am J Med Genet A* 2009; 149A: 1241–8.
3. Merlob P, *et al.* Tetrads of the possible mycophenolate mofetil embryopathy: a review. *Reprod Toxicol* 2009; 28: 105–8.

Interactions

Mycophenolate may compete with other drugs that undergo active renal tubular secretion, resulting in increased concentrations of either drug. Antacids, polycarbophil calcium, sevelamer, or colestyramine may reduce absorption of mycophenolate. Rifampicin decreases exposure to mycophenolate (in patients not also taking ciclosporin); mycophenolic acid (MPA) concentrations should be monitored when rifampicin and mycophenolate are used together. See p. 1963.2 for precautions about use with live vaccines.

Antacids. Although giving mycophenolate mofetil with an antacid mixture (aluminium and magnesium hydroxides) or food both resulted in reductions in peak plasma concentrations of mycophenolic acid (MPA), the differences were small compared with interindividual variation, and were considered unlikely to be clinically significant.[1]

UK licensed product information for mycophenolate sodium states that, although magnesium- or aluminium-containing antacids decrease MPA exposure and peak plasma concentrations, they may be used intermittently for the treatment of occasional dyspepsia; chronic use of antacids is not recommended.

1. Bullingham R, *et al.* Effects of food and antacid on the pharmacokinetics of single doses of mycophenolate mofetil in rheumatoid arthritis patients. *Br J Clin Pharmacol* 1996; 41: 513–16.

Antibacterials. A selective bowel decontamination regimen of *tobramycin, cefuroxime,* and the antifungal *nystatin,* apparently inhibited the enterohepatic recycling of mycophenolic acid (MPA), thereby reducing the bioavailability of mycophenolate in liver transplant recipients.[1] *Norfloxacin, metronidazole,* or a combination of the two, reduced exposure to MPA and mycophenolic acid glucuronide (see Metabolism, p. 1965.2) when given to healthy subjects receiving mycophenolate mofetil. The effect of the antibacterials appeared to be additive.[2] Rapid reductions in MPA concentrations were seen after renal transplant patients stabilised on mycophenolate were given either *ciprofloxacin* or *amoxicillin with clavulanic acid;* MPA concentrations recovered to baseline within 3 days of stopping antibacterial therapy, and the effect was seen to wane with continued dosage of antibacterials for 14 days.[3] *Rifampicin* markedly reduced exposure to MPA in a heart-lung transplant recipient, possibly through induction of mycophenolate glucuronidation.[4] A study in renal transplant recipients given rifampicin confirmed this reduction in MPA exposure, concluding that the mechanism was induction of glucuronidation and inhibition of enterohepatic circulation.[5]

1. Schmidt LE, *et al.* The effect of selective bowel decontamination on the pharmacokinetics of mycophenolate mofetil in liver transplant recipients. *Liver Transpl* 2001; 7: 739–42.
2. Naderer OJ, *et al.* The influence of norfloxacin and metronidazole on the disposition of mycophenolate mofetil. *J Clin Pharmacol* 2005; 45: 219–26.
3. Borrows R, *et al.* The magnitude and time course of changes in mycophenolic acid 12-hour predose levels during antibiotic therapy in mycophenolate mofetil-based renal transplantation. *Ther Drug Monit* 2007; 29: 122–6.
4. Kuypers DRJ, *et al.* Drug interaction between mycophenolate mofetil and rifampin: possible induction of uridine diphosphate-glucuronosyltransferase. *Clin Pharmacol Ther* 2005; 78: 81–8.
5. Naesens M, *et al.* Rifampin induces alterations in mycophenolic acid glucuronidation and elimination: implications for drug exposure in renal allograft recipients. *Clin Pharmacol Ther* 2006; 80: 509–21.

Immunosuppressants. Stopping *ciclosporin* therapy in renal transplant recipients was found to increase serum concentrations of mycophenolic acid (MPA),[1,2] leading to the hypothesis that ciclosporin inhibits the enterohepatic circulation of MPA. In contrast,[3,4] *tacrolimus* therapy increased serum concentrations of MPA, apparently by inhibiting conversion to mycophenolic acid glucuronide (MPAG). While the studies have been criticised,[5] it has been pointed out that an interaction cannot be excluded.[6] An increased incidence of CMV disease has been reported in renal transplant recipients given a triple therapy regimen containing tacrolimus and mycophenolate mofetil.[7] Based on a study[8] in children it has been recommended that mycophenolate mofetil be given in initial doses of 600 mg/m^2 twice daily with ciclosporin but 300 mg/m^2 twice daily with tacrolimus; 500 mg/m^2 twice daily was suggested if no calcineurin inhibitor was given. It is also recommended that dose adjustments are made using therapeutic drug monitoring. However, changes to MPA concentrations may be dose-dependent; a pharmacokinetic study[9] suggested that the ciclosporin dosing schedule used (standard-dose, low-dose, or initial low-dose treatment withdrawn after 6 months) influenced exposure, with MPA exposure tending to increase as ciclosporin exposure decreased. Changes in MPA exposure with tacrolimus have been shown to vary with the dose of mycophenolate mofetil used, an effect that was not adequately reflected by MPA trough concentrations (see Therapeutic Drug Monitoring, p. 1965.2).[10] Another study found marked interindividual variability in MPA and MPAG pharmacokinetics when patients were given ciclosporin microemulsion or tacrolimus in the early stages after renal transplantation. This variability was greater in those given ciclosporin than in those given tacrolimus, and mean total MPA concentrations were about half that of patients in the tacrolimus group.[11] A randomised crossover study compared the effect of ciclosporin microemulsion or tacrolimus on the pharmacokinetics of MPA when each of these were given with enteric-coated mycophenolate sodium to stable renal transplant recipients.[12] In comparison with use with ciclosporin, giving mycophenolate sodium with tacrolimus resulted in a moderate increase in the total exposure of MPA and decreased maximum concentrations and total exposure to the metabolites MPAG and the acyl glucuronide. The results were not statistically significant, and the authors suggested that on this basis, doses of mycophenolate sodium need not be adjusted when converting stable renal transplant patients from one calcineurin inhibitor to the other. However, they recommended that mycophenolate sodium dose adjustments should be based on both the pharmacokinetic data and the clinical situation.

UK licensed product information has stated that ciclosporin reduces MPA exposure, and may decrease MPA concentrations when these two drugs are given together. The exact extent of the decrease is not known for mycophenolate sodium, but may be about 20%, extrapolated from data for mycophenolate mofetil. However, since efficacy studies used this combination, no dose adjustment of mycophenolate is considered necessary. If concomitant ciclosporin therapy is interrupted or stopped, an increase in MPA of about 30% is to be expected, and dosage should be re-evaluated depending on the immunosuppressive regimen. While not commenting on dose adjustment when used with tacrolimus, UK licensed product information for mycophenolate sodium stated that stable renal transplant patients showed increased MPA exposure and decreased MPAG when tacrolimus was substituted for ciclosporin.

Pharmacokinetic analyses found that use of *sirolimus* with mycophenolate led to greater MPA exposure,[13,14] but lower MPAG exposure,[15] when compared with ciclosporin plus mycophenolate. Therapeutic drug monitoring of MPA is recommended in transplant recipients given both mycophenolate and sirolimus;[13,14] guidelines are needed when switching patients from ciclosporin to sirolimus, since the same dose of mycophenolate mofetil would lead on average to a 50% increase in MPA exposure in patients receiving sirolimus compared with ciclosporin.[14]

1. Smak Gregoor PJH, *et al.* Effect of cyclosporine on mycophenolic acid trough levels in kidney transplant recipients. *Transplantation* 1999; 68: 1603–6.
2. Shipkova M, *et al.* Effect of cyclosporine withdrawal on mycophenolic acid pharmacokinetics in kidney transplant recipients with deteriorating renal function: preliminary report. *Ther Drug Monit* 2001; 23: 717–21.
3. Zucker K, *et al.* Unexpected augmentation of mycophenolic acid pharmacokinetics in renal transplant patients receiving tacrolimus and mycophenolate mofetil in combination therapy, and analogous in vitro findings. *Transpl Immunol* 1997; 5: 225–32.
4. Hübner GI, *et al.* Drug interaction between mycophenolate mofetil and tacrolimus detectable within therapeutic mycophenolic acid monitoring in renal transplant patients. *Ther Drug Monit* 1999; 21: 536–9.
5. van Gelder T, *et al.* Drug interaction between mycophenolate mofetil and tacrolimus detectable within therapeutic mycophenolic acid monitoring in renal transplant patients. *Ther Drug Monit* 2000; 22: 639.
6. Hübner GI, Sziegoleit W. Drug interaction between mycophenolate mofetil and tacrolimus detectable within therapeutic mycophenolic acid monitoring in renal transplant patients. *Ther Drug Monit* 2000; 22: 498–9.
7. Kuypers DRJ, *et al.* Role of immunosuppressive drugs in the development of tissue-invasive cytomegalovirus infection in renal transplant recipients. *Transplant Proc* 2002; 34: 1164–70.
8. Filler G, *et al.* Pharmacokinetics of mycophenolate mofetil are influenced by concomitant immunosuppression. *Pediatr Nephrol* 2000; 14: 100–104.
9. Kuypers DR, *et al.* Mycophenolic acid exposure after administration of mycophenolate mofetil in the presence and absence of ciclosporin in renal transplant recipients. *Clin Pharmacokinet* 2009; 48: 329–41.
10. Kuypers DRJ, *et al.* Long-term changes in mycophenolic acid exposure in combination with tacrolimus and corticosteroids are dose dependent and not reflected by trough plasma concentration: a prospective study in 100 de novo renal allograft recipients. *J Clin Pharmacol* 2003; 43: 866–80.
11. Atcheson BA, *et al.* Mycophenolic acid pharmacokinetics and related outcomes early after renal transplant. *Br J Clin Pharmacol* 2005; 59: 271–80.
12. Kaplan B, *et al.* Randomized calcineurin inhibitor cross over study to measure the pharmacokinetics of co-administered enteric-coated mycophenolate sodium. *Clin Transplant* 2005; 19: 551–8.
13. Büchler M, *et al.* Higher exposure to mycophenolic acid with sirolimus than with cyclosporine coreatment. *Clin Pharmacol Ther* 2005; 78: 34–42.
14. Picard N, *et al.* A comparison of the effect of ciclosporin and sirolimus on the pharmokinetics [sic] of mycophenolate in renal transplant patients. *Br J Clin Pharmacol* 2006; 62: 477–84.
15. Pescovitz MD, *et al.* Pharmacokinetics, safety, and efficacy of mycophenolate mofetil in combination with sirolimus or ciclosporin in renal transplant patients. *Br J Clin Pharmacol* 2007; 64: 758–71.

Iron. Absorption of mycophenolate mofetil after oral doses was markedly reduced by iron preparations in a study in 7 healthy subjects:[1] mean peak serum concentrations of mycophenolic acid were reduced from 20.1 to 1.3 micrograms/mL. However, in contrast, a study in 16 healthy subjects found no interaction between iron supplements and mycophenolate mofetil,[2] and 2 studies in renal transplant patients found no significant effect of oral iron supplements on the absorption of mycophenolate mofetil.[3,4]

1. Morii M, *et al.* Impairment of mycophenolate mofetil absorption by iron ion. *Clin Pharmacol Ther* 2000; 68: 613–6.
2. Ducray PS, *et al.* Absence of an interaction between iron and mycophenolate mofetil absorption. *Br J Clin Pharmacol* 2005; 62: 492–5.
3. Mudge DW, *et al.* The effect of oral iron admilnistration [sic] on mycophenolate mofetil absorption in renal transplant recipients: a randomized, controlled trial. *Transplantation* 2004; 77: 206–9.
4. Lorenz M, *et al.* Ferrous sulfate does not affect mycophenolic acid pharmacokinetics in kidney transplant patients. *Am J Kidney Dis* 2004; 43: 1098–1103.

Proton pump inhibitors. Proton pump inhibitors increase gastric pH and may affect the bioavailability of mycophenolate salts. A prospective case-control study[1] found that *pantoprazole* reduced exposure to mycophenolate mofetil in heart transplant recipients. *Omeprazole*[2] and pantoprazole[3] have been reported to reduce the absorption of mycophenolate mofetil but not enteric-coated mycophenolate sodium in healthy subjects.

1. Kofler S, *et al.* Proton pump inhibitors reduce mycophenolate exposure in heart transplant recipients-a prospective case-controlled study. *Am J Transplant* 2009; 9: 1650–6.
2. Kees MG, *et al.* Omeprazole impairs the absorption of mycophenolate mofetil but not of enteric-coated mycophenolate sodium in healthy volunteers. *J Clin Pharmacol* 2011;.
3. Rupprecht K, *et al.* Bioavailability of mycophenolate mofetil and enteric-coated mycophenolate sodium is differentially affected by pantoprazole in healthy volunteers. *J Clin Pharmacol* 2009; 49: 1196–1201.

Sevelamer. Exposure to mycophenolate mofetil was reduced after the use of sevelamer in renal transplant patients, an effect that was thought to be due to sevelamer reducing the absorption of mycophenolate.[1] Licensed product information for sevelamer suggests that it should be given at least 3 hours before or 1 hour after drugs for which a reduction in bioavailability could be clinically significant.

1. Pieper A-K, *et al.* The effect of sevelamer on the pharmacokinetics of cyclosporin A and mycophenolate mofetil after renal transplantation. *Nephrol Dial Transplant* 2004; 19: 2630–3.

Pharmacokinetics

Mycophenolate mofetil is rapidly and extensively absorbed from the gastrointestinal tract; enteric-coated mycophenolate sodium is also extensively absorbed. Mycophenolate undergoes presystemic metabolism to active mycophenolic acid (MPA). MPA undergoes enterohepatic recirculation and secondary increases in plasma MPA concentrations are seen; these have been reported at between 6 to 12 hours after a dose of mycophenolate mofetil, and at between 6 to 8 hours after a dose of mycophenolate sodium. MPA is metabolised by glucuronidation to the inactive mycophenolic acid glucuronide. The majority of a dose of mycophenolate is excreted in the urine as this glucuronide, with negligible amounts of MPA; about 6% of a dose is recovered in faeces. MPA is 97% bound to plasma albumin. The mean half-life of MPA after oral and intravenous doses of mycophenolate mofetil has been reported to be 17.9 hours and 16.6 hours, respectively; an MPA half-life of about 12 hours has been reported for mycophenolate sodium.

References.

1. Bullingham RES, *et al.* Clinical pharmacokinetics of mycophenolate mofetil. *Clin Pharmacokinet* 1998; 34: 429–55.
2. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of mycophenolate in solid organ transplant recipients. *Clin Pharmacokinet* 2007; 46: 13–58.
3. Filler G, *et al.* Pharmacokinetics of mycophenolate mofetil and sirolimus in children. *Ther Drug Monit* 2008; 30: 138–42.
4. Lévesque E, *et al.* Pharmacokinetics of mycophenolate mofetil and its glucuronide metabolites in healthy volunteers. *Pharmacogenomics* 2008; 9: 869–79.
5. de Winter BCM, *et al.* Population pharmacokinetics of mycophenolic acid: a comparison between enteric-coated mycophenolate sodium and mycophenolate mofetil in renal transplant recipients. *Clin Pharmacokinet* 2008; 47: 827–38.
6. Sam W-J, *et al.* Population pharmacokinetics of mycophenolic acid and its 2 glucuronidated metabolites in kidney transplant recipients. *J Clin Pharmacol* 2009; 49: 185–95.
7. Barraclough KA, *et al.* Pharmacogenetic influences on mycophenolate therapy. *Pharmacogenomics* 2010; 11: 369–90.

Bioavailability. A study in renal transplant patients found single doses of mycophenolate sodium 640 mg and 720 mg to be bioequivalent to mycophenolate mofetil 1 g. The 720-mg dose most closely approximated the mycophenolic acid (MPA) exposure of the mycophenolate mofetil dose.[1] The authors noted that since the study was conducted in patients given ciclosporin, bioequivalence of MPA exposure between these two formulations could not be assumed for patients receiving other immunosuppressants. A meta-analysis of 3 studies in stable renal transplant recipients concluded that mycophenolate mofetil and enteric-coated mycophenolate sodium give equivalent mycophenolate exposure in these patients.[2]

1. Arns W, *et al.* Enteric-coated mycophenolate sodium delivers bioequivalent MPA exposure compared with mycophenolate mofetil. *Clin Transplant* 2005; 19: 199–206.
2. Johnston A, *et al.* Bioequivalence of enteric-coated mycophenolate sodium and mycophenolate mofetil: a meta-analysis of three studies in stable renal transplant recipients. *Transplantation* 2006; 82: 1413–18.

Haematopoietic stem cell transplantation. Pharmacokinetic studies have suggested that exposure to mycophenolic acid is lower in adult[1] and paediatric[2] haematopoietic stem cell transplant (HSCT) recipients taking mycophenolate mofetil compared with reference values from renal transplant recipients. Children were found to have similar exposure to mycophenolic acid as adults, despite a 33% higher daily dose.[2]

1. van Hest RM, *et al.* Pharmacokinetics of mycophenolate mofetil in hematopoietic stem cell transplant recipients. *Ther Drug Monit* 2007; 29: 353–60.
2. Jacobson P, *et al.* Higher mycophenolate dose requirements in children undergoing hematopoietic cell transplant (HCT). *J Clin Pharmacol* 2008; 48: 485–94.

Metabolism. Mycophenolate mofetil is rapidly de-esterified in the body to active mycophenolic acid (MPA), which is subsequently converted to inactive mycophenolic acid glucuronide (MPAG) in the gastrointestinal tract, liver and possibly kidney. This conversion to MPAG is considered to be the most important and rate limiting step.[1] MPA undergoes enterohepatic circulation, with MPAG formed in the liver being excreted into bile and converted back to MPA in the gastrointestinal tract. A further metabolite, the acyl glucuronide, has been shown to be active *in vitro*, inhibiting human inosine monophosphate dehydrogenase,[1,2] and may have implications in therapeutic drug monitoring (see below). MPA is extensively bound to albumin in patients with normal renal and hepatic function, but this binding may be affected in transplant patients by several factors such as hypoalbuminaemia, hyperbilirubinaemia, and uraemia. Accumulation of MPAG leads to an increase in unbound MPA, and a subsequent increase in MPA clearance.[2]

A crossover study to compare the metabolism of mycophenolate mofetil with mycophenolate sodium[3] found that the onset of MPA absorption was delayed with mycophenolate sodium, consistent with its enteric-coated formulation. However, MPA exposure was considered to be bioequivalent, and MPA metabolism did not differ significantly between the two formulations. MPAG was confirmed as being the principal metabolite of MPA, and the authors considered that acyl glucuronide exposure was of a sufficient magnitude to potentially contribute to immunosuppression and toxicity.

1. Shaw LM, *et al.* Pharmacokinetic, pharmacodynamic, and outcome investigations as the basis for mycophenolic acid therapeutic drug monitoring in renal and heart transplant patients. *Clin Biochem* 2001; 34: 17–22.
2. Shaw LM, *et al.* Current issues in therapeutic drug monitoring of mycophenolic acid: report of a roundtable discussion. *Ther Drug Monit* 2001; 23: 305–15.
3. Tedesco-Silva H, *et al.* Mycophenolic acid metabolite profile in renal transplant patients receiving enteric-coated mycophenolate sodium or mycophenolate mofetil. *Transplant Proc* 2005; 37: 852–5.

Therapeutic drug monitoring. Mycophenolic acid (MPA) concentration appears to correlate with efficacy and toxicity.[1] Patients with low MPA concentrations may be at increased risk of transplant rejection,[2-5] or graft-versus-host disease,[3] and there is some evidence that a high MPA concentration correlates with increased adverse effects.[4,6] Fixed doses of mycophenolate mofetil have been reported to lead to variable MPA exposure,[7,8] and other immunosuppressants can affect MPA concentrations, see under Interactions, p. 1964.2. Therapeutic drug monitoring of mycophenolate mofetil is therefore considered necessary.[1]

Assay procedures to measure MPA concentrations include HPLC and an enzyme-multiplied immunoassay technique (EMIT). However, the acyl glucuronide metabolite of MPA (see Metabolism, above) may cross-react with the latter method, leading to higher measured concentrations than with HPLC.[8,9] This overestimation of MPA exposure using EMIT was reported to be about 24 to 35%, with the greatest bias seen in kidney recipients early after transplantation. However, in paediatric renal transplant patients, EMIT showed comparable diagnostic efficacy to HPLC, and is an acceptable assay for MPA in this population.[8] Another suggested approach is to measure inosine monophosphate dehydrogenase activity directly, (see Metabolism, above) but this has produced variable results.[10]

A review[9] concluded that while some studies show a correlation between MPA trough concentration (C_0) and acute allograft rejection, MPA area under the concentration-time curve (AUC) is predictive of the risk for rejection, and that both have limitations. An abbreviated AUC involving more practical blood sampling regimens may be more appropriate, and a trough concentration between 1 and 3.5 mg/litre has been proposed. For paediatric transplant recipients, a predose trough concentration, as measured by EMIT assay, of between 1.6 and 3.5 mg/litre has been recommended.[11] However, it has been pointed out[12] that the therapeutic range may be different at different time points after transplantation, and among different patient populations; concomitant drugs may also influence this range. The following target concentrations have been recommended for transplant patients taking mycophenolate mofetil:[13]

- MPA AUC 30 to 60 mg X hours/litre as determined by HPLC in the first 30 days post-transplantation
- for renal transplant recipients on a ciclosporin-based regimen, MPA C_0 greater than or equal to 1.3 mg/litre, as measured by HPLC
- for renal transplant recipients on a tacrolimus-based regimen, MPA C_0 greater than or equal to 1.9 mg/litre, as measured by HPLC
- for cardiac transplant recipients, MPA C_0 greater than or equal to 2 mg/litre, as measured by EMIT, or 1.2 to 3.5 mg/litre as measured by HPLC
- for liver transplant recipients, target concentrations could not be definitively recommended; similar targets to renal transplantation were suggested until more data are available

Some have stated that the contribution of MPA trough level monitoring during mycophenolate mofetil therapy is unproven, given the lack of data in paediatric renal transplant patients, and in cardiac and liver transplantation, and that adherence to recommended target ranges for MPA cannot ensure an improved clinical outcome.[14]

It has also been pointed out that, because of differing pharmacokinetic profiles, algorithms developed for mycophenolate mofetil cannot be used for patients treated with mycophenolate sodium.[15]

Measurements of unbound MPA concentrations may be of benefit in patients with renal or hepatic impairment, as factors such as hypoalbuminaemia and renal dysfunction affect the binding of MPA.[9] In liver transplant patients, plasma protein binding of MPA increased as albumin concentration increased and as bilirubin concentration decreased, leading to decreased unbound fraction of MPA, and contributing to large intra- and interindividual pharmacokinetic variability.[16] A population pharmacokinetic study considered the complexity in determining MPA pharmacokinetics to be underestimated.[17] Bayesian forecasting using only 3 samples has been reported to accurately predict MPA exposure.[18-20]

A study in 6 patients with psoriasis concluded that MPA trough concentrations (measured by EMIT) did not predict efficacy or toxicity, but instead were useful to evaluate compliance.[21]

For the view that MPA trough concentrations may not adequately reflect exposure in patients also receiving tacrolimus, see Immunosuppressants, under Interactions, p. 1964.2.

1. Mourad M, *et al.* Therapeutic monitoring of mycophenolate mofetil in organ transplant recipients: is it necessary? *Clin Pharmacokinet* 2002; 41: 319–27.
2. van Gelder T, *et al.* A randomized double-blind, multicenter plasma concentration controlled study of the safety and efficacy of oral mycophenolate mofetil for the prevention of acute rejection after kidney transplantation. *Transplantation* 1999; 68: 261–6.
3. DeNofrio D, *et al.* Mycophenolic acid concentrations are associated with cardiac allograft rejection. *J Heart Lung Transplant* 2000; 19: 1071–6.
4. Tredger JM, *et al.* Monitoring mycophenolate in liver transplant recipients: toward a therapeutic range. *Liver Transpl* 2004; 10: 492–502.
5. Jacobson P, *et al.* Relationship of mycophenolic acid exposure to clinical outcome after hematopoietic cell transplantation. *Clin Pharmacol Ther* 2005; 78: 486–500.
6. Mourad M, *et al.* Correlation of mycophenolic acid pharmacokinetic parameters with side effects in kidney transplant patients treated with mycophenolate mofetil. *Clin Chem* 2001; 47: 88–94.
7. David-Neto E, *et al.* The need of mycophenolic acid monitoring in long-term renal transplants. *Clin Transplant* 2005; 19: 19–25.
8. Jeong H, Kaplan B. Therapeutic monitoring of mycophenolate mofetil. *Clin J Am Soc Nephrol* 2007; 2: 184–91.
9. Shaw LM, *et al.* Current issues in therapeutic drug monitoring of mycophenolic acid: report of a roundtable discussion. *Ther Drug Monit* 2001; 23: 305–15.
10. Shaw LM, *et al.* Monitoring of mycophenolic acid in clinical transplantation. *Ther Drug Monit* 2002; 24: 68–73.
11. Filler G. Value of therapeutic drug monitoring of MMF therapy in pediatric transplantation. *Pediatr Transplant* 2006; 10: 707–11.
12. Venkataramanan R, Shaw LM. Therapeutic monitoring of mycophenolic acid in liver transplant patients. *Liver Transpl* 2004; 10: 503–5.
13. van Gelder T, *et al.* Therapeutic drug monitoring of mycophenolate mofetil in transplantation. *Ther Drug Monit* 2006; 28: 145–54.
14. Kaplan B. Mycophenolic acid trough level monitoring in solid organ transplant recipients treated with mycophenolate mofetil: association with clinical outcome. *Curr Med Res Opin* 2006; 22: 2355–64.
15. Oellerich M, Armstrong VW. The role of therapeutic drug monitoring in individualizing immunosuppressive drug therapy: recent developments. *Ther Drug Monit* 2006; 28: 720–5.
16. Pisupati J, *et al.* Intraindividual and interindividual variations in the pharmacokinetics of mycophenolic acid in liver transplant patients. *J Clin Pharmacol* 2005; 45: 34–41.
17. Shum B, *et al.* Population pharmacokinetic analysis of mycophenolic acid in renal transplant recipients following oral administration of mycophenolate mofetil. *Br J Clin Pharmacol* 2003; 56: 188–97.
18. Le Guellec C, *et al.* Population pharmacokinetics and Bayesian estimation of mycophenolic acid concentrations in stable renal transplant patients. *Clin Pharmacokinet* 2004; 43: 253–66.

19. Zahr N, *et al.* Pharmacokinetic study of mycophenolate mofetil in patients with systemic lupus erythematosus and design of Bayesian estimator using limited sampling strategies. *Clin Pharmacokinet* 2008; 47: 277–84.
20. Saint-Marcoux F, *et al.* Pharmacokinetic modelling and development of Bayesian estimators for therapeutic drug monitoring of mycophenolate mofetil in reduced-intensity haematopoietic stem cell transplantation. *Clin Pharmacokinet* 2009; 48: 667–75.
21. Daudén E, *et al.* Plasma trough levels of mycophenolic acid do not correlate with efficacy and safety of mycophenolate mofetil in psoriasis. *Br J Dermatol* 2004; 150: 132–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: CellCept; Imuxgen; Metocris; Munotrast; Mycoldosa; Myfortic; *Austral.*: CellCept; Imulate; Myfortic; *Austria*: CellCept; Myfortic; *Belg.*: CellCept; Myfenax; Myfortic; *Braz.*: CellCept; Myfortic; *Canad.*: CellCept; Myfortic; *Chile*: CellCept; Myfortic; *China*: Myfortic (米芙); Saikeping (赛可平); Shun You (顺友); Cz.: CellCept; Limfocept; Mofimutral; Mometil; Mophecen; Myclausen; Mycofenor; Myfenax; Myfortic; Mygref; Trixin; *Denm.*: CellCept; Myclausen; Myfenax; Myfortic; *Fin.*: CellCept; Myfortic; *Fr.*: CellCept; Myfortic; *Ger.*: CellCept; Mycopheno-cell; Myfortic; *Gr.*: CellCept; Mycofen; Myfenax; Myfetil; Myfortic; *Hong Kong*: CellCept; Micocept; Myfortic; *Hung.*: CellCept; Mofimutral; Myfenax; Myfortic; Presumin; *India*: Baxmune; CellCept; Cellmune; MMF; Mofetyl; Mofilet; Mycept; Mycofit; Mycophen; Myfortic; Mygraft; Myotec; *Indon.*: CellCept; Myfortic; *Irl.*: CellCept; Myclausen; Mycolat; Myfenax; Myfortic; *Israel*: CellCept; Mefetil; Myfortic; *Ital.*: CellCept; Myfortic; Rigenol; Rimmunos; *Jpn*: CellCept; *Malaysia*: CellCept; Myfortic; *Mex.*: CellCept; Celprot; Lanfetil; Myfortic; Tevacept; *Neth.*: CellCept; Myclausen; Myfortic; *Norw.*: CellCept; Myfenax; Myfortic; *NZ*: CellCept; Ceptolate; Myaccord; *Philipp.*: CellCept; Mofilet; Mycept; Myfetil; Myfortic; Renocell; *Pol.*: CellCept; Myclausen; Myfenax; Myfortic; *Port.*: CellCept; Myclausen; Myfenax; Myfortic; *Rus.*: CellCept (Селлсепт); Myfortic (Майфортик); Mysept (Майсепт); Supresta (Супреста); *S.Afr.*: CellCept; Myfortic; *Singapore*: CellCept; Myfortic; Refrat; *Spain*: CellCept; Myfenax; Myfortic; *Swed.*: CellCept; Myclausen; Myfenax; Myfortic; *Switz.*: CellCept; Myfortic; *Thai.*: CellCept; Myfortic; *Turk.*: CellCept; Mofecept; Myfortic; *UK*: Arzip; CellCept; Myfortic; *Ukr.*: CellCept (Селлсепт); Myfenax (Мифенакс); Myfortic (Мифортик); *USA*: CellCept; Myfortic; *Venez.*: CellCept; Myfortic.

Pharmacopoeial Preparations
USP 36: Mycophenolate Mofetil Capsules; Mycophenolate Mofetil for Injection; Mycophenolate Mofetil for Oral Suspension; Mycophenolate Mofetil Tablets.

Remestemcel-L *(USAN)*

JR-0301.
Allogeneic human mesenchymal stem cells.

NOTE. The name Prochymal has been used as a trade mark for remestemcel-L.

Profile

Remestemcel-L contains *ex-vivo* cultured allogeneic human mesenchymal stem cells, and is used in the treatment of acute graft-versus-host disease (see Haematopoietic Stem Cell Transplantation, p. 1933.1). It is also under investigation in the management of acute radiation syndrome, Crohn's disease, myocardial infarction, pulmonary disease, and type 1 diabetes mellitus.

References.
1. Kebriaei P, *et al.* Adult human mesenchymal stem cells added to corticosteroid therapy for the treatment of acute graft-versus-host disease. *Biol Blood Marrow Transplant* 2009; 15: 804–11.
2. Hare JM, *et al.* A randomized, double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (Prochymal) after acute myocardial infarction. *J Am Coll Cardiol* 2009; 54: 2277–86.
3. Prasad VK, *et al.* Efficacy and safety of ex vivo cultured adult human mesenchymal stem cells (Prochymal®) in pediatric patients with severe refractory acute graft-versus-host disease in a compassionate use study. *Biol Blood Marrow Transplant* 2011; 17: 534–41.
4. Mannon PJ. Remestemcel-L: human mesenchymal stem cells as an emerging therapy for Crohn's disease. *Expert Opin Biol Ther* 2011; 11: 1249–56.

Reparixin *(USAN, rINN)*

DF-1681; Reparixina; Réparixine; Reparixinum; Repertaxin; Репариксин.
(2*R*)-2-[4-(2-Methylpropyl)phenyl]-*N*-methylsulfonylpropanamide.
$C_{14}H_{21}NO_3S$=283.4.
CAS — 266359-83-5.
UNII — U604E1N83K.

Reparixin Lysine *(rINNM)*

Reparixin L-Lysine; Reparixina lisina; Réparixine Lysine; Reparixinum Lysinum; Repertaxin L-lisina; Repertaxin L-Lysine; Репариксин Лизин.
Reparixin compound with L-lysine (1:1).
$C_{14}H_{21}NO_3S.C_6H_{14}N_2O_2$=429.6
CAS — 266359-93-7.

Profile

Reparixin is an inhibitor of interleukin-8. Reparixin and reparixin lysine have been investigated for the prevention of delayed graft function in organ transplantation.

Sirolimus *(BAN, USAN, rINN)*

AY-022989; AY-22989; NSC-226080; Raparnicina; Rapamycin; Sirolimús; Sirolimusum; Sirolimuusi; Wy-090217; Сиролимус.
(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-[(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4*H*,6*H*,31*H*)-pentone.
$C_{51}H_{79}NO_{13}$=914.2
CAS — 53123-88-9.
ATC — L04AA10.
ATC Vet — QL04AA10.
UNII — W36ZG6FT64.

Uses and Administration

Sirolimus is a macrolide compound obtained from *Streptomyces hygroscopicus* and has potent immunosuppressant properties. Sirolimus binds to a protein (FK binding protein-12; FKBP-12; FKPB-12) and this complex inhibits the activation of the mammalian target of rapamycin (mTOR), a key regulatory kinase for cell cycle progression thus suppressing cytokine-driven T-cell proliferation.

Sirolimus is used for the prevention of graft rejection in kidney transplantation (p. 1935.2), and is being investigated for induction of remission in some auto-immune diseases. Sirolimus-releasing stents have been developed to reduce restenosis after coronary artery stent placement. They are also used in the treatment of severe claudication and critical limb ischaemia of infrapopliteal lesions (which is the most severe form of arterial disease in the leg).

For prevention of graft rejection, sirolimus is given with ciclosporin and corticosteroids as soon as possible after transplantation. A loading dose of 6 mg is given orally, followed by a maintenance dose of 2 mg daily, 4 hours after ciclosporin. In patients 13 years of age or more who weigh less than 40 kg a loading dose of 3 mg/m², followed by initial maintenance doses of 1 mg/m² daily, is recommended. It is recommended that the dose of sirolimus should be adjusted to obtain whole blood trough concentrations of 4 to 12 nanograms/mL (by chromatographic assay), and the doses of ciclosporin and corticosteroids gradually reduced. After 2 to 3 months, ciclosporin should be gradually stopped over 4 to 8 weeks, and the dose of sirolimus adjusted to obtain trough concentrations of about 12 to 20 nanograms/mL. In the USA, ciclosporin may be continued for up to 4 months; sirolimus trough concentrations of 16 to 24 nanograms/mL have been recommended for the first year after transplantation; thereafter, the concentrations should be 12 to 20 nanograms/mL. In patients at high immunological risk (defined as black [Afro-Caribbean] patients and/or repeat renal transplant patients and/or patients with high panel-reactive antibodies), sirolimus may be used with ciclosporin and corticosteroids for the first year after transplantation. A loading dose of up to 15 mg is suggested, followed by an initial maintenance dose of 5 mg daily; adjustments thereafter are made on the basis of whole blood trough concentrations. In patients in whom ciclosporin withdrawal is unsuccessful or cannot be attempted, sirolimus should not be used for more than 3 months after transplantation.

For further information on use in children, and for doses in hepatic impairment, see below.

Sirolimus has been shown to possess antifungal and antineoplastic properties. It is under investigation for gene regulation in gene therapy.

Administration. A study in renal transplant recipients judged the tablet and oral solution formulations of sirolimus to be therapeutically equivalent.[1] Licensed product information states that while 2 mg of oral solution has been shown to be clinically equivalent to 2 mg of the oral tablet formulation, and the two are hence interchangeable, it is unknown whether higher doses of the oral solution are clinically equivalent to the same doses as tablets. When switching patients between formulations, it is recommended to give the same dose and verify the sirolimus trough concentrations 1 to 2 weeks later; verification of trough concentrations is also recommended when switching between different tablet strengths.

1. Mathew TH, *et al.* A comparative study of sirolimus tablet versus oral solution for prophylaxis of acute renal allograft rejection. *J Clin Pharmacol* 2006; 46: 76–87.

Administration in children. In the USA, sirolimus is not licensed for use in children under 13 years of age. For doses in children aged 13 years or older, and weighing under 40 kg, see Uses and Administration, above. In the UK, sirolimus is licensed from 18 years of age, and the *BNFC* recommends local treatment protocols be consulted for details of doses to be used in children; official guidance from NICE recommends that sirolimus be used as a component of immunosuppressive regimens in children and adolescents only if intolerance necessitates the withdrawal of a calcineurin inhibitor.[1]

1. NICE. Immunosuppressive therapy for renal transplantation in children and adolescents (Technology Appraisal 99, issued April 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA099guidance.pdf (accessed 07/02/08)

Administration in hepatic impairment. Exposure to sirolimus and half-life are both increased in patients with mild to moderate hepatic impairment (Child-Pugh category A or B). Licensed product information states that in patients with hepatic impairment, it is not necessary to modify the loading dose of sirolimus, but whole blood trough concentrations should be closely monitored in these patients. US licensed product information states that the maintenance dose should be reduced by about one-third in patients with mild to moderate hepatic impairment; both US and UK licensed product information recommend reducing the dose by about one-half in patients with severe hepatic impairment. A study[1] involving 9 patients with severe hepatic impairment (Child-Pugh category C) indicated that an initial dosage reduction of about 60% followed by therapeutic drug monitoring might be suitable in these patients.

1. Zimmerman JJ, *et al.* Pharmacokinetics of sirolimus (rapamycin) in subjects with severe hepatic impairment. *J Clin Pharmacol* 2008; 48: 285–92.

Inflammatory bowel disease. Sirolimus was added to treatment for severe Crohn's disease in a patient who was losing response to infliximab. An initial oral dose of sirolimus 2 mg daily was adjusted to maintain serum trough concentrations at 5 nanograms/mL; this was achieved on a dose of 4 mg daily. Infliximab infusions continued to be given every 6 weeks. A marked improvement in symptoms, inflammatory markers, and endoscopic appearance was noted after 8 weeks of sirolimus, and after 12 weeks of treatment the interval between infliximab infusions was able to be increased to 8 weeks. Sirolimus was stopped after 6 months and remission maintained with 8-weekly infliximab infusions.[1]

1. Massey DCO, *et al.* Use of sirolimus (rapamycin) to treat refractory Crohn's disease. *Gut* 2008; 57: 1294–6.

Kaposi's sarcoma. Transplant recipients are susceptible to the development of Kaposi's sarcoma (p. 718.1) as a result of long-term immunosuppressive therapy. In 15 renal transplant recipients with biopsy-proven Kaposi's sarcoma, therapy with ciclosporin and mycophenolate was stopped, and sirolimus started. After 1 month, cutaneous lesions had regressed in 12 patients and after 6 months biopsy specimens were negative for Kaposi's sarcoma.[1] While stopping ciclosporin or mycophenolate has led to remission of Kaposi's sarcoma,[2] sirolimus may have an antineoplastic action independent of its immunosuppressive effect.[1] In renal transplant recipients, those who received sirolimus-based therapy after ciclosporin withdrawal at month 3 had a reduced incidence of both skin and non-skin (including Kaposi's sarcoma) malignancies at 5 years after transplantation, compared with those who continued with sirolimus and ciclosporin therapy.[3]

1. Stallone G, *et al.* Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med* 2005; 352: 1317–23.
2. Dantal J, Soulillou J-P. Immunosuppressive drugs and the risk of cancer after organ transplantation. *N Engl J Med* 2005; 352: 1371–3.
3. Campistol JM, *et al.* Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. *J Am Soc Nephrol* 2006; 17: 581–9.

Lymphangioleiomyomatosis. Improvements in left lung function have been noted in a patient with lymphangioleiomyomatosis treated with sirolimus after transplantation of the right lung.[1] For mention of the use of medroxyprogesterone in this rare disease, see Respiratory Disorders, p. 2288.3.

1. Egan JJ, *et al.* Sirolimus for lymphangioleiomyomatosis lesions. *N Engl J Med* 2008; 358: 1963–4.

Organ and tissue transplantation. Sirolimus is used for the prophylaxis of graft rejection in kidney transplantation (p. 1935.2), initially as an adjunct to calcineurin inhibitor-based regimens. It is increasingly used for corticosteroid or calcineurin inhibitor withdrawal, although long-term data

are lacking, and the safety of ciclosporin withdrawal in high-risk patients has not been adequately studied and is not recommended. Sirolimus has been investigated for liver (p. 1936.3), heart (p. 1934.2), pancreas (p. 1938.1), and lung (p. 1937.3) transplantation, although safety has not been established, see Adverse Effects and Precautions below. In *de novo* renal transplant patients, there was an increased risk of rejection in those given sirolimus and mycophenolate and corticosteroids with an interleukin-2 receptor antibody, compared with those not given an interleukin-2 receptor antibody. In a small study of heart transplant recipients switched from standard immunosuppressive therapy with a calcineurin inhibitor, mycophenolate mofetil, and corticosteroids, to sirolimus with mycophenolate mofetil, there was an increased incidence of acute rejection; target sirolimus and mycophenolate concentrations may have been insufficient to maintain adequate immunosuppression.

A few selected references to the use of sirolimus in transplantation are given below.

1. Vasquez EM. Sirolimus: a new agent for prevention of renal allograft rejection. *Am J Health-Syst Pharm* 2000; 57: 437–51.
2. Kahan BD. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicentre study. *Lancet* 2000; 356: 194–202.
3. Ingle GR, *et al.* Sirolimus: continuing the evolution of transplant immunosuppression. *Ann Pharmacother* 2000; 34: 1044–55.
4. Johnson RW. Sirolimus (Rapamune) in renal transplantation. *Curr Opin Nephrol Hypertens* 2002; 11: 603–7.
5. Radovancevic B, Vrtovec B. Sirolimus therapy in cardiac transplantation. *Transplant Proc* 2003; 35 (suppl): 171S–176S.
6. Trotter JF. Sirolimus in liver transplantation. *Transplant Proc* 2003; 35 (suppl): 193S–200S.
7. MacDonald AS. Rapamycin in combination with cyclosporine or tacrolimus in liver, pancreas, and kidney transplantation. *Transplant Proc* 2003; 35 (suppl): 201S–208S.
8. Neff GW, *et al.* Ten years of sirolimus therapy in orthotopic liver transplant recipients. *Transplant Proc* 2003; 35 (suppl): 209S–216S.
9. Dupont P, Warrens AN. The evolving role of sirolimus in renal transplantation. *Q J Med* 2003; 96: 401–9.
10. Kahan BD. Sirolimus: a ten-year perspective. *Transplant Proc* 2004; 36: 71–5.
11. Lo A, *et al.* Comparison of sirolimus-based calcineurin inhibitor-sparing and calcineurin inhibitor-free regimens in cadaveric renal transplantation. *Transplantation* 2004; 77: 1228–35.
12. Kuypers DRJ. Benefit-risk assessment of sirolimus in renal transplantation. *Drug Safety* 2005; 28: 133–81.
13. Mehrabi A, *et al.* The role and value of sirolimus administration in kidney and liver transplantation. *Clin Transplant* 2006; 20 (Suppl 17): 30–43.
14. Mulay AV, *et al.* Conversion from calcineurin inhibitors to sirolimus for chronic renal allograft dysfunction: a systematic review of the evidence. *Transplantation* 2006; 82: 1153–62.
15. Augustine JJ, *et al.* Use of sirolimus in solid organ transplantation. *Drugs* 2007; 67: 369–91.
16. House AA, *et al.* Sirolimus use in recipients of expanded criteria donor kidneys. *Drugs* 2008; 68 (suppl 1): 41–9.
17. Kahan BD. Fifteen years of clinical studies and clinical practice in renal transplantation: reviewing outcomes with de novo use of sirolimus in combination with cyclosporine. *Transplant Proc* 2008; 40 (suppl): S17–S20.
18. Campistol JM, *et al.* Practical recommendations for the early use of m-TOR inhibitors (sirolimus) in renal transplantation. *Transpl Int* 2009; 22: 681–7.
19. Flechner SM. Sirolimus in kidney transplantation indications and practical guidelines: de novo sirolimus-based therapy without calcineurin inhibitors. *Transplantation* 2009; 87 (8 suppl): S1–S6.
20. Patel SJ, *et al.* Considerations in sirolimus use in the early and late post-transplant periods. *Expert Opin Drug Safety* 2009; 8: 421–34.

Psoriasis. Sirolimus has been investigated both systemically[1,2] and topically[3,4] in the treatment of psoriasis (p. 1688.1).

1. Reitamo S, *et al.* A double-blind study in patients with severe psoriasis to assess the clinical activity and safety of rapamycin (sirolimus) alone or in association with a reduced dose of cyclosporine. *Br J Dermatol* 1999; 141: 978–9.
2. Reitamo S, *et al.* Efficacy of sirolimus (rapamycin) administered concomitantly with a subtherapeutic dose of cyclosporin in the treatment of severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2001; 145: 438–45.
3. Ormerod AD, *et al.* Penetration, safety and efficacy of the topical immunosuppressive sirolimus in psoriasis. *Br J Dermatol* 1999; 141: 975.
4. Ormerod AD, *et al.* Treatment of psoriasis with topical sirolimus: preclinical development and a randomized, double-blind trial. *Br J Dermatol* 2005; 152: 758–64.

Reperfusion and revascularisation procedures. Restenosis is a particular problem after percutaneous coronary revascularisation procedures (p. 1259.2) and various drugs have been tried for its prevention. Coronary stents that elute sirolimus effectively reduce restenosis[1–8] and have been widely used. There is some suggestion that sirolimus-eluting stents may be superior to paclitaxel-eluting stents in terms of clinical outcome and rates of restenosis,[9–14] although not all studies have noted differences.[15] The risk of late stent thrombosis may be increased with drug eluting stents,[16] although the evidence is controversial,[17] and their role in complex interventions is not yet established.[18,19] Oral sirolimus may also be effective in preventing restenosis.[20–23]

1. Morice M-C, *et al.* A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; 346: 1773–80.
2. Moses JW, *et al.* Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003; 349: 1315–23.
3. Lemos PA, *et al.* Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes: insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *J Am Coll Cardiol* 2003; 41: 2093–9.
4. Vishnevetsky D, *et al.* Sirolimus-eluting coronary stent. *Am J Health-Syst Pharm* 2004; 61: 449–56.
5. Cheng-Lai A, Prishman WH. Sirolimus-eluting coronary stents: novel devices for the management of coronary artery disease. *Am J Ther* 2004; 11: 218–28.
6. Spaulding C, *et al.* A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007; 356: 989–97.
7. Kastrati A, *et al.* Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007; 356: 1030–9.
8. Weisz G, *et al.* Five-year follow-up after sirolimus-eluting stent implantation: results of the SIRIUS (sirolimus-eluting stent in de-novo native coronary lesions) trial. *J Am Coll Cardiol* 2009; 53: 1488–97.
9. Windecker S, *et al.* Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med* 2005; 353: 653–62.
10. Dibra A, *et al.* Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. *N Engl J Med* 2005; 353: 663–70.
11. Hofma SH, *et al.* One year clinical follow up of paclitaxel eluting stents for acute myocardial infarction compared with sirolimus eluting stents. *Heart* 2005; 91: 1176–80.
12. Stettler C, *et al.* Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet* 2007; 370: 937–48.
13. Lee S-W, *et al.* A randomized comparison of sirolimus- versus paclitaxel-eluting stent implantation in patients with diabetes mellitus: 2-year clinical outcomes of the DES-DIABETES trial. *J Am Coll Cardiol* 2009; 53: 812–13.
14. Zhang P, *et al.* Meta-analysis of five randomized clinical trials comparing sirolimus- versus paclitaxel-eluting stents in patients with diabetes mellitus. *Am J Cardiol* 2010; 105: 64–8.
15. Gallee AM, *et al.* SORT OUT II Investigators. Comparison of paclitaxel- and sirolimus-eluting stents in everyday clinical practice: the SORT OUT II randomized trial. *JAMA* 2008; 299: 409–16.
16. Stone GW, *et al.* Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007; 356: 998–1008.
17. Mauri L, *et al.* Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007; 356: 1020–9.
18. Beohar N, *et al.* Outcomes and complications associated with off-label and untested use of drug-eluting stents. *JAMA* 2007; 297: 1992–2000.
19. Win HK, *et al.* Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA* 2007; 297: 2001–9.
20. Hausleiter J, *et al.* Randomized, double-blind, placebo-controlled trial of oral sirolimus for restenosis prevention in patients with in-stent restenosis: the Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) trial. *Circulation* 2004; 110: 790–5.
21. Waksman R, *et al.* Oral rapamycin to inhibit restenosis after stenting of de novo coronary lesions: the Oral Rapamune to Inhibit Restenosis (ORBIT) study. *J Am Coll Cardiol* 2004; 44: 1386–92.
22. Rodriguez AE, *et al.* ORAR II Investigators. Oral rapamycin after coronary bare-metal stent implantation to prevent restenosis: the Prospective, Randomized Oral Rapamycin in Argentina (ORAR II) Study. *J Am Coll Cardiol* 2006; 47: 1522–9.
23. Rodriguez AE, *et al.* Role of oral rapamycin to prevent restenosis in patients with de novo lesions undergoing coronary stenting: results of the Argentina single centre study (ORAR trial). *Heart* 2005; 91: 1433–7.

Uveitis. Sirolimus has been reported to be effective in the treatment of patients with refractory uveitis.[1]

1. Shanmuganathan VA, *et al.* The efficacy of sirolimus in the treatment of patients with refractory uveitis. *Br J Ophthalmol* 2005; 89: 666–9.

Adverse Effects and Precautions

Commonly reported adverse effects of sirolimus include peripheral oedema, lymphocele, hypokalaemia, hypophosphataemia, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, hyperglycaemia, tachycardia, venous thromboembolism, gastrointestinal disturbances, stomatitis, arthralgia, epistaxis, acne, rash, bone necrosis, fever, hypertension, headache, and pain including abdominal pain. Anaemia, thrombocytopenia, neutropenia or leucopenia are also common.

Immunosuppression, including sirolimus treatment, is associated with an increased incidence of lymphoma and other malignancies, particularly those of the skin, and excess exposure to UV light should be avoided during treatment. There is also an increased risk of infection, including activation of latent viral infections. These include JC virus-associated progressive multifocal leukoencephalopathy (PML), and BK virus-associated nephropathy that can lead to renal graft loss. Antimicrobial prophylaxis is recommended against pneumocystis pneumonia for the first year after transplantation and against CMV for the first 3 months after transplantation.

Thrombotic thrombocytopenic purpura and the haemolytic-uraemic syndrome may occur, as may hypersensitivity, including anaphylactic reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis. There are reports of fluid accumulation, including lymphoedema, pleural effusions, and pericardial effusions. Pulmonary embolism, pulmonary haemorrhage, pancreatitis, and alveolar proteinosis may occur rarely. Renal impairment, proteinuria, focal glomerulosclerosis, or nephrotic syndrome may develop; renal function should be monitored, especially when given with ciclosporin. In patients with delayed graft function, sirolimus may delay recovery of renal function. There are reports of hepatotoxicity, and rarely, fatal hepatic necrosis. Excess mortality, graft loss, and hepatic artery thrombosis has been associated with the use of sirolimus in immunosuppressive regimens in liver transplant recipients and therefore use in such patients is not recommended. Interstitial lung disease has been reported, including some fatalities, although other cases resolved on stopping or reducing the dose of sirolimus. Abnormal wound healing after transplant surgery has been reported with the use of sirolimus, especially in those with a BMI greater than 30 kg/m^2; bronchial anastomotic dehiscence, including some fatal cases, has occurred in lung transplant recipients and use in these patients is not recommended.

Sirolimus may have adverse effects on sperm production azoospermia and infertility have been reported. These effects are usually reversible on stopping sirolimus.

Immunosuppressants may reduce the response to vaccines, and the use of live vaccines should be avoided. Intra-uterine devices should be used with caution during immunosuppressive therapy, as there is an increased risk of infection.

Hypersensitivity reactions and subacute thrombosis have occurred with use of the sirolimus-eluting stent; fatalities have been reported.

Effects on the kidneys. Proteinuria and renal dysfunction have been associated with sirolimus. A review[1] concluded that the vast majority of evidence suggested that proteinuria was mediated by glomerular haemodynamic mechanisms due to withdrawal of other immunosuppressants in kidneys with chronic glomerular injury, as in those transplant patients with chronic allograft dysfunction. Whether sirolimus directly causes proteinuria and/or mediates direct glomerular toxicity remains to be resolved and further studies are needed.

1. Rangan GK. Sirolimus-associated proteinuria and renal dysfunction. *Drug Safety* 2006; 29: 1153–61.

Effects on the liver. A retrospective review of 488 patients noted an increased incidence of veno-occlusive disease of the liver when sirolimus was included in the regimen for prophylaxis against graft-versus-host disease after myeloablative allogeneic stem cell transplant. Incidence was increased further if sirolimus was given with methotrexate after a conditioning regimen using cyclophosphamide and total body irradiation, and was excessively high when sirolimus was used with a busulfan-based conditioning regimen.[1]

1. Cutler C, *et al.* Sirolimus is associated with veno-occlusive disease of the liver after myeloablative allogeneic stem cell transplantation. *Blood* 2008; 112: 4425–31.

Effects on the lungs. Pulmonary toxicity, including interstitial pneumonitis,[1–9] and alveolar haemorrhage,[5,10,11] has been reported with sirolimus. There was some suggestion in one series that the incidence of interstitial pneumonitis might be higher in patients who switched from calcineurin inhibitors to sirolimus than in those who were started on sirolimus after transplantation.[6] Possible risk factors include giving a loading dose, late use of sirolimus compared with initial therapy, and higher sirolimus dose and trough concentrations; additional risk factors include allograft dysfunction, hypervolaemia, and male gender.[7] Acute respiratory distress has been reported in a 1-year-old heart transplant recipient 3 days after starting sirolimus.[12] Pulmonary alveolar proteinosis has also been reported in a renal transplant patient 2 years after starting sirolimus; symptoms resolved markedly upon stopping sirolimus.[13]

Similar toxicity has occurred with everolimus (p. 1959.1).

1. Morelon E, *et al.* Interstitial pneumonitis associated with sirolimus therapy in renal-transplant recipients. *N Engl J Med* 2000; 343: 225–6.
2. Singer SJ, *et al.* Interstitial pneumonitis associated with sirolimus therapy in renal-transplant recipients. *N Engl J Med* 2000; 343: 1815–16.
3. Morelon E, *et al.* Characteristics of sirolimus-associated interstitial pneumonitis in renal transplant patients. *Transplantation* 2001; 72: 787–90.
4. Lennon A, *et al.* Interstitial pneumonitis associated with sirolimus (rapamycin) therapy after liver transplantation. *Transplantation* 2001; 72: 1166–7.
5. Pham P-T T, *et al.* Sirolimus-associated pulmonary toxicity. *Transplantation* 2004; 77: 1215–20.
6. Champion L, *et al.* Brief communication: sirolimus-associated pneumonitis: 24 cases in renal transplant recipients. *Ann Intern Med* 2006; 144: 505–9.
7. Morath C, *et al.* Four cases of sirolimus-associated interstitial pneumonitis: identification of risk factors. *Transplant Proc* 2007; 39: 99–102.
8. García-Luque A, *et al.* Sirolimus-associated pneumonitis in heart transplant recipients. *Ann Pharmacother* 2008; 42: 1143–5.
9. Peegans J, *et al.* Interstitial pneumonitis in the transplant patient: consider sirolimus-associated pulmonary toxicity. *J La State Med Soc* 2009; 161: 166–72.
10. Vlahakis NE, *et al.* Sirolimus-associated diffuse alveolar hemorrhage. *Mayo Clin Proc* 2004; 79: 541–5.
11. Khalife WI, *et al.* Sirolimus-induced alveolar hemorrhage. *J Heart Lung Transplant* 2007; 26: 652–7.
12. Das BB, *et al.* Acute sirolimus pulmonary toxicity in an infant heart transplant recipient: case report and literature review. *J Heart Lung Transplant* 2007; 26: 296–8.
13. Pedroso SL, *et al.* Pulmonary alveolar proteinosis: a rare pulmonary toxicity of sirolimus. *Transpl Int* 2007; 20: 291–6.

Effects on the nervous system. Posterior reversible encephalopathy syndrome (a neurotoxic condition involving oedema of the white matter in the posterior parts of the brain and characterised by headache, confusion, and

visual disturbances) has been reported after use of sirolimus.[1,2]

1. Bodkin CL, Bidelman BH. Sirolimus-induced posterior reversible encephalopathy. *Neurology* 2007; 68: 2039–40.
2. Moskowitz A, *et al.* Posterior reversible encephalopathy syndrome due to sirolimus. *Bone Marrow Transplant* 2007; 39: 653–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sirolimus 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 05/10/11)

Thrombosis. There was an apparent clustering of reports of subacute thrombosis associated with the use of the sirolimus-eluting stent soon after its marketing approval in 2003.[1] However, subsequent studies[2] and additional data from 2063 patients[3] suggest that use of the sirolimus-eluting stent is not associated with an excess risk of subacute thrombosis compared with bare-metal stents.

1. Muni NI, Gross TP. Problems with drug-eluting coronary stents—the FDA perspective. *N Engl J Med* 2004; 351: 1593–5.
2. Jeremias A, *et al.* Stent thrombosis after successful sirolimus-eluting stent implantation. *Circulation* 2004; 109: 1930–2.
3. FDA. FDA public health web notification: final update of information for physicians on sub-acute thromboses (SAT) and hypersensitivity reactions with use of the Cordis CYPHER® sirolimus-eluting coronary stent (issued 18th October 2004). Available at: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/UCM062120 (accessed 05/08/10)

Interactions

Inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole, HIV-protease inhibitors, the NNRTI delavirdine, and diltiazem may increase plasma concentrations of sirolimus. Conversely, inducers of this isoenzyme, such as nevirapine and rifampicin, may reduce plasma concentrations of sirolimus. Use of sirolimus with strong inhibitors or inducers of CYP3A4 and/or P-glycoprotein is not recommended. Grapefruit juice should not be taken with sirolimus. Ciclosporin can affect the rate and extent of sirolimus absorption and it is recommended that these drugs be given 4 hours apart. Use of sirolimus with a calcineurin inhibitor may also increase the risk of calcineurin inhibitor-induced haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, or thrombotic microangiopathy. Use of sirolimus with an ACE inhibitor may increase the risk of developing angioedema. See p. 1967.2 for precautions about use with live vaccines.

Immunosuppressants. Concentrations of sirolimus, and area under the concentration-time curve were significantly higher when sirolimus and *ciclosporin* were given together than when the 2 drugs were given 4 hours apart,[1,2] and a synergistic effect has been suggested.[3] This effect may allow for lower doses[4] or early withdrawal[5] of ciclosporin, resulting in improved renal function and less nephrotoxicity. However, for the risk of increased thrombotic reactions see Interactions, above.

Sirolimus may decrease blood concentrations of *tacrolimus*.

1. Kaplan B, *et al.* The effects of relative timing of sirolimus and cyclosporine microemulsion formulation coadministration on the pharmacokinetics of each agent. *Clin Pharmacol Ther* 1998; 63: 48–53.
2. Zimmerman JJ, *et al.* Pharmacokinetic interactions between sirolimus and microemulsion cyclosporine when orally administered jointly and 4 hours apart in healthy volunteers. *J Clin Pharmacol* 2003; 43: 1168–76.
3. Kahan BD, Kramer WG. Median effect analysis of efficacy versus adverse effects of immunosuppressants. *Clin Pharmacol Ther* 2001; 70: 74–81.
4. Reitamo S, *et al.* Efficacy of sirolimus (rapamycin) administered concomitantly with a subtherapeutic dose of cyclosporin in the treatment of severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2001; 145: 438–45.
5. Johnson RWG, *et al.* Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. *Transplantation* 2001; 72: 777–86.

Pharmacokinetics

Sirolimus is rapidly absorbed after doses of the oral solution, with a time to peak concentration of about 2 hours. Absorption is variably affected by food, especially high-fat meals. Sirolimus is extensively bound to plasma proteins. It is metabolised by the cytochrome P450 isoenzyme CYP3A4. Metabolism occurs by demethylation or hydroxylation, and the majority of a dose is excreted via the faeces, with only about 2% excreted in the urine. In healthy subjects, the bioavailability of a single dose of the tablet formulation is about 27% higher than the oral solution, bioavailability of which is only about 14%. However, this difference is less marked in renal transplant recipients, and when switching between formulations, licensed product information recommends giving the same dose, with trough concentrations verified 1 to 2 weeks later. The terminal half-life in stable renal transplant patients after multiple oral doses has been reported to be about 62 hours; the half-life in men was reported to be significantly longer than in women (about 72 hours compared with about 61 hours).

References.

1. Mahalati K, Kahan BD. Clinical pharmacokinetics of sirolimus. *Clin Pharmacokinet* 2001; 40: 573–85.

Genetic factors. Renal transplant recipients with at least one CYP3A5*1 allele had lower exposure to sirolimus than those patients homozygous for CYP3A5*3, and patients with CYP3A5*1/*1 and *1/*3 genotypes required significantly higher sirolimus daily dosage to achieve the same blood concentrations at steady state as the *3/*3 genotypes.[1] Determination of this cytochrome P450 isoenzyme polymorphism could be useful for individualising doses of sirolimus.

1. Le Meur Y, *et al.* CYP3A5*3 influences sirolimus oral clearance in de novo and stable renal transplant recipients. *Clin Pharmacol Ther* 2006; 80: 51–60.

Therapeutic drug monitoring. The immunosuppressive efficacy and the occurrence and severity of adverse effects of sirolimus correlate with blood concentrations.[1] There is also a good correlation between sirolimus trough concentrations and the area under the concentration-time curve (AUC); the trough concentration is therefore a useful surrogate marker for sirolimus exposure.[2] When sirolimus is used with ciclosporin, whole blood trough concentrations of sirolimus between 4 and 12 nanograms/mL are associated with protection from acute rejection episodes and adverse events. Black patients may require higher doses of sirolimus to achieve a similar exposure to non-black patients; trough concentrations in the higher end of the range are recommended to reduce the risk of rejection.[3] When ciclosporin therapy is stopped, a target trough concentration of sirolimus of about 12 to 20 nanograms/mL is recommended (see also Uses and Administration, p. 1966.2).

Daily monitoring of sirolimus is not necessary due to the relatively long half-life of the drug (about 60 hours). Furthermore, sirolimus concentrations are variable early after transplantation due to physiological changes from surgery and concurrent dose adjustments in other immunosuppressants. The first sample should be taken about 4 days or more after the initial loading dose, and then weekly for the first month and every 2 weeks for the second month.[3] Monitoring is also necessary after changes in the dose of sirolimus or ciclosporin, or of their relative timing.[2,3]

After the first 2 months of dose titration, routine therapeutic drug monitoring is not considered necessary in all patients, although it is considered warranted in patients receiving concurrent CYP3A4 and/or P-glycoprotein inducers or inhibitors. Monitoring may also be needed in those at high risk of rejection, those displaying signs of toxicity, or those in whom compliance is a problem.[3] Patients with liver disease, hyperlipidaemia, or leucopenia should also have their sirolimus blood concentrations determined,[2] and concentrations in children should be monitored.[3] Licensed product information states that the recommended 24-hour trough concentrations for sirolimus are based on chromatographic assay methods, and that these values are not interchangeable with immunoassay methods.

Limited sampling strategies based on two time points within 4 hours after dosing were found to be useful predictors of sirolimus exposure in kidney transplant recipients on calcineurin inhibitor-free immunosuppressive regimens;[4] Bayesian forecasting has also been proposed as an accurate predictor of sirolimus pharmacokinetics.[5,6]

1. Mahalati K, Kahan BD. Clinical pharmacokinetics of sirolimus. *Clin Pharmacokinet* 2001; 40: 573–85.
2. Oellerich M, Armstrong VW. The role of therapeutic drug monitoring in individualizing immunosuppressive drug therapy: recent developments. *Ther Drug Monit* 2006; 28: 720–5.
3. Stenton SB, *et al.* Sirolimus: the evidence for clinical pharmacokinetic monitoring. *Clin Pharmacokinet* 2005; 44: 769–86.
4. Cattaneo D, *et al.* Limited sampling strategies for the estimation of sirolimus daily exposure in kidney transplant recipients on a calcineurin inhibitor-free regimen. *J Clin Pharmacol* 2009; 49: 773–81.
5. Dansirikul C, *et al.* A Bayesian approach for population pharmacokinetic modelling of sirolimus. *Br J Clin Pharmacol* 2006; 62: 420–34.
6. Djebli N, *et al.* Sirolimus population pharmacokinetic/pharmacogenetic analysis and Bayesian modelling in kidney transplant recipients. *Clin Pharmacokinet* 2006; 45: 1135–48.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Rapamune; *Austral.*: Rapamune; *Austria*: Rapamune; *Belg.*: Rapamune; *Braz.*: Rapamune; *Canad.*: Rapamune; *Chile*: Rapamune; *China*: Rapamune (雷帕鸣); Rui Pa Ming (瑞帕明); Saimosi (赛莫司); Yixinke (宜欣可); *Cz.*: Rapamune; *Denm.*: Rapamune; *Fin.*: Rapamune; *Fr.*: Rapamune; *Ger.*: Rapamune; *Gr.*: Rapamune; *Hong Kong*: Rapamune; *Hung.*: Rapamune; *India*: Rapamune; *Irl.*: Rapamune; *Israel*: Rapamune; *Ital.*: Rapamune; *Malaysia*: Rapamune; *Mex.*: P-Hysplan; Rapamune; Renacept; *Neth.*: Rapamune; *Norw.*: Rapamune; *NZ*: Rapamune; *Philipp.*: Rapamune; *Pol.*: Rapamune; *Port.*: Rapamune; *Rus.*: Rapamune (Рапамун); *S.Afr.*: Rapamune; *Singapore*: Rapamune; *Spain*: Rapamune; *Swed.*: Rapamune; *Switz.*: Rapamune; *Thal.*: Rapamune; *Turk.*: Rapamune; *UK*: Rapamune; *USA*: Rapamune; *Venez.*: Rapamune.

Tacrolimus *(BAN, USAN, rINN)*

FK-506; FR-900506; Tacrolimús; Tacrolimusum; Takrolimus; Takrolimuusi; Tsukubaenolide; Такролимус.

(-)-(3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26a*S*)-8-Allyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(*E*)-2-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylvinyl]-14,16,-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3*H*-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4*H*,23*H*)-tetrone monohydrate.

$C_{44}H_{69}NO_{12}.H_2O$=822.0

CAS — 104987-11-3 (anhydrous tacrolimus); 109581-93-3 (tacrolimus monohydrate).

ATC — D11AH01; L04AD02.

ATC Vet — QD11AH01; QL04AD02.

UNII — WM0HAQ4WNM (tacrolimus); Y5L2157C4J (anhydrous tacrolimus).

Pharmacopoeias. In *US*.

USP 36: (Tacrolimus). Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Tacrolimus is a potent macrolide (macrolactam) immunosuppressant derived from *Streptomyces tsukubaensis*, and has actions similar to those of ciclosporin (see p. 1945.3). Tacrolimus binds to an intracellular protein, FKBP-12, and then forms a complex with calcium, calmodulin, and calcineurin, which inhibits the activity of calcineurin. This interferes with the production of lymphokines such as interleukin-2 and inhibits T-lymphocyte activation, resulting in immunosuppression.

Tacrolimus is used to prevent or treat rejection in patients receiving organ transplants, as indicated by the cross references given in Organ and Tissue Transplantation p. 1970.2. Tacrolimus has been tried in a few patients with refractory auto-immune or immune-mediated disorders; in some countries it is licensed for use in myasthenia gravis, in rheumatoid arthritis that is unresponsive to conventional therapy, in lupus nephritis where corticosteroids are ineffective or contra-indicated, and in corticosteroid-refractory ordependent ulcerative colitis. Tacrolimus is also applied topically in the management of moderate to severe atopic eczema. Tacrolimus-releasing stents have been developed to reduce restenosis after coronary artery stent placement.

UK licensed product information recommends that oral tacrolimus should be taken on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximum absorption. Different oral formulations of tacrolimus are not considered interchangeable and should be prescribed by brand name, see Oral Formulations, p. 1969.2.

For **prevention of rejection** after organ transplantation, in adult patients in the UK, the initial *oral* daily doses, to be given as an immediate-release formulation in 2 divided doses, are:

- *liver* transplantation: 100 to 200 micrograms/kg, starting about 12 hours after completion of surgery
- *kidney* transplantation: 200 to 300 micrograms/kg, starting within 24 hours of completion of surgery
- *heart* transplantation: 75 micrograms/kg, after antibody induction, and within 5 days of completion of surgery, and when the patient is stable

Alternatively, tacrolimus has been given within 12 hours of transplantation, in patients without other organ dysfunction, at an initial oral dose of 2 to 4 mg daily, with mycophenolate mofetil and corticosteroids, or with sirolimus and corticosteroids

If the patient's condition does not permit oral use, therapy may be given *intravenously*, by continuous 24-hour infusion, for up to 7 days; suggested initial adult daily doses are:

- *liver* transplantation: 10 to 50 micrograms/kg
- *kidney* transplantation: 50 to 100 micrograms/kg
- *heart* transplantation: 10 to 20 micrograms/kg

For **treatment of rejection**, increased tacrolimus doses, supplemental corticosteroid therapy, and short courses of monoclonal or polyclonal antibodies have been used. In patients being converted to tacrolimus from another immunosuppressant for the treatment of rejection after liver or kidney transplantation, treatment should begin with the initial oral dose recommended for primary immunosuppression. For heart transplant patients converted to tacrolimus, an initial oral dose of 150 micrograms/kg daily, in 2 divided doses, is recommended. UK dose recommendations for rejection therapy in other allografts are based on

limited data. The following initial *oral* daily doses of tacrolimus have been used:
- *lung* transplantation: 100 to 150 micrograms/kg
- *pancreatic* transplantation: 200 micrograms/kg
- *intestinal* transplantation: 300 micrograms/kg

In the USA, the following initial *oral* daily doses, given in 2 divided doses, are recommended for adult patients for the **prevention of rejection:**
- *liver* transplantation: 100 to 150 micrograms/kg, starting no sooner than 6 hours after transplantation
- *kidney* transplantation: 200 micrograms/kg when used with azathioprine, or 100 micrograms/kg when used with mycophenolate mofetil and an interleukin-2 receptor antagonist, starting within 24 hours of transplantation, but delayed if necessary until renal function has recovered
- *heart* transplantation: 75 micrograms/kg, starting no sooner than 6 hours after transplantation

For most transplant patients, initial oral therapy is recommended. If *intravenous* tacrolimus therapy is needed, the recommended starting daily doses, to be given as a continuous infusion, are:
- *liver* transplantation: 30 to 50 micrograms/kg, starting no sooner than 6 hours after transplantation
- *kidney* transplantation: 30 to 50 micrograms/kg, starting within 24 hours of transplantation, but delayed if necessary until renal function has recovered
- *heart* transplantation: 10 micrograms/kg, starting no sooner than 6 hours after transplantation

Tacrolimus doses are usually reduced in the post-transplant period; in some cases other immunosuppressant therapy can be stopped, leading to tacrolimus monotherapy or tacrolimus-based dual therapy. Maintenance dosage should be adjusted according to whole-blood trough concentrations in individual patients: it is suggested that most patients can be satisfactorily maintained at whole-blood trough concentrations below 20 nanograms/mL (for details see Therapeutic Drug Monitoring, p. 1974.2).

A prolonged-release *oral* formulation of tacrolimus is also available in the UK for the prevention of rejection in adult liver or kidney transplantation, and the treatment of allograft rejection (*Advagraf, Astellas*). The same initial daily dose as that recommended for the UK twice-daily immediate-release formulation is given once daily in the morning using prolonged-release capsules. Patients maintained on the twice-daily immediate-release formulation may also be converted to once-daily prolonged-release capsules at the same total daily dose. However, immediate-release and prolonged-release formulations are not considered interchangeable, and tacrolimus trough concentrations should be monitored to ensure similar systemic exposure is maintained. In the USA, a prolonged-release formulation is licensed for the prevention of rejection in kidney transplantation (*Astagraf, Astellas*). When used with basiliximab induction an initial oral dose of 150 micrograms/kg once daily is given before or within 48 hours of the transplant, but may be delayed until renal function has recovered. When basiliximab induction is not used, a pre-operative dose of 100 micrograms/kg is given within 12 hours before reperfusion; an initial postoperative dose of 200 micrograms/kg once daily is given at least 4 hours after the pre-operative dose and within 12 hours of reperfusion.

For doses used in paediatric transplant recipients, see Administration in Children, below.

For the treatment of **atopic eczema**, where conventional therapies are ineffective or unsuitable, *topical* tacrolimus may be applied thinly to the affected areas twice daily as a 0.03 or 0.1% ointment; an attempt should be made to use the lower strength or reduce the frequency of application when possible. For treatment in children, see Administration in Children, below. US licensed product information suggests treatment should be continued only until resolution of signs and symptoms. If clinical manifestations do not improve within 6 weeks, diagnosis of atopic eczema should be confirmed through re-examination. UK licensed product information recommends that if no signs of improvement are seen after 2 weeks of treatment, further treatment options should be considered.

In the UK, tacrolimus is also licensed for maintenance treatment; patients who have responded to up to 6 weeks of twice-daily treatment may thinly apply tacrolimus 0.1% ointment to areas usually affected by eczema twice weekly with 2 to 3 days between applications, for up to 12 months. During a flare, twice-daily treatment may be restarted.

Reviews.
1. Winkler M, Christians U. A risk-benefit assessment of tacrolimus in transplantation. *Drug Safety* 1995; 12: 348–57.
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4. Woo DK, James WD. Topical tacrolimus: a review of its uses in dermatology. *Dermatitis* 2005; 16: 6–21.
5. Simpson D, Noble S. Tacrolimus ointment: a review of its use in atopic dermatitis and its clinical potential in other inflammatory skin conditions. *Drugs* 2005; 65: 827–58.
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8. Chisholm MA, Middleton MD. Modified-release tacrolimus. *Ann Pharmacother* 2006; 40: 270–5.
9. Cross SA, Perry CM. Tacrolimus once-daily formulation: in the prophylaxis of transplant rejection in renal or liver allograft recipients. *Drugs* 2007; 67: 1931–43.
10. First MR. First clinical experience with the new once-daily formulation of tacrolimus. *Ther Drug Monit* 2008; 30: 159–66.

Administration. The mean dose of tacrolimus required to produce a standard trough concentration of 10 to 15 nanograms/mL was reported to be 96% higher in 7 black renal graft recipients than in 20 such patients of white or Asian descent.[1] (For mention of the effect of ethnicity on the bioavailability of tacrolimus see under Pharmacokinetics, p. 1974.1.)

Children generally require relatively higher doses than adults to achieve the same blood concentrations (see Administration in Children, below). There is limited evidence that children with hepatitis C required on average one-third of the dose of tacrolimus needed by children without the virus.[2]

1. Andrews PA, *et al.* Racial variation in dosage requirements of tacrolimus. *Lancet* 1996; 348: 1446.
2. Moreno M, *et al.* Monitoring of tacrolimus as rescue therapy in pediatric liver transplantation. *Ther Drug Monit* 1998; 20: 376–9.

ORAL FORMULATIONS. Tacrolimus has a narrow therapeutic index and even minor differences in blood concentrations have the potential to affect immunosuppression or cause adverse effects; inadvertent switching between different oral formulations has led to acute rejection and toxicity. Additionally, conventional preparations are immediate-release, twice-daily formulations, and these are not interchangeable with, nor licensed for quite the same indications as, the prolonged-release, once daily formulations available in some countries. The two formulations fulfil regulatory criteria for bioequivalence; however, studies in transplant recipients have shown reduced exposure to tacrolimus, with higher rates of acute rejection, on conversion from the conventional preparation to the prolonged-release formulation.[1]

The UK Commission on Human Medicines has advised that all oral tacrolimus products should be prescribed by brand name only.[2]

1. Barraclough KA, *et al.* Once- versus twice-daily tacrolimus: are the formulations truly equivalent? *Drugs* 2011; 71: 1561–77.
2. MHRA/CHM. Oral tacrolimus products: prescribe and dispense by brand name only, to minimise the risk of inadvertent switching between products, which has been associated with reports of toxicity and graft rejection. *Drug Safety Update* 2012; 5(11): A1. Available at: http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con157116.pdf (accessed 06/06/13)

Administration in children. For **prevention of rejection** after organ transplantation in paediatric patients in the UK, tacrolimus is given in the following initial *oral* daily doses, in 2 divided doses:
- *liver* transplantation: 300 micrograms/kg, starting about 12 hours after completion of surgery
- *kidney* transplantation: 300 micrograms/kg, starting within 24 hours of completion of surgery; a lower dose of 200 micrograms/kg has been used in adolescents to prevent very high trough concentrations
- *heart* transplantation, *after antibody induction*: 100 to 300 micrograms/kg, starting within 5 days of the completion of surgery, and when the patient is stable

If the patient's condition does not allow for oral use, therapy may be started *intravenously*, by continuous 24-hour infusion; intravenous therapy may be given for up to 7 days, but should be converted to oral therapy as soon as clinically possible. Suggested daily doses are:
- *liver* transplantation: 50 micrograms/kg
- *kidney* transplantation: 75 to 100 micrograms/kg

For *heart* transplantation *without antibody induction*, patients may be started on intravenous doses of 30 to 50 micrograms/kg daily, as a continuous 24-hour infusion. The first oral dose should be started 8 to 12 hours after stopping intravenous infusion, at a dose of 300 micrograms/kg daily, given in 2 divided doses.

For **treatment of rejection**, increased tacrolimus doses, supplemental corticosteroid therapy, and short courses of monoclonal or polyclonal antibodies have been used. In children being converted to tacrolimus from another immunosuppressant for the treatment of rejection after *liver* or *kidney* transplantation, treatment should begin with the initial oral dose recommended for primary immunosuppression. For paediatric *heart* transplant patients converted to tacrolimus, an initial oral dose of 200 to 300 micrograms/kg daily, in 2 divided doses, is recommended.

In the USA, the following *oral* daily doses, given in 2 divided doses, are recommended for children for the **prevention of rejection:**
- *liver* transplantation: 150 to 200 micrograms/kg, starting about 6 hours after transplantation

The *intravenous* dose is as for adults (see Uses and Administration, p. 1968.3).

Doses are adjusted according to whole-blood trough concentrations (see Therapeutic Drug Monitoring, p. 1974.2); children generally require doses per kg 1½ to 2 times higher than adults to achieve the same concentrations. Different oral formulations of tacrolimus are not considered interchangeable and should be prescribed by brand name, see Oral Formulations, above.

For the treatment of **atopic eczema**, where conventional therapies are ineffective or unsuitable, tacrolimus may be used *topically* in children aged 2 to 16 years as a 0.03% ointment applied thinly to the affected areas twice daily, for up to 3 weeks. In the UK this is then reduced to once daily until lesions clear. The 0.1% ointment is not licensed for use in children under 16, although it has been used (see Eczema, below). Initial treatment duration is as for adults (see Uses and Administration, p. 1968.3).

In the UK, tacrolimus is also licensed for maintenance treatment; children aged 2 to 16 years who have responded to up to 6 weeks of initial treatment may thinly apply tacrolimus 0.03% ointment to the areas commonly affected by eczema twice weekly with 2 to 3 days between applications, for up to 12 months. During a flare, twice-daily treatment may be restarted.

For reference to the development of lentigines in children given long-term treatment with the higher strength preparation see *Effects on the Skin* under Adverse Effects, p. 1972.2.

Children aged 16 years and older are treated as for adults (see Uses and Administration, p. 1968.3).

Eczema. Topical tacrolimus has been found to be safe and effective[1-4] for short-term use in the treatment of moderate to severe atopic eczema (p. 1684.1). In adult patients, 0.1% tacrolimus ointment applied to all affected areas was shown to have similar efficacy to 0.1% hydrocortisone butyrate ointment,[5] and be more effective than fluticasone 0.005% ointment (applied to the face),[6] or a combination of 0.1% hydrocortisone butyrate ointment (applied to the trunk and extremities) and 1% hydrocortisone acetate ointment (applied to the head and neck).[7] In 18 of 19 patients with facial atopic eczema resistant to 0.03% tacrolimus ointment,[8] there was significant improvement upon application of a 0.03% lotion formulation, and 6 patients were positive to a patch test for white petrolatum, an ingredient of the commercial ointment. A meta-analysis concluded that topical tacrolimus 0.1% was as effective as potent topical corticosteroids and more effective than mild topical corticosteroids for the treatment of eczema; however, tacrolimus was significantly more likely to cause skin burning than corticosteroids.[9] Another meta-analysis[10] found that 0.03% and 0.1% tacrolimus ointment were both more effective than topical hydrocortisone acetate 1% or pimecrolimus 1% in effecting remission of eczema in paediatric patients. However, there was no significant difference in efficacy between the two strengths of tacrolimus.

Results from a small, open-label study suggest that long-term intermittent use of tacrolimus ointment may reverse the skin atrophy induced by topical corticosteroids.[11] In other studies,[12,13] adult and paediatric patients (2 to 15 years of age) with atopic eczema were treated continuously or intermittently with twice-daily tacrolimus 0.1% ointment for up to 4 years. Although about half of the patients withdrew from the studies early, there was no indication of an increased risk of adverse effects with the long-term use of tacrolimus, nor was there an indication of an increased risk for any cutaneous infection with increased duration of exposure to tacrolimus.

Maintenance treatment with tacrolimus ointment 0.03% applied two or three times weekly has also been shown to be effective in preventing eczema exacerbations in children for up to 12 months.[14,15]

In general, however, long-term use of topical tacrolimus should be avoided because of concerns about potential carcinogenicity (see under Adverse Effects, p. 1971.2).

1. Gianni LM, Sulli MM. Topical tacrolimus in the treatment of atopic dermatitis. *Ann Pharmacother* 2001; 35: 943–6.
2. Allen BR. Tacrolimus ointment: its place in the therapy of atopic dermatitis. *J Allergy Clin Immunol* 2002; 109: 401–3.
3. Anonymous. Topical tacrolimus—a role in atopic dermatitis? *Drug Ther Bull* 2002; 40: 73–5.
4. Fleischer AB, Boguniewicz M. An approach to pruritus in atopic dermatitis: a critical systematic review of the tacrolimus ointment literature. *J Drugs Dermatol* 2010; 9: 488–98.
5. Reitamo S, *et al.* Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone butyrate ointment in adult patients with atopic dermatitis. *J Allergy Clin Immunol* 2002; 109: 547–55.
6. Doss N, *et al.* Superiority of tacrolimus 0.1% ointment compared with fluticasone 0.005% in adults with moderate to severe atopic dermatitis of the face: results from a randomized, double-blind trial. *Br J Dermatol* 2009; 161: 427–34.
7. Reitamo S, *et al.* A multicentre, randomized, double-blind, controlled study of long-term treatment with 0.1% tacrolimus ointment in adults

with moderate to severe atopic dermatitis. *Br J Dermatol* 2005; 152: 1282–9.
8. Sugiura H, *et al.* An open study of a lotion formulation to improve tolerance of tacrolimus in facial atopic dermatitis. *Br J Dermatol* 2001; 145: 795–8.
9. Ashcroft DM, *et al.* Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. *BMJ* 2005; 330: 516–22.
10. Yan J, *et al.* Meta-analysis of tacrolimus ointment for atopic dermatitis in pediatric patients. *Pediatr Dermatol* 2008; 25: 117–20.
11. Kyllönen H, *et al.* Effects of 1-year intermittent treatment with topical tacrolimus monotherapy on skin collagen synthesis in patients with atopic dermatitis. *Br J Dermatol* 2004; 150: 1174–81.
12. Hanifin JM, *et al.* US Tacrolimus Ointment Study Group. Efficacy and safety of tacrolimus ointment treatment for up to 4 years in patients with atopic dermatitis. *J Am Acad Dermatol* 2005; 53 (suppl 2): S186–S194.
13. Reitamo S, *et al.* 0.1% Tacrolimus Ointment Long-term Follow-up Study Group. A 4-year follow-up study of atopic dermatitis therapy with 0.1% tacrolimus ointment in children and adult patients. *Br J Dermatol* 2008; 159: 942–51.
14. Thaçi D, *et al.* European Tacrolimus Ointment Study Group. Proactive disease management with 0.03% tacrolimus ointment for children with atopic dermatitis: results of a randomized, multicentre, comparative study. *Br J Dermatol* 2008; 159: 1348–56.
15. Paller AS, *et al.* US Tacrolimus Ointment Study Group. Three times weekly tacrolimus ointment reduces relapse in stabilized atopic dermatitis: a new paradigm for use. *Pediatrics* 2008; 122: e1210–e1218.

Encephalitis. Compared with historical untreated controls, 7 patients with Rasmussen encephalitis (a progressive neurological disorder thought to have an auto-immune origin) had a superior outcome in terms of neurological function and progression rate of cerebral hemiatrophy after treatment with tacrolimus, but no better seizure outcome.[1] The control patients had more severe disease, but since only 1 patient on tacrolimus showed a cognitive decline, and none became eligible for hemispherectomy, the authors concluded prospective studies would be useful.

1. Bien CG, *et al.* An open study of tacrolimus therapy in Rasmussen encephalitis. *Neurology* 2004; 62: 2106–9.

Glomerular kidney disease. Tacrolimus has been reported[1–5] to be effective in inducing remission in patients with glomerular kidney disease (p. 1604.3); it has been used as monotherapy from first presentation, as well as in patients refractory to standard therapy, and in those with corticosteroid-dependent disease. However, a small, longitudinal study[6] in children with severe corticosteroid-dependent nephrotic syndrome given tacrolimus after inadequate response to ciclosporin, reported no better management of disease with tacrolimus, although it was beneficial for some children.

1. Segarra A, *et al.* Combined therapy of tacrolimus and corticosteroids in cyclosporin-resistant or -dependent idiopathic focal glomerulosclerosis: a preliminary uncontrolled study with prospective follow-up. *Nephrol Dial Transplant* 2002; 17: 655–62.
2. Duncan N, *et al.* Treatment of focal and segmental glomerulosclerosis in adults with tacrolimus monotherapy. *Nephrol Dial Transplant* 2004; 19: 3062–7.
3. Westhoff TH, *et al.* Tacrolimus in steroid-resistant and steroid-dependent nephrotic syndrome. *Clin Nephrol* 2006; 65: 393–400.
4. Bhimma R, *et al.* Management of steroid-resistant focal segmental glomerulosclerosis in children using tacrolimus. *Am J Nephrol* 2006; 26: 544–51.
5. Praga M, *et al.* Grupo Español de Estudio de la Nefropatía Membranosa. Tacrolimus monotherapy in membranous nephropathy: a randomized controlled trial. *Kidney Int* 2007; 71: 924–30.
6. Sinha MD, *et al.* Treatment of severe steroid-dependent nephrotic syndrome (SDNS) in children with tacrolimus. *Nephrol Dial Transplant* 2006; 21: 1848–54.

Hepatitis. In auto-immune chronic active hepatitis (p. 1602.3), some evidence suggests that tacrolimus may offer an alternative therapy when corticosteroids alone or with azathioprine do not suffice.

Ichthyosis. For mention of the use of tacrolimus in ichthyosis see p. 1685.1.

Inflammatory bowel disease. There are reports of response to tacrolimus in patients with inflammatory bowel disease (IBD; p. 1808.3). Tacrolimus has been given orally,[1–4] intravenously,[1] or topically,[5,6] in the treatment of ulcerative colitis[1,3,4] and Crohn's disease,[1–3,5,6] refractory to standard therapy. A systematic review[7] of 23 reports of tacrolimus use in 286 patients concluded that oral tacrolimus was a reasonable and effective alternative for fistulising Crohn's disease, although the evidence base was poor and comparative studies with infliximab were needed. Tacrolimus was also a possible alternative in IBD cases unresponsive to corticosteroids. Intravenous use was not deemed to confer any advantage over oral dosage; topical tacrolimus might be an option in certain cases.

1. Pellermann K, *et al.* Tacrolimus: a new immunosuppressant for steroid refractory inflammatory bowel disease. *Transplant Proc* 2001; 33: 2247–8.
2. Ierardi E, *et al.* Oral tacrolimus long-term therapy in patients with Crohn's disease and steroid resistance. *Aliment Pharmacol Ther* 2001; 15: 371–7.
3. Bousvaros A, *et al.* Oral tacrolimus treatment of severe colitis in children. *J Pediatr* 2000; 137: 794–9.
4. Ogata H, *et al.* A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut* 2006; 55: 1255–62. Correction. *ibid.*: 1684. [dosage error in abstract]
5. Casson DR, *et al.* Topical tacrolimus may be effective in the treatment of oral and perineal Crohn's disease. *Gut* 2000; 47: 436–40.
6. Hart AL, *et al.* Topical tacrolimus in the treatment of perianal Crohn's disease: exploratory randomized controlled trial. *Inflamm Bowel Dis* 2007; 13: 245–53.
7. Gonzalez-Lama Y, *et al.* The role of tacrolimus in inflammatory bowel disease: a systematic review. *Dig Dis Sci* 2006; 51: 1833–40.

Myasthenia gravis. Tacrolimus has been reported to be effective in the management of myasthenia gravis (p. 684.1) in patients resistant to conventional therapy, or for whom standard therapy is contra-indicated.[1,2] In an open-label study, 79 patients with myasthenia gravis, who had undergone thymectomy and were on high doses of prednisone and ciclosporin, were switched from ciclosporin to tacrolimus. Initial doses of tacrolimus were 100 micrograms/kg daily, given in 2 divided doses. Dosage was subsequently adjusted to achieve plasma concentrations between 7 and 8 nanograms/mL; tacrolimus doses of 6 to 10 mg daily were needed. After 1 year doses were reduced to achieve concentrations of about 6 nanograms/mL. Doses of prednisone were reduced, and finally withdrawn in all but 2 patients; 73 patients received tacrolimus for more than 3 years. All patients were able to resume normal daily activities.[3] Tacrolimus is licensed for use for myasthenia gravis in some countries, in a usual oral dose of 3 mg once daily. In these doses it was reported to reduce corticosteroid use in another small study; treatment was continued long-term and efficacy was maintained for up to 3 years.[4] There is some suggestion that tacrolimus may be more effective in thymomatous myasthenia gravis than in non-thymomatous disease.[5]

Tacrolimus has also been used as first-line adjunctive therapy with prednisolone; it was reported to decrease the daily prednisolone dose, and the need for plasmapheresis and high-dose intravenous methylprednisolone.[6]

1. Evoli A, *et al.* Successful treatment of myasthenia gravis with tacrolimus. *Muscle Nerve* 2002; 25: 111–14.
2. Shimojima Y, *et al.* Tacrolimus in refractory patients with myasthenia gravis: coadministration and tapering of oral prednisolone. *J Clin Neurosci* 2006; 13: 39–44.
3. Ponseti JM, *et al.* Long-term results of tacrolimus in cyclosporine- and prednisone-dependent myasthenia gravis. *Neurology* 2005; 64: 1641–3.
4. Tada M, *et al.* Long-term therapeutic efficacy and safety of low-dose tacrolimus (FK506) for myasthenia gravis. *J Neurol Sci* 2006; 247: 17–20.
5. Mitsui T, *et al.* Beneficial effect of tacrolimus on myasthenia gravis with thymoma. *Neurologist* 2007; 13: 83–6.
6. Nagane Y, *et al.* Efficacy of low-dose FK506 in the treatment of Myasthenia gravis—a randomized pilot study. *Eur Neurol* 2005; 53: 146–50.

Ocular disorders. For mention of the use of tacrolimus in various disorders characterised by ocular lesions such as uveitis, see p. 1932.1.

Organ and tissue transplantation. Tacrolimus has been used both for primary immunosuppression and for the control of graft rejection. Much of the initial experience with the drug was for liver grafts, (p. 1936.3), but it is also used in the transplantation of heart (p. 1934.2), kidney (p. 1935.2), lung (p. 1937.3), pancreas (p. 1938.1), and intestines (p. 1935.1). It has also been tried for the prophylaxis of graft-versus-host disease after bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p. 1933.1).

A few selected references to the use of tacrolimus in transplantation are given below.

1. European FK506 Multicentre Liver Study Group. Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. *Lancet* 1994; 344: 423–8.
2. The US Multicenter FK506 Liver Study Group. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression in liver transplantation. *N Engl J Med* 1994; 331: 1110–15.
3. Gruessner RW. Tacrolimus in pancreas transplantation: a multicenter analysis. *Clin Transplant* 1997; 11: 299–312.
4. Gruessner RWG, *et al.* Suggested guidelines for the use of tacrolimus in pancreas/kidney transplantation. *Clin Transplant* 1998; 12: 260–2.
5. Margreiter R. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre study. *Lancet* 2002; 359: 741–6.
6. O'Grady JG, *et al.* Tacrolimus versus microemulsified ciclosporin in liver transplantation: the TMC randomised controlled trial. *Lancet* 2002; 360: 1119–25.
7. Scott LJ, *et al.* Tacrolimus: a further update of its use in the management of organ transplantation. *Drugs* 2003; 63: 1247–97.
8. Kelly D, *et al.* Tacrolimus and steroids versus ciclosporin microemulsion, steroids, and azathioprine in children undergoing liver transplantation: randomised European multicentre trial. *Lancet* 2004; 364: 1054–61.
9. Webster AC, *et al.* Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. *BMJ* 2005; 331: 810–14.
10. McCormack PL, *et al.* Tacrolimus: in heart transplant recipients. *Drugs* 2006; 66: 2269–79.
11. Haddad E, *et al.* Cyclosporin versus tacrolimus for liver transplanted patients. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 18/03/08).
12. Wente MN, *et al.* Review of the clinical experience with a modified release form of tacrolimus [FK506E (MR4)] in transplantation. *Clin Transplant* 2006; 20 (suppl 17): 80–4.
13. Patel JK, Kobashigawa JA. Tacrolimus in heart transplant recipients: an overview. *BioDrugs* 2007; 21: 139–43.
14. Joseph A, *et al.* Tacrolimus immunosuppression in high-risk corneal grafts. *Br J Ophthalmol* 2007; 91: 51–5.
15. Bowman LJ, Brennan DC. The role of tacrolimus in renal transplantation. *Expert Opin Pharmacother* 2008; 9: 635–43.
16. Wallemacq P, *et al.* Opportunities to optimize tacrolimus therapy in solid organ transplantation: report of the European consensus conference. *Ther Drug Monit* 2009; 31: 139–52.
17. Fortune K, Couriel D. Tacrolimus in hematopoietic stem cell transplantation. *Expert Opin Drug Metab Toxicol* 2009; 5: 835–41.

Psoriasis. Tacrolimus has been shown to be effective in the treatment of psoriasis (p. 1688.1) when used orally[1] or topically.[2–7]

1. The European FK 506 Multicentre Psoriasis Study Group. System tacrolimus (FK 506) is effective for the treatment of psoriasis in a double-blind, placebo-controlled study. *Arch Dermatol* 1996; 132: 419–23.
2. Remitz A, *et al.* Tacrolimus ointment improves psoriasis in a microplaque assay. *Br J Dermatol* 1999; 141: 103–7.
3. Clayton TH, *et al.* Topical tacrolimus for facial psoriasis. *Br J Dermatol* 2003; 149: 419–20.
4. Brune A, *et al.* Tacrolimus ointment is effective for psoriasis on the face and intertriginous areas in pediatric patients. *Pediatr Dermatol* 2007; 24: 76–80.
5. Liao YH, *et al.* Comparison of cutaneous tolerance and efficacy of calcitriol 3 μg g^{-1} ointment and tacrolimus 0.3 mg g^{-1} ointment in chronic plaque psoriasis involving facial or genitofemoral areas: a double-blind, randomized controlled trial. *Br J Dermatol* 2007; 157: 1005–12.
6. Vissers WHPM, *et al.* Topical treatment of mild to moderate plaque psoriasis with 0.3% tacrolimus gel and 0.5% tacrolimus cream: the effect on SUM score, epidermal proliferation, keratinization, T-cell subsets and HLA-DR expression. *Br J Dermatol* 2008; 158: 705–12.
7. Bissonnette R, *et al.* Efficacy and tolerability of topical tacrolimus ointment for the treatment of male genital psoriasis. *J Cutan Med Surg* 2008; 12: 230–4.

Pyoderma gangrenosum. There are reports of response to tacrolimus, given orally,[1–3] or topically,[4–9] or both,[10,11] in patients with pyoderma gangrenosum (p. 1688.3). A small study[12] found topical tacrolimus 0.3% in carmellose sodium paste to be more effective than clobetasol propionate 0.05% for peristomal pyoderma gangrenosum.

Systemic absorption, resulting in tacrolimus blood concentrations equivalent to oral dosing, has been reported in patients with pyoderma gangrenosum in whom tacrolimus was applied directly onto ulcerated areas;[13,14] therapeutic drug monitoring has been suggested for patients treated with topical tacrolimus over large skin areas or with impaired skin barriers.

1. Abu-Elmagd K, *et al.* Resolution of severe pyoderma gangrenosum in a patient with streaking leukocyte factor disease after treatment with tacrolimus (FK 506). *Ann Intern Med* 1993; 119: 595–8.
2. D'Incà R, *et al.* Tacrolimus to treat pyoderma gangrenosum resistant to cyclosporine. *Ann Intern Med* 1998; 128: 783–4.
3. Lyon CC, *et al.* Recalcitrant pyoderma gangrenosum treated with systemic tacrolimus. *Br J Dermatol* 1999; 140: 562–4.
4. Schuppe H-C, *et al.* Topical tacrolimus for pyoderma gangrenosum. *Lancet* 1998; 351: 832.
5. Reich K, *et al.* Topical tacrolimus for pyoderma gangrenosum. *Br J Dermatol* 1998; 139: 755–7.
6. Vidal D, Alomar A. Successful treatment of periostomal pyoderma gangrenosum using topical tacrolimus. *Br J Dermatol* 2004; 150: 387–8.
7. Lally A, *et al.* Penile pyoderma gangrenosum treated with topical tacrolimus. *Arch Dermatol* 2005; 141: 1175–6.
8. Chiba T, *et al.* Topical tacrolimus therapy for pyoderma gangrenosum. *J Dermatol* 2005; 32: 199–203.
9. Kontos AP, *et al.* An open-label study of topical tacrolimus ointment 0.1% under occlusion for the treatment of pyoderma gangrenosum. *Int J Dermatol* 2006; 45: 1383–5.
10. Jolles S, *et al.* Combination oral and topical tacrolimus in therapy resistant pyoderma gangrenosum. *Br J Dermatol* 1999; 140: 564–5.
11. Deckers-Kocken JM, Pasmans SG. Successful tacrolimus (FK506) therapy in a child with pyoderma gangrenosum. *Arch Dis Child* 2005; 90: 531.
12. Lyon CC, *et al.* Topical tacrolimus in the management of peristoma pyoderma gangrenosum. *J Dermatol Treat* 2001; 12: 13–17.
13. Ghislain P-D, *et al.* Efficacy and systemic absorption of topical tacrolimus used in pyoderma gangrenosum. *Br J Dermatol* 2004; 150: 1052–3.
14. Pitarch G, *et al.* Systemic absorption of topical tacrolimus in pyoderma gangrenosum. *Acta Derm Venereol* 2006; 86: 64–5.

Reperfusion and revascularisation procedures. References to the use of tacrolimus-eluting stents.

1. García-Tejada J, *et al.* Carbo-stent liberador de tacrolimus Janus resultados inmediatos y seguimiento clínico a medio plazo. *Rev Esp Cardiol* 2007; 60: 197–200.
2. Han Y-L, *et al.* Midterm outcomes of prospective, randomized, single-center study of the Janus tacrolimus-eluting stent for treatment of native coronary artery lesions. *Chin Med J (Engl)* 2007; 120: 552–6.
3. Tamburino C, *et al.* Real world safety and efficacy of the Janus Tacrolimus-Eluting stent: long-term clinical outcome and angiographic findings from the Tacrolimus-Eluting STent (TEST) registry. *Catheter Cardiovasc Interv* 2009; 73: 243–8.
4. Onuma Y, *et al.* MAHOROBA, first-in-man study: 6-month results of a biodegradable polymer sustained release tacrolimus-eluting stent in de novo coronary stenoses. *Eur Heart J* 2009; 30: 1477–85.

Rheumatoid arthritis. In a small, open-label study[1] of 12 patients with rheumatoid arthritis (p. 13.2) refractory to other disease-modifying antirheumatic drugs including ciclosporin, 7 had significant response to tacrolimus after treatment for 6 months, with 4 of these patients maintaining this response after 2 years of therapy. In a larger controlled study,[2] tacrolimus improved disease activity in patients with rheumatoid arthritis resistant to methotrexate. Similarly, an open-label multicentre study involving 80 patients with active disease inadequately responsive to methotrexate alone, addition of oral tacrolimus 3 mg daily to methotrexate therapy produced a clinical improvement in about half. The regimen was considered to be generally well tolerated.[3] Tacrolimus in an oral dose of 3 mg once daily has been licensed for use in refractory

rheumatoid arthritis in some countries; elderly patients may be given 1.5 mg once daily.[4,5]

1. Gremillion RB, *et al.* Tacrolimus (FK506) in the treatment of severe, refractory rheumatoid arthritis: initial experience in 12 patients. *J Rheumatol* 1999; **26**: 2352–6.
2. Furst DE, *et al.* Efficacy of tacrolimus in rheumatoid arthritis patients who have been treated unsuccessfully with methotrexate: a six-month, double-blind, randomized, dose-ranging study. *Arthritis Rheum* 2002; **46**: 2020–8.
3. Kremer JM, *et al.* Tacrolimus in rheumatoid arthritis patients receiving concomitant methotrexate: a six-month, open-label study. *Arthritis Rheum* 2003; **48**: 2763–8.
4. Curran MP, Perry CM. Tacrolimus: in patients with rheumatoid arthritis. *Drugs* 2005; **65**: 993–1001.
5. Kawai S, Yamamoto K. Safety of tacrolimus, an immunosuppressive agent, in the treatment of rheumatoid arthritis in elderly patients. *Rheumatology (Oxford)* 2006; **45**: 441–4.

Scleroderma. There are reports of response to tacrolimus in patients with scleroderma (p. 1938.3).

Skin disorders. Topical tacrolimus has been used to treat various skin disorders. Aside from its licensed use in eczema (p. 1969.3), and use in psoriasis and pyoderma gangrenosum (see p. 1970.3), there are reports of benefit in granuloma annulare,[1,2] lichen sclerosus,[3] lichen striatus,[4] pityriasis alba,[5] pityriasis lichenoides,[6] seborrhoeic dermatitis,[7] as well as the skin manifestations of angiolymphoid hyperplasia,[8] pruritus due to primary biliary cirrhosis,[9] and facial cutaneous lupus erythematosus.[10]

1. Barth W, Linse R. Topical tacrolimus in granuloma annulare and necrobiosis lipoidica. *Br J Dermatol* 2004; **150**: 792–4.
2. Jain S, Stephens CJM. Successful treatment of disseminated granuloma annulare with topical tacrolimus. *Br J Dermatol* 2004; **150**: 1042–3.
3. Hengge UR, *et al.* Multicentre, phase II trial on the safety and efficacy of topical tacrolimus ointment for the treatment of lichen sclerosus. *Br J Dermatol* 2006; **155**: 1021–8.
4. Sorgentini C, *et al.* Lichen striatus in an adult: successful treatment with tacrolimus. *Br J Dermatol* 2004; **150**: 776–7.
5. Rigopoulos D, *et al.* Tacrolimus ointment 0.1% in pityriasis alba: an open-label, randomized, placebo-controlled study. *Br J Dermatol* 2006; **155**: 152–5.
6. Simon D, *et al.* Successful treatment of pityriasis lichenoides with topical tacrolimus. *Br J Dermatol* 2004; **150**: 1033–5.
7. Braza TJ, *et al.* Tacrolimus 0.1% ointment for seborrhoeic dermatitis: an open-label pilot study. *Br J Dermatol* 2003; **148**: 1242–4.
8. Mashiko M, *et al.* A case of angiolymphoid hyperplasia with eosinophilia successfully treated with tacrolimus ointment. *Br J Dermatol* 2006; **154**: 803–4.
9. Aguilar-Bernier M, *et al.* Successful treatment of pruritus with topical tacrolimus in a patient with primary biliary cirrhosis. *Br J Dermatol* 2005; **152**: 808–9.
10. Tzung T-Y, *et al.* Tacrolimus vs. clobetasol propionate in the treatment of facial cutaneous lupus erythematosus: a randomized, double-blind, bilateral comparison study. *Br J Dermatol* 2007; **156**: 191–2.

Adverse Effects, Treatment, and Precautions

The most common adverse effects after systemic use of tacrolimus include tremor, headache, paraesthesias, nausea and diarrhoea, hypertension, insomnia, and renal impairment. Disturbances of serum electrolytes, notably hyperkalaemia, and hyperglycaemic conditions, including diabetes mellitus, occur frequently. Hyperlipidaemia, hypercholesterolaemia, and hypertriglyceridaemia are common. Anaemia, leucopenia, and thrombocytopenia also occur commonly. Other common adverse effects include mood changes, anxiety, confusion, dizziness, tinnitus and hearing loss, visual disturbances, peripheral neuropathies, and convulsions; constipation, dyspepsia, gastrointestinal perforation and ulceration, and gastrointestinal haemorrhage; dyspnoea, parenchymal lung disorders, pleural effusions, pharyngitis, cough, nasal congestion and inflammation; alopecia, acne, skin rashes, and pruritus; and arthralgia, muscle cramps, asthenia, febrile disorders, oedema, ascites and liver dysfunction.

Thromboembolic and ischaemic events, and tachycardia are common; ventricular arrhythmias, cardiac arrest, heart failure, palpitations, and ECG changes are less frequent. Tacrolimus may prolong the QT interval. Cardiomyopathies, including ventricular hypertrophy have also been reported; most cases have been reversible, and occurred mainly with tacrolimus blood concentrations much higher than the recommended maximum levels. Coagulation disorders, neutropenia, and pancytopenia have occurred, as have asthma, acute respiratory distress syndrome, hypoproteinaemia, dysmenorrhoea, uterine bleeding, deep limb venous thrombosis, paralytic ileus, acute and chronic pancreatitis, peritonitis, and haemolytic uraemic syndrome. There are rare reports of thrombotic thrombocytopenic purpura, hypoprothrombinaemia, and hirsutism. Toxic epidermal necrolysis, Stevens Johnson syndrome, hepatic artery thrombosis, and veno-occlusive liver disease have also occurred rarely.

CNS adverse effects including coma, paralysis, CNS haemorrhage, amnesia, and speech and language abnormalities have been reported with tacrolimus. Posterior reversible encephalopathy syndrome (PRES) has also developed during treatment; symptoms include headache, altered mental status, seizures, and visual disturbances. Magnetic resonance imaging should be carried out in patients with symptoms of PRES, and if diagnosed, tacrolimus treatment should be stopped. Most patients have recovered with supportive treatment such as blood pressure control.

Tacrolimus injection is formulated with polyoxyl castor oil and anaphylactoid reactions have occurred; prophylactic antihistamines may reduce the risk. When given orally, it is important to distinguish controlled-release from immediate-release formulations; serious adverse effects have resulted from confusion between the two.

Dosage reduction may be necessary in patients with hepatic impairment. Care is also required in patients with pre-existing renal impairment, and dosage reduction may prove advisable in such patients. Monitoring of blood concentrations of tacrolimus is recommended in all patients, especially during episodes of diarrhoea as concentrations may be significantly affected. Renal and hepatic function, blood pressure, blood glucose, electrolytes, haematological and cardiac function, as well as neurological and visual status, coagulation values, and plasma protein should be monitored regularly.

Immunosuppression, including tacrolimus treatment, is associated with an increased incidence of EBV-associated lymphoproliferative disorders, lymphoma, and other malignancies, particularly those of the skin. Excess exposure to UV light should be avoided during treatment, particularly with topical tacrolimus (see below). There is also an increased risk of infection, including activation of latent viral infections. These include JC virus-associated progressive multifocal leukoencephalopathy and BK virus-associated nephropathy that can lead to serious or fatal outcomes. Intra-uterine devices should be used with caution during immunosuppressive therapy as there is an increased risk of infection. Immunosuppressants may reduce the response to vaccines and the use of live vaccines should be avoided. Tacrolimus may affect visual or neurological function, and patients so affected should not drive or operate dangerous machinery.

Topical tacrolimus has been associated with local irritation such as burning sensations and pruritus, and skin disorders including acne, rosacea, and an increased incidence of herpes simplex and zoster infections, folliculitis, and impetigo. Lymphadenopathy, headache and 'flu-like' symptoms have also been reported. Facial flushing and skin irritation has been reported after consumption of alcohol. Exposure of the skin to sunlight should be minimised and the use of artificial sources of ultraviolet light avoided.

Skin infections should be treated before starting therapy with topical tacrolimus. It should not be used in immunocompromised patients or those with conditions that might increase systemic absorption of tacrolimus. It must also not be applied to pre-malignant or malignant skin conditions; some malignant skin conditions may mimic eczema.

Breast feeding. Tacrolimus is distributed into breast milk. Tacrolimus concentrations were measured in milk from a liver transplant recipient on a dose of 100 micrograms/kg daily. The authors estimated that the infant would ingest only 0.06% (60 nanograms/kg daily) of the mother's weight-adjusted dose. No adverse effects were noted in the infant at 2.5 months of age.[1]

Licensed product information recommends that women should avoid breast feeding while taking tacrolimus.

1. Prench AE, *et al.* Milk transfer and neonatal safety of tacrolimus. *Ann Pharmacother* 2003; **37**: 815–18.

Calcineurin inhibitor-induced pain syndrome. For discussion of the calcineurin inhibitor-induced pain syndrome, see Ciclosporin, p. 1949.1.

Carcinogenicity. The systemic use of tacrolimus increases the risk of malignancy.

Carcinogenicity studies in *animals* have also reported an increase in the incidence of malignancies associated with the topical calcineurin inhibitors, tacrolimus and pimecrolimus. As of December 2004 the FDA had received reports of 19 cases of lymphoma or cutaneous tumours associated with topical tacrolimus, of which 4 cases were a recurrence or aggravation of a pre-existing malignancy, and 3 other cases were confounded by other possible risk factors. At this same date, the FDA had also received reports of 10 cases of malignancy in patients treated with topical pimecrolimus, including 6 cutaneous tumours. Although the potential for systemic immunosuppression from topical use was unknown and the role of the drug in these cases was uncertain, the FDA recommended that topical calcineurin inhibitors should only be used as a second-line drug for short-term and intermittent treatment of eczema, and that they should not be used in immunocompromised patients or in children younger than 2 years of age.[1,2] Similar warnings have been issued in the European Union.[3] However, there has been some debate about the risk of malignancy associated with the topical use of these drugs, and several groups[4–6] have examined the evidence used by the FDA. They found that after topical application in humans the serum concentrations of these drugs were usually low or undetectable, that there was no evidence of systemic immunosuppression as measured by response to childhood immunisation and delayed hypersensitivity, no evidence of an increase in malignancy in clinical studies or compared with the general population, and that none of the reported lymphoma cases resembled the usual presentation and histology seen with systemic immunosuppression-associated lymphoma. They concluded that based on available data the risk of cancer from topical calcineurin inhibitors was theoretical and unknown. A review[7] of skin cancer risk found that there was no conclusive evidence from *rodent* studies to suggest that topical calcineurin inhibitors were associated with an increase in skin cancers, or a potentiation of UV-associated immunosuppression and carcinogenicity. There was also no evidence of an increased risk of skin cancer in human studies. In general, there seems to be agreement that long-term data are still needed to determine the carcinogenic risk, if there is any, from topical tacrolimus and pimecrolimus. Until long-term safety data are available some[8] consider that it would be prudent if topical calcineurin inhibitors were:

- not used in children under 2 years of age
- not used continuously for more than 6 weeks, with an application-free period of up to 2 weeks
- avoided in immunocompromised patients
- avoided in patients with neoplasia
- avoided in those with skin disorders liable to lead to increased systemic absorption

Patients should also be encouraged to use a broad-spectrum sunscreen daily on all sunlight-exposed skin.

1. FDA. Information for healthcare professionals: tacrolimus (marketed as *Protopic*) (issued June 2006). Available at: *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126497.htm* (accessed 05/08/10)
2. FDA. Alert for healthcare professionals: pimecrolimus (marketed as Elidel) (issued June 2006). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm153525.htm (accessed 05/08/10)
3. CSM/MHRA. Topical tacrolimus (Protopic) and pimecrolimus (Elidel): reports of malignancies. *Current Problems* 2006; **31**: 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 18/03/08)
4. Fonacier L, *et al.* Report of the Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2005; **115**: 1249–53.
5. Bieber T, *et al.* Consensus statement on the safety profile of topical calcineurin inhibitors. *Dermatology* 2005; **211**: 77–8.
6. Berger TG, *et al.* The use of topical calcineurin inhibitors in dermatology: safety concerns. Report of the American Academy of Dermatology Association Task Force. *J Am Acad Dermatol* 2006; **54**: 818–23.
7. Ring J, *et al.* Review of the potential photo-cocarcinogenicity of topical calcineurin inhibitors: position statement of the European Dermatology Forum. *J Eur Acad Dermatol Venereol* 2005; **19**: 663–71.
8. Ring J, *et al.* The US FDA 'black box' warning for topical calcineurin inhibitors: an ongoing controversy. *Drug Safety* 2008; **31**: 185–98.

Effects on the blood. Severe anaemia due to selective depression of erythropoiesis in a patient given tacrolimus resolved when tacrolimus was replaced with ciclosporin.[1] More generalised bone marrow suppression,[2] post-transplant thrombotic microangiopathy,[3] and red cell aplasia[4] have also been reported. Hypoplasia occurring in a liver transplant recipient,[5] was characterised by a slow but complete recovery after substituting tacrolimus with ciclosporin.

1. Winkler M, *et al.* Anaemia associated with FK 506 immunosuppression. *Lancet* 1993; **341**: 1035–6.
2. de-la-Serna-Higuera C, *et al.* Tacrolimus-induced bone marrow suppression. *Lancet* 1997; **350**: 714–15.
3. Trimarchi HM, *et al.* FK506-associated thrombotic microangiopathy: report of two cases and review of the literature. *Transplantation* 1999; **67**: 539–44.
4. Misra S, *et al.* Red cell aplasia in children on tacrolimus after liver transplantation. *Transplantation* 1998; **65**: 575–7.
5. Nosari A, *et al.* Bone marrow hypoplasia complicating tacrolimus (FK506) therapy. *Int J Hematol* 2004; **79**: 130–2.

Effects on carbohydrate metabolism. The development of diabetes mellitus after solid organ transplantation is common,[1,2] which may be attributed to the diabetogenic effects of immunosuppressive drugs. Incidence has appeared to be increased in both adult[3] and paediatric[4] renal transplant recipients given tacrolimus. However, a retrospective review[2] found no significant difference in incidence between patients receiving tacrolimus or ciclosporin but found instead a correlation between the absence of an antiproliferative agent and the development of diabetes. A retrospective study of liver transplant recipients found that, although those given tacrolimus had a greater incidence of diabetes mellitus, hepatitis C infection was the only factor predictive of its development.[1] In contrast, a meta-analysis[5] found the incidence of new-onset diabetes mellitus (NODM) to be significantly higher among patients receiving tacrolimus compared with those receiving ciclosporin after solid organ transplantation. An observational study[6] confirmed this finding, and found it to be unrelated to corticosteroid dosage, although relatively high doses of corticosteroids were used across the study. A

retrospective study[7] found tacrolimus to be significantly more diabetogenic than ciclosporin, even when corticosteroid dosing was lower with tacrolimus. An analysis of data for 8839 patients[8] found the risk of NODM to be greatest with high tacrolimus doses, but the increased risk versus ciclosporin was sustained even with lower tacrolimus doses. Higher corticosteroid doses potentiated the diabetogenic effect of tacrolimus, but even the lowest dosage group for tacrolimus and corticosteroids had higher rates of NODM than all ciclosporin groups; there was no association between corticosteroid dose and NODM for any dosage of ciclosporin. In a small, retrospective study,[9] conversion from tacrolimus to ciclosporin resulted in marked improvement of glucose metabolism, and even reversal of diabetes mellitus in a significant proportion of patients.

1. AlDosary AA, *et al.* Post-liver transplantation diabetes mellitus: an association with hepatitis C. *Liver Transpl* 2002; 8: 356–61.
2. First MR, *et al.* Posttransplant diabetes mellitus in kidney allograft recipients: incidence, risk factors, and management. *Transplantation* 2002; 73: 379–86.
3. Pirsch JD, *et al.* A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. *Transplantation* 1997; 63: 977–83.
4. Al-Uzri A, *et al.* Posttransplant diabetes mellitus in pediatric renal transplant recipients: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Transplantation* 2001; 72: 1020–4.
5. Heisel O, *et al.* New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. *Am J Transplant* 2004; 4: 583–95.
6. Kamar N, *et al.* Diapason Study Group. Diabetes mellitus after kidney transplantation: a French multicentre observational study. *Nephrol Dial Transplant* 2007; 22: 1986–93.
7. Hoitsma AJ, Hilbrands LB. Relative risk of new-onset diabetes during the first year after renal transplantation in patients receiving tacrolimus or cyclosporine immunosuppression. *Clin Transplant* 2006; 20: 659–64.
8. Burroughs TE, *et al.* Influence of early posttransplantation prednisone and calcineurin inhibitor dosages on the incidence of new-onset diabetes. *Clin J Am Soc Nephrol* 2007; 2: 517–23.
9. Bouchta NB, *et al.* Conversion from tacrolimus to cyclosporin is associated with a significant improvement of glucose metabolism in patients with new-onset diabetes mellitus after renal transplantation. *Transplant Proc* 2005; 37: 1857–60.

Effects on the cardiovascular system. Hypertrophic cardiomyopathy, and in some cases heart failure, has been described in paediatric patients receiving tacrolimus after organ grafting (small bowel or liver).[1] Symptoms largely resolved on stopping or reducing dosage. A similar case had been found *post mortem* in an adult,[2] and the UK CSM[3] was aware of 29 reported cases worldwide as of July 1995. Echocardiographic monitoring of patients receiving tacrolimus has been recommended, with dose reduction or withdrawal in those who developed hypertrophic changes.[3] However, echocardiographic abnormalities may be quite common after orthotopic liver transplantation in adults, with no obvious relationship to the use of tacrolimus,[4] and a retrospective analysis concluded that tacrolimus is not a risk factor for hypertrophic cardiomyopathy in adult transplant recipients.[5]

Severe hypertension was documented in 5 out of 10 paediatric patients who received intravenous tacrolimus after renal transplant surgery. All patients responded to intravenous labetalol. By contrast none of 11 children who received ciclosporin at the same institution developed hypertension.[6] However, a review[7] concluded that tacrolimus causes less hypertension than ciclosporin, resulting in a better cardiovascular risk profile in renal transplant recipients, and possibly ultimately prolonging graft survival.

1. Atkison P, *et al.* Hypertrophic cardiomyopathy associated with tacrolimus in paediatric transplant patients. *Lancet* 1995; 345: 894–6.
2. Natazuka T, *et al.* Immunosuppressive drugs and hypertrophic cardiomyopathy. *Lancet* 1995; 345: 1644.
3. CSM/MCA. Tacrolimus (Prograf) and hypertrophic cardiomyopathy in transplant patients. *Current Problems* 1995; 21: 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 18/03/08)
4. Dollinger MM, *et al.* Tacrolimus and cardiotoxicity in adult liver transplant recipients. *Lancet* 1995; 346: 507.
5. Coley KC, *et al.* Lack of tacrolimus-induced cardiomyopathy. *Ann Pharmacother* 2001; 35: 985–9.
6. Booth CJ, *et al.* Intravenous tacrolimus may induce severe hypertension in renal transplant recipients. *Arch Dis Child* 1999; 80 (suppl 1): A27.
7. Koomans HA, Ligtenberg G. Mechanisms and consequences of arterial hypertension after renal transplantation. *Transplantation* 2001; 72 (suppl): S9–12.

Effects on the kidneys. A comparison in patients who had undergone liver transplantation suggested that nephrotoxicity was more of a problem in those receiving tacrolimus than in those given a ciclosporin-based regimen.[1] In particular intravenous tacrolimus during the first week after transplantation was associated with acute renal failure in 4 of 20 patients. Furthermore, on follow-up for 1 year, GFR was somewhat lower in the tacrolimus-treated group. A small study compared GFR and effective renal plasma flow (ERPF), at various stages after transplantation, in renal and liver transplant recipients given tacrolimus.[2] In renal transplant patients, the GFR, although lower than normal, was increased after transplant, and remained stable over 3 months. ERPF, however, was significantly lower at 3 months. In liver transplant recipients, despite being lower than normal, GFR and ERPF were unchanged at 1 year post-transplant.

1. Porayko MK, *et al.* Nephrotoxic effects of primary immunosuppression with FK-506 and cyclosporine regimens after liver transplantation. *Mayo Clin Proc* 1994; 69: 105–11.
2. Agarwala S, *et al.* Evaluation of renal function in transplant patients on tacrolimus therapy. *J Clin Pharmacol* 2002; 42: 798–805.

Effects on the nervous system. Although many of the symptoms of neurotoxicity induced by tacrolimus are similar to those of ciclosporin (p. 1950.2), some symptoms such as headaches, tremor, and sleep disturbances, appear to be more prevalent with tacrolimus, and the incidence of tacrolimus-induced neurotoxicity appears to be higher in liver transplant recipients.[1]

Severe peripheral neuropathy with signs of cerebral dysfunction has been reported in 2 patients receiving tacrolimus.[2] Among other central effects, tacrolimus has also been associated with speech disorders, including severe dysarthria and mutism;[3-6] some degree of speech dysfunction, in the form of an apparent Norwegian accent in one case,[3] may persist long-term.[3,5]

Encephalopathy, sometimes occurring within the reversible posterior leukoencephalopathy syndrome (RPLS), has been reported with use of tacrolimus.[7-11] Presenting symptoms included acute severe headache, seizures, cortical blindness, disorientation, and hypertension.

Miller Fisher syndrome, a variant of Guillain-Barré syndrome, has been attributed to tacrolimus use in a liver transplant recipient.[12] Clinical manifestations included ataxia, ophthalmoplegia, and areflexia.

1. Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. *Transpl Int* 2000; 13: 313–26.
2. Ayres RCS, *et al.* Peripheral neurotoxicity with tacrolimus. *Lancet* 1994; 343: 862–3.
3. Boeve BF, *et al.* Dysarthria and apraxia of speech associated with FK-506 (tacrolimus). *Mayo Clin Proc* 1996; 71: 969–72.
4. Bronster DJ, *et al.* Tacrolimus-associated mutism after orthotopic liver transplantation. *Transplantation* 2000; 70: 979–82.
5. Sokol DK, *et al.* Tacrolimus (FK506)-induced mutism after liver transplant. *Pediatr Neurol* 2003; 28: 156–8.
6. Chegounchi M, *et al.* Progressive neurological disease induced by tacrolimus in a renal transplant recipient: case presentation. *BMC Nephrol* 2006; 7: 7.
7. Klemenčič IM, *et al.* Acute headache as a presenting symptom of tacrolimus encephalopathy. *J Neurol Neurosurg Psychiatry* 2003; 74: 1126–7.
8. Nakazato T, *et al.* Reversible posterior leukoencephalopathy syndrome associated with tacrolimus therapy. *Intern Med* 2003; 42: 624–5.
9. Frühauf NR, *et al.* Late onset of tacrolimus-related posterior leukoencephalopathy after living donor liver transplantation. *Liver Transpl* 2003; 9: 983–5.
10. Schuuring J, *et al.* Severe tacrolimus leukoencephalopathy after liver transplantation. *Am J Neuroradiol* 2003; 24: 2085–8.
11. Lavigne CM, *et al.* Tacrolimus leukoencephalopathy: a neuropathologic confirmation. *Neurology* 2004; 63: 1132–3.
12. Kaushik P, *et al.* Miller Fisher variant of Guillain-Barré syndrome requiring a cardiac pacemaker in a patient on tacrolimus after liver transplantation. *Ann Pharmacother* 2005; 39: 1124–7.

Effects on skeletal muscle. Severe acute rhabdomyolysis, leading to fatal acute renal failure, developed in an 18-month-old child given tacrolimus after bone marrow transplantation.[1] Seizures, severe rhabdomyolysis, and acute renal failure were reported in a renal transplant patient taking tacrolimus and a monoclonal antibody.[2]

1. Hibi S, *et al.* Severe rhabdomyolysis associated with tacrolimus. *Lancet* 1995; 346: 702.
2. Fontana I, *et al.* Severe rhabdomyolysis and acute renal failure in a kidney transplant patient treated with tacrolimus and chimaeric CD25 monoclonal antibody. *Transplant Proc* 2004; 36: 711–2.

Effects on the skin. Three children developed lentigines (small pigmented macules) while receiving long-term (9 months to 4 years) treatment with topical tacrolimus 0.1% for eczema. The lesions developed mainly in the areas where tacrolimus had been applied. Despite withdrawal of tacrolimus, the lentigines still persisted at review 6 to 18 months later. The authors noted that use of tacrolimus was outside the product's licensed indications, and that the clinical implications of their findings remained uncertain.[1]

1. Hickey JR, *et al.* Does topical tacrolimus induce lentigines in children with atopic dermatitis? A report of three cases. *Br J Dermatol* 2005; 152: 152–4.

Hepatitis. For the suggestion that dosage requirements of tacrolimus may be reduced in children with hepatitis C see Administration, p. 1969.2.

Infection. For a report of an increased incidence of CMV disease in renal transplant recipients given a regimen combining tacrolimus and mycophenolate mofetil see under Interactions, p. 1964.2.

Overdosage. A report[1] of 12 cases of acute overdose with tacrolimus described overdoses of up to 30 times the prescribed dose. Three patients were asymptomatic, while 7 showed mild transient renal and hepatic impairment, nausea, and mild hand tremors. One patient suffered renal failure, histoplasmosis, and sepsis 48 hours after admission for the overdose. The outcome was unknown in one patient. All 8 symptomatic patients recovered when tacrolimus concentrations returned to normal. No specific treatment regimen has been recommended, but patients have been treated with gastric lavage, oral activated charcoal, and phenytoin. The latter is used both to prevent seizures and to enhance tacrolimus metabolism by stimulation of cytochrome P450. Patients should be closely monitored for known signs and symptoms of tacrolimus toxicity. In a further series of 5 cases,[2] acute ingestion of tacrolimus was reported to be well tolerated, and adequately managed with conservative treatment.

1. Curran CF, *et al.* Acute overdoses of tacrolimus. *Transplantation* 1996; 62: 1376.
2. Mrvos R, *et al.* Tacrolimus (FK 506) overdose: a report of five cases. *J Toxicol Clin Toxicol* 1997; 35: 395–9.

Porphyria. Data are limited on the use of tacrolimus in patients with porphyria. There has been a report of a patient with acute intermittent porphyria given tacrolimus for 5 days before renal transplantation, and maintenance tacrolimus post-transplantation, without exacerbation of symptoms.[1] The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tacrolimus as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[2]

1. Barone GW, *et al.* The tolerability of newer immunosuppressive medications in a patient with acute intermittent porphyria. *J Clin Pharmacol* 2001; 41: 113–5.
2. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Pregnancy. Tacrolimus crosses the placenta. Licensed product information states that, although *systemic* tacrolimus has shown abortifacient and teratogenic properties in *animal* studies, limited data in humans show no evidence of an increased risk of adverse effects on the course and outcome of pregnancy compared with other immunosuppressants. However, use of tacrolimus has been associated with neonatal hyperkalaemia, which appears to normalise spontaneously, and neonatal renal dysfunction; the neonate should be monitored for potential adverse effects.

There are no adequate data from the use of *topical* tacrolimus in pregnancy.

Further references.

1. Kainz A, *et al.* Review of the course and outcome of 100 pregnancies in 84 women treated with tacrolimus. *Transplantation* 2000; 70: 1718–21.
2. Jain AB, *et al.* Pregnancy after liver transplantation with tacrolimus immunosuppression: a single center's experience update at 13 years. *Transplantation* 2003; 76: 827–32.
3. Baumgart DC, *et al.* Uneventful pregnancy and neonatal outcome with tacrolimus in refractory ulcerative colitis. *Gut* 2005; 54: 1822–3.

Interactions

Increased nephrotoxicity may result if tacrolimus is given with other potentially nephrotoxic drugs: use with ciclosporin should be avoided for this reason. Similarly, concurrent use with neurotoxic drugs should be avoided. High potassium intake or potassium-sparing diuretics should also be avoided in patients receiving tacrolimus. Tacrolimus is extensively bound to plasma proteins and so has the potential to interact with other drugs that are highly protein bound.

Tacrolimus is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme system, such as azole antifungals, bromocriptine, calcium-channel blockers, cimetidine, some corticosteroids, ciclosporin, danazol, HIV-protease inhibitors, macrolide antibacterials, and metoclopramide, may produce increased blood concentrations of tacrolimus. The metabolism of tacrolimus may also be inhibited by grapefruit juice and they should not be taken together. Equally, inducers of this enzyme system (such as carbamazepine, phenobarbital, phenytoin, rifampicin, and St John's wort) may reduce blood concentrations of tacrolimus. Sirolimus can also decrease blood concentrations of tacrolimus. Corticosteroids may increase or decrease tacrolimus concentrations. Nevirapine and the NNRTI delavirdine may also affect tacrolimus concentrations. For a warning concerning the use of live vaccines in patients receiving immunosuppressants see Adverse Effects and Precautions, p. 1971.1.

Facial flushing or skin irritation may occur if alcohol is consumed by patients using topical tacrolimus.

The cytochrome P450 isoenzyme subfamily CYP3A, and P-glycoprotein, are involved in the pharmacokinetic pathways of tacrolimus.[1] Drugs that interact with these systems will probably affect tacrolimus concentrations, mainly by influencing oral bioavailability rather than clearance.[2] A study[3] *in vitro* found that metabolism of tacrolimus by CYP3A in human liver microsomes was inhibited by bromocriptine, corticosterone, dexamethasone, ergotamine, erythromycin, ethinylestradiol, josamycin, ketoconazole, miconazole, midazolam, nifedipine, omeprazole, tamoxifen, troleandomycin, and verapamil. No effect on tacrolimus metabolism was seen with aspirin, amphotericin B, captopril, cefotaxime, ciprofloxacin, diclofenac, diltiazem, doxycycline, furosemide, glibenclamide,

imipramine, lidocaine, paracetamol, prednisolone, progesterone, ranitidine, sulfamethoxazole, trimethoprim, or vancomycin.

1. van Gelder T. Drug interactions with tacrolimus. *Drug Safety* 2002; 25: 707–12.
2. Christians U, *et al.* Mechanisms of clinically relevant drug interactions associated with tacrolimus. *Clin Pharmacokinet* 2002; 41: 813–51.
3. Christians U, *et al.* Identification of drugs inhibiting the in vitro metabolism of tacrolimus by human liver microsomes. *Br J Clin Pharmacol* 1996; 41: 187–90.

Antibacterials. Increased concentrations of tacrolimus in plasma have been reported with *erythromycin*;[1] the interaction was accompanied by some evidence of nephrotoxicity. A similar interaction has been reported between tacrolimus and *clarithromycin*.[2,3] For reference to the effects of macrolides on tacrolimus metabolism *in vitro* see p. 1972.3.

Treatment with *rifampicin* has been found to substantially decrease tacrolimus concentrations.[4,5] A pharmacokinetic study found that rifampicin induces metabolism of tacrolimus in both the liver and intestine, probably by induction of the cytochrome P450 isoenzyme subfamily CYP3A and P-glycoprotein.[6] Both *metronidazole*[7,8] and *chloramphenicol*[9,10] increased the blood concentrations of tacrolimus. This is probably due to inhibition of metabolism, and dosage reduction of the immunosuppressant may be necessary when either drug is given with tacrolimus. A pharmacokinetic study[11] found that *levofloxacin* partially inhibited the metabolism of tacrolimus, and recommended that drug concentrations be monitored when these 2 drugs are used together.

Plasma concentrations of tacrolimus are also increased by *quinupristin/dalfopristin*.

1. Jensen C, *et al.* Interaction between tacrolimus and erythromycin. *Lancet* 1994; 344: 825.
2. Wolter K, *et al.* Interaction between FK 506 and clarithromycin in a renal transplant patient. *Eur J Clin Pharmacol* 1994; 47: 207–8.
3. Ibrahim RB, *et al.* Tacrolimus-clarithromycin interaction in a patient receiving bone marrow transplantation. *Ann Pharmacother* 2002; 36: 1971–2.
4. Purlan V, *et al.* Interactions between FK506 and rifampicin or erythromycin in pediatric liver recipients. *Transplantation* 1995; 59: 1217–18.
5. Chenhsu R-Y, *et al.* Renal allograft dysfunction associated with rifampin-tacrolimus interaction. *Ann Pharmacother* 2000; 34: 27–31.
6. Hebert MF, *et al.* Effects of rifampin on tacrolimus pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 1999; 39: 91–6.
7. Herzig K, Johnson DW. Marked elevation of blood cyclosporin and tacrolimus levels due to concurrent metronidazole therapy. *Nephrol Dial Transplant* 1999; 14: 521–3.
8. Page RL, *et al.* Potential elevation of tacrolimus trough concentrations with concomitant metronidazole therapy. *Ann Pharmacother* 2005; 39: 1109–13.
9. Schulman SL, *et al.* Interaction between tacrolimus and chloramphenicol in a renal transplant recipient. *Transplantation* 1998; 65: 1397–8.
10. Mathis AS, *et al.* Interaction of chloramphenicol and the calcineurin inhibitors in renal transplant recipients. *Transpl Infect Dis* 2002; 4: 169–74.
11. Federico S, *et al.* Pharmacokinetic interaction between levofloxacin and ciclosporin or tacrolimus in kidney transplant recipients: ciclosporin, tacrolimus and levofloxacin in renal transplantation. *Clin Pharmacokinet* 2006; 45: 169–75.

Antidepressants. Tacrolimus trough concentrations reduced sharply in a patient who took *St John's wort*, and returned to previous levels on stopping the St John's wort.[1] St John's wort induces cytochrome P450 isoenzyme CYP3A4, enhancing the metabolism of tacrolimus. A pharmacokinetic study[2] confirmed this, finding an increase in tacrolimus clearance; the authors concluded that potential consequences of this interaction in transplant recipients are rejection and graft loss.

1. Bolley R, *et al.* Tacrolimus-induced nephrotoxicity unmasked by induction of the CYP3A4 system with St John's wort. *Transplantation* 2002; 73: 1009.
2. Hebert MF, *et al.* Effects of St. John's wort (Hypericum perforatum) on tacrolimus pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2004; 44: 89–94.

Antiepileptics. For the effect of tacrolimus on *phenytoin* plasma concentrations, see Immunosuppressants in Phenytoin, p. 545.1.

Antifungals. Elevated plasma-tacrolimus concentrations have been reported in patients given *clotrimazole*,[1] *fluconazole*,[2] or *voriconazole*[3]; a reduction in the dose of tacrolimus was likely to be necessary if it were given with an azole antifungal. A study involving tacrolimus and *ketoconazole* suggested that an increase in the oral bioavailability of tacrolimus from a mean of 14 to 30% when given with the azole was probably due to decreased cytochrome P450 isoenzyme CYP3A4 metabolism in the gut wall, or improved absorption due to inhibition of P-glycoprotein mediated efflux, rather than an effect on hepatic metabolism.[4] Similarly, a 50% reduction in tacrolimus dosage was found to be necessary when the drug was given with *itraconazole*.[5] It has been suggested that the interaction could be exploited to reduce the cost of immunosuppressant regimens.[6] In another study of itraconazole with tacrolimus,[7] 1 patient required a 20% increase in the dose of tacrolimus, 3 patients required no dose adjustment, and 5 patients required tacrolimus dose reductions, ranging from 20 to 76.5%. The authors concluded that the magnitude of the dose reduction is dependent on the initial tacrolimus serum concentration and the final target concentration.

1. Mieles L, *et al.* Interaction between FK506 and clotrimazole in a liver transplant recipient. *Transplantation* 1991; 52: 1086–7.
2. Mañez R, *et al.* Fluconazole therapy in transplant recipients receiving FK506. *Transplantation* 1994; 57: 1521–3.
3. Venkataramanan R, *et al.* Voriconazole inhibition of the metabolism of tacrolimus in a liver transplant recipient and in human liver microsomes. *Antimicrob Agents Chemother* 2002; 46: 3091–3.
4. Floren LC, *et al.* Tacrolimus oral bioavailability doubles with coadministration of ketoconazole. *Clin Pharmacol Ther* 1997; 62: 41–9.
5. Capone D, *et al.* Effects of itraconazole on tacrolimus blood concentrations in a renal transplant recipient. *Ann Pharmacother* 1999; 33: 1124–5.
6. Kramer MR, *et al.* Dose adjustment and cost of itraconazole prophylaxis in lung transplant recipients receiving cyclosporine and tacrolimus (FK506). *Transplant Proc* 1997; 29: 2657–9.
7. Leather H, *et al.* Pharmacokinetic evaluation of the drug interaction between intravenous itraconazole and intravenous tacrolimus or intravenous cyclosporin A in allogeneic hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant* 2006; 12: 325–34.

Antivirals. Ten- to fiftyfold reductions in tacrolimus dosage were necessary to maintain therapeutic tacrolimus trough concentrations, in 6 HIV-positive liver transplant recipients receiving tacrolimus-based immunosuppressive therapy, when antiretroviral therapy including an HIV-protease inhibitor was started postoperatively.[1] This effect was more pronounced with *nelfinavir* than *indinavir*. In contrast, 4 HIV-positive kidney transplant recipients given antiretroviral therapy without HIV-protease inhibitors required only conventional doses of tacrolimus. The authors caution that some HIV-protease inhibitors can act as both inducers and inhibitors of the cytochrome P450 isoenzyme CYP3A4. While the inhibitory effect appears to predominate when given with tacrolimus, if the HIV-protease inhibitor is withdrawn suddenly the CYP3A4 system may remain induced, and a sudden decrease in tacrolimus concentration may occur; this had occurred in one case. For this reason, they concluded that great caution and frequent tacrolimus monitoring are necessary when HIV-protease inhibitors are introduced or withdrawn in transplant recipients receiving tacrolimus.

The potential interaction between tacrolimus and *atazanavir* in an HIV-positive renal transplant recipient was managed by monitoring serum concentrations of tacrolimus and modifying the tacrolimus dose accordingly; metabolism and elimination of tacrolimus were impaired in the presence of atazanavir.[2]

Dramatic increases in tacrolimus blood concentrations have been reported after addition of *lopinavir/ritonavir* in HIV-positive liver transplant recipients.[3-5] Some patients did not need further tacrolimus for up to 3 weeks, even with normal hepatic function; with hepatic dysfunction, 1 mg of tacrolimus provided a therapeutic concentration for up to 5 weeks, and in one patient the tacrolimus concentration increased for the next few days with the introduction of lopinavir/ritonavir without any additional dose of tacrolimus. The authors recommended a pre-emptive decrease in tacrolimus dose by at least 50% one day before starting therapy with lopinavir/ritonavir, and withholding tacrolimus for the next few days; therapy should then be guided by therapeutic drug monitoring of tacrolimus blood concentrations.[4] The usual dose of tacrolimus while a patient is on lopinavir/ritonavir is expected to be about 0.5 to 1 mg weekly.[3,4] In contrast, *efavirenz* did not appreciably affect tacrolimus pharmacokinetics.[5]

1. Jain AKB, *et al.* The interaction between antiretroviral agents and tacrolimus in liver and kidney transplant patients. *Liver Transpl* 2002; 8: 841–5.
2. Tsapepas DS, *et al.* Managing the atazanavir-tacrolimus drug interaction in a renal transplant recipient. *Am J Health-Syst Pharm* 2011; 68: 138–42.
3. Schonder KS, *et al.* Tacrolimus and lopinavir/ritonavir interaction in liver transplantation. *Ann Pharmacother* 2003; 37: 1793–6.
4. Jain AB, *et al.* Effect of coadministered lopinavir and ritonavir (Kaletra) on tacrolimus blood concentration in liver transplantation patients. *Liver Transpl* 2003; 9: 954–60.
5. Teicher E, *et al.* Effect of highly active antiretroviral therapy on tacrolimus pharmacokinetics in hepatitis C virus and HIV co-infected liver transplant recipients in the ANRS HC-08 study. *Clin Pharmacokinet* 2007; 46: 941–52.

Calcium-channel blockers. Dosage requirements for tacrolimus were substantially reduced in 22 liver graft recipients who also received *nifedipine*, compared with 28 patients given tacrolimus alone, in a 1-year retrospective study.[1]

Tacrolimus toxicity has been reported in a liver transplant patient shortly after starting *diltiazem*.[2]

1. Seifeldin RA, *et al.* Nifedipine interaction with tacrolimus in liver transplant recipients. *Ann Pharmacother* 1997; 31: 571–5.
2. Hebert MF, Lam AY. Diltiazem increases tacrolimus concentrations. *Ann Pharmacother* 1999; 33: 680–2.

Danazol. Nephrotoxicity and tremors associated with elevated concentrations of tacrolimus developed in a patient given danazol with the immunosuppressant.[1] The effect might have been due to inhibition of the metabolism of tacrolimus.

1. Shapiro R, *et al.* FK 506 interaction with danazol. *Lancet* 1993; 341: 1344–5.

Deoxyschizandrin. Mean blood concentrations of tacrolimus in 12 healthy subjects rose from 22.2 to 66.4 nanograms/mL after they had received 13 days of treatment with SchE (*Hezheng Pharmaceutical Company, China*), an extract of *Schisandra sphenanthera* containing amongst other ingredients deoxyschizandrin.[1] During the study the area under the concentration-time curve (AUC) of tacrolimus also rose by 164.2% while oral clearance fell by 49%. It was suggested that constituents of *Schisandra sphenanthera* may act as inhibitors of the cytochrome P450 isoenzyme CYP3A4 and/or P-glycoprotein.

1. Xin H-W, *et al.* Effects of *Schisandra sphenanthera* extract on the pharmacokinetics of tacrolimus in healthy volunteers. *Br J Clin Pharmacol* 2007; 64: 469–75.

Gastrointestinal drugs. In 2 renal transplant recipients, tacrolimus trough concentrations increased markedly after introduction of *lansoprazole* and returned to normal after it was stopped.[1,2] One of the patients was later given *rabeprazole* with no effect on tacrolimus concentration.[2] The same effects were apparent in a study of healthy subjects,[3] with lansoprazole increasing the concentration and decreasing the clearance of tacrolimus, but the degree of interaction was found to depend, at least partly, upon the genetic status of the patients. The authors supposed that certain ethnic groups might be at higher risk for this interaction. In contrast, rabeprazole appears less affected by genotypic status, and had minimal effect on tacrolimus pharmacokinetics; the authors considered it a safer proton pump inhibitor than lansoprazole for those with cytochrome P450 isoenzyme CYP2C19 gene mutation who were receiving tacrolimus. An *in-vitro* study suggested that omeprazole inhibited the metabolism of tacrolimus.[4] Despite a study reporting no clinically relevant interaction between omeprazole and tacrolimus in renal transplant recipients,[5] increased tacrolimus concentrations were reported when a paediatric liver transplant patient was started on omeprazole.[6]

1. Takahashi K, *et al.* Lansoprazole-tacrolimus interaction in Japanese transplant recipient with CYP2C19 polymorphism. *Ann Pharmacother* 2004; 38: 791–4.
2. Homma M, *et al.* Effects of lansoprazole and rabeprazole on tacrolimus blood concentration: case of a renal transplant recipient with CYP2C19 gene mutation. *Transplantation* 2002; 73: 303–4.
3. Itagaki F, *et al.* Effect of lansoprazole and rabeprazole on tacrolimus pharmacokinetics in healthy volunteers with CYP2C19 mutations. *J Pharm Pharmacol* 2004; 56: 1055–9.
4. Christians U, *et al.* Identification of drugs inhibiting the in vitro metabolism of tacrolimus by human liver microsomes. *Br J Clin Pharmacol* 1996; 41: 187–90.
5. Pascual J, *et al.* Interaction between omeprazole and tacrolimus in renal allograft recipients: a clinical-analytical study. *Transplant Proc* 2005; 37: 3752–3.
6. Moreau C, *et al.* Interaction between tacrolimus and omeprazole in a pediatric liver transplant recipient. *Transplantation* 2006; 81: 487–8.

Immunosuppressants. *Sirolimus* may decrease blood concentrations of tacrolimus; in stable renal transplant recipients given both drugs, mean exposure and trough concentrations of tacrolimus decreased by about 30% relative to tacrolimus alone. Tacrolimus may inhibit *ciclosporin* metabolism *in vitro*, with the possibility of increased nephrotoxicity (see under Ciclosporin, p. 1954.3). Tacrolimus may also increase concentrations of mycophenolic acid, a metabolite of *mycophenolate mofetil* (see under Mycophenolate Mofetil, p. 1964.2), and the risk of infection may be increased if used together.

Sevelamer. There was a progressive reduction in tacrolimus concentrations in a renal transplant patient after starting sevelamer, which was thought to be due to binding of tacrolimus in the gut.[1] Licensed product information for sevelamer suggests that it should be given at least 3 hours before or 1 hour after drugs for which a reduction in bioavailability could be clinically significant.

1. Merkle M, *et al.* The effect of sevelamer on tacrolimus target levels. *Transplantation* 2005; 80: 707.

Pharmacokinetics

Absorption of tacrolimus after oral doses is reported to be erratic. Oral bioavailability varies very widely; the mean value is in the range of 20 to 25%. The rate and extent of absorption of tacrolimus is decreased by the presence of food, with the effect most pronounced after a high-fat meal. There is little or no systemic exposure to tacrolimus after topical use (but see Absorption, p. 1974.1). After intravenous doses it is widely distributed to the tissues; it is extensively bound to erythrocytes in the blood, and variations in red cell binding account for much of the variability in pharmacokinetics. The portion in plasma is about 99% bound to plasma proteins. Tacrolimus is extensively metabolised in the liver, mainly by cytochrome P450 isoenzyme CYP3A4, and excreted, primarily in bile,

almost entirely as metabolites. Considerable metabolism also occurs in the intestinal wall. Whole-blood elimination half-life has been reported to average 43 hours in healthy subjects, and to range from about 12 to 16 hours in transplant patients.

References.
1. Gruber SA, *et al.* Pharmacokinetics of FK506 after intravenous and oral administration in patients awaiting renal transplantation. *J Clin Pharmacol* 1994; 34: 859–64.
2. Jusko WJ, *et al.* Pharmacokinetics of tacrolimus in liver transplant patients. *Clin Pharmacol Ther* 1995; 57: 281–90.
3. Venkataramanan R, *et al.* Clinical pharmacokinetics of tacrolimus. *Clin Pharmacokinet* 1995; 29: 404–30.
4. Wallemacq PE, Verbeeck RK. Comparative clinical pharmacokinetics of tacrolimus in paediatric and adult patients. *Clin Pharmacokinet* 2001; 40: 283–95.
5. Bekersky I, *et al.* Comparative tacrolimus pharmacokinetics: normal versus mildly hepatically impaired subjects. *J Clin Pharmacol* 2001; 41: 628–35.
6. Reding R, *et al.* Efficacy and pharmacokinetics of tacrolimus oral suspension in pediatric liver transplant recipients. *Pediatr Transplant* 2002; 6: 124–6.
7. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. *Clin Pharmacokinet* 2004; 43: 623–53.
8. Iwasaki K. Metabolism of tacrolimus (FK506) and recent topics in clinical pharmacokinetics. *Drug Metab Pharmacokinet* 2007; 22: 328–35.
9. Antignac M, *et al.* Population pharmacokinetics and bioavailability of tacrolimus in kidney transplant patients. *Br J Clin Pharmacol* 2007; 64: 750–7.
10. Undre NA, *et al.* Skin and systemic pharmacokinetics of tacrolimus following topical application of tacrolimus ointment in adults with moderate to severe atopic dermatitis. *Br J Dermatol* 2009; 160: 665–9.
11. Reitamo S, *et al.* The pharmacokinetics of tacrolimus after first and repeated dosing with 0.03% ointment in infants with atopic dermatitis. *Int J Dermatol* 2009; 48: 348–55.
12. Zhao W, *et al.* Population pharmacokinetics and pharmacogenetics of tacrolimus in de novo pediatric kidney transplant recipients. *Clin Pharmacol Ther* 2009; 86: 609–18.
13. Benkali K, *et al.* Tacrolimus population pharmacokinetic-pharmacogenetic analysis and Bayesian estimation in renal transplant recipients. *Clin Pharmacokinet* 2009; 48: 805–16.
14. Zheng S, *et al.* Pharmacokinetics of tacrolimus during pregnancy. *Ther Drug Monit* 2012; 34: 660–70.
15. Guy-Viterbo V, *et al.* Population pharmacokinetic analysis of tacrolimus in the first year after pediatric liver transplantation. *Eur J Clin Pharmacol* 2013; 69: 1533–42.

Absorption. A single topical application of a 0.1% tacrolimus ointment to an infant for the treatment of chronic dermatitis, resulted in high serum-tacrolimus concentrations (24 nanograms/mL). Tacrolimus levels decreased over 7 days, after which another smaller, single application of 0.03% tacrolimus ointment again resulted in high serum concentrations. The authors cautioned against its use in young children and diseases with decreased skin barrier function.[1] In another report,[2] elevated blood tacrolimus concentrations were seen after application of 0.1% tacrolimus ointment to a large area of the body of a patient with erythroderma; again, caution in conditions where the skin barrier is disrupted was advised.

1. Kameda G, *et al.* Unexpected high serum levels of tacrolimus after a single topical application in an infant. *J Pediatr* 2003; 143: 280. Correction. *ibid.*: 462.
2. Teshima D, *et al.* Increased topical tacrolimus absorption in generalized leukemic erythroderma. *Ann Pharmacother* 2003; 37: 1444–7.

Bioavailability. Bioavailability of tacrolimus appears to be influenced by the type and timing of meals. Food, particularly high-fat meals, significantly reduced bioavailability, compared with the fasting state.[1] Ingestion of tacrolimus up to 1.5 hours after a meal also considerably reduced absorption.[2] UK licensed product information states that tacrolimus should be taken on an empty stomach, or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption. Gastrointestinal metabolism of tacrolimus is thought to be extensive, significantly affecting its bioavailability,[3] and differences in this metabolism may account for apparent differences in availability according to ethnic origin.[4]

1. Bekersky I, *et al.* Effect of low- and high-fat meals on tacrolimus absorption following 5 mg single oral doses to healthy human subjects. *J Clin Pharmacol* 2001; 41: 176–82.
2. Bekersky I, *et al.* Effect of time of meal consumption on bioavailability of a single oral 5 mg tacrolimus dose. *J Clin Pharmacol* 2001; 41: 289–97.
3. Tuteja S, *et al.* The effect of gut metabolism on tacrolimus bioavailability in renal transplant recipients. *Transplantation* 2001; 71: 1301–7.
4. Mancinelli LM, *et al.* The pharmacokinetics and metabolic disposition of tacrolimus: a comparison across ethnic groups. *Clin Pharmacol Ther* 2001; 69: 24–31.

Genetic factors. Renal transplant recipients homozygous for CYP3A5*3 required lower doses to reach target trough concentrations of tacrolimus compared with CYP3A5*1 allele carriers;[1] the latter group can be expected to have a tacrolimus clearance 25 to 45% greater than that of homozygotes.[2] Determination of the cytochrome P450 isoenzyme genotype before transplantation may identify patients at risk for underimmunosuppression or toxicity.

1. Hesselink DA, *et al.* Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. *Clin Pharmacol Ther* 2003; 74: 245–54.
2. Utrecht KN, *et al.* Effects of genetic polymorphisms on the pharmacokinetics of calcineurin inhibitors. *Am J Health-Syst Pharm* 2006; 63: 2340–8.

Therapeutic drug monitoring. There is a good correlation between tacrolimus trough concentrations and systemic exposure, and analysis at other time points is not considered to offer any advantage.[1] However, since tacrolimus concentrations appear to be generally higher in the morning than the evening, some have suggested that the morning might be the best time for therapeutic drug monitoring.[2]

Microparticle enzyme immunoassay (MEIA) and enzyme-linked immunosorbent assay (ELISA) have both been used to measure tacrolimus whole blood concentrations. A study[3] of liver transplant recipients found that increasing trough tacrolimus concentrations, as measured by the ELISA, correlated with decreasing risk of acute rejection, but increasing risk of nephrotoxicity. The authors suggested a trough blood concentration of less than 15 nanograms/mL to minimise nephrotoxicity. While several studies have shown that adverse effects are more closely correlated with tacrolimus concentrations than with dose, the correlation between concentrations and allograft rejection has not been established. There is some suggestion that measuring the unbound concentration of tacrolimus may be a better correlate for rejection than whole blood concentrations.[4]

Licensed product information states that blood trough concentrations of tacrolimus should be monitored during the post-transplantation period; blood should be drawn just before the next dose. Samples which are not analysed immediately should be stored at room temperature or in a refrigerator and assayed within 7 days; if samples are to be kept for longer they may be frozen at -20 degrees for up to 6 months. The frequency of monitoring is based on clinical need; about twice-weekly during the early post-transplant period is recommended, followed by periodic monitoring during maintenance therapy. Trough concentrations should also be monitored after dose adjustment, although it may take several days before changes become apparent. Monitoring is also recommended when signs of toxicity or acute rejection are seen, after changes in the immunosuppressive regimen, or when other drugs are given which may alter tacrolimus blood concentrations. The majority of patients can be successfully managed if blood concentrations are maintained below 20 nanograms/mL. In practice, in the early post-transplant period, whole blood trough concentrations have generally been in the range of 5 to 20 nanograms/mL in liver transplant recipients, and 10 to 20 nanograms/mL in kidney and heart transplant recipients. A higher target range of 15 to 25 nanograms/mL is recommended in children after heart transplantation, when tacrolimus is given intravenously and antibody induction is not used. During maintenance therapy, blood concentrations have generally been between 5 and 15 nanograms/mL in liver, kidney, and heart transplant patients, although when tacrolimus is used with everolimus in liver transplantation, a lower tacrolimus target range of 3 to 5 nanograms/mL is recommended.

Bayesian forecasting[5,6] and limited sampling strategies (with samples taken 1.5 hours postdose and immediately predose)[7] have also been used to predict exposure to tacrolimus.

Licensed product information states that the relationship between tacrolimus trough concentrations and systemic exposure is similar for the standard formulation (*Prograf, Astellas*) and the prolonged-release formulation (*Advagraf* or *Astagraf, Astellas*), although they are not interchangeable (see Oral Formulations, p. 1969.2).

1. Oellerich M, Armstrong VW. The role of therapeutic drug monitoring in individualizing immunosuppressive drug therapy: recent developments. *Ther Drug Monit* 2006; 28: 720–5.
2. Baraldo M, Furlanut M. Chronopharmacokinetics of ciclosporin and tacrolimus. *Clin Pharmacokinet* 2006; 45: 775–88.
3. Venkataramanan R, *et al.* Clinical utility of monitoring tacrolimus blood concentrations in liver transplant patients. *J Clin Pharmacol* 2001; 41: 542–51.
4. Zahir H, *et al.* Factors affecting variability in distribution of tacrolimus in liver transplant recipients. *Br J Clin Pharmacol* 2004; 57: 298–309.
5. Fukudo M, *et al.* Forecasting of blood tacrolimus concentrations based on the Bayesian method in adult patients receiving living-donor liver transplantation. *Clin Pharmacokinet* 2003; 42: 1161–78.
6. Fukudo M, *et al.* Prospective evaluation of the Bayesian method for individualizing tacrolimus dose early after living-donor liver transplantation. *J Clin Pharmacol* 2009; 49: 789–97.
7. Mathew BS, *et al.* A limited sampling strategy for tacrolimus in renal transplant patients. *Br J Clin Pharmacol* 2008; 66: 467–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Litacro; Prograf; Protopic Tacraf†; Tacro-Tic; Tacroinmun; *Austral.*: Prograf; *Austria*: Advagraf; Prograf; Protopic; *Belg.*: Advagraf; Prograf; Protopic; *Braz.*: Prograf; Protopic; *Canad.*: Advagraf; Prograf; Protopic; *Chile*: Cromidin; Prograf; Protopic; T-Inmun; *China*: Advagraf (新普乐可复); Prograf (普乐可复); Protopic (普特彼); *Cz.*: Advagraf; Gecrol; Lecron; Modigraf; Prograf; Protopic; Tacni; *Denm.*: Advagraf; Prograf; Protopic; *Fin.*: Prograf; Protopic; Tacni; *Fr.*: Advagraf; Modigraf; Prograf; Protopic; *Ger.*: Advagraf; Modigraf; Prograf; Protopic; Tacpan; Tacro-cell; *Gr.*: Advagraf; Prograf; Protopic; *Hong Kong*: Advagraf; Prograf; Protopic; *Hung.*: Advagraf; Prograf; Protopic; *India*: Crolim; Mustopic; Olmis; PanGraf; Tacroz; *Indon.*: Prograf; Protopic; *Irl.*: Advagraf; Modigraf; Prograf; Protopic; Tacni; *Israel*: Prograf; Protopic; Tacrocel; *Ital.*: Advagraf; Lecron; Prograf; Protopic; *Jpn*: Graceptor; Prograf; Protopic; *Malaysia*: Prograf; Protopic; *Mex.*: Pramebin; Limustin; Lytomi-C; Octralin; Proalid; Prograf; Protopic; Traderma; *Neth.*: Advagraf; Modigraf; Prograf; Prograft; Protopic; Tacni; *Norw.*: Advagraf; Modigraf; Prograf; Protopic; Tacni; *NZ*: Prograf; *Philipp.*: Prograf; Protopic; Tacrocin; Tagraf; Vingraf; *Pol.*: Advagraf; Modigraf; Prograf; Protopic; *Port.*: Advagraf; Modigraf; Prograf; Protopic; *Rus.*: Advagraf (Адваграф); Prograf (Програф); Protopic (Протопик); *S.Afr.*: Prograf; Protopic; *Singapore*: Prograf; Protopic; *Spain*: Adoport; Advagraf; Modigraf; Prograf; Protopic; Tartrime; *Swed.*: Advagraf; Prograf; Protopic; Tacni; *Switz.*: Advagraf; Prograf; Protopic; *Thail.*: Advagraf; Prograf; Protopic; *Turk.*: Prograf; Protopic; *UK*: Adoport; Advagraf; Capexion; Modigraf; Perixis; Prograf; Protopic; Tacni; *Ukr.*: Prograf (Програф); Protopic (Протопик); *USA*: Astagraf; Prograf; Protopic; *Venez.*: Prograf.

Pharmacopoeial Preparations
USP 36: Tacrolimus Capsules; Tacrolimus Oral Suspension.

Umirolimus *(USAN, rINN)*

Biolimus; TRM-986; Umirolimús; Umirolimusum; Биолимус; Умиролимус.

(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-3-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-(2-Ethoxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-3,4,9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-octadecahydro-23,27-epoxy-5*H*-pyrido[2,1-*c*][1,4]oxazacyclohentriacontine-1,5,11,28,29(6*H*,31*H*)-pentone.

$C_{55}H_{87}NO_{14}$=986.3

CAS — 851536-75-9.

NOTE. The names Biolimus A9 and BA9 have been used as trade marks for umirolimus.

Profile

Umirolimus is an analogue of sirolimus (p. 1966.2). A umirolimus-eluting stent has been developed to reduce restenosis after coronary artery stent placement.

References.
1. Windecker S, *et al.* Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 2008; 372: 1163–73.
2. Ostojic M, *et al.* The pharmacokinetics of Biolimus A9 after elution from the Nobori stent in patients with coronary artery disease: the NOBORI PK study. *Catheter Cardiovasc Interv* 2008; 72: 901–8.
3. Verheye S, *et al.* 9-month clinical, angiographic, and intravascular ultrasound results of a prospective evaluation of the Axxess self-expanding biolimus A9-eluting stent in coronary bifurcation lesions: the DIVERGE (Drug-Eluting Stent Intervention for Treating Side Branches Effectively) study. *J Am Coll Cardiol* 2009; 53: 1031–9.
4. Wykrzykowska JJ, *et al.* Biolimus-eluting biodegradable polymer versus sirolimus-eluting permanent polymer stent performance in long lesions: results from the LEADERS multicentre trial substudy. *EuroIntervention* 2009; 5: 310–17.
5. Wykrzykowska JJ, *et al.* Impact of vessel size on angiographic and clinical outcomes of revascularization with biolimus-eluting stent with biodegradable polymer and sirolimus-eluting stent with durable polymer: the LEADERS trial substudy. *JACC Cardiovasc Interv* 2009; 2: 861–70.

Voclosporin *(USAN, rINN)*

ISA-247; ISATX-247; LX-211; R-1524; Voclosporina; Voclosporine; Voclosporinum; Вокльоспорин.

Cyclo(L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-[(2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)nona-6,8-dienoyl]-(2*S*)-2-aminobutanoyl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl).

$C_{63}H_{111}N_{11}O_{12}$=1214.6

CAS — 515814-01-4.

ATC — L04AD03.

ATC Vet — QL04AD03.

UNII — 2PN063X681.

NOTE. The name Luveniq has been used as a trade mark for voclosporin.

Profile

Voclosporin is an analogue of ciclosporin (p. 1945.2) that is under investigation for the treatment of uveitis, psoriasis, and for the prevention of rejection in organ transplantation.

References.
1. Dumont FJ. ISAtx-247 (Isotechnika/Roche). *Curr Opin Investig Drugs* 2004; 5: 542–50.

2. Anonymous. ISA 247: trans-ISA 247, trans-R 1524, ISA(TX)247, ISATx 247, ISATx247, LX 211, LX211, R 1524, R-1524. *Drugs R D* 2007; 8: 103–12.
3. Papp K, *et al.* Efficacy of ISA247 in plaque psoriasis: a randomised, multicentre, double-blind, placebo-controlled phase III study. *Lancet* 2008; 371: 1337–42.
4. Anglade E, *et al.* A new agent for the treatment of noninfectious uveitis: rationale and design of three LUMINATE (Lux Uveitis Multicenter Investigation of a New Approach to Treatment) trials of steroid-sparing voclosporin. *Clin Ophthalmol* 2008; 2: 693–702.
5. Deuter CME. Systemisches Voclosporin bei Uveitis. *Ophthalmologe* 2010; 107: 672–5.

Zotarolimus *(USAN, rINN)*

ABT-578; Zotarolimusum; Зотаролимус.

(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,27-Dihydroxy-10,21-dimethoxy-3-[(2*R*)-1-[(1*S*,3*R*,4*S*)-3-methoxy-4-(1*H*-tetrazol-1-yl)cyclohexyl]propan-2-yl]-6,8,12,14,20,26-hexamethyl-3,4,9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-octadecahydro-5*H*-23,27-epoxypyrido[2,1-*c*][1,4]oxaazahentriacontine-1,5,11,28,29(6*H*,31*H*)-pentone.

$C_{52}H_{79}N_5O_{12}$=966.2

CAS — 221877-54-9.

UNII — H4GXR80IZE.

Profile

Zotarolimus is an analogue of sirolimus (p. 1966.2) that is used in the form of a drug-eluting stent to reduce the risk of restenosis after percutaneous coronary stenting.

Reperfusion and revascularisation procedures. References to the use of zotarolimus-eluting stents.

1. Burke SE, *et al.* Zotarolimus (ABT-578) eluting stents. *Adv Drug Deliv Rev* 2006; 58: 437–46.
2. Fajadet J, *et al.* ENDEAVOR II Investigators. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation* 2006; 114: 798–806.
3. Kandzari DE, Leon MB. Overview of pharmacology and clinical trials program with the zotarolimus-eluting endeavor stent. *J Interv Cardiol* 2006; 19: 405–13.
4. Korovesis S, *et al.* Subacute thrombosis following implantation of zotarolimus-eluting stent. *Hellenic J Cardiol* 2006; 47: 310–2.
5. Kandzari DE, *et al.* ENDEAVOR III Investigators. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. *J Am Coll Cardiol* 2006; 48: 2440–7.
6. Chen Y-W, *et al.* Zotarolimus, a novel sirolimus analogue with potent anti-proliferative activity on coronary smooth muscle cells and reduced potential for systemic immunosuppression. *J Cardiovasc Pharmacol* 2007; 49: 228–35.
7. Gershlick A, *et al.* ENDEAVOR Investigators. Zotarolimus-eluting stents in patients with native coronary artery disease: clinical and angiographic outcomes in 1,317 patients. *Am J Cardiol* 2007; 100 (suppl 2): S45–S55.
8. Meredith IT, *et al.* Four-year clinical follow-up after implantation of the endeavor zotarolimus-eluting stent: ENDEAVOR I, the first-in-human study. *Am J Cardiol* 2007; 100 (suppl 2): S56–S61.
9. Jain AK, *et al.* Real-world safety and efficacy of the endeavor zotarolimus-eluting stent: early data from the E-Five Registry. *Am J Cardiol* 2007; 100 (suppl 2): S77–S83.
10. Brugaletta S, *et al.* Zotarolimus for the treatment of coronary artery disease: pathophysiology, DES design, clinical evaluation and future perspective. *Expert Opin Pharmacother* 2009; 10: 1047–58.
11. Meredith IT, *et al.* RESOLUTE Investigators. Clinical and angiographic results with the next-generation resolute stent system: a prospective, multicenter, first-in-human trial. *JACC Cardiovasc Interv* 2009; 2: 977–85.
12. Meredith IT, *et al.* ENDEAVOR I Investigators. Five-year clinical follow-up after implantation of the endeavor zotarolimus-eluting stent: ENDEAVOR I, first-in-human study. *Catheter Cardiovasc Interv* 2009; 74: 989–95.

Local Anaesthetics

Local anaesthetics produce reversible loss of function or sensation by preventing or diminishing the conduction of nerve impulses near to the site of their application or injection. Because their mode of action is to decrease permeability of the nerve cell membrane to sodium ions, they also have a membrane stabilising effect.

Most clinically useful local anaesthetics have the same general chemical configuration of an amine portion joined to an aromatic residue by an ester or amide link. The type of linkage is important in determining the properties of the drug.

For a classification of local anaesthetics, see Table 1, below.

Table 1. Classification of local anaesthetics.

Amide type	Ester type
Articaine	*Esters of benzoic acid*
Bupivacaine	Amylocaine
Cinchocaine	Cocaine
Ethyl parapiperidino-acetylaminobenzoate	Propanocaine
Levobupivacaine	*Esters of meta-aminobenzoic acid*
Lidocaine	Proxymetacaine
Mepivacaine	*Esters of para-aminobenzoic acid*
Oxetacaine	Benzocaine
Prilocaine	Butyl aminobenzoate
Ropivacaine	Chloroprocaine
Tolycaine	Oxybuprocaine
Trimecaine	Procaine
Miscellaneous	Propoxycaine
Dyclonine	Tetracaine
Ethyl chloride	Tricaine
Ketocaine	
Myrtecaine	
Pramocaine	
Quinisocaine	

Uses and Administration

Local anaesthetics act by preventing the generation and transmission of impulses along nerve fibres and at nerve endings: depolarisation and ion-exchange are inhibited. The effects are reversible. They are used for the local relief of painful conditions, and to prevent pain and discomfort of various medical and surgical procedure (see below). In general, loss of pain (analgesia) occurs before loss of sensory and autonomic function (anaesthesia) and loss of motor function (paralysis), but this may depend on the drug used and the site into which it is given.

Local anaesthetics vary in their potency and speed of onset and duration of action. The anaesthetic must penetrate the lipoprotein nerve sheath in its unionised form before it can act and therefore drugs with high lipid-solubility tend to have a greater potency and duration of action and a faster onset than drugs with low lipid-solubility. The most protein-bound drugs tend to have the longest duration of action.

The potency of local anaesthetics is traditionally compared against that of procaine, which is low; chloroprocaine, lidocaine, mepivacaine, and prilocaine are similar or somewhat more potent; bupivacaine and ropivacaine highly potent, and tetracaine extremely potent.

Speed of onset and duration of action also depend on the technique used (see Local Anaesthetic Techniques, p. 1977.2), the type of block, and the site of administration.

The speed of onset and duration of action of local anaesthetics may be increased by the addition of a vasoconstrictor, which has the effect of reducing the uptake of the local anaesthetic into the circulation from the injection site. Solutions containing adrenaline 1 in 200 000 are generally advocated, although higher concentrations such as 1 in 80 000 may be used in dentistry where the total dose is small. The total amount of adrenaline injected should not exceed 500 micrograms although the amount of adrenaline absorbed varies considerably with the site of injection; some consider that the maximum dose should be 200 micrograms. Other vasoconstrictors including noradrenaline are also used, but the 2002 *Dental Practitioners' Formulary* in the UK considered that noradrenaline should not be used since it presented no advantages and when given at relatively high concentrations had occasionally been associated with severe hypertensive episodes. Vasoconstrictors should not be used when producing a nerve block in an appendage such as a digit, as gangrene may occur. Vasoconstrictors have been added to injections for spinal block, but their use is not recommended because of the danger of reducing the blood supply to the spinal cord.

Local anaesthetics are generally given as acidic solutions of the water-soluble hydrochloride salts; alkalinisation of these solutions or formulation as a carbonated base may increase the speed of onset (below).

The dosage of individual local anaesthetics depends on the injection site and the procedure used. The smallest effective dose and the lowest effective concentration should be used. Smaller doses are usually needed in the elderly, in children, in debilitated patients, and in cardiac disease. Doses should also be reduced in the presence of hepatic disease. Meticulous attention to technique is essential particularly in nerve block and spinal procedures. Injections for central nerve blocks, such as epidural (including caudal block) and spinal block should not contain preservatives.

Action. The intrinsic vasoactivity of a local anaesthetic can influence its rate of removal from the site of action and therefore its duration of action. Ester-type local anaesthetics such as tetracaine and procaine are more likely to produce vasodilatation than amide-type local anaesthetics such as cinchocaine, lidocaine, mepivacaine, and prilocaine after intradermal doses.[1] However, cocaine differs from other ester-type local anaesthetics in that it produces vasoconstriction. The amide-type local anaesthetics can produce vasoconstriction but, apart from prilocaine, their vasoconstrictor activity has generally been found to decline with increasing concentration,[1,2] and, in a study, lidocaine and bupivacaine produced more vasodilatation than vasoconstriction at the higher concentrations tested.[2] Mepivacaine has produced greater and more consistent vasoconstriction than lidocaine, cinchocaine, or prilocaine after intradermal injection[1] but this greater vasoactivity is not always evident.[3]

1. Willatts DG, Reynolds F. Comparison of the vasoactivity of amide and ester local anaesthetics: an intradermal study. *Br J Anaesth* 1985; 57: 1006–11.
2. Aps C, Reynolds F. The effect of concentration on vasoactivity of bupivacaine and lignocaine. *Br J Anaesth* 1976; 48: 1171–4.
3. Goebel WM, *et al.* Comparative circulatory levels of 2 per cent mepivacaine and 2 per cent lignocaine. *Br Dent J* 1980; 148: 261–4.

Administration. Systemic toxic effects of local anaesthetics are related to blood concentrations and, as absorption varies considerably according to the site of injection, it has been suggested[1,2] that recommendation of a single maximum dose without regard to the site of the procedure is meaningless. If a plasma-lidocaine concentration of 5 micrograms/mL were required for toxicity then this would be achieved by injection of 300 mg in the intercostal area, 500 mg epidurally, 600 mg in the region of the brachial plexus, or 1 g subcutaneously. The reduction of peak concentrations obtained by the addition of adrenaline was also dependent on the site of injection. Furthermore, most cases of severe toxicity did not result from overdosage but from inadvertent intravascular injection or too rapid injection.

1. Scott DB. "Maximum recommended doses" of local anaesthetic drugs. *Br J Anaesth* 1989; 63: 373–4.
2. Scott DB. Safe use of lignocaine. *BMJ* 1989; 299: 56.

CARBONATED SOLUTIONS. The use of carbonated solutions of local anaesthetics instead of the usual hydrochloride salts has been discussed in several reviews.[1-3] Although some early studies indicated that carbonated solutions of bupivacaine, lidocaine, or prilocaine produced earlier onset of anaesthesia and improved the quality of epidural or brachial plexus blocks not all subsequent studies have confirmed these results. A method for preparing carbonated solutions has been published[4] but proprietary preparations of such solutions of bupivacaine or lidocaine may be available in some countries.

1. Covino BG. Pharmacology of local anaesthetic agents. *Br J Anaesth* 1986; 58: 701–16.
2. Burm AGL. Clinical pharmacokinetics of epidural and spinal anaesthesia. *Clin Pharmacokinet* 1989; 16: 283–311.
3. Carrie LES. Extradural, spinal or combined block for obstetric surgical anaesthesia. *Br J Anaesth* 1990; 65: 225–33.
4. Bromage PR. Improved conduction blockade in surgery and obstetrics: carbonated local anesthetics. *Can Med Assoc J* 1967; 97: 1377–84.

PH OF SOLUTIONS. The pain associated with infiltration of local anaesthetics can be reduced by buffering the solution to physiological pH with sodium bicarbonate.[1,2] Although buffering itself does not appear to compromise the efficacy of anaesthesia,[2] alkalinisation of the solution may reduce the solubility of the local anaesthetic and cause precipitation.[2-4] To enhance stability local anaesthetic solutions are usually prepared at an acidic pH and it is therefore recommended that if solutions are buffered they should be used immediately.[2] (Solutions containing adrenaline require an acidic pH.)

Similar pH adjustments of solutions for intravenous regional anaesthesia have been reported to reduce the amount of local venous irritation and thrombophlebitis[5] and to increase the speed of onset and the duration of the block.[6] However, it has been noted that at alkaline pH lidocaine can lower surface tension, thereby altering drop size and potentially resulting in a decreased dose if such solutions are infused via a drop counting device rather than a volume pump.[7] Alkalinisation of a solution used for epidural block for caesarean section has been reported to result in a more rapid onset of action and denser block.[8]

Alkalinisation has also been used to hasten the onset of peripheral nerve block[9] by increasing the proportion of the lipid-soluble nonionised free base but the effect in epidural block has been inconsistent.[10,11]

1. McKay W, *et al.* Sodium bicarbonate attenuates pain on skin infiltration with lidocaine, with or without epinephrine. *Anesth Analg* 1987; 66: 572–4.
2. Cristoph RA, *et al.* Pain reduction in local anesthetic administration through pH buffering. *Ann Emerg Med* 1988; 17: 117–20.
3. Nakano NI. Temperature-dependent aqueous solubilities of lidocaine, mepivacaine, and bupivacaine. *J Pharm Sci* 1979; 68: 667–8.
4. Bourget P, *et al.* Factors influencing precipitation of pH-adjusted bupivacaine solutions. *J Clin Pharm Ther* 1990; 15: 197–204.
5. Yudenfreund SM, *et al.* pH-Buffered 2-chloroprocaine for intravenous regional anesthesia. *DICP Ann Pharmacother* 1989; 23: 614–15.
6. Armstrong P, *et al.* Effect of alkalinization of prilocaine on IV regional anaesthesia. *Br J Anaesth* 1989; 63: 625P–626P.
7. Leor R, *et al.* The influence of pH on the intravenous delivery of lidocaine solutions. *Eur J Clin Pharmacol* 1990; 39: 521–3.
8. Fernando R, Jones HM. Comparison of plain and alkalinized local anaesthetic mixtures of lignocaine and bupivacaine for elective extradural caesarean section. *Br J Anaesth* 1991; 67: 699–703.
9. Coventry DM, Todd JG. Alkalinization of bupivacaine for sciatic nerve blockade. *Br J Anaesth* 1989; 62: 227P.
10. Burm AGL. Clinical pharmacokinetics of epidural and spinal anaesthesia. *Clin Pharmacokinet* 1989; 16: 283–311.
11. Carrie LES. Extradural, spinal or combined block for obstetric surgical anaesthesia. *Br J Anaesth* 1990; 65: 225–33.

Anorectal disorders. See under Surface Anaesthesia, p. 1977.3.

Cough. Drugs such as lidocaine or bupivacaine have been given by inhalation in severe intractable cough (p. 1651.2), including cough caused by malignant neoplasms.[1-4] Cough suppression is produced by an indirect peripheral action on sensory receptors, but as all protective pulmonary reflexes may be lost and bronchospasm may be induced, nebulised local anaesthetics should be used in controlled circumstances only; there may also be temporary loss of the swallowing reflex.

Intravenous lidocaine has also been tried for the prevention of fentanyl-induced cough.[5-7]

1. Howard P, *et al.* Lignocaine aerosol and persistent cough. *Br J Dis Chest* 1977; 71: 19–24.
2. Stewart CJ, Coady TJ. Suppression of intractable cough. *BMJ* 1977; 1: 1660–1.
3. Sanders RV, Kirkpatrick MB. Prolonged suppression of cough after inhalation of lidocaine in a patient with sarcoid. *JAMA* 1984; 252: 2456–7.
4. Brown RC, Turton CWG. Cough and angiotensin converting enzyme inhibition. *BMJ* 1988; 296: 1741.
5. Lin C-S, *et al.* Intravenous lidocaine and ephedrine, but not propofol, suppress fentanyl-induced cough. *Can J Anesth* 2004; 51: 654–9.
6. Pandey CK, *et al.* Intravenous lidocaine suppresses fentanyl-induced coughing: a double-blind, prospective, randomized placebo-controlled study. *Anesth Analg* 2004; 99: 1696–8.
7. Pandey CK, *et al.* Intravenous lidocaine 0.5 mg.kg^{-1} effectively suppresses fentanyl-induced cough. *Can J Anesth* 2005; 52: 172–5.

Endoscopy. Local anaesthetics such as lidocaine are sometimes used before endoscopy to improve patient comfort and facilitate passage of the endoscope. As mentioned in the discussion on drugs used in endoscopy (see p. 1032.3) some consider that the use of local anaesthetics for procedures such as gastrointestinal endoscopy should probably be reserved for those patients who prefer not to be sedated as their use in addition to premedication with opioids or benzodiazepines appears to serve little purpose.

References.

1. Chuah SY, *et al.* Topical anaesthesia in upper gastrointestinal endoscopy. *BMJ* 1991; 303: 695.
2. Jameson JS, *et al.* Topical anaesthesia improves toleration for upper gastrointestinal endoscopy. *Gut* 1992; 33 (suppl): S51.
3. Randell T, *et al.* Topical anaesthesia of the nasal mucosa for fibreoptic airway endoscopy. *Br J Anaesth* 1992; 68: 164–7.

Mouth ulceration. For the role of local anaesthetics in the management of mouth ulceration, see p. 1811.2.

Pain. Pain and its general management are discussed on p. 4.1. Local anaesthetics are used in a variety of situations for the management of pain. They are usually given by local injection or applied topically but are sometimes used intravenously in techniques such as intravenous regional anaesthesia, which involves the continuous infusion of local anaesthetics such as lidocaine to produce general

analgesia. However, the technique is potentially dangerous and seldom used.

NERVE BLOCKS. Nerve blocks produce analgesia by interrupting the nervous transmission of pain signals either by temporary inhibition of conduction or by destruction of the nerve. Nerve blocks may be used alone or with analgesics in the management of acute or chronic pain associated with a well-defined anatomical site, especially when the pain is unresponsive to or not adequately controlled by conventional therapy. The route of administration and method used depend on the site to be blocked but may include peripheral nerve block, autonomic nerve blocks such as sympathetic nerve blocks and coeliac plexus block, and central nerve blocks such as epidural (including caudal) and spinal block. **Local anaesthetics** are used when a temporary effect is required. **Neurolytics** such as phenol or alcohol or freezing of the nerve (cryoanalgesia) produce more prolonged block, but even so the effects may last no more than a few months, and the variable and non-selective neural damage produced correlates poorly with pain relief; some consider the risk of complications to outweigh the benefits obtained.[1]

The use of nerve blocks in the *management of cancer* (see Cancer Pain, p. 7.1) has declined following the refinement of the use of conventional analgesics. Some consider that their value may be limited to patients with a life expectancy of 3 months or less[2] and that the main benefit of nerve blocks in cancer is to produce maximum pain relief rapidly. However, others consider that chemical and thermal neurolysis can provide long-term control of severe cancer pain without a substantial incidence of adverse effects.[3] Neurolytic blocks may be of particular value in cancer pain syndromes involving the viscera or the torso, but are rarely applicable in the management of extremity pain.[4] Neuropathic pain is rarely helped by somatic neural block and may even be aggravated,[1] but block of the splanchnic nerves or coeliac plexus with alcohol or phenol is reputed to be effective in relieving severe intractable pain caused by cancer of the pancreas, stomach, small intestine, gallbladder, or other abdominal viscera, especially when the cancer has not spread to the parietal peritoneum.[5]

Similar neurolytic blocks preceded by a local anaesthetic have also been used in patients with *severe intractable pain* of chronic pancreatitis, postcholecystectomy syndrome, or other chronic abdominal visceral diseases unrelieved by medical or surgical therapy.

Central nerve blocks using local anaesthetics with or without **opioids** are used for the *management of acute pain* such as labour pain (p. 8.3) and postoperative pain (p. 6.1) including that in children (p. 5.2); they are also sometimes used for cancer pain.[1,6]

Sympathetic nerve blocks using repeated injections of local anaesthetics or neurolytics have been used for sympathetically maintained pain. Intravenous regional sympathetic block is an alternative when a single limb is involved;[1] guanethidine is one of the drugs that has been used.[7]

Injections of local anaesthetics with or without **corticosteroids** are often used for blocks of localised painful joints. Nerve blocks are also used to block localised painful trigger areas[8] such as postoperative or post-traumatic neuroma formation and for focal muscle pain.

For the role of nerve blocks in the management of low back pain, see p. 9.2.

1. Hanks GW, Justins DM. Cancer pain: management. *Lancet* 1992; 339: 1031–6.
2. WHO. Cancer pain relief and palliative care: report of a WHO expert committee. *WHO Tech Rep Ser 804*,1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_804.pdf (accessed 11/08/08)
3. American Society of Anesthesiologists Task Force on Pain Management, Cancer Pain Section. Practice guidelines for cancer pain management. *Anesthesiology* 1996; 84: 1243–7. Also available at: http://www.asahq.org/publicationsAndServices/cancer.html (accessed 11/08/08)
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5. Bonica JJ. Management of pain with regional analgesia. *Postgrad Med J* 1984; 60: 897–904.
6. Hunt R, Massolino J. Spinal bupivacaine for the pain of cancer. *Med J Aust* 1989; 150: 350.
7. Hannington-Kiff JG. Relief of causalgia in limbs by regional intravenous guanethidine. *BMJ* 1979; 2: 367–8.
8. Foley KM. The treatment of cancer pain. *N Engl J Med* 1985; 313: 84–95.

Postherpetic neuralgia. For the role of local anaesthetics in the management of postherpetic neuralgia, see p. 10.3.

Premature ejaculation. A cream containing lidocaine 2.5% and prilocaine 2.5% has been applied topically to the penis for a desensitising effect in the management of premature ejaculation (p. 2350.2). The cream is usually applied to the penis and covered with a condom for a period of time, then washed off before sexual intercourse. It has been reported to increase intravaginal ejaculatory latency time compared with a placebo cream,[1] and a study[2] of different application times found 20 minutes to be the optimum. Longer application times were associated with erection loss because of numbness of the penis, and delayed ejaculation. Decreased vaginal sensitivity in female partners, from residual anaesthetic, has also been reported.[1]

1. Busato W, Galindo CC. Topical anaesthetic use for treating premature ejaculation: a double-blind, randomized, placebo-controlled study. *BJU Int* 2004; 93: 1018–21.
2. Atikeler MK, *et al.* Optimum usage of prilocaine-lidocaine cream in premature ejaculation. *Andrologia* 2002; 34: 356–9.

Soft-tissue rheumatism. For the adjunctive use of local anaesthetics in the management of soft-tissue rheumatism, see p. 14.2.

Spasticity. The management of spasticity (p. 2014.2) involves physiotherapy and the use of antispastic drugs. Other approaches to treatment include nerve blocks with local anaesthetics; these can improve spasticity but should generally only be used when further muscle relaxation would not increase disability.

Stuttering. Local anaesthetics have been tried in the treatment of stuttering (p. 1078.1).

Local Anaesthetic Techniques

Local anaesthetics are used in several techniques. In order of increasing level of anaesthesia they are:

- surface or topical anaesthesia
- infiltration anaesthesia
- regional nerve block, including peripheral nerve block, sympathetic nerve block, and central nerve block, which includes epidural and spinal (intrathecal or subarachnoid) block

Local anaesthetics may also be given intravenously for regional anaesthesia in the extremities.

Infiltration anaesthesia

Infiltration anaesthesia is produced by injection of a local anaesthetic such as lidocaine or bupivacaine directly into and around the field of operation without attempting to identify individual nerves. The drug used should not be absorbed too rapidly otherwise the anaesthesia will wear off too quickly for practical use; some local anaesthetics require the addition of a vasoconstrictor in low concentrations, which can increase the duration of infiltration anaesthesia and reduce peak plasma concentrations of the local anaesthetic. Infiltration anaesthesia is extensively used in dentistry.

Anaesthesia of small areas by infiltration techniques requires a relatively large amount of local anaesthetic, which is not a problem for minor surgery but would be for more extensive areas that required anaesthesia. The amount of local anaesthetic used can be reduced and the duration of anaesthesia increased by blocking specific nerves that innervate the area. This may be carried out at several levels. In *field block* anaesthesia subcutaneous injection of a local anaesthetic close to the nerves around the area to be anaesthetised blocks sensory nerve paths. This is a form of infiltration anaesthesia, but the technique requires less drug for a given area to be anaesthetised.

Intravenous regional anaesthesia

Intravenous regional anaesthesia (Bier's block) involves injection of a dilute solution of local anaesthetic into a suitable limb vein after exsanguination and application of a tourniquet, in order to produce anaesthesia distal to it. Arterial flow must remain occluded for at least 20 minutes after injection and adrenaline should not be used. Intravenous regional anaesthesia may be used for short procedures where postoperative pain is not marked, such as manipulation of fractures and minor surgical procedures to the limbs. Although a safe procedure when performed correctly, complications have arisen; there have been fatalities associated with the use of bupivacaine, and prilocaine is the drug of choice. Facilities for resuscitation should be available.

Regional nerve block

Regional nerve block anaesthesia involves specific blocks at the levels of major nerves or spinal roots, and may include peripheral nerve block, sympathetic nerve block, and central nerve block including epidural and spinal block. For a discussion of the use of nerve blocks in the management of pain, see Nerve Blocks, above.

Central nerve block. Central nerve block includes epidural and spinal block.

Epidural block (also referred to as *extradural* or *peridural block*) is widely used to provide analgesia or anaesthesia in surgical and obstetric procedures. It involves injecting a local anaesthetic such as lidocaine, bupivacaine, or ropivacaine, alone or with a small dose of an opioid analgesic into the epidural space in the lumbar, sacral (*caudal block*), thoracic, or cervical regions. Introduction of a cannula into the epidural space enables prolonged analgesia or anaesthesia (epidural anaesthesia) to be provided through the use of 'top-up' doses or continuous infusion of the drugs. A vasoconstrictor is sometimes added to reduce systemic exposure to the local anaesthetic. A test dose at the intended injection site is recommended before starting epidural anaesthesia to ensure that the main dose is not accidentally injected intravascularly or into the subarachnoid space.

Spinal block (also referred to as *subarachnoid* or *intrathecal block*) is produced by injecting a solution of a suitable drug such as bupivacaine within the spinal subarachnoid space, causing temporary paralysis of the nerves with which it comes into contact. It may be used, for example, to produce spinal anaesthesia in surgical procedures on the lower body. Vasoconstrictors have been added to prolong the duration of the block but the effect is not always clinically useful and there is a danger of restricting the blood supply to the spinal cord; therefore this practice is not recommended. The somatic level at which anaesthesia occurs depends on many factors including the specific gravity or baricity of the anaesthetic solution used and the positioning of the patient.

For the adverse effects of and precautions for central block, see p. 1978.1 and p. 1979.2, respectively.

Peripheral nerve block. Peripheral nerve block anaesthesia involves injection into or around a peripheral nerve or plexus supplying the part to be anaesthetised; motor fibres may be blocked as well as sensory fibres. *Brachial plexus block* is widely used for procedures involving the arm; lower limb blocks are less simple although *sciatic* and *femoral blocks* may be combined to permit surgery below the knee. Other peripheral nerve blocks such as those for the head and neck, or *intercostal* or *paravertebral blocks* for local anaesthesia of the trunk, are mostly highly specialised techniques. Lidocaine, prilocaine, bupivacaine, or ropivacaine have all been widely used for peripheral nerve blocks. Adrenaline is often added as a vasoconstrictor.

Pudendal block (usually with prilocaine) may be useful in obstetrics before forceps delivery, but as mentioned under Labour Pain on p. 8.3, the technique of *paracervical local anaesthetic block* has largely fallen out of favour because of the high incidence of serious adverse effects on the fetus.

Sympathetic nerve block. Sympathetic nerve block such as *stellate ganglion blockade* and *lumbar sympathectomy* is used in the management of a range of painful conditions and vascular diseases (see under Complex Regional Pain Syndrome on p. 8.1). Temporary block is obtained using local anaesthetics such as lidocaine or bupivacaine but permanent block may be produced with use of neurolytic agents such as phenol (see Pain, p. 1764.1) or alcohol (see Pain, p. 1733.2).

Surface anaesthesia

Surface or topical anaesthesia blocks the sensory nerve endings in the skin or mucous membranes. Many local anaesthetics are effective surface anaesthetics, a notable exception being procaine. Penetration of intact skin by most local anaesthetics is poor whereas absorption through mucous membranes may be rapid. However, reliable percutaneous anaesthesia can be achieved by application of a eutectic mixture of lidocaine and prilocaine to intact skin (see under Surface Anaesthesia in Lidocaine, p. 1989.3). Eutectic mixtures may be of value in providing surface anaesthesia for various minor medical or surgical procedures. Tetracaine also provides reliable percutaneous anaesthesia. Other methods of dermal delivery of local anaesthetics include a transdermal patch of lidocaine (either alone or with tetracaine), and an iontophoretic drug delivery system incorporating lidocaine and adrenaline. Anaesthesia of the skin and subcutaneous tissues is also discussed under Infiltration Anaesthesia, above.

There are several special uses of topical anaesthesia including anaesthetising the cornea during ophthalmological procedures, and the throat and larynx before intubation and bronchoscopy. Absorption from the respiratory tract is rapid and care is essential to avoid giving a toxic dose. Great care is also necessary when using local anaesthetics to anaesthetise the urethra: if trauma has occurred, rapid absorption of the drug may occur and give rise to serious adverse effects.

Local anaesthetics have been included in topical preparations to relieve the pain of haemorrhoids (p. 1808.1) but good evidence of their efficacy is lacking. Similar uses include pain relief in pruritus ani and anal fissure. Excessive application of local anaesthetics to the rectal mucosa should be avoided as absorption can occur; use for periods of no longer than a few days is recommended to prevent sensitisation of the anal skin. Local anaesthetics are sometimes included in topical preparations for the relief of pruritus (p. 1687.3). However, they are only marginally effective and can very occasionally cause sensitisation. The use of local anaesthetics in rubefacient and topical analgesic preparations is mentioned on p. 6.3.

Adverse Effects

Adverse effects apparent after local anaesthesia may be caused by the anaesthetic or errors in technique, or may be the result of blockade of the sympathetic nervous system. Local anaesthetics may produce systemic adverse effects as a result of raised plasma concentrations that occur when the rate of uptake into the circulation exceeds the rate of breakdown, for example, after

- accidental intravascular injection
- excessive or too rapid doses
- absorption of large amounts through mucous membranes or damaged skin
- absorption of large amounts from inflamed or highly vascular areas

The systemic toxicity of local anaesthetics mainly involves the CNS and the cardiovascular system. Excitation of the CNS may be manifested by restlessness, excitement, nervousness, paraesthesias, dizziness, tinnitus, blurred vision, nausea and vomiting, muscle twitching and tremors, and convulsions. Numbness of the tongue and perioral region, and lightheadedness followed by sedation may appear as early signs of systemic toxicity. Excitation when it occurs may be transient and followed by depression with drowsiness, respiratory failure, and coma. There may be effects on the cardiovascular system with myocardial depression and peripheral vasodilatation resulting in hypotension and bradycardia; arrhythmias and cardiac arrest may occur. Hypotension often accompanies spinal and epidural anaesthesia; inappropriate positioning of the patient may be a contributory factor for women in labour.

Hypersensitivity reactions are rare and generally limited to local anaesthetics of the ester type. There appears to be no cross-sensitivity between ester- and amide-type local anaesthetics. Idiosyncrasy to local anaesthetics has been reported. Hypersensitivity reactions to preservatives in local anaesthetic preparations have also occurred.

Some local anaesthetics cause methaemoglobinaemia.

Fetal intoxication has occurred after the use of local anaesthetics in labour, either as a result of transplacental diffusion or after accidental injection of the fetus.

Prolonged use of topical anaesthetics in the eye causes corneal damage.

Adverse effects may also be caused by vasoconstrictors given with the anaesthetic.

Reviews.

1. McCaughey W. Adverse effects of local anaesthetics. *Drug Safety* 1992; 7: 178–189.
2. Berde CB. Toxicity of local anesthetics in infants and children. *J Pediatr* 1993; 122 (suppl): S14–S20.
3. Naguib M, *et al.* Adverse effects and drug interactions associated with local and regional anaesthesia. *Drug Safety* 1998; 18: 221–50.
4. Dalens BJ, Mazoit J-X. Adverse effects of regional anaesthesia in children. *Drug Safety* 1998; 19: 251–68.
5. Cox B, *et al.* Toxicity of local anaesthetics. *Best Pract Res Clin Anaesthesiol* 2003; 17: 111–36.
6. Fuzier R, *et al.* French Association of Regional Pharmacovigilance Centres. Adverse drug reactions to local anaesthetics: a review of the French pharmacovigilance database. *Drug Safety* 2009; 32: 345–56.

Adverse effects of central block. Central nerve block (see under Local Anaesthetic Techniques, p. 1977.2), comprising spinal or epidural block, is very widely used and certain adverse effects are particularly associated with the technique. Systemic effects (see Adverse Effects, above) are more likely with epidural than with spinal block, because of the larger doses used.

Total spinal anaesthesia from extreme spread of a block or accidental penetration of the dura during an epidural block produces unconsciousness, hypotension, and respiratory arrest. Less extensive spread to the cervical region is usually associated with nausea, agitation, and hypotension.

Hypotension (associated with venodilatation and decreased cardiac output secondary to sympathetic block) is the **cardiovascular** effect most often associated with the technique, and may be especially problematic in pregnancy. Other cardiovascular complications may include bradycardia or heart block; cardiac arrest has also been reported unexpectedly after spinal anaesthesia.

Post-dural puncture headache (see under Treatment of Adverse Effects, p. 1979.1) is probably the most common **neurological complication** related to these procedures and may be accompanied by tinnitus or photophobia. Headache after spinal block may rarely be caused by meningitis. Backache is a frequent postoperative complication of epidural, spinal, or general anaesthesia. Cranial nerve lesions and reversible loss of hearing in the low frequency range, usually affecting both ears, have been reported rarely following spinal block. Neurological complications associated with these blocks may also rarely include paraplegia caused by arachnoiditis, or trauma or compression of the spinal cord after development of a haematoma or abscess. Transient radicular irritation involving the lower back, buttocks, and thighs may develop within 24 hours of spinal block; recovery is usually within 1 week. Cauda equina syndrome, the symptoms of which include urinary retention, loss of perineal sensation, loss of sexual function, and faecal incontinence, is also a rare complication which can present many months after spinal block. There is some evidence that, although still rare, the incidence of neurotoxic complications after spinal anaesthesia is greater with lidocaine than with other commonly used local anaesthetics such as bupivacaine and tetracaine. The incidence of persistent lumbosacral neuropathy may be as high as 1 in 200 after continuous spinal anaesthesia with lidocaine.

Perioperative shivering has been associated with epidural block.

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2. Wildsmith JAW, Lee JA. Neurological sequelae of spinal anaesthesia. *Br J Anaesth* 1989; 63: 505–7.
3. Parnass SM, Schmidt KJ. Adverse effects of spinal and epidural anaesthesia. *Drug Safety* 1990; 5: 179–94.
4. Anonymous. Perioperative shivering. *Lancet* 1991; 338: 547–8.
5. Broome IJ. Hearing loss and dural puncture. *Lancet* 1993; 341: 667–8.
6. Russell R, *et al.* Assessing long term backache after childbirth. *BMJ* 1993; 306: 1299–1303.
7. Harding SA, *et al.* Meningitis after combined spinal-extradural anaesthesia in obstetrics. *Br J Anaesth* 1994; 73: 545–7.
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10. Johnson ME. Potential neurotoxicity of spinal anesthesia with lidocaine. *Mayo Clin Proc* 2000; 75: 921–32.
11. Zaric D, Pace NL. Transient neurologic symptoms (TNS) following spinal anaesthesia with lidocaine versus other local anaesthetics. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 24/12/09).

Effects on the ears. Symptoms such as vertigo, nausea, and nystagmus, which have been reported after the use of local anaesthetics in the external[1] or middle ear,[2] may result from penetration of the local anaesthetic into the inner ear. For reference to hearing disturbances associated with spinal block, see under Adverse Effects of Central Block, above.

1. Raine NMN, Whittet HB. Emla cream and induced vertigo. *Br J Hosp Med* 1994; 51: 614–15.
2. Blair Simmons P, *et al.* Lidocaine in the middle ear: a unique cause of vertigo. *Arch Otolaryngol* 1973; 98: 42–3.

Effects on the joints. Between 2006 and 2008, the FDA[1] received 35 reports of chondrolysis (mainly in the shoulder) occurring in postoperative patients after the unlicensed use of continuous intra-articular infusions of local anaesthetics via elastomeric infusers. Of these, 30 had received bupivacaine (with or without adrenaline), 2 had received bupivacaine and ropivacaine, and 2 had received bupivacaine as a single injection with an intra-articular infusion of lidocaine. The average infusion time was between 48 and 72 hours. Symptoms of chondrolysis appeared as early as 2 months (median of 5 months), and diagnosed within a median of 8.5 months, after infusion. A further 4 reports have subsequently been received. Similar reports have also been received by Health Canada.[2]

1. FDA. Information for healthcare professionals: chondrolysis reported with continuously infused local anesthetics (marketed as bupivacaine, chlorprocaine, lidocaine, mepivacaine, procaine and ropivacaine) (issued 13th November, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm190302.htm (accessed 06/08/10)
2. Health Canada. Local anesthetic infusion with postoperative pain pumps and articular chondrolysis. *Can Adverse React News* 2009; 19 (1): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v19n1-eng.php#ar1 (accessed 24/12/09)

Effects on wound healing. A review of the literature[1] found evidence that local infiltration of local anaesthetics can have detrimental effects on the first two stages of wound healing. The size of the effect on mature wound strength remains to be determined.

1. Brower MC, Johnson ME. Adverse effects of local anesthetic infiltration on wound healing. *Reg Anesth Pain Med* 2003; 28: 233–40.

Hypersensitivity. Local anaesthetics may provoke types I and IV hypersensitivity reactions. Type I reactions (e.g. anaphylaxis) to local anaesthetics are generally rare. They occur more often with the ester-type than with the amide-type drugs, probably because of the metabolism of the former to para-aminobenzoic acid (PABA). Nevertheless, severe or fatal reactions have been associated not only with ester-type local anaesthetics such as tetracaine[1] and procaine[2] but also with the amide-type local anaesthetics lidocaine[3-7] and prilocaine.[3] Intolerance may also have been the cause of death in a patient who received mepivacaine for paracervical anaesthesia.[8] Hypotension during dental anaesthesia is usually a vasovagal response unrelated to the type of local anaesthetic used and may be prevented by the use of diazepam. Patients sensitised by topical application may then develop anaphylactic reactions when treated systemically.[9] The use of drugs such as benzocaine or tetracaine in lozenges or throat sprays may also sensitise patients.[10]

Some patients diagnosed as being hypersensitive to local anaesthetics may have reacted to preservatives in the preparations.[11] Cross-hypersensitivity reactions may also occur between some ester-type local anaesthetics and topical preparations, such as sunscreens, that contain PABA or related compounds.[12]

Skin testing may be of benefit in patients who will require future local anaesthesia and when a patient's history does not rule out a possible allergic reaction. However, testing itself can cause severe or anaphylactic reactions.[9,13]

Type IV reactions (i.e. delayed reactions) to local anaesthetics have also been reported, albeit rarely.[14-17]

For reports of the incidence of allergy to local anaesthetics determined by patch testing, see under individual monographs.

1. Moriwaki K, *et al.* A case report of anaphylactic shock induced by tetracaine used for spinal anesthesia. *Masui* 1986; 35: 1279–84.
2. MacLachlan D, Forrest AL. Procaine and malignant hyperthermia. *Lancet* 1974; i: 355.
3. Fisher MM, Pennington JC. Allergy to local anaesthesia. *Br J Anaesth* 1982; 54: 893–4.
4. Howard JJ, *et al.* Adult respiratory distress syndrome following administration of lidocaine. *Chest* 1982; 81: 644–5.
5. Promisloff RA, DuPont DC. Death from ARDS and cardiovascular collapse following lidocaine administration. *Chest* 1983; 83: 585.
6. Ruffles SP, Ayres JG. Fatal bronchospasm after topical lignocaine before bronchoscopy. *BMJ* 1987; 294: 1658–9.
7. Ball IA. Allergic reactions to lignocaine. *Br Dent J* 1999; 186: 224–6.
8. Grimes DA, Cates W. Deaths from paracervical anesthesia used for first-trimester abortion, 1972–1975. *N Engl J Med* 1976; 295: 1397–9.
9. Mulvey PM. Allergy to local anaesthetics. *Med J Aust* 1980; 1: 386.
10. Verbov J. Drug eruptions. *Practitioner* 1979; 222: 400–9.
11. Wildsmith JAW, *et al.* Alleged allergy to local anaesthetic drugs. *Br Dent J* 1998; 184: 507–10.
12. Parnass SM, Schmidt KJ. Adverse effects of spinal and epidural anesthesia. *Drug Safety* 1990; 5: 179–94.
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14. Klein CE, Gall H. Type IV allergy to amide-type local anesthetics. *Contact Dermatitis* 1991; 25: 45–8.
15. Craft DV. Good RP. Delayed hypersensitivity reaction of the knee after injection of arthroscopy portals with bupivacaine (Marcaine). *Arthroscopy* 1994; 10: 305–8.
16. Bircher AJ, *et al.* Delayed-type hypersensitivity to subcutaneous lidocaine with tolerance to articaine: confirmation by in vivo and in vitro tests. *Contact Dermatitis* 1996; 34: 387–9.
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Methaemoglobinaemia. Methaemoglobinaemia has been reported with several local anaesthetics including tetracaine,[1] benzocaine,[1-6] and lidocaine[1,7] but is more commonly associated with the use of prilocaine.[8-11] It may occur after local injection or topical use. It has been suggested that the effect is due to the presence of an aniline group in the structure or, in the case of lidocaine and prilocaine, metabolism to an aniline-like structure. Methaemoglobinaemia may result from the use of usual doses as well as exposure to toxic concentrations of local anaesthetic[1,10] with prilocaine doses of 8 mg/kg or more [above recommended maxima] usually produce symptoms.[12]

Methaemoglobinaemia has occurred after the topical application of a eutectic preparation of prilocaine and lidocaine.[8,11] Although increases in methaemoglobin concentrations are generally small after the use of this mixture in infants[13,14] and children,[15] some infants may be particularly susceptible to induced methaemoglobinaemia during the first 3 months of life probably due to their limited enzyme capacity.[13] In some countries, including the UK and USA, the cream is licensed for limited use in neonates (see also Surface Anaesthesia under Lidocaine, p. 1989.3).

Use with drugs such as sulfonamides[8] or antimalarials[12] may predispose to methaemoglobinaemia. Patients with haemoglobinopathies or G6PD deficiency may also be at greater risk.[1]

1. Olson ML, McEvoy GK. Methemoglobinemia induced by local anesthetics. *Am J Hosp Pharm* 1981; 38: 89–93.
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3. Tush GM, Kuhn RJ. Methemoglobinemia induced by an over-the-counter medication. *Ann Pharmacother* 1996; 30: 1251–4.
4. LeClaire AC, *et al.* Methemoglobinemia secondary to topical benzocaine use in a lung transplant patient. *Ann Pharmacother* 2005; 39: 373–6.
5. FDA. FDA Public Health Advisory: benzocaine sprays marketed under different names, including Hurricaine, Topex, and Cetacaine (issued 10th February, 2006). Available at: http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm124350.htm (accessed 06/08/10)
6. Dahshan A, Donovan GK. Severe methemoglobinemia complicating topical benzocaine use during endoscopy in a toddler: a case report and review of the literature. Abstract: *Pediatrics* 2006; 117: 1415–16. Full version: http://pediatrics.aappublications.org/cgi/reprint/117/4/e806 (accessed 24/12/09)
7. Karim A, *et al.* Methemoglobinemia complicating topical lidocaine used during endoscopic procedures. *Am J Med* 2001; 111: 150–3.
8. Jakobsson B, Nilsson A. Methemoglobinemia associated with a prilocaine-lidocaine cream and trimetoprim-sulphamethoxazole: a case report. *Acta Anaesthesiol Scand* 1985; 29: 453–5.
9. Mandel S. Methemoglobinemia following neonatal circumcision. *JAMA* 1989; 261: 702.
10. Knobeloch L, *et al.* CDC. Prilocaine-induced methemoglobinemia—Wisconsin, 1993. *MMWR* 1994; 43: 655–7.
11. Parker JP, *et al.* EMLA toxicity after application for allergy skin testing. *Pediatrics* 2004; 113: 410–11.
12. Reynolds F. Adverse effects of local anaesthetics. *Br J Anaesth* 1987; 59: 78–95.
13. Nilsson A, *et al.* Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy. *Br J Anaesth* 1990; 64: 72–6.

14. Brisman M, *et al.* Methaemoglobin formation after the use of EMLA cream in term neonates. *Acta Paediatr* 1998; 87: 1191–4.
15. Frayling IM, *et al.* Methaemoglobinaemia in children treated with prilocaine-lignocaine cream. *BMJ* 1990; 301: 153–4.

Pregnancy. As mentioned under Adverse Effects of Central Block, p. 1978.1, hypotension may be particularly problematic for patients receiving epidural or spinal block for analgesia during labour. In addition it has been suggested that patients receiving epidural analgesia during labour may have an increased risk of pyrexia, which can lead to fetal compromise.[1]

The use of paracervical block has fallen out of favour because of serious adverse effects on the fetus.

1. Fusi L, *et al.* Maternal pyrexia associated with the use of epidural analgesia in labour. *Lancet* 1989; i: 1250–2.

Treatment of Adverse Effects

At the first signs of local anaesthetic toxicity from parenteral dosage, the injection should be stopped; in some cases it may also be possible to apply a tourniquet to limit further systemic absorption. Subsequent management, regardless of the route, is supportive. If systemic reactions develop, steps should be taken to maintain the circulation and respiration and to control convulsions. A patent airway must be established and oxygen given, with assisted ventilation if necessary. The circulation should be maintained with infusions of intravenous fluids. Vasopressors have been suggested in the treatment of marked hypotension although their use is accompanied by a risk of CNS excitation. Ephedrine is preferred for the management of hypotension associated with spinal or epidural block, particularly in pregnancy. Cardiotoxicity, particularly with some local anaesthetics such as bupivacaine, may be refractory (for the suggested use of lipid emulsions see Soya Oil, p. 2093.1). Vasopressors should not be given to patients receiving oxytocic drugs. Convulsions may be controlled with intravenous benzodiazepines such as diazepam although these drugs may also depress respiration and the circulation. Intravenous phenobarbital is used for persistent convulsions.

Methaemoglobinaemia may be treated with intravenous methylthioninium chloride.

Post-dural puncture headache. Headache after puncture of the dura mater during procedures such as lumbar puncture or central nerve blocks is thought to be caused by subsequent leakage of CSF. The incidence of such post-dural puncture headache is significantly reduced by the use of small, blunt needles, which produce a smaller hole in the dura and separate its fibres rather than cutting them.

When treatment is necessary conservative therapy such as analgesics and hydration will relieve symptoms in the majority of patients with mild post-dural puncture headache within 1 to 2 days. Bed rest does not reduce the incidence but once headache develops the patient may feel some relief when recumbent. If the headache persists for a further 24 hours measures such as epidural saline or dextran 40 or the use of intravenous caffeine and sodium benzoate may be effective; oral caffeine has also been shown to be of benefit. However, perhaps the most widely favoured measure, despite a lack of good evidence, is the epidural injection of autologous blood to form a blood patch over the dural puncture. There have been anecdotal reports of success using corticotropin or tetracosactide but such reports of relief with sumatriptan were not confirmed by a controlled study.

References.

1. Choi A, *et al.* Pharmacologic management of postdural puncture headache. *Ann Pharmacother* 1996; 30: 831–9.
2. Broadley SA, Fuller GN. Lumbar puncture needn't be a headache. *BMJ* 1997; 315: 1324–5.
3. Serpell MG, *et al.* Prevention of headache after lumbar puncture: questionnaire survey of neurologists and neurosurgeons in United Kingdom. *BMJ* 1998; 316: 1709–10.
4. Evans RW, *et al.* Assessment: prevention of post-lumbar puncture headaches: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2000; 55: 909–14. Also available at: http://www.neurology.org/cgi/reprint/55/7/909.pdf (accessed 11/08/08)
5. Boonmak P, Boonmak S. Epidural blood patching for preventing and treating post-dural puncture headache. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 06/08/10).
6. Turnbull DK, Shepherd DB. Post-dural puncture headache: pathogenesis, prevention and treatment. *Br J Anaesth* 2003; 91: 718–29.
7. Armon C, Evans RW. Addendum to assessment: prevention of post-lumbar puncture headaches: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2005; 65: 510–12. Also available at: http://www.neurology.org/cgi/reprint/65/4/510.pdf (accessed 11/08/08)

Precautions

As with any drug local anaesthetics are contra-indicated in patients with known hypersensitivity. However, it might be possible to avoid reactions by using a local anaesthetic of the alternative chemical type. Facilities for resuscitation should be available when local anaesthetics are given parenterally.

Local anaesthetics should not be used in patients with complete heart block. They should be given cautiously to the elderly, to the debilitated, to children, and to patients with epilepsy, impaired cardiac conduction or respiratory function, shock, or hepatic impairment; patients with myasthenia gravis are particularly susceptible to the effects of local anaesthetics. Ester-type local anaesthetics are contra-indicated in patients with low plasma-cholinesterase concentrations. Techniques such as epidural or spinal block should not be used in patients with cerebrospinal diseases, cardiogenic or hypovolaemic shock, or altered coagulation status. Because of the risk of transmitting infection into the CNS these techniques should not be employed where there is pyogenic infection of the skin at or adjacent to the injection site.

Because of the risk of systemic adverse effects when local anaesthetics are absorbed too rapidly, they should not be injected into or applied to inflamed or infected tissues or to damaged skin or mucosa. For similar reasons, the rate of injection should not be too rapid and great care must be taken to avoid inadvertent intravascular injection. The risk of adverse effects from the uptake of local anaesthetics into the circulation may be reduced by the inclusion of adrenaline to produce vasoconstriction, but the lowest effective concentration of adrenaline should be used. Solutions containing adrenaline should not, however, be used for producing anaesthesia in appendages such as digits, because the profound ischaemia that follows may lead to gangrene. Mepivacaine and prilocaine tend to produce less vasodilatation at low concentrations than other local anaesthetics and may be useful where the addition of vasoconstrictors is contra-indicated (but see also under Action, p. 1976.2).

When used in the mouth or throat, local anaesthetics may impair swallowing and increase the risk of aspiration. Patients who have received local anaesthetics for procedures such as laryngoscopy or tracheoscopy should be cautioned not to eat or drink for at least 3 to 4 hours after the anaesthetic.

The cornea may be damaged by prolonged topical application of local anaesthetics, particularly cocaine. Patients should be warned not to rub or touch the eye while anaesthesia persists and the anaesthetised eye should be protected from dust and bacterial contamination.

Local anaesthetics may be ototoxic and should not be instilled into the middle ear.

The application of local anaesthetics to the skin for prolonged periods or to extensive areas should be avoided.

Precautions for central block. Epidural or spinal block may rarely result in paraplegia caused by an induced haematoma or abscess, and have thus been considered unsuitable in patients with pre-existing neurological disease, infection at the puncture site, or blood disorders, or in those receiving aspirin or full-dose anticoagulant therapy. Such therapy may be stopped at an appropriate time before surgery if central block is planned. It is necessary to balance the risk of withholding anticoagulation against the risk of bleeding in the individual patient. Epidural or spinal block in patients given low-dose anticoagulant therapy to prevent postoperative deep-vein thrombosis is still controversial. For further discussion and recommendations see Spinal Anaesthesia, p. 1400.1.

A study in the USA[1] involving 891 patients found that low-dose aspirin during pregnancy did not increase the risk of bleeding complications during epidural anaesthesia compared with placebo; it was considered that the recommendation to stop aspirin 7 to 10 days before delivery was unjustified.

1. Sibai BM, *et al.* Low-dose aspirin in correlation between bleeding time and maternal-neonatal bleeding complications. *Am J Obstet Gynecol* 1995; 172: 1553–7.

Inappropriate use. The FDA[1] has expressed concern over the inappropriate use of topical local anaesthetics, such as lidocaine gel, which can lead to excessive systemic absorption and cause life-threatening adverse effects such as irregular heartbeat, seizures, breathing difficulties, and coma. Such use may include applying too much, applying to a large area of skin or to irritated or broken skin, or covering the skin with a wrap or using a heating pad after application. The FDA[2] has also warned against the use of standardised compounded creams that often contain high doses, and/or a combination, of local anaesthetics after 2 deaths due to improper use of a compounded lidocaine and tetracaine cream before laser hair removal were reported.[3]

For details of inappropriate intra-articular use, see Effects on the Joints, p. 1978.2.

1. FDA. Public Health Advisory: potential hazards of skin products containing numbing ingredients for relieving pain from mammography and other medical tests and conditions (issued 16th January, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm110625.htm (accessed 26/05/10)
2. FDA. News Release: FDA warns five firms to stop compounding topical anesthetic creams (issued 5th December, 2006). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108793.htm (accessed 26/05/10)
3. FDA. Public Health Advisory: life-threatening side effects with the use of skin products containing numbing ingredients for cosmetic procedures (issued 6th February, 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm054718.htm (accessed 26/05/10)

Tachyphylaxis. The effect of successive epidural injections of 2% solutions of lidocaine, mepivacaine, or prilocaine was reduced by 25 to 30% with each injection when the interval between the disappearance of analgesia and re-injection was more than 10 minutes but anaesthesia was augmented if this interval was less than 10 minutes.[1] Such tachyphylaxis, associated with the prolonged epidural use of all local anaesthetics, has also been reviewed.[2]

1. Bromage PR, *et al.* Tachyphylaxis in epidural analgesia 1: augmentation and decay of local anesthesia. *J Clin Pharmacol* 1969; 9: 30–8.
2. Mogensen T. Tachyphylaxis to epidural local anaesthetics. *Dan Med Bull* 1995; 42: 141–6.

Test dose. A test dose is recommended in epidural block to check for accidental intravenous or intrathecal injection but negative results should be treated with caution.[1] Accidental intravenous placement of the needle is notoriously more difficult to detect than inadvertent subarachnoid placement. Adrenaline has been added to the test solution to aid detection of intravenous injection but is considered by some to be of little value.[2,3]

1. Scott DB. Test doses in extradural block. *Br J Anaesth* 1988; 61: 129–30.
2. Thornburn J. Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia. *Br J Anaesth* 1989; 62: 578–81.
3. Narchi P, *et al.* Heart rate response to an iv test dose of adrenaline and lignocaine with and without atropine pretreatment. *Br J Anaesth* 1991; 66: 583–6.

Interactions

The metabolism of ester-type local anaesthetics may be inhibited by anticholinesterases, increasing the risk of systemic toxicity.

Ester derivatives such as tetracaine, benzocaine, or procaine that are hydrolysed to para-aminobenzoic acid may antagonise the activity of aminosalicylic acid or sulfonamides. Ester-type local anaesthetics such as procaine and cocaine that are hydrolysed by plasma cholinesterase may competitively enhance the neuromuscular blocking activity of suxamethonium; the amide local anaesthetic, lidocaine may have a similar effect.

There is an increased risk of myocardial depression when amide-type local anaesthetics such as bupivacaine, levobupivacaine, lidocaine, or ropivacaine are given with antiarrhythmics.

If local anaesthetics containing adrenaline are given for epidural or paracervical block during labour the use of an oxytocic drug post partum may lead to severe hypertension. Although there is no clinical evidence of dangerous interactions between adrenaline-containing local anaesthetics and MAOIs or tricyclic antidepressants, great care should nevertheless be taken to avoid inadvertent intravenous doses of the local anaesthetic preparation.

For further details of interactions between local anaesthetics and other drugs, see under individual monographs.

Pharmacokinetics

Most local anaesthetics are readily absorbed through mucous membranes, and through damaged skin. Local anaesthetics are weak bases and at tissue pH can diffuse through connective tissue and cellular membranes to reach the nerve fibre where ionisation can occur.

Anaesthetics of the ester type are hydrolysed by esterases in the plasma and, to a lesser extent, in the liver. The effect of spinal anaesthetics lasts until the drug is taken up into the blood circulation since there is little esterase in the spinal fluid.

Amide-type anaesthetics are metabolised in the liver and, in some cases, the kidneys. While there is little protein binding with most ester-type anaesthetics, the amide types are considerably bound.

References.

1. Tucker GT. Pharmacokinetics of local anaesthetics. *Br J Anaesth* 1986; 58: 717–31.
2. Burm AGL. Clinical pharmacokinetics of epidural and spinal anaesthesia. *Clin Pharmacokinet* 1989; 16: 283–311.
3. Smith C. Pharmacology of local anaesthetic agents. *Br J Hosp Med* 1994; 52: 455–60.
4. Mazoit J-X, Dalens BJ. Pharmacokinetics of local anaesthetics in infants and children. *Clin Pharmacokinet* 2004; 43: 17–32.

Amylocaine Hydrochloride *(BANM)*

Amilocaína, hidrocloruro de; Amyleinii Chloridum; Amylocain Hydrochlor.; Chlorhydrate d'Amyléine; Амилокаина Гидрохлорид

(*RS*)-1-(Dimethylaminomethyl)-1-methylpropyl benzoate hydrochloride.

$C_{14}H_{21}NO_2$,HCl=271.8

CAS — 532-59-2 (amylocaine hydrochloride); 644-26-8 (amylocaine hydrochloride).
UNII — 224EF0K14Q.

Profile

Amylocaine, a benzoic acid ester, is a local anaesthetic (p. 1976.1) used mainly as the hydrochloride in a range of preparations for application to the skin or mucous membranes. It has also been used in preparations for the relief of painful anorectal conditions and has been included in oral mixtures for the relief of coughs.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Dolodent.

Multi-ingredient Preparations. *Belg.*: Dentophar†; Rectovasol; *Braz.*: Fonergin; Hemodotti†; *Cz.*: Avenoc†; *Fr.*: Avenoc; Dentobaume; Elenol†; Paracamf; Pulmoll†; Sedaplaie†; *Hong Kong*: Prazoline†; *Ital.*: Dentinale; Proctosedyl; *Mon.*: Bronchodermine; *Thai.*: Bacal; Basina; Citacin; Izac; Lobacin; Medcin†; Mybacin; Novacin; Thrody.

Homoeopathic Preparations. *Canad.*: Avenoc†; *Port.*: Avenoc†.

Articaine Hydrochloride *(BANM, USAN, rINNM)*

4004S; Articaína, hidrocloruro de; Articaïne, Chlorhydrate d'; Articainhydrochlorid; Articaini Hydrochloridum; Artikaiinihydrokloridi; Artikain Hidroklorür; Artikain-hidroklorid; Artikainhydrochlorid; Artikainhydroklorid; Artikaino hidrochloridas; Carticaine Hydrochloride; Carticaini Hydrochloridum; Hidrocloruro de articaína; Hoe-045; Karticainhydroklorid; Kartikaiinihydrokloridi; Kartikain Hidroklorür; Артикаина гидрохлорид.

Methyl 4-methyl-3-(2-propylaminopropionamido)thiophene-2-carboxylate hydrochloride.

$C_{13}H_{20}N_2O_3S,HCl$=320.8

CAS — 23964-58-1 (articaine); 23964-57-0 (articaine hydrochloride).
ATC — N01BB08.
ATC Vet — QN01BB08.
UNII — QS9014Q792.

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

Ph. Eur. 8: (Articaine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in alcohol. A 1% solution in water has a pH of 4.2 to 5.2. Protect from light.

USP 36: (Articaine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in alcohol. Protect from light.

Profile

Articaine hydrochloride is an amide local anaesthetic (p. 1976.1). It has been used as a 1 or 2% solution with or without adrenaline for infiltration and regional anaesthesia. A 4% solution of articaine hydrochloride with adrenaline is used similarly in dentistry. A hyperbaric solution of articaine hydrochloride with glucose has been used for spinal block.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies articaine 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 05/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Bucanest; Deltazine; Septanest; *Austria*: Septanest; Sopira Citocartin; Ubistesin; Ultracain Dental; *Canad.*: Astracaine†; Septanest; Ultracaine D-S; Zorcaine; *China*: Primacaine Adrenaline (必兰); *Cz.*: Septanest S; Supracain; Ubistesin; *Denm.*: Dentocaine; Septanest; Septocaine; Sopira Citocartin; Ubistesin; *Fin.*: Dentocaine; Septocaine; Ubistesin; Ultracain D-Suprarenin; *Fr.*: Alphacaine; Articadent; Artinibsa; Bucanest†; Deltazine; Primacaine; Septanest; Ubistesin Adrenalinee; *Ger.*: Sopira Citocartin; Ubistesin; Ultracain D-S; Ultracain Suprarenin; Ultracain; *Gr.*: Artikamine; Septanest; Ubistesin; *Hong Kong*: Ubistesin; *Hung.*: Ubistesin; Ultracain D-S; *Irl.*: Espestesin; *Israel*: Septanest; Ubistesin; *Ital.*: Alfacaina; Cartidont; Citocartin; Sarticain; Septanest; Ubistesin; *Neth.*: Citocartin; Loncarti; Septanest; Ubistesin; Ultracain D-S; *Norw.*: Septocaine; *NZ*: Septanest; Ubistesin; *Port.*: Alphacaine†; Artinibsa; Artinostrum; Meganest; Septanest; Ubistesin; *Rus.*: Alphacaine (Альфакаин); Artifrin (Артифрин); Brilocaine (Брилокаин); Citocartin (Цитокартин); Primacaine Adrenaline (Примакаин С Адреналином); Septanest (Септанест); Ubistesin (Убистезин); Ultracain (Ультракаин); *Singapore*: Ubistesin; *Spain*: Artinibsa; Meganest; Septanest; Ubistesin; Ultracain; *Swed.*: Septocaine; Ubistesin; *Switz.*: Alphacaine; Rudocain; Septanest; Ubistesin; Ultracaine D-S; *Turk.*: Ultracain; *UK*: Septanest; *Ukr.*: Artifrin (Артифрин); Ultracain D-S (Ультракаин Д-С); *USA*: Orabloc; Septocaine.

Pharmacopoeial Preparations
USP 36: Articaine Hydrochloride and Epinephrine Injection.

Benzocaine *(BAN, rINN)*

Anaesthesinum; Anestezin; Anesthamine; Bensokain; Bentsokaiini; Benzocaïn; Benzocaína; Benzocaïne; Benzocainum; Benzokain; Benzokaína; Benzokainas; Ethoform; Éthoforme; Ethyl Aminobenzoate; Ethylis Aminobenzoas; Бензокаин.

Ethyl 4-aminobenzoate.

$C_9H_{11}NO_2$=165.2

CAS — 94-09-7.
ATC — C05AD03; D04AB04; N01BA05; R02AD01.
ATC Vet — QC05AD03; QD04AB04; QN01AX92; QN01BA05; QR02AD01.
UNII — U3RSY48JW5.

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

Coco snow; Procrystal; Pro-crystal.

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

Ph. Eur. 8: (Benzocaine). Colourless crystals or a white or almost white, crystalline powder. M.p. 89 degrees to 92 degrees. Very slightly soluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Benzocaine). Small, white crystals or a white odourless crystalline powder. M.p. 88 degrees to 92 degrees. Soluble 1 in 2500 of water, 1 in 5 of alcohol, 1 in 2 of chloroform, 1 in 4 of ether, and 1 in 30 to 50 of almond oil or olive oil; dissolves in dilute acids.

Uses and Administration

Benzocaine, a para-aminobenzoic acid ester, is a local anaesthetic used for surface anaesthesia (p. 1977.3); it has low potency and low systemic toxicity. It is used, often with other drugs such as analgesics, antiseptics, antibacterials, antifungals, and antipruritics, for the temporary local relief of pain associated with dental conditions, oropharyngeal disorders, haemorrhoids, anal pruritus, and ear pain.

Lozenges containing benzocaine in usual doses of up to 10 mg are used for the relief of sore throat. Gels, pastes, solutions, and sprays containing benzocaine in concentrations of up to 20% have been used for surface anaesthesia of the mouth and throat.

Benzocaine is used in ear drops, creams, ointments, lotions, solutions, sprays, gels, and suppositories in concentrations of up to 20% for topical analgesia and anaesthesia.

Benzocaine has also been used as the hydrochloride.

Obesity. It has been reported[1] that despite the inclusion of benzocaine in some over-the-counter appetite suppressants there is no good evidence of its value in obesity (p. 2315.1).

1. Anonymous. A nasal decongestant and a local anesthetic for weight control? *Med Lett Drugs Ther* 1979; 21: 65–6.

Adverse Effects and Treatment

As for Local Anaesthetics in general, p. 1978.1.

Abuse. Benzocaine has been used as an adulterant or 'cutting' agent in the preparation of cocaine for illicit use and adverse effects such as methaemoglobinaemia have been seen after cocaine overdosage as a result of the benzocaine content.[1]

1. McKinney CD, *et al.* Benzocaine-adultered street cocaine in association with methemoglobinemia. *Clin Chem* 1992; 38: 596–7.

Hypersensitivity. The incidence of positive reactions in patients patch tested with benzocaine has ranged from 3.3 to 5.9%.[1,2] Patch testing with benzocaine has been recommended by The International Contact Dermatitis Research Group as an indicator of contact hypersensitivity to local anaesthetics. However, it was found that of 40 patients who had had positive reactions to benzocaine with tetracaine and cinchocaine, 21 were not allergic to benzocaine alone.[3]

1. Rudzki E, Kleniewska D. The epidemiology of contact dermatitis in Poland. *Br J Dermatol* 1970; 83: 543–5.
2. Bandmann H-J, *et al.* Dermatitis from applied medicaments. *Arch Dermatol* 1972; 106: 335–7.
3. Beck MH, Holden A. Benzocaine—an unsatisfactory indicator of topical local anaesthetic sensitization for the UK. *Br J Dermatol* 1988; 118: 91–4.

Precautions

As for Local Anaesthetics in general, p. 1979.1.

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Pharmacokinetics

See under Local Anaesthetics, p. 1979.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lodoc; *Austral.*: Appli caine†; *Austria*: Anaestherit; *Braz.*: Solarcaine; *Canad.*: Anbesol Baby; Anbesol Extra Strength; Anbesol; Baby Orajel; Comfortcaine†; Dermine†; First Aid Spray; ManDelay†; Oragard-B Orajel; Swabplus Insect Bite Relief†; Swabplus Mouth Pain Relief†; Swabplus Teething pain Relief†; Ultracare; *Chile*: Anbesol†; BBdent Gel Topico; Dentispray†; Foille; Kalmafta *China*: Ou Ji (欧吉); *Cz.*: Babydent†; *Fr.*: Prothyl†; Topex; *Ger.*: Anaesthesin N†; Anaesthesin; Labocaine†; *Hung.*: Babydent†; *India*: Mamdew Baby Gel; ManDelay; Mucopain; *Irl.*: Burneze Lanacane; *Israel*: Anadent; Baby Gel; Hurricaine; Lanacane† Maintain; Oramed†; UltraCare; *Mex.*: Auralyt; Gomas Garde B Graneodin B; *NZ*: Solarcaine†; *Pol.*: Baby Orajel†; Orajel† *Port.*: Dentispray; Topigel; *Rus.*: Relief Advance (Релиф Адванс); *S.Afr.*: Kiddigum†; *Spain*: Dentispray; Gartricin; Hurricaine; Lanacane; Nani Pre Dental; Topispray; *Turk.*: Undo Pate; *UK*: AAA; Burneze; Lanacane; Orajel; Ultra Chloraseptic Ultracare; *Ukr.*: Babydent (Бебиденг)†; *USA*: Americaine First Aid; Americaine; Anbesol Jr; Baby Anbesol; Baby Orajel; Benz-O-Sthetic; Benzodent; Cepacol Dual Relief Sore Throat Spray Cepacol Fizzlers; Chigger-Tox†; Dent's Extra Strength Toothache Gum; Dent's Maximum Strength Toothache Drops; Dent-O-Kain; Dermoplast; Detane†; Hurricaine; Ivy-Rid; Kank-A Soothing Beads; Lanacane; Mediconet; Mycinettes; Orabase Baby; Orabase Dental; Orabase-B; Orajel; Oral Pain Relief; Ora-Magic Plus; Otocain; Pinnacaine; SensoGARD; Trocaine; Zilactin-B Medicated.

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

Pharmacopoeial Preparations
USP 36: Antipyrine and Benzocaine Otic Solution; Antipyrine, Benzocaine, and Phenylephrine Hydrochloride Otic Solution; Benzocaine and Menthol Topical Aerosol; Benzocaine Cream; Benzocaine Gel; Benzocaine Lozenges; Benzocaine Ointment; Benzocaine Otic Solution; Benzocaine Topical Aerosol; Benzocaine Topical Solution; Benzocaine, Butamben, and Tetracaine Hydrochloride Gel; Benzocaine, Butamben, and Tetracaine Hydrochloride Ointment; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Aerosol; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Solution.

Bupivacaine *(BAN, USAN, rINN)*

Bupivacaína; Bupivacaïne; Bupivacainum; Bupivakaiini; Bupivakain; SKY-0402; Бупивакаин.

(±)-(1-Butyl-2-piperidyl)formo-2',6'-xylidide.

$C_{18}H_{28}N_2O$=288.4

CAS — 2180-92-9; 38396-39-3.
ATC — N01BB01.
ATC Vet — QN01BB01.
UNII — Y8335394RO.

Bupivacaine Hydrochloride

(BANM, USAN, rINNM)

AH-2250; Bupivacaína, hidrocloruro de; Bupivacaïne, Chlorhydrate de; Bupivacainhydrochlorid; Bupivacaini Hydrochloridum; Bupivacaini Hydrochloridum Monohydricum; Bupivakaiinihydrokloridi; Bupivakain Hidroklorür; Bupivakain-hidroklorid; Bupivakain-hydrochlorid monohydrát; Bupivakainhydroklorid; Bupivakaino hidrochloridas; Bupiwakainy chlorowodorek; Hidrocloruro de bupivacaína; LAC-43; Win-11318; Бупивакаина гидрохлорид.

$C_{18}H_{28}N_2O,HCl,H_2O$=342.9

CAS — 18010-40-7 (anhydrous bupivacaine hydrochloride); 14252-80-3 (bupivacaine hydrochloride monohydrate); 73360-54-0 (bupivacaine hydrochloride monohydrate).
ATC — N01BB01.
ATC Vet — QN01BB01.
UNII — 7TQO7W3VT8.

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

Ph. Eur. 8: (Bupivacaine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Soluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Bupivacaine Hydrochloride). A white, odourless, crystalline powder. Freely soluble in water and in alcohol; slightly soluble in acetone and in chloroform. A 1% solution in water has a pH of 4.5 to 6.0.

Stability of solutions. For a discussion of the effect that pH has on the stability of local anaesthetic solutions and the pain associated with their injection, see p. 1976.2.

For reference to the stability of admixtures of bupivacaine and fentanyl in solution, with or without adrenaline, see under Fentanyl, p. 60.1.

Uses and Administration

Bupivacaine hydrochloride is a local anaesthetic of the amide type with actions and uses similar to those described on p. 1976.1. It has a slow onset and a long duration of action. The speed of onset and duration of action are increased by the addition of a vasoconstrictor, and absorption into the circulation from the site of injection is reduced. Slow accumulation occurs with repeated doses. It is used mainly for infiltration anaesthesia and regional nerve blocks, particularly epidural block, but is contra-indicated for obstetric paracervical block and for use in intravenous regional anaesthesia (Bier's block). The 0.75% solution is contra-indicated for epidural block in obstetrics. (Local anaesthetic techniques are discussed on p. 1977.2.) At high doses bupivacaine produces surgical anaesthesia, whereas at lower doses it is used for the management of acute pain such as labour pain (below) and in postoperative analgesia (p. 6.1).

Bupivacaine is a racemic mixture but the *S* (-)-isomer levobupivacaine (see p. 1987.2) is also used. A carbonated solution of bupivacaine is available for injection in some countries (see p. 1976.2). An injectable liposomal formulation of bupivacaine is also used for postoperative analgesia (see below).

In recommended doses bupivacaine produces complete sensory blockade but the concentration of bupivacaine solution used affects the extent of motor blockade achieved. A 0.25% solution generally produces incomplete motor block, a 0.5% solution will usually produce motor block and some muscle relaxation, and complete motor block and muscle relaxation can be achieved with a 0.75% solution.

The dosage of bupivacaine used depends on the site of injection and the procedure used, as well as the status of the patient. Bupivacaine is usually given as the hydrochloride monohydrate salt although doses are expressed in terms of the anhydrous hydrochloride; bupivacaine hydrochloride monohydrate 10.55 mg is equivalent to about 10 mg anhydrous bupivacaine hydrochloride. Bupivacaine is also given as the base in a liposomal suspension; however, different formulations are not bioequivalent and doses cannot be directly converted from any other formulation to the liposomal suspension.

In the UK the suggested general **maximum single** dose of bupivacaine hydrochloride is 150 mg with or without adrenaline followed if necessary by doses of up to 50 mg every 2 hours. In the USA the recommended maximum single dose is 175 mg of the plain preparation or 225 mg when given with adrenaline; doses may be repeated at intervals of not less than 3 hours but the total daily dose should not exceed 400 mg. The dose should be reduced in the elderly, in children (see also below), in debilitated patients, and in cardiac or hepatic disease.

A test dose of bupivacaine, preferably with adrenaline, should be given before starting epidural block to detect inadvertent intravascular injection. Subsequent doses should be given in small increments.

Solutions with or without adrenaline may be used for most **local anaesthetic techniques** and procedures apart from dental infiltration, when adrenaline is added to the solution (see below).

- For **surgical anaesthesia**, bupivacaine hydrochloride is given by *infiltration* as a 0.25% solution in doses up to the recommended maximum (see above). When a longer duration of anaesthesia is required, as in dental or surgical procedures of the maxillary and mandibular area, a 0.5% solution with adrenaline 1 in 200 000 has been used but a total dose of 90 mg (18 mL) should not be exceeded over a single dental sitting.
- For *peripheral nerve block* the usual dose is 12.5 mg (5 mL) as a 0.25% solution or 25 mg (5 mL) as a 0.5% solution, although doses up to the recommended maximum single dose (see above) may also be given. A 0.375% solution is also available. A 0.75% solution has been used for *retrobulbar block* in ophthalmic surgery in a dose of 15 to 30 mg (2 to 4 mL).
- For *sympathetic nerve block* 50 to 125 mg (20 to 50 mL) as a 0.25% solution is recommended.
- For *lumbar epidural block* in surgery a 0.25% solution of bupivacaine hydrochloride may be used in a dose of 25 to 50 mg (10 to 20 mL) or as a 0.5% solution in a dose of 50 to 100 mg (10 to 20 mL). A 0.75% solution is also used for induction of lumbar epidural block in non-obstetric surgery in a single dose of 75 to 150 mg (10 to 20 mL). For *caudal block* in surgery 37.5 to 75 mg (15 to 30 mL) as a 0.25% solution or 75 to 150 mg (15 to 30 mL) as a 0.5% solution may be used.
- Hyperbaric solutions of bupivacaine hydrochloride without adrenaline may be used for *spinal block*. Preparations containing 0.5% are available and are given in doses of 10 to 20 mg (2 to 4 mL).
- In the management of **acute pain** bupivacaine may be given as an epidural bolus or by continuous infusion. For analgesia during *labour*, doses of 15 to 30 mg (6 to 12 mL) as a 0.25% solution, 22.5 to 45 mg (6 to 12 mL) as a 0.375% solution, or 30 to 60 mg (6 to 12 mL) as a 0.5% solution have been recommended as a bolus for lumbar block. Alternatively, when given as an infusion, a dose of 10 to 15 mg (10 to 15 mL) per hour as a 0.1% solution or 10 to 15 mg (8 to 12 mL) per hour as a 0.125% solution has been recommended for lumbar block. Bupivacaine may also be given as a bolus caudal injection for labour pain; doses of 25 to 50 mg (10 to 20 mL) as a 0.25% solution, 37.5 to 75 mg (10 to 20 mL) as a 0.375% solution, or 50 to 100 mg (10 to 20 mL) as a 0.5% solution are recommended.
- For *postoperative pain* bupivacaine may be given as an epidural infusion in doses of 4 to 15 mg (4 to 15 mL) per hour as a 0.1% solution or 5 to 15 mg (4 to 12 mL) per hour as a 0.125% solution. A liposomal suspension containing bupivacaine 1.3% is available for local infiltration into the surgical site to produce post-surgical analgesia; the recommended dose is based on the site and the volume required to cover the area. For bunionectomy, a single dose of 106 mg (8 mL) is given: 7 mL into the tissues surrounding the osteotomy and 1 mL into the subcutaneous tissue. For haemorrhoidectomy, a single dose of 266 mg (20 mL) is diluted to 30 mL with preservative-free sodium chloride 0.9% for injection and infiltrated around the anal sphincter in 6 equally divided portions.

Action. Addition of potassium chloride 0.2 mmol to 40 mL of bupivacaine 0.25% solution resulted in a more rapid onset of sensory loss than the same dose of plain bupivacaine in patients undergoing brachial plexus block for forearm or hand surgery.[1]

Hyaluronidase did not increase the speed of onset of brachial plexus block produced by bupivacaine 0.5%, with or without adrenaline, but did reduce the duration of anaesthesia.[2]

Bupivacaine encapsulated in liposomes can prolong postsurgical analgesic action without motor block.[3,4]

For a comparison of the vasoactivity of bupivacaine and some other local anaesthetics, see p. 1976.2.

1. Parris MR, Chambers WA. Effects of the addition of potassium to prilocaine or bupivacaine: studies on brachial plexus blockade. *Br J Anaesth* 1986; **58**: 297–300.
2. Keeler JF, *et al.* Effect of addition of hyaluronidase to bupivacaine during axillary brachial plexus block. *Br J Anaesth* 1992; **68**: 68–71.
3. Boogaerts S, *et al.* Epidural administration of liposomal bupivacaine for the management of postsurgical pain. *Br J Anaesth* 1993; **70**: (suppl 1): 104.
4. Boogaerts JG, *et al.* Pharmacokinetic-pharmacodynamic specific behaviour of liposome-associated bupivacaine in humans. *Br J Anaesth* 1995; **74** (suppl 1): 74.

Administration in children. The *BNFC* recommends that the dose of bupivacaine in children should be adjusted according to physical status and the nature of the procedure.

Bupivacaine 0.25%, injected intra-operatively at the wound site, up to a maximum dose of 1.5 mg/kg with adrenaline has been used in infants for the control of postoperative pain due to pyloromyotomy and appears to attenuate some of the cardiac and respiratory effects associated with the use of general anaesthesia alone.[1] Doses of 2.5 mg of bupivacaine for each year of age, as a 0.5% solution, have been used for ilioinguinal nerve block in children undergoing herniotomy.[2] A study[3] in infants undergoing abdominal surgery found that an epidural infusion of bupivacaine produced comparable analgesia to an intravenous infusion of morphine. It was considered that bupivacaine might be preferable to morphine in neonates and young infants who are particularly prone to respiratory depression, but older children might require additional sedation or analgesia to prevent postoperative restlessness.

1. McNicol LR, *et al.* Peroperative bupivacaine for pyloromyotomy pain. *Lancet* 1990; **335**: 54–5.
2. Smith BAC, Jones SEF. Analgesia after herniotomy in a paediatric day unit. *BMJ* 1982; **285**: 1466.
3. Wolf AR, Hughes D. Pain relief for infants undergoing abdominal surgery: comparison of infusions of IV morphine and extradural bupivacaine. *Br J Anaesth* 1993; **70**: 10–16.

Headache. Small amounts of bupivacaine 0.5% have been injected into the lower cervical paraspinal muscles for the emergency treatment of headache.[1,2]

1. Mellick LB, *et al.* Treatment of headaches in the ED with lower cervical intramuscular bupivacaine injections: a 1-year retrospective review of 417 patients. *Headache* 2006; **46**: 1441–9.
2. Mellick LB, Pleasant MR. Do pediatric headaches respond to bilateral lower cervical paraspinous bupivacaine injections? *Pediatr Emerg Care* 2010; **26**: 192–6.

Labour pain. For a discussion of the management of labour pain, including mention of the use of local anaesthetics, see p. 8.3.

Early experience in nearly 1000 patients suggested that 8 mL of a 0.5% solution of bupivacaine with adrenaline was the optimum dose for epidural block during labour;[1] pain relief lasted for about 2 hours. Decreasing the concentration of the final dose to 0.25% reduced the persistence of sensory and motor nerve block after delivery. Others[2] found that bupivacaine 0.375% was the most suitable concentration for epidural analgesia when using a regimen of regular 'top-up' doses of 500 micrograms/kg about every 90 minutes. However, the use of low doses of bupivacaine 0.25% for epidural analgesia in primiparous women was associated with a lower incidence of forceps delivery and oxytocin augmentation.[3] Although an even lower concentration of bupivacaine (0.0625%) used with sufentanil[4] produced analgesia similar to that with 0.125% bupivacaine used alone, the duration of the second stage of labour and the incidence of instrumental and surgical delivery were not reduced. Similar results were obtained using bupivacaine 0.0625% with diamorphine 0.005%; in addition pruritus and drowsiness produced by diamorphine were considered to be troublesome in many patients.[5] However, a large UK study[6,7] compared a traditional epidural regimen using 10 mL boluses of bupivacaine 0.25% given up to every hour, with two lower-dose regimens using bupivacaine 0.1% with fentanyl 2 micrograms/mL, and found the lower dose techniques were at least as effective and were associated with a lower incidence of instrumental delivery.

Combined spinal-epidural blocks, in which an initial intrathecal injection of bupivacaine or bupivacaine with an opioid is given before starting the epidural, are also used,[6-9] and have been found to give excellent results,[7] although they may have no advantages over a low-dose epidural technique.[10]

Intrathecal injections containing bupivacaine have also been given alone[11,12] for the management of labour pain but the use of this route alone is usually associated with anaesthesia and management of postoperative pain in caesarean section. Bupivacaine has also been tried with lidocaine for epidural anaesthesia in caesarean section in order to reduce the dose of bupivacaine and minimise cardiotoxicity.[13]

1. Crawford JS. Lumbar epidural block in labour: a clinical analysis. *Br J Anaesth* 1972; **44**: 66–74.
2. Purdy G, *et al.* Continuous extradural analgesia in labour: comparison between "on demand" and regular "top-up" injections. *Br J Anaesth* 1987; **59**: 319–24.
3. Turner MJ, *et al.* Primiparous women using epidural analgesia. *BMJ* 1990; **300**: 123.
4. Auroy Y, Benhamou D. Extradural analgesia for labour: 0.125% bupivacaine vs 0.0625% bupivacaine with 0.2 micrograms mL^{-1} sufentanil. *Br J Anaesth* 1995; **74** (suppl 1): 105–6.
5. Bailey CR, *et al.* Diamorphine-bupivacaine mixture compared with plain bupivacaine for analgesia. *Br J Anaesth* 1994; **72**: 58–61.
6. Comparative Obstetric Mobile Epidural Trial (COMET) Study Group UK. Effect of low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial. *Lancet* 2001; **358**: 19–23.
7. Comparative Obstetric Mobile Epidural Trial (COMET) Study Group UK. Randomized controlled trial comparing traditional with two "mobile" epidural techniques: anesthetic and analgesic efficacy. *Anesthesiology* 2002; **97**: 1567–75.
8. Stacey RGW, *et al.* Single space combined spinal-extradural technique for analgesia in labour. *Br J Anaesth* 1993; **71**: 499–502.
9. Collis RE, *et al.* Randomised comparison of combined spinal-epidural and standard epidural analgesia in labour. *Lancet* 1995; **345**: 1413–16.
10. Simmons SW, *et al.* Combined spinal-epidural versus epidural analgesia in labour. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 01/02/08).
11. Kestin IG, *et al.* Analgesia for labour and delivery using incremental diamorphine and bupivacaine via a 32-gauge intrathecal catheter. *Br J Anaesth* 1992; **68**: 244–7.
12. McHale S, *et al.* Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour. *Br J Anaesth* 1992; **69**: 634–6.
13. Howell P, *et al.* Comparison of four local extradural anaesthetic solutions for elective Caesarean section. *Br J Anaesth* 1990; **65**: 648–53.

Adverse Effects and Treatment

As for Local Anaesthetics in general, p. 1978.1 and p. 1979.1.

Bupivacaine appears to be more cardiotoxic than other local anaesthetics. Cardiac arrest due to bupivacaine can be resistant to electrical defibrillation and a successful outcome may require prolonged resuscitative efforts. For reports suggesting that infusion of a lipid emulsion may be of benefit, and a suggested protocol for its use, see Cardiotoxicity, under Soya Oil, p. 2093.1.

For reference to the toxic threshold for bupivacaine plasma concentrations, see Absorption under Pharmacokinetics, p. 1982.2.

Effects on the cardiovascular system. Bupivacaine[1,2] appears to be more cardiotoxic than most other commonly used local anaesthetics and marked cardiovascular depression may occur at plasma concentrations only slightly above those for CNS toxicity.[2] Fatalities have occurred. Simultaneous seizures and cardiovascular collapse may develop rapidly on inadvertent intravascular injection and even prompt oxygenation and blood pressure support might not prevent cardiac arrest.[2] Ventricular fibrillation which is very resistant to normal methods of defibrillation may develop. Since lidocaine and the other local anaesthetics have additive effects on the CNS bretylium may be preferable to lidocaine for the treatment of induced arrhy-

thmias.[1] Seizures and life-threatening ventricular fibrillation have also been reported after systemic absorption of bupivacaine solutions in an adolescent patient undergoing wound debridement.[3] Fatal cardiotoxicity has occurred after the use of bupivacaine in intravenous regional anaesthesia, possibly due to leakage past the tourniquet, and the use of bupivacaine in this technique should be avoided.[1] Fatalities have also been associated with the use of 0.75% solutions for epidural anaesthesia in obstetric patients and this strength is no longer recommended for obstetric anaesthesia. See also Labour Pain under Uses and Administration, p. 1981.2.

1. Anonymous. Cardiotoxicity of local anaesthetic drugs. *Lancet* 1986; ii: 1192–4.
2. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979; 51: 285–7.
3. Yan AC, Newman RD. Bupivacaine-induced seizures and ventricular fibrillation in a 13-year-old girl undergoing wound debridement. *Pediatr Emerg Care* 1998; 14: 354–5.

Effects on the eyes. Bilateral retinal haemorrhages developed in a 47-year-old woman[1] after receiving a caudal block with bupivacaine 0.5%. The haemorrhages cleared and her usual vision returned by 3 months.

1. Ling C, *et al.* Bilateral retinal haemorrhages following epidural injection. *Br J Ophthalmol* 1993; 77: 316–17.

Prolonged block. Use of bupivacaine in regional anaesthesia may result in prolonged block.[1,2]

1. Pathy GV, Rosen M. Prolonged block with recovery after extradural analgesia for labour. *Br J Anaesth* 1975; 47: 520–2.
2. Brockway MS, *et al.* Prolonged brachial plexus block with 0.42% bupivacaine. *Br J Anaesth* 1989; 63: 604–5.

Precautions

As for Local Anaesthetics in general, p. 1979.1.

Bupivacaine is contra-indicated for use in intravenous regional anaesthesia (Bier's block) and for paracervical block in obstetrics. The 0.75% solution is contra-indicated for epidural block in obstetrics.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bupivacaine 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 05/10/11)

Renal impairment. Spinal block was more rapid in onset and of shorter duration in patients with chronic renal failure given 3 mL of bupivacaine 0.75% than in control patients.[1]

1. Ocko R, *et al.* Subarachnoid anaesthesia with 0.75% bupivacaine in patients with chronic renal failure. *Br J Anaesth* 1986; 58: 605–9.

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Antiarrhythmics. There is an increased risk of myocardial depression when bupivacaine and antiarrhythmics are given together.

Beta blockers. *Propranolol* reduced the clearance of bupivacaine by 35% in 6 healthy subjects.[1] There is a risk of increased bupivacaine toxicity if these drugs are used together.

1. Bowdle TA, *et al.* Propranolol reduces bupivacaine clearance. *Anesthesiology* 1987; 66: 36–8.

Calcium-channel blockers. There is a theoretical risk that the adverse effects of bupivacaine on the heart might be enhanced in patients taking calcium-channel blockers, but evidence of a clinical problem is lacking.

Histamine H_2-antagonists. Studies of the effect of H_2-antagonists on the pharmacokinetics of bupivacaine have yielded variable results. While a group of workers[1] found that pretreatment with *cimetidine* decreased the clearance of bupivacaine, others have failed to find any significant pharmacokinetic effects.[2,3] Similarly, pretreatment with *ranitidine* has either increased plasma concentrations of bupivacaine[4] or had no significant effect.[3]

1. Noble DW, *et al.* Effects of H-2 antagonists on the elimination of bupivacaine. *Br J Anaesth* 1987; 59: 735–7.
2. Pihlajamäki KK. Lack of effect of cimetidine on the pharmacokinetics of bupivacaine in healthy subjects. *Br J Clin Pharmacol* 1988; 26: 403–6.
3. Flynn RJ, *et al.* Does pretreatment with cimetidine and ranitidine affect the disposition of bupivacaine? *Br J Anaesth* 1989; 62: 87–91.
4. Wilson CM. Plasma bupivacaine concentrations associated with extradural anaesthesia for caesarean section: influence of pretreatment with ranitidine. *Br J Anaesth* 1986; 58: 1330P–1331P.

Local anaesthetics. For reference to the effect of bupivacaine on the protein binding of *lidocaine* and *mepivacaine*, see p. 1991.2 and p. 1992.3, respectively.

Pharmacokinetics

Bupivacaine is about 95% bound to plasma proteins. Reported half-lives are from 1.5 to 5.5 hours in adults and about 8 hours in neonates. It is metabolised in the liver and is excreted in the urine mainly as metabolites with only 5 to 6% as unchanged drug.

Bupivacaine is distributed into breast milk in small quantities. It crosses the placenta but the ratio of fetal concentrations to maternal concentrations is relatively low. Bupivacaine also diffuses into the CSF.

See also under Local Anaesthetics, p. 1979.3.

Absorption. The toxic threshold for bupivacaine plasma concentrations is considered by some[1] to lie in the range of 2 to 4 micrograms/mL and in the UK the maximum single recommended dose for anhydrous bupivacaine hydrochloride is 150 mg (equivalent to about 2 mg/kg). Giving bupivacaine for *regional anaesthesia* of the head and neck in a mean total dose of 3.4 mg/kg has produced mean peak plasma concentrations of 3.56 micrograms/mL (with adrenaline) and 4.95 micrograms/mL (without adrenaline), without producing toxicity.[2] Similarly, *intrapleural* bupivacaine 0.5% in a dose of 2.5 mg/kg has produced mean peak plasma concentrations of 2.57 and 3.22 micrograms/mL (with or without adrenaline, respectively) without producing toxicity.[3] A further study[4] in which a 72-hour interpleural infusion of bupivacaine hydrochloride with adrenaline was given to cholecystectomy patients showed appreciable interpatient variability in steady-state plasma drug concentrations (range 1.3 to 3.2 micrograms/mL; mean 2.1 micrograms/mL); no patient suffered any adverse effects. Bilateral *intercostal* nerve blocks using bupivacaine 2 mg/kg have also produced concentrations within the presumed toxic range without adverse effects but the use of adrenaline with this block did not reliably reduce peak plasma-bupivacaine concentrations.[5]

Stellate ganglion block with bupivacaine 0.25% has produced a mean peak plasma concentration of 340 and 470 nanograms/mL after doses of 10 or 20 mL, respectively.[6] Giving bupivacaine 0.5% in a dose of 3 mg/kg with or without adrenaline for *sciatic* and *femoral nerve block* produced mean peak plasma concentrations below 800 nanograms/mL.[7]

Intra-articular bupivacaine is rapidly absorbed from the synovial membrane of the knee during arthroscopy but plasma concentrations did not exceed 350 nanograms/mL after controlled pressure-irrigation with isotonic solutions containing up to 200 mg.[8] Although a group of workers found that the peak plasma concentrations of bupivacaine after intra-articular injection of 30 mL of a 0.5% solution for arthroscopy was 875 nanograms/mL they suggested that adrenaline should probably be added to minimise absorption.[9]

1. Tucker GT. Pharmacokinetics of local anaesthetics. *Br J Anaesth* 1986; 58: 717–31.
2. Neill RS, Watson R. Plasma bupivacaine concentrations during combined regional and general anaesthesia for resection and reconstruction of head and neck carcinomata. *Br J Anaesth* 1984; 56: 485–92.
3. Gin T, *et al.* Effect of adrenaline on venous plasma concentrations of bupivacaine after interpleural administration. *Br J Anaesth* 1990; 64: 662–6.
4. Kastrissios H, *et al.* The disposition of bupivacaine following a 72h interpleural infusion in cholecystectomy patients. *Br J Clin Pharmacol* 1991; 32: 251–4.
5. Bodenham A, Park GR. Plasma concentrations of bupivacaine after intercostal nerve block in patients after orthotopic liver transplantation. *Br J Anaesth* 1990; 64: 436–41.
6. Hardy PAJ, Williams NE. Plasma concentrations of bupivacaine after stellate ganglion block using two volumes of 0.25% bupivacaine plain solution. *Br J Anaesth* 1990; 65: 243–4.
7. Misra U, *et al.* Plasma concentrations of bupivacaine following combined sciatic and femoral 3 in 1 nerve blocks in open knee surgery. *Br J Anaesth* 1991; 66: 310–13.
8. Debruyne D, *et al.* Monitoring serum bupivacaine levels during arthroscopy. *Eur J Clin Pharmacol* 1985; 27: 733–5.
9. Butterworth JF, *et al.* Effect of adrenaline on plasma concentrations of bupivacaine following intra-articular injection of bupivacaine for knee arthroscopy. *Br J Anaesth* 1990; 65: 537–9.

SURFACE ANAESTHESIA. Studies of the absorption of bupivacaine after surface application.

1. McBurney A, *et al.* Absorption of lignocaine and bupivacaine from the respiratory tract during fibreoptic bronchoscopy. *Br J Clin Pharmacol* 1984; 17: 61–6.

Pregnancy. Bupivacaine crosses the placenta to a lesser degree than lidocaine or mepivacaine after maternal injection. Values of 0.2 to 0.4 have been reported[1,2] for the ratio of fetal to maternal concentrations for bupivacaine compared with values of 0.5 to 0.7 quoted[2,3] for lidocaine and mepivacaine. The greater degree of protein-binding of bupivacaine compared with these other drugs not only limits the amount of bupivacaine available to cross the placenta but also reduces the relative amount of free drug in the fetal circulation[2] (see also under Protein Binding, below). Addition of adrenaline to the injection does not appear to affect the placental transfer rate of bupivacaine.[4] Measurement of a beta-phase half-life of 25 hours in the neonate compared with 1.25 hours in mothers suggest that the neonate is less able to metabolise bupivacaine.[5]

1. Denson DD, *et al.* Serum bupivacaine concentrations in term parturient following continuous epidural analgesia for labor and delivery. *Ther Drug Monit* 1984; 6: 393–8.
2. Blogg CE, Simpson BR. Obstetric analgesia and the newborn baby. *Lancet* 1974; i: 1283.
3. Poppers PJ. Evaluation of local anaesthetic agents for regional anaesthesia in obstetrics. *Br J Anaesth* 1975; 47: 322–7.
4. Reynolds F, *et al.* Effect of time and adrenaline on the feto-materna distribution of bupivacaine. *Br J Anaesth* 1989; 63: 509–14.
5. Caldwell J, *et al.* Pharmacokinetics of bupivacaine administered epidurally during childbirth. *Br J Clin Pharmacol* 1976; 3: 956P–957P.

Protein binding. The two major binding proteins for bupivacaine in the blood are α_1-acid glycoprotein, the influence of which is predominant at low concentrations, and albumin, which plays the major role at high concentrations. Reduction in pH from 7.4 to 7.0 decreases the affinity of the α_1-acid glycoprotein for bupivacaine but has no effect on albumin affinity.[1] Binding of bupivacaine is reduced during pregnancy but it is considered that the increase in free bupivacaine concentrations is unlikely to cause a clinically significant increase in the risk of CNS or cardiovascular toxicity.[2]

As fetal plasma contains little α_1-acid glycoprotein the binding capacity for bupivacaine is reduced and this may contribute to the difference between maternal and fetal plasma concentration at delivery[3] (see also under Pregnancy, above).

Ageing, uncomplicated by disease, does not affect the protein binding of bupivacaine.[4]

1. Denson D, *et al.* Alpha$_1$-acid glycoprotein and albumin in human serum bupivacaine binding. *Clin Pharmacol Ther* 1984; 35: 409–15.
2. Denson DD, *et al.* Bupivacaine protein binding in the term parturient: effects of lactic acidosis. *Clin Pharmacol Ther* 1984; 35: 702–9.
3. Petersen MC, *et al.* Relationship between the transplacental gradients of bupivacaine and α_1-acid glycoprotein. *Br J Clin Pharmacol* 1981; 12: 859–62.
4. Veering BT, *et al.* Age does not influence the serum protein binding of bupivacaine. *Br J Clin Pharmacol* 1991; 32: 501–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bupicaina; Bupigobbi; Bupinex; Caina G; Duracaine; *Austral.*: Marcain; *Austria*: Bucain; Carbostesin; Dolanaest; *Belg.*: Marcaine; *Braz.*: Bupiabbott Plus; Bupiabbott; Bupstesic; Dorcaina; Marcaina; Neocaina; *Canad.*: Marcaine; Sensorcaine; Vivacaine; *Cz.*: Marcaine; *Denm.*: Marcain; *Fin.*: Bicain; Marcain; *Fr.*: Bupiforan†; *Ger.*: Bucain; Carbostesin; Dolanaest; *Gr.*: Marcaine; *Hong Kong*: Marcain; *Hung.*: Bucain; Marcain; *India*: Anawin; Bupivan; Marcain; Sensorcaine; *Indon.*: Bucain; Bunascan; Buvanest; Decain; Marcain; Recain; Regivell; *Irl.*: Marcain; *Israel*: Kamacaine; Marcaine; *Ital.*: Bupibil; Bupicain; Bupiforan; Bupisen; Bupisolver; Bupixamol; Marcaina; *Malaysia*: Marcain; *Mex.*: Buvacaina†; *Neth.*: Marcaine; *Norw.*: Marcain; *NZ*: Marcain; *Philipp.*: Ascain; Marcaine; Senpicaine; Senpivac; Sensorcaine; *Pol.*: Marcaine; *Port.*: Bupinostrum; Marcaina; *Rus.*: Anekain (Анекаин)†; Bloccoc (Блоккос); Marcain (Маркаин); *S.Afr.*: Macaine; Regibloc†; *Singapore*: Marcain; *Spain*: Inibsacain; *Swed.*: Marcain; *Switz.*: Carbostesin; Duracain†; *Thai.*: Marcaine; Regivell; *Turk.*: Marcaine; *UK*: Marcain; *Ukr.*: Bucain (Букаин); Marcaine (Маркаин); Omnikain (Омникаин); *USA*: Exparel; Marcaine; Sensorcaine; *Venez.*: Duracaina.

Multi-ingredient Preparations. *Austral.*: Marcain with Fentanyl; *Fin.*: Solomet c bupivacain hydrochlorid; *NZ*: Bupafen; Marcain with Fentanyl; *UK*: Bufyl; *USA*: Duocaine.

Pharmacopoeial Preparations

BP 2014: Bupivacaine and Adrenaline Injection; Bupivacaine and Diamorphine Injection; Bupivacaine and Fentanyl Injection; Bupivacaine Heavy Injection; Bupivacaine Injection;
USP 36: Bupivacaine Hydrochloride in Dextrose Injection; Bupivacaine Hydrochloride Injection.

Butyl Aminobenzoate

Butamben (USAN); Butilaminobenzoato; Butoforme; Бутиламинобензоат.

Butyl 4-aminobenzoate.

$C_{11}H_{15}NO_2$=193.2

CAS — 94-25-7.

UNII — EFW857872Q.

Pharmacopoeias. In *Fr.* and *US.*

USP 36: (Butamben). A white, odourless, crystalline powder. M.p. 57 degrees to 59 degrees. Soluble 1 in 7000 of water; soluble in alcohol, in ether, in chloroform, in fixed oils, and in dilute acids. It slowly hydrolyses when boiled with water.

Butyl Aminobenzoate Picrate

Abbott-34842; Butamben Picrate (USAN); Butilaminobenzoato, picrato de.

$(C_{11}H_{15}NO_2)_2C_6H_3N_3O_7$=615.6

CAS — 577-48-0.
UNII — D4ZFB7ZH5Y.

Profile

Butyl aminobenzoate, a para-aminobenzoic acid ester, is a local anaesthetic (p. 1976.1) that has been used for surface anaesthesia of the skin and mucous membranes. It has also been used for relief of pain and pruritus associated with anorectal disorders. A suspension of butyl aminobenzoate 5 or 10% has been given epidurally.

Butyl aminobenzoate picrate has been applied to the skin as an ointment.

References.

1. Korsten HR, *et al.* Long-lasting epidural sensory blockade by n-butyl-p-aminobenzoate in the terminally ill intractable cancer pain patient. *Anesthesiology* 1991; 75: 950–60.
2. Armstrong DG, Kanat IO. Analgesic efficacy of topical butamben picrate. *J Am Podiatr Med Assoc* 1995; 85: 738–40.
3. Shulman M, *et al.* Nerve blocks with 5% butamben suspension for the treatment of chronic pain syndromes. *Reg Anesth Pain Med* 1998; 23: 395–401.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Unguento Picrato de Butesin.

Multi-ingredient Preparations. *Canad.*: Cetacaine; *Chile*: Butesin†; *Fr.*: Nestosyl†; Nestosyl; *India*: Proctosedyl; *Ital.*: Prurex; *Rus.*: Proctosedyl (Проктоседил); Proctosedyl M (Проктоседил М); *Spain*: Alvogil†; *Switz.*: Alvogyl; *USA*: Cetacaine.

Pharmacopoeial Preparations
USP 36: Benzocaine, Butamben, and Tetracaine Hydrochloride Gel; Benzocaine, Butamben, and Tetracaine Hydrochloride Ointment; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Aerosol; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Solution; Erythromycin Ethylsuccinate Injection.

Chloroprocaine Hydrochloride *(rINNM)*

Chloroprocaine, Chlorhydrate de; Chloroprocaini Hydrochloridum; Cloroprocaína, hidrocloruro de; Hidrocloruro de cloroprocaína; Хлоропрокаина Гидрохлорид.

2-Diethylaminoethyl 4-amino-2-chlorobenzoate hydrochloride.

$C_{13}H_{19}ClN_2O_2.HCl$=307.2

CAS — 133-16-4 (chloroprocaine); 3858-89-7 (chloroprocaine hydrochloride).
ATC — N01BA04.
ATC Vet — QN01BA04.
UNII — LT7Z1YW11H.

Pharmacopoeias. In *US*.

USP 36: (Chloroprocaine Hydrochloride). A white odourless crystalline powder. Soluble 1 in 20 of water and 1 in 100 of alcohol; very slightly soluble in chloroform; practically insoluble in ether. Solutions are acid to litmus.

pH of solutions. For a discussion of the effect that pH has on the stability of local anaesthetic solutions and the pain associated with their injection, see p. 1976.2.

Uses and Administration

Chloroprocaine, a para-aminobenzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p. 1976.1. It has properties similar to those of procaine (p. 1994.3). It has a rapid onset (6 to 12 minutes) and short duration (one hour) of action.

Chloroprocaine is used as the hydrochloride for infiltration, peripheral nerve block, and central nerve block including lumbar and caudal epidural blocks. It may be given, if necessary, with adrenaline 1 in 200 000 to delay absorption and reduce toxicity. Chloroprocaine is not an effective surface anaesthetic. It should not be used for spinal anaesthesia. (Local anaesthetic techniques are discussed on p. 1977.2.)

The dosage of chloroprocaine used depends on the site of injection and the procedure used. In adults the **maximum single dose** of chloroprocaine hydrochloride without adrenaline should not exceed 800 mg; when given with adrenaline 1 in 200 000 the maximum single dose should not exceed 1 g. A test dose of chloroprocaine, preferably with adrenaline, should be given before starting epidural block to detect inadvertent intravascular injection. Doses for various procedures include:

- *mandibular nerve block*: 40 to 60 mg (2 to 3 mL) as a 2% solution
- *infra-orbital nerve block*: 10 to 20 mg (0.5 to 1 mL) as a 2% solution
- *brachial plexus block*: 600 to 800 mg (30 to 40 mL) as a 2% solution
- *digital nerve block*: 30 to 40 mg (3 to 4 mL) as a 1% solution without adrenaline
- in obstetrics a dose of 200 mg (10 mL) per side as a 2% solution is suggested for *pudendal block* and for a *paracervical block* a 1% solution in a dose of 30 mg (3 mL) at each of 4 sites
- *lumbar epidural block*: 40 to 50 mg (2 to 2.5 mL) as a 2% solution or 60 to 75 mg (2 to 2.5 mL) as a 3% solution for each segment to be anaesthetised, the usual total dose being 300 to 750 mg with smaller repeat doses being given at intervals of 40 to 50 minutes
- *caudal block*: 300 to 500 mg (15 to 25 mL) as a 2% solution or 450 to 750 mg (15 to 25 mL) as a 3% solution may be given and repeated at intervals of 40 to 60 minutes

Dosages should be reduced in children, elderly or debilitated patients, and those with cardiac or liver disease. For children concentrations of 0.5 to 1% are suggested for infiltration and 1 to 1.5% for nerve block procedures.

Administration in children. For brief details on the use of chloroprocaine hydrochloride in children, see above.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p. 1978.1. Chloroprocaine is said to be unsuitable for intravenous regional anaesthesia (Bier's block) because of a high incidence of thrombophlebitis associated with such use. It is also contra-indicated in spinal anaesthesia due to potential neurotoxicity.

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Pharmacokinetics

Chloroprocaine is hydrolysed rapidly in the circulation by plasma cholinesterase. It has a half-life of 19 to 26 seconds in adults. It is excreted in the urine mainly as metabolites.

See also under Local Anaesthetics, p. 1979.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Nesacaine; *China*: Kai Ning (凯宁); Ke Pu Nuo (可普诺); *Switz.*: Ivracain; *UK*: Ampres; *USA*: Nesacaine.

Pharmacopoeial Preparations
USP 36: Chloroprocaine Hydrochloride Injection.

Cinchocaine *(BAN, rINN)*

Cincainum; Cinchocaïne; Cinchocainum; Cincocaína; Cinkokain; Dibucaine; Sinkokaiini; Цинхокаин.

2-Butoxy-*N*-(2-diethylaminoethyl)cinchoninamide; 2-Butoxy-*N*-(2-diethylaminoethyl)quinoline-4-carboxamide.

$C_{20}H_{29}N_3O_2$=343.5

CAS — 85-79-0.
ATC — C05AD04; D04AB02; N01BB06; S01HA06.
ATC Vet — QC05AD04; QD04AB02; QN01BB06; QS01HA06.
UNII — L6JW2TJG99.

Pharmacopoeias. In *US*.

USP 36: (Dibucaine). A white to off-white powder, with a slight characteristic odour. M.p. 62.5 degrees to 66 degrees. Soluble 1 in 4600 of water, 1 in 0.7 of alcohol, 1 in 0.5 of chloroform, and 1 in 1.4 of ether; soluble in 1N hydrochloric acid. It darkens on exposure to light. Store in airtight containers. Protect from light.

Cinchocaine Hydrochloride *(BANM, rINNM)*

Cincaini Chloridum; Cinchocaïne, Chlorhydrate de; Cinchocainhydrochlorid; Cinchocaini hydrochloridum; Cinchokain-hidroklorid; Cinchokain-hydrochlorid; Cinchokaino hidrochloridas; Cincocaína, hidrocloruro de; Cinkokainhydroklorid; Dibucaine Hydrochloride; Dibucainium Chloride; Hidrocloruro de cincocaína; Percainum; Sinkokaiinihydrokloridi; Sinkokain Hidroklorür; Sovcainum; Цинхокаина Гидрохлорид.

$C_{20}H_{29}N_3O_2.HCl$=379.9

CAS — 61-12-1.
ATC — C05AD04; D04AB02; N01BB06; S01HA06.
ATC Vet — QC05AD04; QD04AB02; QN01BB06; QS01HA06.
UNII — Z97702A5DG.

NOTE. This compound was originally marketed under the name Percaine, but accidents occurred owing to the confusion of this name with procaine.

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

Ph. Eur. 8: (Cinchocaine Hydrochloride). A white or almost white, crystalline powder or colourless crystals; it is hygroscopic. It agglomerates very easily. Very soluble in water; freely soluble in alcohol, in acetone, and in dichloromethane. A 2% solution in water has a pH of 5.0 to 6.0. Store in airtight containers. Protect from light.

USP 36: (Dibucaine Hydrochloride). Colourless or white to off-white crystals or white to off-white, crystalline powder. It is odourless, somewhat hygroscopic, and darkens on exposure to light. Freely soluble in water, in alcohol, in acetone, and in chloroform. Its solutions have a pH of about 5.5. Store in airtight containers. Protect from light.

Profile

Cinchocaine is an amide local anaesthetic (p. 1976.1) that is now generally only used for surface anaesthesia. It is one of the most potent and toxic of the long-acting local anaesthetics and its parenteral use was restricted to spinal anaesthesia.

For surface anaesthesia cinchocaine has been used, as the base or hydrochloride, in creams and ointments containing up to 1% and in suppositories for the temporary relief of pain and itching associated with skin and anorectal conditions. Cinchocaine benzoate has also been used topically.

Action. For a comparison of the vasoactivity of cinchocaine and some other local anaesthetics, see p. 1976.2.

Plasma cholinesterase deficiency. For mention of the use of cinchocaine in the determination of plasma cholinesterase activity, see under Precautions of Suxamethonium Chloride, p. 2039.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cinchocaine as not porphyrinogenic when used for surface anaesthesia of the cornea; 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 05/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Nupercainal; *Canad.*: Nupercainal; *Denm.*: Cincain; *Fin.*: Orodrops; *Ger.*: DoloPosterine N; *Gr.*: Nupercainal; *India*: Nupercainal†; *Port.*: Nupercainal; *Swed.*: Cincain; *UK*: Nupercainal; *USA*: Nupercainal.

Multi-ingredient Preparations. *Arg.*: Procto Venart; Proctyl; Scheriproct; Ultraproct; *Austral.*: Proctosedyl; Rectinol HC†; Rectinol; Scheriproct; Ultraproct†; *Austria*: Scheriproct; *Belg.*: Scheriproct; Trihistalex; Ultraproct; *Braz.*: Proctox-H; Proctyl; Ultraproct; *Canad.*: Nupercainal; Proctol; Proctomyxin HC; Proctosedyl; ratio-Proctosone; *Chile*: Scheriproct; Ultraproct; *Cz.*: Faktu; Otobacid N; Spofax; *Denm.*: Proctosedyl; *Fin.*: Proctosedyl; Scheriproct; *Fr.*: Deliproct; Ultraproct; *Ger.*: Faktu†; Otobacid N; *Gr.*: Hemorrocort; Proctosedyl-N; Scheriproct Neo; *Hong Kong*: Borraginol-N†; Decatylen; Faktu; *India*: Faktu; Otogesic; *Indon.*: Borraginol-N; Faktu; Ultraproct†; *Irl.*: Proctosedyl; Scheriproct; Ultraproct; *Ital.*: Ultraproct; *Jpn*: Una A Gel†; Una A; *Malaysia*: Decatylen; Proctosedyl; *Mex.*: Proctoacid; Scheriproct; Ultraproct; *Neth.*: Proctosedyl; *Norw.*: Proctosedyl; Scheriproct; *NZ*: Proctosedyl; Ultraproct; *Philipp.*: Faktu; Proctosedyl; Ultraproct; *Pol.*: Proctosone†; Proktosedon; *Port.*: Decatyleno; Faktu; Scheriproct; *Rus.*: Ultraproct (Ультрапрокт); *S.Afr.*: Medi-Keel A; Proctosedyl; Scheriproct; *Singapore*: Decatylen; Faktu; Proctosedyl; *Spain*: Anestesia Local Braun S/A; Ruscus; *Swed.*: Proctosedyl†; Scheriproct N; *Switz.*: Decatylene Neo; Faktu; Locaseptil-Neo; Scheriproct; *Thai.*: Proctosedyl; *Turk.*: Ultraproct; *UAE*: Supraproct-S; *UK*: Proctosedyl; Scheriproct; Ultraproct; Uniroid-HC; *Ukr.*: Decatylen (Декатилен); Ultraproct (Ультрапрокт); *USA*: Corticaine†; *Venez.*: Scheriproct.

Pharmacopoeial Preparations
USP 36: Dibucaine Cream; Dibucaine Hydrochloride Injection; Dibucaine Ointment.

Coca ⊗

Coca Leaves; Hoja de Coca; Кока.

Profile

Coca is the dried leaves of *Erythroxylum coca* (Bolivian or Huanuco leaf) or of *E. truxillense* (Peruvian or Truxillo leaf) (Erythroxylaceae), indigenous to Bolivia and Peru and cultivated in Colombia and Indonesia.

Coca leaves contain about 0.7 to 1.5% of total alkaloids, of which cocaine, cinnamyl-cocaine, and α-truxilline are the most important.

Coca was formerly used for its stimulant action and for the relief of gastric pain, nausea, and vomiting, but it has no place in modern medicine. The practice of coca leaf chewing still continues in South America.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Fr.*: Tabacum Compose.

Cocaine *(BAN)* ⊗

Cocaína; Cocaïna; Cocainum; Kokaiini; Kokain; Methyl Benzoylecgonine; Кокаин.

(1*R*,2*R*,3*S*,5*S*)-2-(Methoxycarbonyl)tropan-3-yl benzoate.

$C_{17}H_{21}NO_4$=303.4.

CAS — 50-36-2.

ATC — N01BC01; R02AD03; S01HA01; S02DA02.

ATC Vet — QN01BC01; QR02AD03; QS01HA01; QS02DA02.

UNII — I5Y540LHVR.

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

24-7; 151; 256; A1-Yola; All-American drug; Angie; Apple jacks; Aspirin; Aunt; Aunt Nora; Baby T; Bad; Badrock; Bah-say; Baise; Ball; Balls Mahoney; Bane; Barbs; Basa; Base; Baseball; Basing; Basuco; Batman; Bazooka; Bazulco; Beak; Beam; Beamers; Beans; Beat; Beautiful boulders; Bebe; Beemers; Berni; Bernice; Bernie; Bernie's flakes; Bernie's gold dust; Big bloke; Big C; Big flake; Big rush; Bill blass; Billie hoke; Bing; Bing Crosby; Bings; Birdie powder; Biscuits; Bjs; BJ's; B.J.'s; Black rock; Blanca; Blanco; Blast; Blizzard; Blotter; Blow; Blowcaine; Blowout; Blue; Bobo; Bogota Bullion; Bolivian; Bolivian marching powder; Bollo; Bolo; Bomb; Bonecrusher; Bones; Booger; Booger Sugar; Boost; Booth; Bopper; Botray; Boubou; Boulder; Boulya; Bouncing powder; Boutros; Boy; Branco; Breakfast of champions; Brick; Brooke Shields; Bubble gum; Bugar sugar; Buger sugar; Bullia capital; Bullion; Bump; Bumper; Bunk; Burese; Burnese; Bush; Butler; Butter; Butter Sandwich; Butter Sandwiches; Butu; C; Cabello; Cadillac; Caine; Cakes; California cornflakes; Came; Candy; Candy C; Candy cane; Candy sugar; Candycaine; Cane; Cap; Caps; Capsula; Carnie; Carrie; Carrie Nation; Casper; Casper the ghost; Cat's pee; Caviar; CDs; C-dust; Cecil; C-game; Cha; Chabbie; Chach; Chalk; Champagne; Champagne of drugs; Chan; Chandi; Chang; Charlie; Charlie girl; Chaz; Cheap basing; Cheddar; Cheese; Chemical; Chewies; Chez; Chinese Sky Candy; Ching; Chippy; Choe; Cholly; Climax; Cloud; Cloud nine; Coc; Co-ca-ee-na; Coca; Coca-Cola; Coco; Coconut; Cokane; Coke; Cola; Colombian Dancing Dust; Colombian Foot Soldiers; Colombian Marching Powder; Colombo; Colorado; Combol; Cookie; Cookies; Coover; Coovers; Corine; Cornbread; Corrine; Corrinne; Crack; Crackers; Crank; Crib; Crill; Cristaux; Crow; Crumbs; Crunch & Munch; Crusty treats; Crystal; Cubes; Cuch; Dama blanca; Demo; Demolish; Devil drug; Devil's dandruff; Devilsmoke; Dice; Dime; Dime special; Dip; Dirty basing; Divits; DOA; Double bubble; Double yoke; Dream; Duct; Dust; Dutch Bliss; Eastside player; Egg; Eggs; El Perico; Electric kool-aid; Esnortiar; Eve; Everclear; Eye opener; Eye openers; Famous dimes; Farlopa; Fast white lady; Fat bags; Fifty-one; Fish scales; Flake; Flave; Florida snow; Foo Foo; Foo foo stuff; Foo-foo dust; Foolish powder; Freebase; Freeze; French fries; Fries; Friskie powder; Fry; Gak; Garbage rock; Gas; Gear; Geek; Get your own; Gift-of-the-sun; Gift-of-the-sun-god; Gin; Girl; Girlfriend; Glad stuff; Glo; Gold; Gold dust; Gold star; Golf ball; Golf balls; Gooka; Gravel; Green gold; Grit; Grits; Groceries; Gulosa; Gutter glitter; Hail; Half track; Hamburger; Hamburger helper; Hamburgers; Handball; Happy dust; Happy powder; Happy trails; Hard; Hard ball; Hard line; Hard rock; Hardball; Have a dust; Haven dust; Heaven; Heaven dust; Heavy stuff; Hell; Henry VIII; Her; Hit; Hocus-Pocus; Hollywood; Homer; Hooter; Hoove; Hotcakes; How do you like me now?; Hubba; Hubba, I am back; Hubbas; Hunter; I am back; Ice; Ice cube; Icing; Inca message; Incentive; Issues; Ivory flakes; Jam; Jejo; Jelly; Jelly beans; Jessica Simpson; "Jiffy"; Johnny; Johnson; Joy powder; Junk; Kangaroo; Kangoroo; Kate; Kibbles & Bits; King; King's habit; Kitty; Kokomo; Kryptonite; Kubba; Kubs; Kuff; Lady; Lady C; Lady caine; Lady snow; Late night; Leaf; Lido; Line; Lines; Liquid lady; Llello; Love; Love affair; Lucifer Left-Nostril; Ma'a; Mama coca; Marching dust; Marching powder; Mayo; Merca; Merck; Merk; Mighty white; Mix; Mixed jive; Mobbeles; Mojo; Monster; Mosquitos; Movie star drug; Mr. B.; Mujer; Munch; Neige; Neve; New addition; Nieve; Nighttrain; Nose; Nose candy; Nose powder; Nose stuff; Nuggets; Number 3; One-fifty-one; One-to-one; Oyster stew; Pala; Paradise; Paradise white; Pariba; Parlay; Partying; Pasta; Paste; Patico; Pearl; Pebbles; Pee Wee; Pepsi; Percia; Percio; Perico; Peruvian; Peruvian flake; Peruvian lady; Peruvian Marching Powder; P.F.; Picnic in Stevenage; Piece; Piedra; Piedras; Pile; Piles; Pimp; Polvo blanco; Pony; Pop; Powder; Powder diamonds; Press; Prime time; Primo; Product; Purple caps; Purple haze; Quick; Quik; Quill; Race horse Charlie; Racehorse Charlie; Railers; Rane; Raw; Ready rock; Real tops; Red caps; Regular "P"; Rest in peace; Ringer; Ringers; Roca; Rock; Rock attack; Rocks; Rocks of hell; Rocky III; Rooster; Rox; Roxanne; Royalty; Roz; Rush; Schmeck; Schoolboy; Schoolcraft; Scorpion; Scottie; Scotty; Scrabble; Scramble; Scruples; Serpico 21; Seven-Up; Sevenup; Shabu; Shake; She; Sherms; Shit; Shnazzle; Shneg; Shootin' Caine; Showbiz Sherbert; Shrile; Sightball; Skeeter; Skeezell; Slab; Sleet; Sleigh ride; Smack; Smoke; Snai; Sniff; Snort; Snow; Snow bird; Snow coke; Snow cone; Snow soke; Snow toke; Snow Train; Snow white; Snowcones; Soap; Society high; Soda; Soft; Soup; Space; Space dust; Speed; Speed boat; Square time Bob; Squares; Squib; Squirrel; Star; Star dust; Star-spangled powder; Stardust; Stone; Stones; Strawberry; Street Caviar; Studio fuel; Suga buga; Sugar; Sugar block; Sugar boogers; Super cloud; Sutta; Sweet stuff; Swell up; T; Talco; Tardust; Teenager; Teeth; Tension; The champagne of stimulants; The devil; The great white hope; Thing; Tissue; Tony; Toot; Tootie; Top gun; Topo; Tornado; Toss up; Toss-ups; Trails; Trey; Troop; Turkey; Turtle stuff; Tutti-frutti; Tweaks; Twenty rock; Twinkie; Ultimate; Uptown; Uzi; Wacky dust; Wash; Washed rock; Wave; Weasel dust; Whack; White; White ball; White boy; White cloud; White Devil; White dragon; White dust; White ghost; White girl; White horse; White lade; White lady; White Lion; White mosquito; White Pony; White powder; White stuff; White sugar; White tornado; Whites; Whiz bang; Window pane; Wings; Witch; Woolies; Wrecking crew; Yada; Yadidi; Yahoo; Yak; Yale; Yam; Yams; Ya Yo; Yao; Yay; Yayo; Yayoo; Yay-yo; Yeah-O; Yeaho; Yee Yoo; Yeo; Yeyo; Yimyom; Yiz; Yola; Zing; Zip; Zulu.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Cocaine). It may be obtained from the leaves of *Erythroxylum coca* and other spp. of *Erythroxylum*, or by synthesis. Colourless crystals or a white, crystalline powder. It is slightly volatile. M.p. 96 degrees to 98 degrees. Practically insoluble in water; freely soluble in alcohol and in ether; very soluble in chloroform; soluble in arachis oil; slightly soluble in liquid paraffin.

USP 36: (Cocaine). Colourless to white crystals or white, crystalline powder. M.p. 96 degrees to 98 degrees. Soluble 1 in 600 of water, 1 in 7 of alcohol, 1 in 1 of chloroform, 1 in 3.5 of ether, 1 in 12 of olive oil, and 1 in 80 to 100 of liquid paraffin. A saturated solution in water is alkaline to litmus. Protect from light.

Cocaine Hydrochloride *(BANM)* ⊗

Chloridrato de Cocaína; Cocaïna, hidrocloruro de; Cocaïne, chlorhydrate de; Cocaine Hydrochlor.; Cocainhydrochlorid; Cocaini hydrochloridum; Cocainium Chloratum; Kokaiinihydrokloridi; Kokain-hidroklorid; Kokain-hydrochlorid; Kokain-hydrokloríd; Kokaino hidrochloridas; Kokainy chlorowodorek.

$C_{17}H_{21}NO_4$.HCl=339.8

CAS — 53-21-4.

ATC — N01BC01; R02AD03; S01HA01; S02DA02.

ATC Vet — QN01BC01; QR02AD03; QS01HA01; QS02DA02.

UNII — XH8T8T6WZH.

NOTE. CCN is a code approved by the BP 2014 for use on single unit doses of eye drops containing cocaine hydrochloride where the individual containers may be too small to bear all the appropriate labelling information.

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

Ph. Eur. 8: (Cocaine Hydrochloride). Colourless crystals or a white or almost white crystalline powder. M.p. about 197 degrees with decomposition. Very soluble in water; freely soluble in alcohol. Protect from moisture and light.

USP 36: (Cocaine Hydrochloride). Colourless crystals or white, crystalline powder. Soluble 1 in 0.5 of water, 1 in 3.5 of alcohol, and 1 in 15 of chloroform; soluble in glycerol; insoluble in ether. Protect from light.

Stability in solutions. *ALKALIS.* Solutions of cocaine hydrochloride are adversely affected by alkalis.

PHENOL. A stability study[1] was conducted in response to queries over conflicting data on the incompatibility of cocaine hydrochloride solutions and phenol. Some pharmacists had reported that cocaine hydrochloride eye drops preserved with phenol had shown no sign of physical incompatibility. The BPC 1973 states that cocaine hydrochloride is incompatible with phenol but suggests that cocaine hydrochloride solutions may be preserved with chlorocresol. The study found that there was no sign of physical incompatibility in aqueous solutions containing cocaine hydrochloride 5% and phenol 0.5% stored for a year at temperatures of 0 degrees to 37 degrees but there was a fall in pH, greatest at the higher temperatures, which was suggestive of chemical change. It was recommended that such solutions should be stored in a cool place.

1. *PSGB Lab Report P/73/14* 1975.

Uses and Administration

Cocaine, a benzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p. 1976.1. It is used as a surface anaesthetic but, because of systemic adverse effects and its abuse potential, its use is now almost entirely restricted to surgery of the ear, nose, and throat. It has been largely replaced by other drugs in ophthalmology because of its corneal toxicity, although it may still be useful in removal or debridement of the corneal epithelium. Cocaine also blocks the uptake of catecholamines at adrenergic nerve endings and potentiates the action of catecholamines. Its sympathomimetic actions cause tachycardia, peripheral vasoconstriction, a rise in blood pressure, and mydriasis. The use of cocaine with sympathomimetics such as adrenaline increases the risk of cardiac arrhythmias. Despite this hazard some use this combination in otolaryngology to improve the operative field and reduce absorption.

When applied to mucous membranes, surface anaesthesia develops rapidly and persists for 30 minutes or longer depending on the concentration of cocaine used, the dose, and on the vascularity of the tissue.

Cocaine hydrochloride is used in aqueous solutions; cocaine hydrochloride 1.12 g is equivalent to about 1 g of cocaine. Solutions containing up to 4% have been used in ophthalmology (but precautions for ophthalmic use should be considered, see p. 1986.2).

Solutions containing up to 10% of cocaine are applied to the nasal mucosa in otolaryngological procedures. Pastes containing up to 25% of cocaine have also been applied.

In order to avoid systemic effects, the usual maximum total dose recommended for application to the nasal mucosa in healthy adults is 1.5 mg/kg. It should be used only by those skilled in the precautions needed to minimise absorption and the consequent risk of arrhythmias.

Cocaine was used with diamorphine or morphine for the relief of severe pain, especially in terminal illness, but this use is now obsolete.

Cocaine solutions should *never* be given by injection; other local anaesthetics are equally effective and much safer.

References.

1. Middleton RM, Kirkpatrick MB. Clinical use of cocaine: a review of the risks and benefits. *Drug Safety* 1993; 9: 212–17.
2. Latorre F, Klimek L. Does cocaine still have a role in nasal surgery? *Drug Safety* 1999; 20: 9–13.

Adverse Effects

Because the therapeutic use of cocaine is now very restricted many reports of adverse effects occur in the context of abuse. However, both systemic and local effects have followed its use as a surface anaesthetic. Although some effects are similar to those of other local anaesthetics (p. 1978.1), cocaine differs in that it acts as a potent indirect-acting sympathomimetic. It stimulates the CNS causing agitation, dilated pupils, tachycardia, hypertension, hallucinations, hypertonia, and hyperreflexia. Convulsions, coma, and metabolic acidosis may develop. Symptoms of CNS stimulation and sympathetic overactivity are very marked in overdosage with cocaine. A single 1-g oral dose may be fatal, but some persons have a cocaine idiosyncrasy and severe toxicity may occur after doses of only 10 mg intravenously. Systemic absorption of small doses may slow the heart, but with increasing doses tachycardia, hypertension, and ventricular fibrillation occur.

High concentrations of cocaine should not be used topically as, in addition to risks of systemic toxicity after absorption, lasting local damage may occur.

Topical application of cocaine to the cornea can cause corneal damage with clouding, pitting, sloughing, and occasionally ulceration. Topical application to the nose or mouth has been reported to cause loss of smell and taste respectively.

Prolonged use of cocaine by nasal inhalation may cause mucosal damage or perforation of the nasal septum.

Abuse. Cocaine abuse and its effects have been reviewed.[1-4]

Cocaine abuse was once only in the form of chewing of coca leaves containing small amounts of cocaine, but processing of the leaves has led to abuse with a variety of more dangerous preparations containing higher concentrations of cocaine.[7] Coca paste, produced by maceration of the leaves with petrol and sulfuric acid, contains about 40 to 90% of cocaine sulfate and is smoked with tobacco or cannabis. Treatment of coca paste with hydrochloric acid produces cocaine hydrochloride, which is abused by intravenous injection, either alone or with diamorphine, or by sniffing to achieve nasal absorption. Alkaloidal cocaine (cocaine base; 'freebase'), which is abused by smoking, is produced by treating cocaine hydrochloride with alkali, followed either by heating (to form 'crack' cocaine) or by extracting the base from ether or another organic solvent. Other types of cocaine, which are prepared and consumed locally in South America and have a high content of contaminants such as car battery acid, lime, petrol, or kerosene, include 'Merla' and 'Oxi'.[8] The route by which cocaine is taken determines the rate and extent of its absorption, and hence the abuse potential, although once

absorbed, the pharmacokinetics are independent of route. Intravenous cocaine hydrochloride and smoked cocaine base have a greater potential for abuse than intranasal cocaine hydrochloride because of their greater rapidity and intensity of effects.

The psychological effects of cocaine abuse may be described by a cycle of initial euphoria followed by dysphoria and finally schizophreniform psychosis.[7,9] Euphoria may be accompanied by other symptoms of stimulation such as sexual arousal, anorexia, insomnia, hyperexcitability, loquacity, and grandiosity, and users may appear manic. After a short time these feelings are replaced by symptoms of dysphoria including considerable anxiety, fear, depression, apathy, irritability, and suspiciousness. Dysphoria may be ameliorated by repeated use, so the user develops the need to take the drug continuously to feel relatively well, but repeated use appears to diminish the intensity of the effects.[7] During euphoria and dysphoria users may develop varied physical symptoms including palpitations, headache, dizziness, gastrointestinal effects, hyperhidrosis, tremors, tachycardia, hypertension, fever, and myoclonic jerks. Seizures can also occur after repeated use. In chronic abusers psychological deterioration may eventually occur, resulting in loss of mental function, compulsive disorders, suicidal ideation, psychopathic disorders, and ultimately a psychosis resembling acute paranoid schizophrenia similar to that seen with amfetamines.[7,9] Symptoms may include paranoia, stereotyped behaviour, delusions, loss of impulse control, violence, and visual, olfactory, auditory, gustatory, and tactile hallucinations. Overdosage can result in death due to status epilepticus, hyperthermia, ventricular tachycardia, and cardiac or respiratory arrest.[7]

For further details of the adverse effects of cocaine abuse, including effects due to use during pregnancy, see below.

1. Johanson C-E, Fischman MW. The pharmacology of cocaine related to its abuse. *Pharmacol Rev* 1989; 41: 3–52.
2. Warner EA. Cocaine abuse. *Ann Intern Med* 1993; 119: 226–35.
3. Strang J, *et al.* Cocaine in the UK—1991. *Br J Psychiatry* 1993; 162: 1–13.
4. Das G. Cocaine abuse in North America: a milestone in history. *J Clin Pharmacol* 1993; 33: 296–310.
5. Hatsukami DK, Fischman MW. Crack cocaine and cocaine hydrochloride: are the differences myth or reality? *JAMA* 1996; 276: 1580–8.
6. Brownlow HA, Pappachan J. Pathophysiology of cocaine abuse. *Eur J Anaesthesiol* 2002; 19: 395–414.
7. Arif A, ed. *Adverse health consequences of cocaine abuse.* Geneva: WHO, 1987.
8. Bastos FI, *et al.* Smoked crack cocaine in contemporary Brazil: the emergence and spread of 'oxi'. *Addiction* 2011; 106: 1191–2.
9. Leikin JB, *et al.* Clinical features and management of intoxication due to hallucinogenic drugs. *Med Toxicol Adverse Drug Exp* 1989; 4: 324–50.

ADULTERATION. For a report of methaemoglobinaemia as a result of the ingestion of cocaine adulterated with *benzocaine*, see Abuse under Adverse Effects of Benzocaine, p. 1980.2. For reports of severe neutropenia and agranulocytosis as a result of the abuse of cocaine adulterated with *levamisole*, see under Precautions of Levamisole, p. 158.2.

BREAST FEEDING. The American Academy of Pediatrics[1] has stated that, when used as a drug of abuse by breast-feeding mothers, cocaine has caused signs of intoxication in the infant, notably diarrhoea, vomiting, irritability, seizures, and tremulousness.

Acute intoxication has been reported in a breast-fed child whose mother was using cocaine intranasally.[2]

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 02/06/04)
2. Chasnoff IJ, *et al.* Cocaine intoxication in a breast-fed infant. *Pediatrics* 1987; 80: 836–8.

EFFECTS ON THE BLOOD. Severe thrombocytopenia has occurred in 6 males who abused cocaine;[1] 5 of the cases involved intravenous abuse while the sixth patient took by inhaling.

See also Adulteration, above.

1. Leissinger CA. Severe thrombocytopenia associated with cocaine use. *Ann Intern Med* 1990; 112: 708–10.

EFFECTS ON THE CARDIOVASCULAR SYSTEM. There appears to be no relationship between underlying heart disease and the risk of cocaine-induced cardiac effects and cardiac events can occur regardless of the route of abuse.[1] Cardiovascular toxicity due to cocaine may be related to individual sensitivity and therefore may not be predictable or dose dependent.[2] Patients with plasma cholinesterase deficiency are particularly at risk for sudden death.[3] Other risk factors for cardiovascular disease, such as cigarette smoking or pre-existing atherosclerosis, may exacerbate the cardiotoxicity of cocaine.[4-6] Cocaine blocks reuptake of catecholamines at adrenergic nerve endings and thus produces sympathetic stimulation of the cardiovascular system. Accumulation of catecholamines predisposes the myocardium to arrhythmias,[7] and sinus tachycardia, supraventricular or ventricular tachyarrhythmias, myocarditis, and sudden arrhythmic death may occur.[7-9] Severe hypertension can lead to cerebrovascular accidents and stroke has occurred even in young adults without other predisposing conditions.[10,11] However, the exact mechanism of cocaine-induced stroke remains unclear and other implicated effects include vasospasm, cerebral vasculitis, enhanced platelet aggregation, and cardioembolism.[12] Aortic dissection and rupture of the aorta have also occurred.[6] Up to 25% of emergency admissions to US urban hospitals with nontraumatic chest pain have detectable amounts of cocaine or its metabolites in their urine, but only a minority of these have myocardial infarction,[6] as chest pain without signs of myocardial infarction also commonly occurs.[8] Asymptomatic myocardial ischaemia manifesting as episodes of ST-segment elevation has also been reported during withdrawal of cocaine.[13] The mechanism for these changes is probably multifactorial, including increased myocardial oxygen demand, coronary vasoconstriction, and enhanced platelet aggregation and thrombus formation.[6,14] The immediate vasoconstrictor effect of cocaine may be followed by delayed or recurrent vasoconstriction due to its active metabolites, benzoylecgonine and ethyl methyl ecgonine.[6]

Vasoconstriction may also produce ischaemia in the fingers, toes, spinal cord,[8] spleen,[15] and intestines.[16] Renal ischaemia and infarction may also occur.[17,18] Other reported cardiovascular effects include dilated cardiomyopathy and premature atherosclerosis.[6]

Guidance[19] has been issued on the management of cocaine-associated chest pain and myocardial infarction.

1. VanDette JM, Cornish LA. Medical complications of illicit cocaine use. *Clin Pharm* 1989; 8: 401–11.
2. Thadani PV. Cardiovascular toxicity of cocaine: underlying mechanisms. *J Appl Cardiol* 1990; 5: 317–20.
3. Cregler LL, Mark H. Medical complications of cocaine abuse. *N Engl J Med* 1986; 315: 1495–1500.
4. Mollterno DJ, *et al.* Coronary-artery vasoconstriction induced by cocaine, cigarette smoking, or both. *N Engl J Med* 1994; 330: 454–9.
5. Higgins ST, *et al.* Influence of cocaine use on cigarette smoking. *JAMA* 1994; 272: 1724.
6. Lange RA, Hillis LD. Cardiovascular complications of cocaine use. *N Engl J Med* 2001; 345: 351–8. Correction. *ibid.*: 1432.
7. Loper KA. Clinical toxicology of cocaine. *Med Toxicol Adverse Drug Exp* 1989; 4: 174–85.
8. Anonymous. Acute reactions to drugs of abuse. *Med Lett Drugs Ther* 1990; 32: 92–4.
9. Bauman JL, *et al.* Cocaine-related sudden cardiac death: a hypothesis correlating basic science and clinical observations. *J Clin Pharmacol* 1994; 34: 902–11.
10. Kaku DA, Lowenstein DH. Emergence of recreational drug abuse as a major risk factor for stroke in young adults. *Ann Intern Med* 1990; 113: 821–7.
11. Levine SR, *et al.* Cerebrovascular complications of the use of the "crack" form of alkaloidal cocaine. *N Engl J Med* 1990; 323: 699–704.
12. Treadwell SD, Robinson TG. Cocaine use and stroke. *Postgrad Med J* 2007; 83: 389–94.
13. Nademanee K, *et al.* Myocardial ischemia during cocaine withdrawal. *Ann Intern Med* 1989; 111: 876–80.
14. Rezkalla SH, Kloner RA. Cocaine-induced acute myocardial infarction. *Clin Med Res* 2007; 5: 172–6.
15. Novielli KD, Chambers CV. Splenic infarction after cocaine use. *Ann Intern Med* 1991; 114: 251–2.
16. Freudenberger RS, *et al.* Intestinal infarction after intravenous cocaine administration. *Ann Intern Med* 1990; 113: 715–16.
17. Sharff JA. Renal infarction associated with intravenous cocaine use. *Ann Emerg Med* 1984; 13: 1145–7.
18. Bemanian S, *et al.* Cocaine-induced renal infarction: report of a case and review of the literature. *BMC Nephrol* 2005; 6: 10. Available at: http://www.biomedcentral.com/1471-2369/6/10 (accessed 22/06/06)
19. McCord J, *et al.* Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. *Circulation* 2008; 117: 1897–1907. Also available at: http://www.circ.ahajournals.org/cgi/reprint/117/14/1897 (accessed 21/12/09)

EFFECTS ON THE CNS. Severe CNS depression with deep coma has been seen in a few cocaine abusers after prolonged binges.[1]

1. Roberts JR, Greenberg ML. Cocaine washout syndrome. *Ann Intern Med* 2000; 132: 679–80.

EFFECTS ON THE KIDNEYS. For reference to renal failure following rhabdomyolysis associated with cocaine abuse, see under Effects on the Muscles, below. There has been a report[1] of acute renal failure occurring in a 16-year-old girl secondary to cocaine abuse but without evidence of rhabdomyolysis.

For reference to renal ischaemia and infarction due to cocaine abuse, see under Effects on the Cardiovascular System, above.

1. Leblanc M, *et al.* Cocaine-induced acute renal failure without rhabdomyolysis. *Ann Intern Med* 1994; 121: 721–2.

EFFECTS ON THE LUNGS. Smoking the free base has resulted in pulmonary complications not seen with other methods of abuse for cocaine. Associated adverse effects have included pulmonary oedema, hypersensitivity pneumonitis, pulmonary haemorrhage, obliterative bronchiolitis, abnormalities of pulmonary function, pneumomediastinum, and pneumothorax.[1] Severe or life-threatening exacerbations of asthma have also been reported.[2]

1. Ettinger NA, *et al.* A review of the respiratory effects of smoking cocaine. *Am J Med* 1989; 87: 664–8.
2. Rubin RB, Neugarten J. Cocaine-associated asthma. *Am J Med* 1990; 88: 438–9.

EFFECTS ON THE MOUTH. Abuse of cocaine can produce several adverse effects in the oral cavity including perforation of the palate (usually after perforation of the nasal septum), gingival lesions, and erosions of the teeth.[1]

1. Brand HS, *et al.* Cocaine and oral health. *Br Dent J* 2008; 204: 365–9.

EFFECTS ON THE MUSCLES. Rhabdomyolysis, sometimes progressing to renal failure, has been associated with free-base smoking or injection of cocaine hydrochloride.[1-3]

1. Roth D, *et al.* Acute rhabdomyolysis associated with cocaine intoxication. *N Engl J Med* 1988; 319: 673–7.
2. Herzlich BC, *et al.* Rhabdomyolysis related to cocaine abuse. *Ann Intern Med* 1988; 109: 335–6.
3. Pogue VA, Nurse HM. Cocaine-associated acute myoglobinuric renal failure. *Am J Med* 1989; 86: 183–6.

EFFECTS ON SEXUAL FUNCTION. While the initial euphoria of cocaine abuse may be accompanied by sexual arousal, sexual dysfunction can occur[1] and male infertility has been reported.[2] Priapism associated with cocaine abuse has also occurred.[3]

1. Cregler LL, Mark H. Medical complications of cocaine abuse. *N Engl J Med* 1986; 315: 1495–1500.
2. Bracken MB, *et al.* Association of cocaine use with sperm concentration, motility, and morphology. *Fertil Steril* 1990; 53: 315–22.
3. Altman AL, *et al.* Cocaine associated priapism. *J Urol* 1999; 161: 1817–18.

EFFECTS ON THE SKIN. Urticarial vasculitis occurred in a young man after intranasal abuse of cocaine.[1]

1. Hofbauer GFL, *et al.* Urticarial vasculitis following cocaine use. *Br J Dermatol* 1999; 141: 600–601.

OVERDOSAGE. References to fatal overdosage from cocaine abuse.

1. Greenland VC, *et al.* Vaginally administered cocaine overdose in a pregnant woman. *Obstet Gynecol* 1989; 74: 476–7.
2. Peretti FJ, *et al.* Cocaine fatality: an unexplained blood concentration in a fatal overdose. *Forensic Sci Int* 1990; 48: 135–8.
3. Karch SB, *et al.* Relating cocaine blood concentrations to toxicity–an autopsy study of 99 cases. *J Forensic Sci* 1998; 43: 41–5.

PREGNANCY. The effects of cocaine abuse during pregnancy have been reviewed.[1-4] Women who abuse cocaine during pregnancy appear to have an increased risk of spontaneous abortion,[5] abruptio placentae[6,7] and associated stillbirths,[8] premature labour,[9-11] and other birth complications.[9-11] These effects may be due to vasoconstriction by cocaine increasing maternal blood pressure and reducing placental blood flow.[12] Uterine rupture[13] during pregnancy and rupture of ectopic pregnancies[14] have also been associated with cocaine. Neonates born to mothers abusing cocaine have an increased risk of intra-uterine growth retardation and may have lower birth-weight, smaller head size, and shorter length.[6,8-10,15-17] Cocaine is possibly teratogenic and congenital abnormalities associated with abuse include cardiovascular abnormalities,[9,18,19] limb reduction defects,[20] intestinal atresia or infarction,[20] skull defects,[8] and genito-urinary tract anomalies.[21] Neurobehavioural impairment[22] and signs of transient CNS irritability[23] may also occur. Some workers[24,25] have found effects on cognition and motor delays while others have found effects on arousal and attention regulation rather than cognitive processes.[26,27] Cocaine can increase neonatal cerebral blood flow[28] and cerebral infarction and associated seizures have occurred in neonates whose mothers took cocaine near to the onset of labour.[29] Evidence on the risk of intraventricular haemorrhage is conflicting.[7,25]

1. Slutsker L. Risks associated with cocaine use during pregnancy. *Obstet Gynecol* 1992; 79: 778–89.
2. Volpe JJ. Effects of cocaine use on the fetus. *N Engl J Med* 1992; 327: 399–407. Correction. *ibid.*: 1039.
3. Wiggins RC. Pharmacokinetics of cocaine in pregnancy and effects on fetal maturation. *Clin Pharmacokinet* 1992; 22: 85–93.
4. Fajemirokun-Odudeyi O, Lindow SW. Obstetric implications of cocaine use in pregnancy: a literature review. *Eur J Obstet Gynecol Reprod Biol* 2004; 112: 2–8.
5. Chasnoff IJ, *et al.* Cocaine use in pregnancy. *N Engl J Med* 1985; 313: 666–9.
6. Dombrowski MP, *et al.* Cocaine abuse is associated with abruptio placentae and decreased birth weight, but not shorter labor. *Obstet Gynecol* 1991; 77: 139–41.
7. Dusick AM, *et al.* Risk of intracranial hemorrhage and other adverse outcomes after cocaine exposure in a cohort of 323 very low birth weight infants. *J Pediatr* 1993; 122: 438–45.
8. Bingol N, *et al.* Teratogenicity of cocaine in humans. *J Pediatr* 1987; 110: 93–6.
9. Little BB, *et al.* Cocaine abuse during pregnancy: maternal and fetal implications. *Obstet Gynecol* 1989; 73: 157–60.
10. Mastrogiannis DS, *et al.* Perinatal outcome after recent cocaine usage. *Obstet Gynecol* 1990; 76: 8–11.
11. Spence MR, *et al.* The relationship between recent cocaine use and pregnancy outcome. *Obstet Gynecol* 1991; 78: 326–9.
12. Farrar HC, Kearns GL. Cocaine: clinical pharmacology and toxicology. *J Pediatr* 1989; 115: 665–75.
13. Gonsoulin W, *et al.* Rupture of unscarred uterus in primigravid woman in association with cocaine abuse. *Am J Obstet Gynecol* 1990; 163: 526–7.
14. Thatcher SS, *et al.* Cocaine use and acute rupture of ectopic pregnancies. *Obstet Gynecol* 1989; 74: 478–9.
15. Zuckerman B, *et al.* Effects of maternal marijuana and cocaine use on fetal growth. *N Engl J Med* 1989; 320: 762–8.
16. Chasnoff IJ, *et al.* Temporal patterns of cocaine use in pregnancy: perinatal outcome. *JAMA* 1989; 261: 1741–4.
17. Little BB, Snell LM. Brain growth among fetuses exposed to cocaine in utero: asymmetrical growth retardation. *Obstet Gynecol* 1991; 77: 361–4.
18. Lipshultz SE, *et al.* Cardiovascular abnormalities in infants prenatally exposed to cocaine. *J Pediatr* 1991; 118: 44–51.
19. Shaw GM, *et al.* Maternal use of cocaine during pregnancy and congenital cardiac anomalies. *J Pediatr* 1991; 118: 167–8.
20. Hoyme HE, *et al.* Prenatal cocaine exposure and fetal vascular disruption. *Pediatrics* 1990; 85: 743–7.
21. Chávez GF, *et al.* Maternal cocaine use during early pregnancy as a risk factor for congenital urogenital anomalies. *JAMA* 1989; 262: 795–8.
22. Singer LT, *et al.* Neurobehavioural sequelae of fetal cocaine exposure. *J Pediatr* 1991; 119: 667–72.

23. Dobercznk TM, *et al.* Neonatal neurologic and electroencephalographic effects of intrauterine cocaine exposure. *J Pediatr* 1988; 113: 354–8.
24. Azuma SD, Chasnoff IJ. Outcome of children prenatally exposed to cocaine and other drugs: a path analysis of three-year data. *Pediatrics* 1993; 92: 396–402.
25. Singer LT, *et al.* Increased incidence of intraventricular hemorrhage and developmental delay in cocaine-exposed, very low birth weight infants. *J Pediatr* 1994; 124: 765–71.
26. Mayes LC, *et al.* Information processing and developmental assessments in 3-month-old infants exposed prenatally to cocaine. *Pediatrics* 1995; 95: 539–45.
27. Ackerman JP, *et al.* A review of the effects of prenatal cocaine exposure among school-aged children. *Pediatrics* 2010; 125: 554–65.
28. van der Bor M, *et al.* Increased cerebral blood flow velocity in infants of mothers who abuse cocaine. *Pediatrics* 1990; 85: 733–6.
29. Chasnoff IJ, *et al.* Perinatal cerebral infarction and maternal cocaine use. *J Pediatr* 1986; 108: 456–9.

Treatment of Adverse Effects

As for Local Anaesthetics in general, p. 1979.1.

Cocaine overdosage. In the emergency management of overdosage with cocaine the general aims are to establish adequate ventilation and support the circulation. If oral ingestion of a large amount is suspected activated charcoal should be considered. A tourniquet may be applied to limit absorption if the drug was injected. Patients who have swallowed packages containing cocaine for the purpose of smuggling, may be given laxatives but surgical intervention may be required if signs of toxicity appear.

Sedation with intravenous diazepam may be sufficient to manage the symptoms of cocaine overdose. Sedation with benzodiazepines may also be appropriate initial therapy for hypertension or tachyarrhythmias since the excessive sympathetic tone is largely centrally mediated. If hypertension persists, intravenous nitrates should be given; calcium-channel blockers such as diltiazem, nifedipine, or verapamil are an alternative. Phentolamine or sodium nitroprusside may also be tried in patients with hypertension without any evidence of cardiac ischaemia. The use of pure beta blockers should be avoided because of the risk of paradoxical hypertension and coronary vasoconstriction, presumably due to unopposed α-adrenergic stimulation effects of cocaine. However, the beta blocker labetalol which has both α- and β-adrenergic effects may be considered. (For discussion on the use of beta blockers in cocaine-induced myocardial ischaemia, see Cocaine Toxicity under Precautions of Beta Blockers, p. 1320.3.) Chest pain should initially be treated with diazepam or buccal or sublingual nitrates; aspirin should also be given. Persistent pain may require treatment with calcium-channel blockers such as verapamil or intravenous nitrates. Verapamil may also be tried in narrow complex tachycardia. Broad complex tachycardia is treated with sodium bicarbonate; lidocaine may be tried in unresponsive patients. However, there is concern about the use of lidocaine for the treatment of cocaine-induced arrhythmias as lidocaine may enhance toxicity. Diazepam or lorazepam should be used to manage seizures but if they cannot be controlled, propofol or phenytoin can be tried. Hyperthermia should be treated with physical cooling but the use of dantrolene may also be necessary. Control of anxiety and agitation with benzodiazepines when combined with rapid cooling may also have the effect of decreasing heat production in hyperthermic patients. Metabolic acidosis should be monitored and treated where necessary. Short-acting barbiturates or benzodiazepines may be used for dysphoric agitation but drugs that lower the seizure threshold or aggravate hyperthermia such as phenothiazines or haloperidol should be avoided.

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1. Loper KA. Clinical toxicology of cocaine. *Med Toxicol Adverse Drug Exp* 1989; 4: 174–85.
2. Ramrakha P, Barton I. Drug smuggler's delirium. *BMJ* 1993; 306: 470–1.
3. Anonymous. Acute reactions to drugs of abuse. *Med Lett Drugs Ther* 1996; 38: 43–6.
4. Perrar RC, Kearns GL. Cocaine: clinical pharmacology and toxicology. *J Pediatr* 1989; 115: 665–75.
5. Hollander JE. The management of cocaine-associated myocardial ischemia. *N Engl J Med* 1995; 333: 1267–72.

Cocaine withdrawal syndrome. Cocaine can produce psychological dependence but does not produce a major physical withdrawal syndrome. The management of cocaine abuse and dependence has been reviewed.[1-3] There is no advantage to gradual withdrawal and it is best for the patient to stop the drug abruptly.[1,4] The three major psychiatric complications associated with cocaine withdrawal are dysphoric agitation, severe depression, and psychotic symptoms.[1] Such complications are initially managed with psychosocial treatments. However patients with more severe dependence or those who fail to respond to psychosocial treatments should be considered for drug therapies. Dysphoric agitation is best treated with diazepam; propranolol may also be used in more persistent cases. Depressive symptoms during the acute post-cocaine phase are usually transient and require no treatment other than close observation. Desipramine has been used with equivocal results; it appears to be of most benefit in patients who have antecedent or consequent symptoms of severe depression.[3] Trazodone and imipramine have also been tried but had more adverse effects than desipramine.[3] Furthermore, a systematic review has concluded that there was no evidence to support the use of antidepressants[5] in the treatment of cocaine dependence. Antipsychotics such as chlorpromazine, haloperidol, and promazine have been used to manage patients with psychotic symptoms associated with cocaine dependence.[1] However, a systematic review[6] of 7 small studies concluded that there was no evidence to support the use of antipsychotics in the treatment of cocaine dependence; the drugs studied were haloperidol, olanzapine, and risperidone.

Several drugs have been tried in the maintenance of abstinence from cocaine.[1] Lithium may be useful in patients with bipolar disorder or cyclothymic personality. Methylphenidate may be helpful in patients with attention deficit disorders but has potential for abuse itself. Phenothiazine derivatives have been tried in the control of impulsive behaviour and to decrease cocaine craving, although adverse effects may limit their acceptability. Carbamazepine has been reported to suppress the craving for cocaine although this has not been supported by subsequent studies.[3] Furthermore, a systematic review[7] has concluded that there was no evidence to support the use of anticonvulsants (i.e. carbamazepine, gabapentin, lamotrigine, phenytoin, tiagabine, topiramate, and valproate) in the treatment of cocaine dependence. Buprenorphine has been investigated to suppress cocaine and opioid use in patients dependent on both drugs.[3] Anxiolytics or antidepressants are considered unlikely to be of benefit in maintaining abstinence.[3] MAOIs such as phenelzine have been used in a manner analogous to the use of disulfiram in alcohol abuse to provoke unpleasant reactions if patients relapse.[8] Disulfiram itself has also been tried with some success (see below).

There is evidence to suggest that cocaine use affects the dopaminergic modulation of CNS function, and several drugs that interact with the dopamine system have been tried in the treatment of cocaine abuse and dependence.[3,9] For most drugs the results have been disappointing or equivocal although disulfiram and selegiline may warrant further investigation.[9]

A vaccine is under investigation for the treatment of cocaine dependence.

1. Arif A, ed. *Adverse health consequences of cocaine abuse.* Geneva: WHO, 1987.
2. Kleber HD. Pharmacotherapy, current and potential, for the treatment of cocaine dependence. *Clin Neuropharmacol* 1995; 18 (suppl 1): S96–S109.
3. Mendelson JH, Mello NK. Management of cocaine abuse and dependence. *N Engl J Med* 1996; 334: 965–72.
4. DoH (England) and the devolved administrations (2007). *Drug misuse and dependence: UK guidelines on clinical management* (updated September 2007). London: Department of Health (England), the Scottish Government, Welsh Assembly Government and Northern Ireland Executive. Also available at: http://www.nta.nhs.uk/uploads/clinical_guidelines_2007.pdf (accessed 06/08/10)
5. de Lima MS, *et al.* Antidepressants for cocaine dependence. [Withdrawn]. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 17/08/10).
6. Amato L, *et al.* Antipsychotic medications for cocaine dependence. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 21/12/09).
7. Minozzi S, *et al.* Anticonvulsants for cocaine dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 21/12/09).
8. Brewer C. Cocaine and crack. *BMJ* 1989; 299: 792.
9. Gorelick DA, *et al.* Agents in development for the management of cocaine abuse. *Drugs* 2004; 64: 1547–73.

Precautions

As for Local Anaesthetics in general, p. 1979.1.

Since some patients have a marked sensitivity to cocaine, giving a test dose before use on mucous membranes has been suggested. Cocaine should not be applied to damaged mucosa because of the risk of systemic toxicity from enhanced absorption. Ophthalmic preparations of cocaine should not be applied to the eyes for prolonged periods as damage to the cornea may occur not only from the local action of cocaine, but also from loss of the protective eyelid reflexes. As with other mydriatics, there is also a risk of cocaine precipitating angle-closure glaucoma in patients predisposed to the condition. Patients receiving cocaine for surface anaesthesia should be monitored for possible cardiovascular effects. Cocaine should be used with great caution in patients with hypertension, cardiovascular disease, or thyrotoxicosis. It is not recommended for use during pregnancy or breast feeding.

Abuse. Cocaine is subject to abuse. See under Adverse Effects, p. 1984.3.

Gilles de la Tourette's syndrome. Gilles de la Tourette's syndrome, which had been well controlled for 10 years by haloperidol, was precipitated in a 27-year-old man after intranasal use of cocaine on one occasion.[1]

1. Mesulam M-M. Cocaine and Tourette's syndrome. *N Engl J Med* 1986; 315: 398.

Myasthenia gravis. Report of a patient in whom cocaine abuse first unmasked and then exacerbated myasthenia gravis.[1]

1. Berciano J, *et al.* Myasthenia gravis unmasked by cocaine abuse. *N Engl J Med* 1991; 325: 892.

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Cocaine and adrenaline enhance each other's sympathomimetic effects and should preferably not be used together. Caution is needed if cocaine is used with other drugs that may also potentiate the action of catecholamines such as guanethidine or MAOIs.

Adrenaline. In a report[1] of 3 cases of arrhythmias associated with the use of a paste containing cocaine 25% and adrenaline 0.18% for local anaesthesia of the nasal mucosa, the amount of cocaine applied to the nasal mucosa ranged from about 2.5 to 4.5 mg/kg. The maximum recommended dose of cocaine alone in healthy adults is 1.5 mg/kg.

1. Nicholson KEA, Rogers JEG. Cocaine and adrenaline paste: a fatal combination? *BMJ* 1995; 311: 250–1.

Alcohol. In the presence of alcohol, cocaine is metabolised to its ethyl homologue cocaethylene.[1] Cocaethylene appears to have the same stimulant effects as cocaine but it has a longer half-life and *animal* studies suggest that it is more toxic than the parent drug. However, a review of the literature concluded that the use of cocaine with alcohol did not cause more cardiovascular problems than expected from the additive effects of each drug.[2]

1. Randall T. Cocaine, alcohol mix in body to form even longer lasting, more lethal drug. *JAMA* 1992; 267: 1043–4.
2. Pennings EJM, *et al.* Effects of concurrent use of alcohol and cocaine. *Addiction* 2002; 97: 773–83.

Beta blockers. *Propranolol* potentiated cocaine-induced coronary vasoconstriction after intranasal dosage of cocaine in a placebo-controlled study.[1] Because of a possible risk of paradoxical hypertension associated with the use of propranolol to manage arrhythmias associated with cocaine overdosage some prefer the use of labetalol for this indication (see under Treatment of Adverse Effects, above).

1. Lange RA, *et al.* Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic blockade. *Ann Intern Med* 1990; 112: 897–903.

Haloperidol. For the effect of haloperidol in cocaine abusers, see under Chlorpromazine, p. 1053.1.

Pharmacokinetics

Cocaine may be slowly absorbed from some sites because of the vasoconstriction it produces, but absorption occurs from all sites of application, including mucous membranes and the gastrointestinal tract, and may be enhanced when there is inflammation. Cocaine is rapidly absorbed when smoked.

Cocaine is rapidly metabolised by plasma esterases and hepatic esterases to ecgonine methyl ester. Benzoylecgonine, another major metabolite of cocaine, may be produced by spontaneous hydrolysis. Cocaine is also demethylated to the active metabolite norcocaine which is not excreted but undergoes further metabolism. There is considerable interindividual variation in the plasma half-life of cocaine possibly due to differences in esterase activity.

Cocaine and its metabolites are excreted in the urine, about 10% appearing as unchanged drug; they may be detectable in urine for several days or even weeks after use. Cocaine crosses the blood-brain barrier and accumulates within the CNS. It does not appear to undergo rapid metabolism within the brain and concentrations in the CNS after acute intoxication may greatly exceed those in plasma.

Cocaine crosses the placenta and the presence of its metabolites in neonatal hair has been used to indicate intrauterine exposure. Cocaine is distributed into breast milk.

See also under Local Anaesthetics, p. 1979.3.

References.
1. Busto U, *et al.* Clinical pharmacokinetics of non-opiate abused drugs. *Clin Pharmacokinet* 1989; 16: 1–26.
2. Graham K, *et al.* Determination of gestational cocaine exposure by hair analysis. *JAMA* 1989; 262: 3328–30.
3. Burke WM, Ravi NV. Urinary excretion of cocaine. *Ann Intern Med* 1990; 112: 548–9.
4. Ravi NV, Burke WM. Cocaine and traffic accident fatalities in New York City. *JAMA* 1990; 263: 2887.
5. Schenker S, *et al.* The transfer of cocaine and its metabolites across the term human placenta. *Clin Pharmacol Ther* 1993; 53: 329–39.

Absorption. Cocaine is rapidly absorbed from the pulmonary vasculature when smoked and the speed of onset of its effects is similar to that obtained after intravenous injection.[1] Absorption from mucous membranes is delayed by vasoconstriction and peak plasma concentrations of up to 474 nanograms/mL have occurred 15 to 120 minutes after application of doses of 1.5 to 2 mg/kg to the nasal mucosa as a 10% cocaine hydrochloride solution;[2,3] coc-

aine may still be detectable in the nose several hours later and this may result in prolonged systemic absorption.[2] In a study it was estimated that only 5% of the total dose of cocaine hydrochloride used before nasal surgery was absorbed from the nasal mucosa after application of 500 mg of cocaine hydrochloride as a 25% paste with adrenaline or 200 mg as a 10% solution with adrenaline (Moffett's solution) and blood concentrations were well below those associated with toxicity[4] (but see also Adrenaline, under Interactions, p. 1986.3). Peak serum concentrations of cocaine have been obtained 50 to 90 minutes after oral use and are similar to those obtained with nasal application.[3]

1. Farrar HC, Kearns GL. Cocaine: clinical pharmacology and toxicology. *J Pediatr* 1989; 115: 665–75.
2. Van Dyke C, *et al.* Cocaine: plasma concentrations after intranasal application in man. *Science* 1976; 191: 859–61.
3. Van Dyke C, *et al.* Oral cocaine: plasma concentrations and central effects. *Science* 1978; 200: 211–13.
4. Quiney RE. Intranasal topical cocaine: Moffett's method or topical cocaine paste? *J Laryngol Otol* 1986; 100: 279–83.

Preparations

Pharmacopoeial Preparations
BP 2014: Adrenaline and Cocaine Intranasal Solution; Cocaine Eye Drops; Cocaine Paste;
USP 36: Cocaine and Tetracaine Hydrochlorides and Epinephrine Topical Solution; Cocaine Hydrochloride Tablets for Topical Solution.

Dyclonine Hydrochloride *(BANM, rINNM)*

Diclonina, hidrocloruro de; Dyclocaine Hydrochloride; Dyclocaini Chloridum; Dyclonine, Chlorhydrate de; Dyclonini Hydrochloridum; Hidrocloruro de diclonina; Диклонина Гидрохлорид.
4′-Butoxy-3-piperidinopropiophenone hydrochloride.
$C_{18}H_{27}NO_2$,HCl=325.9
CAS — 586-60-7 (dyclonine); 536-43-6 (dyclonine hydrochloride).
ATC — N01BX02; R02AD04.
ATC Vet — QN01BX02; QR02AD04.
UNII — ZEC193879Q.

Pharmacopoeias. In *US.*

USP 36: (Dyclonine Hydrochloride). White crystals or white crystalline powder, with a slight odour. Soluble 1 in 60 of water, 1 in 24 of alcohol, and 1 in 2.3 of chloroform; soluble in acetone; practically insoluble in ether and in hexane. A 1% solution in water has a pH of 4.0 to 7.0. Store in airtight containers. Protect from light.

Profile

Dyclonine hydrochloride is a local anaesthetic (p. 1976.1) used topically for surface anaesthesia of the skin and mucous membranes. Lozenges containing up to 3 mg and throat sprays containing 0.1% of dyclonine hydrochloride have been used for the temporary relief of pain associated with sore throats or mouth irritation; a gel has also been used. It may cause irritation at the site of application.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Cepacol Spray†; Sucrets for Kids; Sucrets Vapor†; Sucrets†; *China*: Da Ji Su (达己苏); *USA*: Sucrets Childrens Formula; Sucrets Original Formula Sore Throat Wild Cherry; Sucrets Throat Spray.

Multi-ingredient Preparations. *Canad.*: Sucrets Complete; *USA*: Cepacol Maximum Strength Sore Throat†; Skin Shield; Sucrets Complete; Sucrets Maximum Strength Sore Throat; Tanac.

Pharmacopoeial Preparations
USP 36: Dyclonine Hydrochloride Gel; Dyclonine Hydrochloride Topical Solution.

Ethyl Chloride

Ethyli Chloridum; Aethylium Chloratum; Chlorethyl; Cloruro de Etilo; Ethylis Chloridum; Etylklorid; Etylu chlorek; Etyylikloridi; Hydrochloric Ether; Monochlorethane; Этилхлорид; Хлористый Этил.
Chloroethane.
C_2H_5Cl=64.51
CAS — 75-00-3.
ATC — N01BX01.
ATC Vet — QN01BX01.
UNII — 46U771ERWK.

Pharmacopoeias. In *Pol.* and *US.*

USP 36: (Ethyl Chloride). A colourless, mobile, very volatile liquid at low temperatures or under pressure, with a characteristic ethereal odour. B.p. 12 degrees to 13 degrees. Slightly soluble in water; freely soluble in alcohol and in ether. Store in airtight containers, preferably hermetically sealed.

Stability. Ethyl chloride is highly flammable and mixtures of the gas with 5 to 15% of air are explosive.

Uses and Administration

Owing to its low boiling-point and the intense cold produced by evaporation, ethyl chloride has been used as a local anaesthetic in minor surgery but such use is not generally recommended. It has also been used topically for the relief of pain and to test the efficacy of regional anaesthesia. Ethyl chloride was formerly used as an inhalational anaesthetic but has no place in modern anaesthetic practice.

Adverse Effects and Precautions

As for Chloroform, p. 1898.2.

Cutaneous sensitisation can occur rarely. Thawing of frozen tissue following surgery may be painful and prolonged spraying onto the skin can cause chemical frostbite. Freezing may also distort the histological structure of biopsy specimens. Ethyl chloride should not be applied to broken skin or mucous membranes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: ShiBo (施博); *Ger.*: Chlorethyl Dr Henning; *Hong Kong*: WariActiv; *Israel*: Chloraethyl Dr Henning; *Mex.*: Traumazol; *Spain*: Cloretilo Chemirosa; *Switz.*: Chlorethyl†; *UK*: Cryogesic.

Multi-ingredient Preparations. *USA*: Fluro-Ethyl†.

Ethyl *p*-Piperidinoacetylaminobenzoate

EPAB; *p*-Piperidinoacetilaminobenzoato de etilo; SA-7.
4-[(1-Piperidinylacetyl)amino]benzoic acid ethyl ester.
$C_{16}H_{22}N_2O_3$=290.4
CAS — 41653-21-8.
UNII — 6M452G7O1F.

NOTE. The name Nichicaine has been used as a trade mark for ethyl *p*-piperidinoacetylaminobenzoate.

Profile

Ethyl *p*-piperidinoacetylaminobenzoate is an amide local anaesthetic (p. 1976.1) that has been given orally for the symptomatic relief of gastritis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Sulcain.

Ketocaine Hydrochloride *(rINNM)*

Chetocaina Cloridrata; Hidrocloruro de ketocaína; Ketocaína, hidrocloruro de; Kétocaïne, Chlorhydrate de; Ketocaini Hydrochloridum; Кетокаина Гидрохлорид.
2′-(2-Di-isopropylaminoethoxy)butyrophenone hydrochloride.
$C_{18}H_{29}NO_2$,HCl=327.9
CAS — 1092-46-2 (ketocaine); 1092-47-3 (ketocaine hydrochloride).

Profile

Ketocaine hydrochloride is a local anaesthetic (p. 1976.1) that has been used as a surface anaesthetic in suppositories or ointments for anorectal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Proctolyn.

Levobupivacaine *(BAN, rINN)*

S (-)-Bupivacaine; Levobupivacaína; Lévobupivacaïne; Levobupivacainum; Levobupivakaiini; Levobupivakain; Левобупивакаин.
(*S*)-1-Butyl-2-piperidylformo-2′,6′-xylidide.
$C_{18}H_{28}N_2O$=288.4
CAS — 27262-47-1.
ATC — N01BB10.
ATC Vet — QN01BB10.
UNII — A5H73K9U3W.

Levobupivacaine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de levobupivacaína; Levobupivacaína, hidrocloruro de; Lévobupivacaïne, Chlorhydrate de; Levobupivacaini Hydrochloridum; Levobupivakain Hidroklorür; Левобупивакаина Гидрохлорид.
$C_{18}H_{28}N_2O$,HCl=324.9
CAS — 27262-48-2.
ATC — N01BB10.
ATC Vet — QN01BB10.
UNII — J998RDZ51I.

Uses and Administration

Levobupivacaine is a local anaesthetic of the amide type with actions and uses similar to those described on p. 1976.1. It is the *S*-enantiomer of bupivacaine (p. 1980.3). Levobupivacaine is given as the hydrochloride for infiltration anaesthesia and regional nerve blocks including epidural block; however, it is contra-indicated for obstetric paracervical block and for use in intravenous regional anaesthesia (Bier's block). The 0.75% solution is also contra-indicated for epidural blocks in obstetrics. (Local anaesthetic techniques are discussed on p. 1977.2.)

Levobupivacaine hydrochloride is available in solutions containing the equivalent of 0.0625 to 0.75% of levobupivacaine. The dosage depends on the site of injection and the procedure used as well as the status of the patient. The recommended **maximum single dose** is 150 mg. The total daily dose should not exceed 400 mg. A test dose of a suitable local anaesthetic, preferably with adrenaline, should be given before starting epidural block with levobupivacaine to detect inadvertent intravascular injection. Subsequent doses of levobupivacaine should be given in small increments. Levobupivacaine should be given in reduced doses to elderly, debilitated, or acutely ill patients.

- For **surgical anaesthesia** doses of levobupivacaine for *epidural block* are 50 to 100 mg (10 to 20 mL) as a 0.5% solution, or 75 to 150 mg (10 to 20 mL) as a 0.75% solution; for caesarean section, doses are 75 to 150 mg (15 to 30 mL) as a 0.5% solution. The dose for *spinal block* is 15 mg (3 mL) as a 0.5% solution.
- For *peripheral nerve blocks*, doses are 2.5 to 150 mg as a 0.25 or 0.5% solution; a volume of 40 mL should not be exceeded.
- For *infiltration anaesthesia* up to 150 mg (60 mL) as a 0.25% solution may be used. For peribulbar block in *ophthalmic* procedures 37.5 to 112.5 mg (5 to 15 mL) as a 0.75% solution may be given. For ilioinguinal or iliohypogastric blocks in **children** under 12 years of age, doses of levobupivacaine are 0.625 to 2.5 mg/kg (0.25 to 0.5 mL/kg) as a 0.25 or 0.5% solution.
- In the management of **acute pain** levobupivacaine may be given as an epidural bolus or by continuous infusion. For pain relief during *labour* 15 to 50 mg (6 to 20 mL) as a 0.25% solution is given as a bolus. Alternatively, levobupivacaine may be given as an infusion in a dose of 5 to 12.5 mg per hour as a 0.125% solution (4 to 10 mL per hour) or as a 0.0625% solution (8 to 20 mL per hour). For *postoperative pain*, an epidural infusion may be given in a dose of 12.5 to 18.75 mg per hour as a 0.25% solution (5 to 7.5 mL per hour), a 0.125% solution (10 to 15 mL per hour), or a 0.0625% solution (20 to 30 mL per hour).

In some countries such as the UK, licensed product information recommends that a lower concentration such as the 0.125% solution should be used if other analgesics are also given for pain relief. When necessary, dilutions should be made with sodium chloride 0.9%.

Reviews

1. Foster RH, Markham A. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. *Drugs* 2000; 59: 551–79.
2. Sanford M, Keating GM. Levobupivacaine: a review of its use in regional anaesthesia and pain management. *Drugs* 2010; 70: 761–91.

Action. A comparison[1] of epidural bupivacaine with levobupivacaine in women in labour found that levobupivacaine had 98% of the potency of the racemate, a clinically insignificant difference. However it was pointed out that whereas the concentration of bupivacaine solutions was expressed in terms of the hydrochloride, solutions of levobupivacaine had their strength expressed in terms of the free base. When calculations were made in terms of molar equivalents levobupivacaine appeared to be 13% less potent than racemic bupivacaine. The difference in expression should be borne in mind when evaluating comparative studies.

1. Lyons G, *et al.* Epidural pain relief in labour: potencies of levobupivacaine and racemic bupivacaine. *Br J Anaesth* 1998; 81: 899–901.

Administration in children. The *BNFC* recommends that the dose of levobupivacaine in children should be adjusted

according to physical status and the nature of the procedure.

For the licensed dosage of levobupivacaine hydrochloride for ilioinguinal or iliohypogastric blocks in children, see p. 1987.3.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p. 1978.1, p. 1979.1, and p. 1979.1, respectively.

Levobupivacaine is contra-indicated for use in intravenous regional anaesthesia (Bier's block) and for paracervical block in obstetrics. The 0.75% solution is also contra-indicated for epidural block in obstetrics.

Effects on the cardiovascular system. It has been suggested[1] that levobupivacaine may have a lower risk of causing cardiotoxicity than bupivacaine (for the effects of bupivacaine on the cardiovascular system see p. 1981.3).

1. Mather LE, Chang DH. Cardiotoxicity with modern local anaesthetics: is there a safer choice? *Drugs* 2001; 61: 333–42.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies levobupivacaine 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 05/10/11)

Interactions

For interactions associated with local anaesthetics, see p. 1979.3. Plasma concentrations of levobupivacaine may be reduced by enzyme-inducing drugs such as rifampicin. Levobupivacaine is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP1A2 and there is a theoretical possibility that substrates for or inhibitors of these isoenzymes may adversely alter plasma concentrations of levobupivacaine.

Pharmacokinetics

The pharmacokinetics of levobupivacaine are similar to those of the racemic form, bupivacaine (p. 1982.2). Levobupivacaine is at least 97% bound to plasma proteins. After intravenous doses the mean half-life is about 80 minutes. Levobupivacaine is extensively metabolised and excreted as its metabolites mainly in the urine, with smaller amounts appearing in the faeces. 3-Hydroxylevobupivacaine is a major metabolite and its formation is mediated by the cytochrome P450 isoenzyme CYP1A2; the isoenzyme CYP3A4 is also involved in the metabolism of levobupivacaine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Chirocaine; *Austria*: Chirocaine; *Belg.*: Chirocaine; *Braz.*: Novabupi; *Chile*: Chirocaina; *China*: Ao Gui Ren (奥桂仁); Chirocaine (凯乐); Su Ka (速卡); Yi Jie Ka (伊捷卡); *Cz.*: Chirocaine; *Fin.*: Chirocaine; *Fr.*: Chirocaine; *Gr.*: Chirocaine; *Hong Kong*: Chirocaine; *Hung.*: Chirocaine†; *Irl.*: Chirocaine; *Ital.*: Chirocaine; *Jpn*: Popscaine; *Mex.*: Quirocaine†; *Neth.*: Chirocaine; *Philipp.*: SensiBloq; *Port.*: Chirocaine; *S.Afr.*: Chirocaine; *Singapore*: Chirocaine; *Spain*: Chirocaine; *Swed.*: Chirocaine; *Switz.*: Chirocaine; *Thai.*: Chirocaine; *Turk.*: Chirocaine; *UK*: Chirocaine; *Venez.*: Chirocaina.

Lidocaine *(BAN, rINN)*

Lidocain; Lidocaína; Lidocaine; Lidocainum; Lidokaiini; Lidokain; Lidokaina; Lidokainas; Lignocaína; Lignocaine; Лидокаин

2-Diethylaminoacet-2',6'-xylidide.

$C_{14}H_{22}N_2O$=234.34.

CAS — 137-58-6.

ATC — C01BB01; C05AD01; D04AB01; N01BB02; R02AD02; S01HA07; S02DA01.

ATC Vet — QC01BB01; QC05AD01; QD04AB01; QN01BB02; QR02AD02; QS01HA07; QS02DA01.

UNII — 98PI200987.

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

Ph. Eur. 8: (Lidocaine). A white or almost white, crystalline powder. M.p. 66 degrees to 70 degrees. Practically insoluble in water; very soluble in alcohol and in dichloromethane.

USP 36: (Lidocaine). A white to slightly yellow crystalline powder with a characteristic odour. M.p. 66 degrees to 69 degrees. Practically insoluble in water; very soluble in alcohol and in chloroform; freely soluble in ether and in benzene; dissolves in oils.

Eutectic mixture. Lidocaine forms a mixture with prilocaine that has a melting-point lower than that of either ingredient. This eutectic mixture is used in the preparation of topical dosage forms.

Lidocaine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de lidocaína; Hidrocloruro de lignocaína; Lidocaína, hidrocloruro de; Lidocaine, Chlorhydrate de; Lidocainhydrochlorid; Lidocaini hydrochloridum; Lidocaini Hydrochloridum Monohydricum; Lidokainihydroklorid; Lidokain Hidroklorür; Lidokain-hidroklorid; Lidokain-hydrochlorid monohydrát; Lidokainhydroklorid; Lidokaino hidrochloridas; Lidokainy chlorowodorek; Lignoc. Hydrochlor; Lignocaine Hydrochloride; Lignokain Hidroklorür; Лидокаина гидрохлорид.

$C_{14}H_{22}N_2O.HCl.H_2O$=288.8

CAS — 73-78-9 (anhydrous lidocaine hydrochloride); 6108-05-0 (lidocaine hydrochloride monohydrate).

ATC — C01BB01; C05AD01; D04AB01; N01BB02; R02AD02; S01HA07; S02DA01.

ATC Vet — QC01BB01; QC05AD01; QD04AB01; QN01BB02; QR02AD02; QS01HA07; QS02DA01.

UNII — V13007Z41A (lidocaine hydrochloride monohydrate); EC2CNF7XFP (anhydrous lidocaine hydrochloride).

NOTE. LIDFLN is a code approved by the BP 2014 for use on single unit doses of eye drops containing lidocaine hydrochloride and fluorescein sodium where the individual container may be too small to bear all the appropriate labelling information.

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

Ph. Eur. 8: (Lidocaine Hydrochloride). A white, or almost white, crystalline powder. M.p. 74 degrees to 79 degrees. Very soluble in water; freely soluble in alcohol. A 0.5% solution in water has a pH of 4.0 to 5.5. Protect from light.

USP 36: (Lidocaine Hydrochloride). A white, odourless, crystalline powder. M.p. 74 degrees to 79 degrees. Very soluble in water and in alcohol; soluble in chloroform; insoluble in ether.

Incompatibility. Lidocaine hydrochloride has been reported to be incompatible in solution with amphotericin B,[1] sulfadiazine sodium,[2] methohexital sodium,[2] cefazolin sodium,[3] or phenytoin sodium.[4]

Acid stable drugs such as adrenaline hydrochloride, noradrenaline acid tartrate, or isoprenaline may begin to deteriorate within several hours of admixture with lidocaine hydrochloride as lidocaine solutions may raise the pH of the final solution above the maximum pH for their stability. Such extemporaneous mixtures should be used promptly after preparation.[5]

1. Whiting DA. Treatment of chromoblastomycosis with high local concentrations of amphotericin B. *Br J Dermatol* 1967; 79: 345–51.
2. Riley BB. Incompatibilities in intravenous solutions. *J Hosp Pharm* 1970; 28: 228–40.
3. Kleinberg ML, *et al.* Stability of antibiotics frozen and stored in disposable hypodermic syringes. *Am J Hosp Pharm* 1980; 37: 1087–8.
4. Kirschenbaum HL, *et al.* Stability and compatibility of lidocaine hydrochloride with selected large-volume parenterals and drug additives. *Am J Hosp Pharm* 1982; 39: 1013–15.
5. Parker EA. Xylocaine hydrochloride 2% injection. *Am J Hosp Pharm* 1971; 28: 805.

pH of solutions. For the effect pH has on the surface tension and administration of lidocaine solutions by infusion, see under Administration in Uses and Administration, p. 1976.2. For its effect on the stability of local anaesthetic solutions and the pain associated with their injection, see p. 1976.2.

Stability. Although there was no decrease in the lidocaine content of lidocaine hydrochloride and adrenaline injection during transport and storage under tropical conditions, the content of adrenaline fell to almost zero in some samples after several months; supply of the injection as a dry powder and separate solvent should be considered for the tropics.[1]

The lidocaine content of buffered cardioplegic solutions has been reported[2] to decrease when stored in PVC containers at ambient temperature, but not when stored at 4 degrees. This loss appeared to result from pH-dependent sorption of lidocaine onto the plastic and did not occur when lidocaine solutions were stored in glass bottles.

1. Abu-Reid IO, *et al.* Stability of drugs in the tropics: a study in Sudan. *Int Pharm J* 1990; 4: 6–10.
2. Lackner TE, *et al.* Lidocaine stability in cardioplegic solution stored in glass bottles and polyvinyl chloride bags. *Am J Hosp Pharm* 1983; 40: 97–101.

Uses and Administration

Lidocaine is a local anaesthetic of the amide type with actions and uses similar to those described on p. 1976.1. It is used for infiltration anaesthesia and regional nerve blocks. It has a rapid onset of action and anaesthesia is obtained within a few minutes; it has an intermediate duration of action. The speed of onset and duration of action of lidocaine are increased by the addition of a vasoconstrictor and absorption into the circulation from the site of injection is reduced. It is generally given as the hydrochloride. Lidocaine hydrochloride monohydrate 1.23 g or anhydrous lidocaine hydrochloride 1.16 g are both equivalent to about 1 g of lidocaine. A carbonated solution of lidocaine is also available in some countries for injection (see p. 1976.2). Lidocaine is also a useful surface anaesthetic but it may be rapidly and extensively absorbed following topical application to mucous membranes, and systemic effects may occur. Hyaluronidase (p. 2527.2) has been added to preparations of lidocaine used for surface and infiltration anaesthesia but it may enhance systemic absorption. (Local anaesthetic techniques are discussed on p. 1977.2.)

Lidocaine is included in some injections, such as depot corticosteroids, to prevent pain, itching, and other local irritation. Lidocaine sodium has also been included in intramuscular injections of some antibacterials to reduce the pain on injection.

Lidocaine is also a class Ib antiarrhythmic used in the treatment of ventricular arrhythmias, especially after myocardial infarction. It has been given by intravenous infusion in the treatment of refractory status epilepticus.

USE IN LOCAL ANAESTHESIA.

The dose of lidocaine hydrochloride used for local anaesthesia depends on the site of injection and the procedure used. Specific doses for individual procedures are not always available in UK licensed product information, although US product information often includes them (see below). When given with adrenaline, the suggested general **maximum single dose** of lidocaine hydrochloride is 500 mg; without adrenaline, the recommended maximum single dose in the UK is 200 mg and in the USA, 300 mg except for spinal anaesthesia (see below). Lidocaine hydrochloride solutions containing adrenaline 1 in 200 000 are used for infiltration anaesthesia and nerve blocks including epidural block; higher concentrations of adrenaline are seldom necessary, except in dentistry, where solutions of lidocaine hydrochloride with adrenaline 1 in 80 000 are widely used. Doses should be reduced in children, the elderly, and in debilitated patients. A test dose, preferably with adrenaline, should be given before starting epidural block to detect inadvertent intravascular or subarachnoid dosage.

The following doses have been recommended for individual **local anaesthetic procedures** in the USA:

- For percutaneous *infiltration anaesthesia*, 5 to 300 mg (1 to 60 mL of a 0.5% solution, or 0.5 to 30 mL of a 1% solution).
- The dosage in *peripheral nerve block* depends on the route. For brachial plexus block 225 to 300 mg (15 to 20 mL) as a 1.5% solution is used; for dental nerve block a 2% solution may be used in doses of 20 to 100 mg (1 to 5 mL); for intercostal nerve block 30 mg (3 mL) is given as a 1% solution; for paracervical block a 1% solution is used in a dose of 100 mg (10 mL) on each side, repeated not more frequently than every 90 minutes; for paravertebral block a 1% solution may be used in doses of 30 to 50 mg (3 to 5 mL); a 1% solution is recommended for pudendal block in doses of 100 mg (10 mL) on each side; for retrobulbar block a 4% solution may be used in doses of 120 to 200 mg (3 to 5 mL).
- For *sympathetic nerve block* a 1% solution is recommended; doses are 50 mg (5 mL) for cervical block and 50 to 100 mg (5 to 10 mL) for lumbar block.
- For *epidural anaesthesia* 2 to 3 mL of solution is needed for each dermatome to be anaesthetised but usual total doses and recommended concentrations are: lumbar epidural 250 to 300 mg (25 to 30 mL) as a 1% solution for analgesia and 225 to 300 mg (15 to 20 mL) as a 1.5% solution or 200 to 300 mg (10 to 15 mL) as a 2% solution for anaesthesia, and for thoracic epidural a 1% solution may be used at doses of 200 to 300 mg (20 to 30 mL). In obstetric caudal analgesia 200 to 300 mg (20 to 30 mL) is used as a 1% solution and in surgical caudal anaesthesia a 1.5% solution may be used in doses of 225 to 300 mg (15 to 20 mL). For continuous epidural or caudal anaesthesia, the maximum doses should not be repeated more frequently than every 90 minutes.
- A hyperbaric solution of 1.5% or 5% lidocaine hydrochloride in glucose 7.5% solution is available for *spinal anaesthesia*; adrenaline should not be used. Doses of up to 50 mg (1 mL) as a 5% solution and 9 to 15 mg (0.6 to 1 mL) as a 1.5% solution have been used during labour for a normal vaginal delivery. Up to 75 mg (1.5 mL) as the 5% solution has been used for caesarean section and 75 to 100 mg (1.5 to 2 mL) for other surgical procedures.
- For *intravenous regional anaesthesia* a 0.5% solution without adrenaline has been used in doses of 50 to 300 mg (10 to 60 mL); a maximum dose of 4 mg/kg has been recommended for adults.

Lidocaine may be used in a variety of formulations for **surface anaesthesia.**

- Lidocaine ointment is used for *anaesthesia of skin and mucous membranes* with a maximum recommended total

dose of 20 g of 5% ointment (equivalent to 1 g of lidocaine base) in 24 hours.

- A 4% foam may be applied to the skin up to 3 or 4 times daily for the *relief of pain* caused by minor cuts or burns, abrasions, sunburn, and insect bites.
- Gels are used for *anaesthesia of the urinary tract* and the dose used varies in different countries. UK licensed product information recommends instilling about 120 to 220 mg (6 to 11 mL) of lidocaine hydrochloride as a 2% gel into the urethra several minutes before examination. The doses used in the USA are as follows: in females 60 to 100 mg of lidocaine hydrochloride as a 2% gel is inserted into the urethra several minutes before examination; in males 100 to 200 mg is used before catheterisation and 600 mg before sounding or cystoscopy.

  A 2% gel may also be used as *anaesthetic lubrication for endotracheal intubation*; a moderate amount is applied to the external surface of the endotracheal tube shortly before use.

  A eutectic gel containing lidocaine base 2.5% and prilocaine base 2.5% is used for *anaesthesia of the periodontal pockets* during dental scaling and/or root planing. Typically, 1.7 g of gel, or less, will be sufficient for one quadrant of dentition; the maximum recommended quantity per treatment session is 8.5 g.
- Topical solutions are used for *surface anaesthesia of mucous membranes of the mouth, throat, and upper gastrointestinal tract.* For painful conditions of the mouth and throat a 2% solution may be used: 300 mg (15 mL) may be rinsed and ejected or, for pharyngeal pain, the solution is gargled and swallowed if necessary; it should not be used more frequently than every 3 hours to a maximum daily dose of 2.4 g. Doses of 40 to 200 mg as a 4% solution (1 to 5 mL) are used before bronchoscopy, bronchography, laryngoscopy, oesophagoscopy, endotracheal intubation, and biopsy in the mouth and throat. Lidocaine in a strength of 10% has also been used as a spray for application to mucous membranes for the prevention of pain during various procedures including use in otorhinolaryngology, dentistry, introduction of instruments into the respiratory and gastrointestinal tracts, and in obstetrics. The dose depends on the extent of the site to be anaesthetised; 10 to 50 mg is generally sufficient for dentistry and otorhinolaryngology; for other procedures, the maximum dose in a 24-hour period is 200 mg. For laryngotracheal anaesthesia 160 mg of lidocaine hydrochloride as a 4% solution is sprayed or instilled as a single dose into the lumen of the larynx and trachea.
- Lidocaine is used *rectally* as suppositories, sprays, ointments, and creams in the treatment of haemorrhoids and other painful perianal conditions.
- *Eye drops* containing lidocaine hydrochloride 4% with fluorescein are used in tonometry.

  An *ophthalmic gel* containing lidocaine hydrochloride 3.5% is used for surface anaesthesia during ophthalmological procedures.
- A *eutectic mixture* containing lidocaine base 2.5% and prilocaine base 2.5% is applied as a cream under an occlusive dressing to produce *surface anaesthesia of the skin* before procedures requiring needle puncture, surgical treatment of localised lesions, and split skin grafting; it has been used similarly, but without an occlusive dressing, before removal of genital warts (see also under Surface Anaesthesia, below).
- Other methods of dermal delivery include a *transdermal patch* of lidocaine 5% for the symptomatic relief of neuropathic pain associated with postherpetic neuralgia, and an *iontophoretic drug delivery system* incorporating lidocaine and adrenaline. A transdermal patch containing lidocaine 70 mg with tetracaine 70 mg is also available for surface anaesthesia.

USE IN ARRHYTHMIAS.

For the treatment of **ventricular arrhythmias** lidocaine is given *intravenously* as the hydrochloride. It may be used in advanced cardiac life support for cardiac arrest due to ventricular fibrillation and pulseless ventricular tachycardia when direct current shocks (together with adrenaline) have failed to restore a normal rhythm. For adults, a usual dose of 1 to 1.5 mg/kg can be given and repeated as necessary to a maximum total dose of 3 mg/kg. The *endotracheal* route has been used when intravenous access cannot be obtained, although doses should probably be larger than those given intravenously; the precise endotracheal dose has not yet been established, however.

Lidocaine is also used in other ventricular arrhythmias in which the patient is in a more stable condition. In these circumstances lidocaine hydrochloride is usually given as a loading dose followed by an infusion. Usual doses are 50 to 100 mg or 1 to 1.5 mg/kg as a direct *intravenous injection* at a rate of 25 to 50 mg/minute. If no effect is seen within 5 to 10 minutes of this loading dose, it may be repeated once or twice to a maximum dose of 200 to 300 mg in 1 hour. A *continuous intravenous infusion* is usually started after loading, at a dose of 1 to 4 mg/minute. It is rarely necessary to continue this infusion for longer than 24 hours, but in the event that a longer infusion is required, the dose may need to be reduced to avoid potential toxicity resulting from an increase in the half-life. Dosage may need to be reduced in the elderly and in patients with heart failure or liver disorders.

In emergency situations, lidocaine hydrochloride has also been given for arrhythmias by *intramuscular* injection into the deltoid muscle in a dose of 300 mg, repeated if necessary after 60 to 90 minutes.

Action. For a comparison of the vasoactivity of lidocaine and some other local anaesthetics, see p. 1976.2.

Administration in children. The *BNFC* recommends that the dose of lidocaine in children should be adjusted according to physical status and the nature of the procedure.

Burns. Lidocaine given intravenously has been reported to have produced pain relief in a few patients with second-degree burns.[1]

1. Jönsson A, *et al.* Inhibition of burn pain by intravenous lignocaine infusion. *Lancet* 1991; 338: 151–2.

Cardiac arrhythmias. Lidocaine is classified as a class Ib antiarrhythmic drug (p. 1243.1) and may be used in the treatment of ventricular arrhythmias, including those associated with cardiac arrest and myocardial infarction, although other drugs are usually preferred (see Cardiac Arrhythmias, p. 1266.1). It is usually given intravenously (see p. 1988.2). Lidocaine may also be used during advanced cardiac life support (see Cardiac Arrest, p. 1268.3).

Lidocaine has been considered for the *prophylaxis* of ventricular fibrillation in patients with proven or suspected myocardial infarction. However, while some studies have identified a protective effect of lidocaine,[1,2] in others it was not shown to reduce mortality and might even have increased it,[3,4] and thus is no longer generally recommended.

It has been suggested that the increased mortality sometimes seen with lidocaine might be associated with the duration of treatment; a study[5] found that patients who received a bolus dose of lidocaine followed by a 40-hour continuous infusion for prophylaxis of ventricular arrhythmias had more episodes of heart failure than patients who received the bolus dose followed by an 8-hour infusion.

1. Horwitz RI, Feinstein AR. Improved observational method for studying therapeutic efficacy: suggestive evidence that lidocaine prophylaxis prevents death in acute myocardial infarction. *JAMA* 1981; 246: 2455–9.
2. Koster RW, Dunning AJ. Intramuscular lidocaine for prevention of lethal arrhythmias in the prehospitalization phase of acute myocardial infarction. *N Engl J Med* 1985; 313: 1105–10.
3. MacMahon S, *et al.* Effects of prophylactic lidocaine in suspected acute myocardial infarction: an overview of results from the randomized, controlled trials. *JAMA* 1988; 260: 1910–16.
4. Eline LK, *et al.* Meta-analytic evidence against prophylactic use of lidocaine in acute myocardial infarction. *Ann Intern Med* 1989; 149: 2694–8.
5. Pharand C, *et al.* Lidocaine prophylaxis for fatal ventricular arrhythmias after acute myocardial infarction. *Clin Pharmacol Ther* 1995; 57: 471–8.

Hiccup. For the management of intractable hiccups see under Chlorpromazine, p. 1046.3. Lidocaine is one of a large number of drugs that has been tried in the treatment of hiccups without strong evidence of their efficacy. It has been given intravenously, or in the form of a 2% viscous solution taken orally. Nebulised lidocaine has also been tried.[1]

1. Neeno TA, Rosenow EC. Intractable hiccups: consider nebulized lidocaine. *Chest* 1996; 110: 1129–30.

Intubation. Lidocaine has produced conflicting results when used to attenuate the pressor response and rise in intra-ocular pressure induced by procedures such as tracheal intubation.[1–5] For an overall discussion of this problem, see under Anaesthesia, p. 2028.1.

1. Tam S, *et al.* Attenuation of circulatory responses to endotracheal intubation using intravenous lidocaine: a determination of the optimal time of injection. *Can Anaesth Soc J* 1985; 32: S65.
2. Murphy DF, *et al.* Intravenous lignocaine pretreatment to prevent intraocular pressure rise following suxamethonium and tracheal intubation. *Br J Ophthalmol* 1986; 70: 596–8.
3. Drenger B, Pe'er J. Attenuation of ocular and systemic responses to tracheal intubation by intravenous lignocaine. *Br J Ophthalmol* 1987; 71: 546–8.
4. Miller CD, Warren SJ. IV lignocaine fails to attenuate the cardiovascular response to laryngoscopy and tracheal intubation. *Br J Anaesth* 1990; 65: 216–19.
5. Mostafa SM, *et al.* Effects of nebulized lignocaine on the intraocular pressure responses to tracheal intubation. *Br J Anaesth* 1990; 64: 515–17.

Migraine and cluster headache. Despite periodic interest, lidocaine has so far failed to find an accepted role in the management of migraine (p. 670.3) or cluster headache (p. 670.1). Lidocaine has been tried for the emergency parenteral treatment of migraine, but in a comparative study with dihydroergotamine or chlorpromazine it was found to be less effective than either.[1] While some workers have found that intranasal instillation of lidocaine has produced rapid relief of headache in some patients with acute migraine (though early relapse was common)[2] others have found it to be ineffective.[3] It has also been reported to be effective in aborting individual attacks of headache during cluster periods in patients with cluster headache.[4,5] However, most patients do not appear to obtain complete pain relief.

1. Bell R, *et al.* A comparative trial of three agents in the treatment of acute migraine headache. *Ann Emerg Med* 1990; 19: 1070–82.
2. Maizels M, *et al.* Intranasal lidocaine for treatment of migraine: a randomized, double-blind, controlled trial. *JAMA* 1996; 276: 319–21.
3. Blanda M, *et al.* Intranasal lidocaine for the treatment of migraine headache: a randomized, controlled trial. *Acad Emerg Med* 2001; 8: 337–42.
4. Kittrelle JP, *et al.* Cluster headache: local anesthetic abortive agents. *Arch Neurol* 1985; 42: 496–8.
5. Robbins L. Intranasal lidocaine for cluster headache. *Headache* 1995; 35: 83–4.

Neuropathic pain syndromes. Lidocaine may be useful in the management of some types of neuropathic pain syndromes (p. 10.1). The pain of *postherpetic neuralgia* has been significantly reduced by the application of lidocaine 5% transdermal patches[1-3] although a systematic review[4] found insufficient evidence to recommend its use as first-line therapy; intravenous lidocaine[5] and a eutectic mixture of lidocaine and prilocaine (see Surface Anaesthesia below) have also been of benefit. Other syndromes where intravenous lidocaine therapy has been tried include *diabetic neuropathy*[6] and *central neuropathic pain* associated with stroke or spinal cord injury.[7]

1. Rowbotham MC, *et al.* Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. *Pain* 1996; 65: 39–44.
2. Comer AM, Lamb HM. Lidocaine patch 5%. *Drugs* 2000; 59: 245–9.
3. Davies PS, Galer BS. Review of lidocaine patch 5% studies in the treatment of postherpetic neuralgia. *Drugs* 2004; 64: 937–47.
4. Khaliq W, *et al.* Topical lidocaine for the treatment of postherpetic neuralgia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 22/04/08).
5. Attal N, *et al.* Systemic lidocaine in pain due to peripheral nerve injury and predictors of response. *Neurology* 2004; 62: 218–25.
6. Kastrup J, *et al.* Treatment of chronic painful diabetic neuropathy with intravenous lidocaine infusion. *BMJ* 1986; 292: 173.
7. Attal N, *et al.* Intravenous lidocaine in central pain: a double-blind, placebo-controlled, psychophysical study. *Neurology* 2000; 54: 564–74.

Pleurodesis. Lidocaine has been instilled intrapleurally as a 1% solution in doses of up to 300 mg to relieve the severe chest pain associated with the use of tetracycline for pleurodesis.[1-3] While the larger doses were significantly more effective[2] toxic plasma concentrations were less likely to occur if a dose of 3 mg/kg or less was used.[3]

1. Harbecke RG. Intrapleurally given tetracycline with lidocaine. *JAMA* 1980; 244: 1899–1900.
2. Sherman S, *et al.* Optimum anesthesia with intrapleural lidocaine during chemical pleurodesis with tetracycline. *Chest* 1988; 93: 533–6.
3. Wooten SA, *et al.* Systemic absorption of tetracycline and lidocaine following intrapleural instillation. *Chest* 1988; 94: 960–3.

Status epilepticus. Lidocaine hydrochloride may be used to control status epilepticus (p. 510.2) resistant to more conventional treatment, particularly in those with respiratory disease. It has a rapid onset of action but its effect is short-lived and continuous infusion may be necessary.[1] It should also be noted that doses producing high plasma concentrations of lidocaine can result in CNS toxicity including seizures.[1] Recurrence of seizures associated with the withdrawal of prolonged lidocaine therapy may be due to its accumulated metabolites exerting an excitatory effect on the nervous system when the inhibitory effect of lidocaine is being reduced.[2]

Lidocaine was used instead of diazepam for 42 episodes of status epilepticus in 36 patients who either had limited pulmonary reserve or who had not responded to intravenous diazepam.[3] Lidocaine 1.5 to 2 mg/kg (usually a dose of 100 mg) was given as a single intravenous dose over 2 minutes. This dose was repeated once if there was no positive response to the first dose (11 episodes) or if the seizures recurred (19 episodes). Subsequently a continuous infusion of lidocaine at a rate of 3 to 4 mg/kg per hour was given in the 7 episodes that recurred after the second dose; 5 of these showed a positive response. The 11 episodes not responding to the first dose did not respond to the second dose or to a continuous infusion. In a retrospective analysis[4] of 37 children with status epilepticus, lidocaine was effective in only 19 of 53 episodes; however, in a few cases it was effective where other drugs had failed, and those patients who responded did so rapidly (within 5 minutes of being given the drug).

1. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; 1: 26–44.
2. Wallin A, *et al.* Lidocaine treatment of neonatal convulsions, a therapeutic dilemma. *Eur J Clin Pharmacol* 1989; 36: 583–6.
3. Pascual J, *et al.* Role of lidocaine (lignocaine) in managing status epilepticus. *J Neurol Neurosurg Psychiatry* 1992; 55: 49–51.
4. Hamano S-I, *et al.* Intravenous lidocaine for status epilepticus during childhood. *Dev Med Child Neurol* 2006; 48: 220–2.

Surface anaesthesia. *EUTECTIC MIXTURES.* A cream containing lidocaine 2.5% and prilocaine 2.5% as a eutectic mixture can produce local anaesthesia when applied topically to intact skin. It appears to be of value in *adults* and *chil-*

dren,[1-3] in minor medical or surgical procedures such as venepuncture, intravenous or arterial cannulation, retrobulbar injections, lumbar puncture, curettage of molluscum contagiosum lesions, genital wart removal, split skin grafting, laser treatment, extracorporeal shock wave therapy, separation of preputial adhesions, and circumcision. It has also been tried as an anaesthetic for the ear drum in preparation for otological procedures such as myringotomy and grommet insertion but is potentially ototoxic and should not be used in the presence of a perforation. Postherpetic neuralgia (p. 10.3) has also been treated with some success.[4,5]

The eutectic cream is usually applied to skin under an occlusive dressing for at least 60 minutes although it has been suggested that for children aged 1 to 5 years 30 minutes may be sufficient.[6] The manufacturers suggest a maximum application time of 5 hours. The onset and duration of the effect may be affected by the site of application.[2] When used for the removal of genital warts an occlusive dressing is not necessary and the application time recommended by the manufacturer is 5 to 10 minutes. The level of anaesthesia begins to decline after 10 to 15 minutes when applied to the genital mucosa and any procedure should be started immediately.

Eutectic mixtures of lidocaine and prilocaine have also been used in *neonates* to reduce the pain of puncture procedures[7] and for circumcision,[8] and appear to be safe and effective. However, there has been concern that excessive absorption (particularly of prilocaine) might lead to methaemoglobinaemia (see p. 1978.3). Nonetheless, in some countries, including the UK and USA, the cream is licensed for use in neonates provided that their gestational age is at least 37 weeks, and that methaemoglobin values are monitored in those aged 3 months or less; it should not be used in infants under 1 year who are receiving methaemoglobin-inducing drugs.

Systemic absorption of both drugs from the eutectic cream appears to be minimal across intact skin[6] even after prolonged or extensive use.[9] However, it should not be used on wounds or mucous membranes except for genital warts in adults. It should not be applied to or near the eyes because it causes corneal irritation, and it should not be instilled in the middle ear. It should be used with caution in patients with atopic dermatitis, anaemia, or congenital or acquired methaemoglobinaemia. Transient paleness, redness, and oedema may occur following application.

Some studies suggest that a topical gel formulation of tetracaine 4% can produce longer and more rapid anaesthesia than the above lidocaine with prilocaine cream (see Surface Anaesthesia, under Uses and Administration of Tetracaine, p. 1997.1). It has also been suggested[10] that topical tetracaine may have practical advantages over the eutectic mixture of lidocaine and prilocaine, which has to be applied for at least one hour, and causes vasoconstriction at the site of application which can make venepuncture difficult.

For reference to the use of a eutectic mixture of lidocaine and prilocaine for the management of premature ejaculation in adults, see p. 1977.1.

1. Lee JJ, Rubin AP. Emla cream and its current uses. *Br J Hosp Med* 1993; 50: 463–6.
2. Buckley MM, Benfield P. Eutectic lidocaine/prilocaine cream: a review of the topical anaesthetic/analgesic efficacy of a eutectic mixture of local anaesthetics (EMLA). *Drugs* 1993; 46: 126–51.
3. Koren G. Use of the eutectic mixture of local anesthetics in young children for procedure-related pain. *J Pediatr* 1993; 122 (suppl): S30–S35.
4. Litman SJ, *et al.* Use of EMLA cream in the treatment of post-herpetic neuralgia. *J Clin Anesth* 1996; 8: 54–7.
5. Kost RG, Straus SE. Postherpetic neuralgia—pathogenesis, treatment, and prevention. *N Engl J Med* 1996; 335: 32–42.
6. Hanks GW, White I. Local anaesthetic creams. *BMJ* 1988; 297: 1215–16.
7. Gourrier E, *et al.* Use of EMLA cream in a department of neonatology. *Pain* 1996; 68: 431–4.
8. Brady-Fryer, B *et al.* Pain relief for neonatal circumcision. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2004 (accessed 16/06/05).
9. Scott DB. Topical anaesthesia of intact skin. *Br J Parenter Ther* 1986; 7: 134–5.
10. Russell SCS, Doyle E. Paediatric anaesthesia. *BMJ* 1997; 314: 201–3.

Tinnitus. Tinnitus is the perception of a noise that arises or appears to arise within the head.

Objective tinnitus may be audible to others and arises from lesions outside the auditory system. Subjective tinnitus (tinnitus aurium) originates from sites within the auditory system and is perceived only by the patient. A simple and remediable cause of tinnitus can be impacted ear wax. Tinnitus is often associated with head injury, vertigo, and hearing loss, including age-related and noise-induced hearing loss. It may also be a symptom of an underlying disorder such as Ménière's disease, may be associated with anxiety or depressive disorders, or may be a manifestation of drug toxicity (for example with aspirin or quinine). In such cases, treatment of the underlying disorder or removal of the offending drug can resolve the tinnitus.

Treatment of tinnitus is difficult although reassurance and counselling are often effective in helping patients to tolerate their condition. Maskers or, if the tinnitus is associated with hearing loss, hearing aids are also used; surgery is rarely indicated. Intravenous lidocaine has proven to be effective in reducing or eliminating tinnitus but the effect only lasts for a few hours and is, therefore, impractical for most patients. Efforts to find an effective oral analogue of lidocaine have not, so far, been successful. Other drugs that have been tried include acamprosate, benzodiazepines such as alprazolam and clonazepam, the antiepileptics carbamazepine and phenytoin, tricyclic antidepressants, and the loop diuretic furosemide, but adverse effects limit their use. Ginkgo biloba has been tried but there are doubts about its value.

References.
1. Luxon LM. Tinnitus: its causes, diagnosis, and treatment. *BMJ* 1993; 306: 1490–1.
2. Robson AK, Birchall JP. Management of tinnitus. *Prescribers' J* 1994; 34: 1–7.
3. Coles RRA. Drug treatment of tinnitus in Britain. In: Reich GE, Vernon JA, eds. *Proceedings of the fifth international tinnitus seminar*. Portland: American Tinnitus Association, 1995.
4. Vesterager V. Tinnitus—investigation and management. *BMJ* 1997; 314: 728–31.
5. Simpson JJ, Davies WE. Recent advances in the pharmacological treatment of tinnitus. *Trends Pharmacol Sci* 1999; 20: 12–18.
6. Dobie RA. A review of randomized clinical trials in tinnitus. *Laryngoscope* 1999; 109: 1202–11.
7. Lockwood AH, *et al.* Tinnitus. *N Engl J Med* 2002; 347: 904–10.

Adverse Effects and Treatment

As for Local Anaesthetics in general, p. 1978.1 and p. 1979.1.

Effects on the CNS. Suspected psychotic reactions have been reported in 6 patients given intravenous lidocaine for the treatment of cardiac disorders.[1] In another case,[2] 2 patients developed signs of cerebral ataxia after topical use of lidocaine for endoscopy.

When compared with other local anaesthetics, lidocaine may be associated with an increased risk of neurotoxic complications when used for spinal anaesthesia, (see under Adverse Effects of Central Block, p. 1978.1).

1. Turner WM. Lidocaine and psychotic reactions. *Ann Intern Med* 1982; 97: 149–50.
2. Perney P, *et al.* Transitory ataxia related to topically administered lidocaine. *Ann Pharmacother* 2004; 38: 828–30.

Effects on the skin. Erythema and pigmentation of the upper lip in a child after local dental infiltration of lidocaine was attributed to a type of fixed drug eruption.[1] Erythema may also occur after topical use of some lidocaine formulations, such as transdermal patches, while transient blanching of the skin is frequent after application of eutectic lidocaine/prilocaine mixtures to the skin.[2] Erythema nodosum and erythema multiforme occurring simultaneously after the use of lidocaine spray and further exacerbated by local lidocaine injection has been reported.[3]

True hypersensitivity reactions, including dermatitis, are rare (see also Hypersensitivity, p. 1978.2) but can occur.[4]

1. Curley RK, *et al.* An unusual cutaneous reaction to lignocaine. *Br Dent J* 1987; 162: 113–14.
2. Villada G, *et al.* Local blanching after epicutaneous application of EMLA cream: a double-blind randomized study among 50 healthy volunteers. *Dermatologica* 1990; 181: 38–40.
3. Rodríguez-Carreón AA, *et al.* Simultaneous erythema nodosum and erythema multiforme after local lidocaine injection. *Ann Pharmacother* 2008; 42: 127–30.
4. Bircher AJ, *et al.* Delayed-type hypersensitivity to subcutaneous lidocaine with tolerance to articaine: confirmation by in vivo and in vitro tests. *Contact Dermatitis* 1996; 34: 387–9.

Overdosage. The most serious effects of lidocaine intoxication are on the CNS and cardiovascular system and overdosage can result in severe hypotension, asystole, bradycardia, apnoea, seizures, coma, cardiac arrest, respiratory arrest, and death. Intoxication with lidocaine is relatively common and can occur as a result of acute overdosage after poor control of intravenous maintenance infusions or accidental injection of concentrated solutions. However, it more commonly results from inadvertent intravascular dosage during regional anaesthesia, or from too rapid injection of antiarrhythmic doses, particularly in patients with circulatory insufficiency, or when clearance is reduced due to heart failure, liver disease, old age, or through interaction with other drugs.[1] Seizures have also been reported after excessive doses given subcutaneously.[2] Although the bioavailability of lidocaine is low it may be sufficient to result in significant toxicity when swallowed[1] and there have been reports of CNS effects, seizures, and death in children[3-7] and adults[8-10] after the ingestion of topical solutions and after the use of viscous preparations in the mouth. Death has also ensued after gargling with a 4% lidocaine solution.[11] Lidocaine is absorbed from mucous membranes and serious toxicity has been reported after urethral[12] or rectal[13] instillation of lidocaine preparations.

1. Denaro CP, Benowitz NL. Poisoning due to class 1B antiarrhythmic drugs: lignocaine, mexiletine and tocainide. *Med Toxicol Adverse Drug Exp* 1989; 4: 412–28.
2. Pelter MA, *et al.* Seizure-like reaction associated with subcutaneous lidocaine injection. *Clin Pharm* 1989; 8: 767–8.
3. Sakai RI, Lattin JE. Lidocaine ingestion. *Am J Dis Child* 1980; 134: 32.
4. Rothstein P, *et al.* Prolonged seizures associated with the use of viscous lidocaine. *J Pediatr* 1982; 101: 461–3.
5. Mofenson HC, *et al.* Lidocaine toxicity from topical mucosal application. *Clin Pediatr (Phila)* 1983; 22: 190–2.
6. Giard MJ, *et al.* Seizures induced by oral viscous lidocaine. *Clin Pharm* 1983; 2: 110.
7. Amital Y, *et al.* Death following accidental lidocaine overdose in a child. *N Engl J Med* 1986; 314: 182–3.
8. Pruncillo RJ, *et al.* CNS toxicity after ingestion of topical lidocaine. *N Engl J Med* 1982; 306: 426–7.
9. Parish RC, *et al.* Seizures following oral lidocaine for esophageal anesthesia. *Drug Intell Clin Pharm* 1985; 19: 199–201.
10. Geraets DR, *et al.* Toxicity potential of oral lidocaine in a patient receiving mexiletine. *Ann Pharmacother* 1992; 26: 1380–1.
11. Zuberi BF, *et al.* Lidocaine toxicity in a student undergoing upper gastrointestinal endoscopy. *Gut* 2000; 46: 435.
12. Dix VW, Tresidder GC. Collapse after use of lignocaine jelly for urethral anaesthesia. *Lancet* 1963; 1: 890.
13. Pottage A, Scott DB. Safety of "topical" lignocaine. *Lancet* 1988; 1: 1003

Pregnancy. Serious adverse effects of epidural anaesthesia are rare but lidocaine may have transient effects on the neonatal auditory system.[1]

1. Borzynski MEA, *et al.* Effect of prenatal lignocaine on auditory brain stem evoked response. *Arch Dis Child* 1989; 64: 934–8.

Precautions

As for Local Anaesthetics in general, p. 1979.1.

In general lidocaine should not be given to patients with hypovolaemia, heart block or other conduction disturbances, and should be used with caution in patients with congestive heart failure, bradycardia, or respiratory depression. Lidocaine is metabolised in the liver and must be given with caution to patients with hepatic impairment. The plasma half-life of lidocaine may be prolonged in conditions that reduce hepatic blood flow such as cardiac and circulatory failure. Metabolites of lidocaine may accumulate in patients with renal impairment.

The intramuscular injection of lidocaine may increase creatine phosphokinase concentrations that can interfere with the diagnosis of acute myocardial infarction.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving lidocaine, and the American Academy of Pediatrics[1] considers 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 02/06/04)

Cerebrovascular disorders. Lidocaine 5 mg/kg by intravenous infusion over 30 minutes was associated with a 12% reduction in cerebral blood flow in healthy subjects although this returned to normal within 60 minutes.[1] Cerebral blood flow in patients with diabetes was lower than in healthy subjects, but was unaffected by lidocaine infusion, indicating reduced cerebrovascular reactivity.

1. Kastrup J, *et al.* Intravenous lidocaine and cerebral blood flow: impaired microvascular reactivity in diabetic patients. *J Clin Pharmacol* 1990; 30: 318–23.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lidocaine as probably not porphyrinogenic when used in local anaesthetic procedures, for surface anaesthesia of the skin and mucous membranes, and as an antiarrhythmic; 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 07/10/11)

Renal impairment. The pharmacokinetics of lidocaine and its metabolite monoethylglycinexylidide appear to be unaffected in patients with renal failure on chronic haemodialysis except that accumulation of the metabolite glycinexylidide may occur during infusions of 12 hours or more.[1] A later pharmacokinetic study[2] of lidocaine in healthy subjects, patients with moderate or severe renal impairment, and anephric patients undergoing haemodialysis found that the clearance of lidocaine was decreased by an average of 18 and 49% in those with moderate and severe impairment, respectively, but was unchanged in those undergoing haemodialysis; there was, however, considerable interindividual variation in the clearance of lidocaine in patients with renal impairment. The authors suggested starting lidocaine infusions at the lower end of the usual dose range with close monitoring for toxicity; no reduction in loading doses appeared necessary. Data to predict the amount of lidocaine and glycinexylidide removed during haemodialysis have been provided.[3,4] Lidocaine does not appear to be removed during haemofiltration.[5]

1. Collinsworth KA, *et al.* Pharmacokinetics and metabolism of lidocaine in patients with renal failure. *Clin Pharmacol Ther* 1975; 18: 59–64.

2. De Martin S, *et al.* Differential effect of chronic renal failure on the pharmacokinetics of lidocaine in patients receiving and not receiving hemodialysis. *Clin Pharmacol Ther* 2006; 80: 597–606.
3. Gibson TP, Nelson HA. Drug kinetics and artificial kidneys. *Clin Pharmacokinet* 1977; 2: 403–26.
4. Lee CC, Marbury TC. Drug therapy in patients undergoing haemodialysis: clinical pharmacokinetic considerations. *Clin Pharmacokinet* 1984; 9: 42–66.
5. Salma S, *et al.* Negligible removal of lidocaine during arteriovenous hemofiltration. *Ther Drug Monit* 1990; 12: 154–6.

Smoking. The effects of smoking on lidocaine therapy are unclear. Studies in a limited number of patients have found reduced systemic bioavailability suggestive of induction of drug-metabolising activity[1] and an inconsistent effect on protein binding.[2,3]

1. Huet P-M, Lelorier J. Effects of smoking and chronic hepatitis B on lidocaine and indocyanine green kinetics. *Clin Pharmacol Ther* 1980; 28: 208–15.
2. McNamara PJ, *et al.* Effect of smoking on binding of lidocaine to human serum proteins. *J Pharm Sci* 1980; 69: 749–51.
3. Davis D, *et al.* The effects of age and smoking on the plasma protein binding of lignocaine and diazepam. *Br J Clin Pharmacol* 1985; 19: 261–5.

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

The clearance of lidocaine may be reduced by propranolol and cimetidine (see below). The cardiac depressant effects of lidocaine are additive with those of beta blockers and of other antiarrhythmics. Additive cardiac effects may also occur when lidocaine is given with intravenous phenytoin; however, the long-term use of phenytoin and other enzyme-inducers may increase dosage requirements of lidocaine (see Antiepileptics, below). Hypokalaemia produced by acetazolamide, loop diuretics, and thiazides antagonises the effect of lidocaine.

Antiarrhythmics. Lidocaine toxicity, arising from the use of an oral preparation containing lidocaine, has been reported[1] in a patient who was receiving *mexiletine*. There are individual reports of seizures or heart failure and cardiac arrest in patients who received intravenous lidocaine with *ajmaline*,[2] *amiodarone*,[3,4] or *tocainide*.[5] Delirium has been reported in a patient who received lidocaine with *procainamide*.[6]

1. Geraets DR, *et al.* Toxicity potential of oral lidocaine in a patient receiving mexiletine. *Ann Pharmacother* 1992; 26: 1380–1.
2. Bleifeld W. Side effects of antiarrhythmic drugs. *Naunyn Schmiedebergs Arch Pharmacol* 1971; 269: 282–97.
3. Siegmund JB, *et al.* Amiodarone interaction with lidocaine. *J Cardiovasc Pharmacol* 1993; 21: 513–15.
4. Keidar S, *et al.* Sinoatrial arrest due to lidocaine injection in sick sinus syndrome during amiodarone administration. *Am Heart J* 1982; 104: 1384–5.
5. Porrence R, *et al.* A seizure induced by concurrent lidocaine-tocainide therapy—is it just a case of additive toxicity? *Drug Intell Clin Pharm* 1986; 20: 56–9.
6. Ilyas M, *et al.* Delirium induced by a combination of anti-arrhythmic drugs. *Lancet* 1969; ii: 1368–9.

Antiepileptics. Studies in healthy subjects and patients with epilepsy[1,2] suggest that long-term use of drugs such as *phenytoin* or *barbiturates* may increase dosage requirements for lidocaine due to induction of drug-metabolising microsomal enzymes. Phenytoin can also increase plasma concentrations of α_1-acid glycoprotein and thereby reduce the free fraction of lidocaine in plasma.[3]

The cardiac depressant effects of lidocaine may be dangerously enhanced by intravenous phenytoin.[4]

1. Heinonen J, *et al.* Plasma lidocaine levels in patients treated with potential inducers of microsomal enzymes. *Acta Anaesthesiol Scand* 1970; 14: 89–95.
2. Perucca E, Richens A. Reduction of oral bioavailability of lignocaine by induction of first pass metabolism in epileptic patients. *Br J Clin Pharmacol* 1979; 8: 21–31.
3. Routledge PA, *et al.* Lignocaine disposition in blood in epilepsy. *Br J Clin Pharmacol* 1981; 12: 663–6.
4. Wood RA. Sinoatrial arrest: an interaction between phenytoin and lignocaine. *BMJ* 1971; 1: 645.

Beta blockers. Significant increases in plasma-lidocaine concentrations have occurred with *propranolol*,[1–4] owing to a reduction in the clearance of lidocaine from plasma. A similar interaction has occurred with *nadolol*[3] and *metoprolol*,[2] although in another study[5] metoprolol did not alter the pharmacokinetics of lidocaine. The hepatic metabolism of lidocaine may be reduced as a result of a fall in hepatic blood flow associated with reduced cardiac output or it may be caused by direct inhibition of hepatic microsomal enzymes.[6] Significant impairment of lidocaine clearance would therefore be most likely to occur with those drugs that lack intrinsic sympathomimetic activity and have a greater effect on cardiac output or with the more lipid-soluble drugs that have greater effects on microsomal oxygenases. The reduction in clearance produced by propranolol seems to be mainly by direct inhibition of metabolism rather than by lowering of hepatic blood flow.[4]

Although some licensed product information suggest a reduction in the dosage of lidocaine injection when used with beta blockers, others consider that potentially toxic plasma concentrations occur when lidocaine is given in repeated high doses and such an interaction should be of no clinical significance after short-term treatment with lidocaine at recommended doses.

1. Ochs HR, *et al.* Reduction in lidocaine clearance during continuous infusion and by coadministration of propranolol. *N Engl J Med* 1980; 303: 373–7.
2. Conrad KA, *et al.* Lidocaine elimination: effects of metoprolol and of propranolol. *Clin Pharmacol Ther* 1983; 33: 133–8.
3. Schneck DW, *et al.* Effects of nadolol and propranolol on plasma lidocaine clearance. *Clin Pharmacol Ther* 1984; 36: 584–7.
4. Bax NDS, *et al.* The impairment of lignocaine clearance by propranolol—major contribution from enzyme inhibition. *Br J Clin Pharmacol* 1985; 19: 597–603.
5. Miners JO, *et al.* Failure of 'therapeutic' doses of β-adrenoceptor antagonists to alter the disposition of tolbutamide and lignocaine. *Br J Clin Pharmacol* 1984; 18: 853–60.
6. Tucker GT, *et al.* Effects of β-adrenoceptor antagonists on the pharmacokinetics of lignocaine. *Br J Clin Pharmacol* 1984; 17 (suppl 1): 21S–28S.

H_2-antagonists. The interaction between *cimetidine* and lidocaine has been considered[1–4] but differences between the studies make interpretation of the overall clinical significance of the results difficult. Cimetidine appears to reduce the hepatic metabolism of lidocaine; it may also reduce its clearance by decreasing hepatic blood flow. Significant increases in plasma-lidocaine concentrations have been reported. Changes in protein binding are not generally important but patients with myocardial infarction who have increased levels of α_1-acid glycoprotein may be partially protected from increases in concentrations of free lidocaine.[5] Since it is not possible to identify those patients at risk all patients receiving both drugs should be closely monitored for signs of toxicity. Some licensed product information suggest a reduction in the dosage of lidocaine injection when used with cimetidine; however, others consider that potentially toxic plasma concentrations occur when lidocaine is given in repeated high doses and such an interaction should be of no clinical significance after short-term treatment with lidocaine at recommended doses.

The use of other H_2-antagonists may be preferable. In studies in healthy subjects *ranitidine* either had no effect on lidocaine kinetics[6] or produced changes consistent with small reductions in hepatic blood flow.[7]

1. Feely J, *et al.* Increased toxicity and reduced clearance of lidocaine by cimetidine. *Ann Intern Med* 1982; 96: 592–4.
2. Knapp AB, *et al.* The cimetidine-lidocaine interaction. *Ann Intern Med* 1983; 98: 174–7.
3. Bauer LA, *et al.* Cimetidine-induced decrease in lidocaine metabolism. *Am Heart J* 1984; 108: 413–15.
4. Patterson JH, *et al.* Influence of a continuous cimetidine infusion on lidocaine plasma concentrations in patients. *J Clin Pharmacol* 1985; 25: 607–9.
5. Berk SL, *et al.* The effect of oral cimetidine on total and unbound serum lidocaine concentrations in patients with suspected myocardial infarction. *Int J Cardiol* 1987; 14: 91–4.
6. Feely J, Guy E. Lack of effect of ranitidine on the disposition of lignocaine. *Br J Clin Pharmacol* 1983; 15: 378–9.
7. Robson RA, *et al.* The effect of ranitidine on the disposition of lignocaine. *Br J Clin Pharmacol* 1985; 20: 170–3.

Local anaesthetics. Although several drugs were shown to reduce the amount of lidocaine bound to α_1-acid glycoprotein only the displacement produced by *bupivacaine* was considered to be of possible clinical significance.[1]

There is concern about the use of lidocaine to treat *cocaine*-induced arrhythmias as lidocaine may enhance toxicity.[2]

1. Goolkasian DL, *et al.* Displacement of lidocaine from serum α_1-acid glycoprotein binding sites by basic drugs. *Eur J Clin Pharmacol* 1983; 25: 413–17.
2. Hollander JE. The management of cocaine-associated myocardial ischemia. *N Engl J Med* 1995; 333: 1267–72.

Neuromuscular blockers. The possible interaction between neuromuscular blockers and antiarrhythmics including lidocaine is discussed under Atracurium, p. 2031.3.

Oral contraceptives. For mention of the effect of oral contraceptives on the protein binding of lidocaine, see under Protein Binding in Pharmacokinetics, below.

Pharmacokinetics

Lidocaine is readily absorbed from the gastrointestinal tract, from mucous membranes, and through damaged skin. Absorption through intact skin is poor. It is rapidly absorbed from injection sites including muscle.

After an intravenous dose lidocaine is rapidly and widely distributed into highly perfused tissues followed by redistribution into skeletal muscle and adipose tissue. Lidocaine is bound to plasma proteins, including α_1-acid glycoprotein (AAG). The extent of binding is variable but is about 66%. Plasma protein binding of lidocaine depends in part on the concentrations of both lidocaine and AAG. Any alteration in the concentration of AAG can greatly affect plasma concentrations of lidocaine (see under Protein Binding, below).

Plasma concentrations decline rapidly after an intravenous dose with an initial half-life of less than 30 minutes; the elimination half-life is 1 to 2 hours but may be prolonged if infusions are given for longer than 24 hours or if hepatic blood flow is reduced.

Lidocaine is largely metabolised in the liver and any alteration in liver function or hepatic blood flow can have a significant effect on its pharmacokinetics and dosage requirements. First-pass metabolism is extensive and bioavailability is about 35% after oral doses. Metabolism in the liver is rapid and about 90% of a given dose is dealkylated to form monoethylglycinexylidide and glycinexylidide. Both of these metabolites may contribute to the therapeutic and toxic effects of lidocaine and since their half-lives are longer than that of lidocaine, accumulation, particularly of glycinexylidide, may occur during prolonged infusions. Further metabolism occurs and metabolites are excreted in the urine with less than 10% of unchanged lidocaine. Reduced clearance of lidocaine has been found in patients with heart failure, alcoholic liver disease, or chronic or viral hepatitis. Drugs that alter hepatic blood flow or induce drug-metabolising microsomal enzymes can also affect the clearance of lidocaine (see Interactions, above). Renal impairment may affect the clearance of lidocaine (see p. 1990.3); accumulation of its active metabolites can also occur.

Lidocaine crosses the placenta and blood-brain barrier; it is distributed into breast milk.

See also under Local Anaesthetics, p. 1979.3.

References.
1. Nattel S, *et al.* The pharmacokinetics of lignocaine and β-adrenoceptor antagonists in patients with acute myocardial infarction. *Clin Pharmacokinet* 1987; 13: 293–316.

Absorption. *SURFACE APPLICATION.* Serum-lidocaine concentrations were usually so low as to be unmeasurable in patients who gargled and expectorated 15 mL (300 mg) of a 2% viscous solution before endoscopy[1] and mean peak serum concentrations of lidocaine were below those associated with toxicity following endotracheal application of 100 mg of lidocaine by spray.[2] The relative bioavailability of lidocaine has been found to be higher when applied to the upper respiratory tract than after administration to the lower respiratory tract.[3] Acceptably low plasma-lidocaine concentrations were noted with the following regimen used before bronchoscopy: a 4% lidocaine solution gargled for 30 seconds, a 2% solution sprayed onto the oropharynx, a 2% jelly applied to the oropharynx and nasal passages, and a 1% solution injected through a bronchoscope.[4] However, a fatality has been reported following the use of lidocaine as a gargle (see Overdosage, p. 1990.2); the absorption of intranasal lidocaine can also be highly variable.[5] For bronchoscopy, inhalation of lidocaine from a nebuliser rather than a direct spray may result in lower peak serum concentrations.[6]

Absorption of lidocaine is generally poor through intact skin. However, there is some evidence that absorption may be greater after application to the skin of preterm infants.[7]

1. Fazio A, *et al.* Lidocaine serum concentrations following endoscopy. *Drug Intell Clin Pharm* 1987; 21: 752–3.
2. Scott DB, *et al.* Plasma lignocaine concentrations following endotracheal spraying with an aerosol. *Br J Anaesth* 1976; 48: 899–902.
3. McBurney A, *et al.* Absorption of lignocaine and bupivacaine from the respiratory tract during fibreoptic bronchoscopy. *Br J Clin Pharmacol* 1984; 17: 61–6.
4. Ameer B, *et al.* Systemic absorption of topical lidocaine in elderly and young adults undergoing bronchoscopy. *Pharmacotherapy* 1989; 9: 74–81.
5. Scavone JM, *et al.* The bioavailability of intranasal lignocaine. *Br J Clin Pharmacol* 1989; 28: 722–4.
6. Labedzki L, *et al.* Reduced systemic absorption of intrabronchial lidocaine by high-frequency nebulization. *J Clin Pharmacol* 1990; 30: 795–7.
7. Barrett DA, Rutter N. Percutaneous lignocaine absorption in newborn infants. *Arch Dis Child* 1994; 71: F122–F124.

Protein binding. Lidocaine is markedly bound to α_1-acid glycoprotein (AAG), a plasma protein which is increased after trauma, surgery, burns, myocardial infarction, in chronic inflammatory disorders such as Crohn's disease, and in cancer. Protein binding may therefore be greatly increased in these conditions and reduced in neonates, the nephrotic syndrome, and in liver disease when AAG concentrations are lower than normal. This can result in an eightfold variation in the free fraction of lidocaine between these conditions.[1] Measurement of free drug concentrations may be a better guide to dosage requirements than measurement of total plasma concentrations.[2] AAG concentrations may also be reduced by oestrogens[3] leading to a higher free fraction of lidocaine in women than in men and the free fraction is further increased during pregnancy and in women taking oral contraceptives.[3,4] Protein binding may also be affected by other concomitant drug therapy or smoking (for further details, see Antiepileptics under Interactions, above, and Precautions, Smoking, above).

1. Routledge PA. Pharmacological terms: protein binding. *Prescribers' J* 1988; 28: 34–5.

2. Shand DG. α 1-Acid glycoprotein and plasma lidocaine binding. *Clin Pharmacokinet* 1984; 9 (suppl 1): 27–31.
3. Routledge PA, *et al.* Sex-related differences in the plasma protein binding of lignocaine and diazepam. *Br J Clin Pharmacol* 1981; 11: 245–50.
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.*: Fidecaina; Gobbicaina; Indican; Lafecaina; Larjancaina; Lidanest; LMX 4; Regiocaina; Solvente Indoloro; Xylocaina; *Austral.*: Nurocain†; Stud 100; Xylocaine Special Adhesive; Xylocaine; Xylocard; *Austria*: Lidocorit; Neo-Xylestesin; Versatis; Xylanaest; Xylocain; Xylocard†; Xyloneural; *Belg.*: Linisol; Otalgan; Otipax; Otocalmine; Versatis; Xylocaine Visqueuse; Xylocaine; Xylocaine; Xylocard; *Braz.*: Dermomax; Gel-Lido†; Labcaina; Lidial; Lidocabbott; Lidoflex†; Lidogel; Lidojet; Lidopass; Lidospray; Lidoston; Xylestesin; Xylocaina; *Canad.*: After Sun; Afterburn; Banana Boat Soothacaine†; Band-Aid Antiseptic Betacaine; Burn Cream; Burn Relief; Caribbean Breeze Burn Relief; Hawaiian Tropic After Sun; Lidodan; Lidomax; Maxilene; Octocaine; Pre-Wax†; Preattached; Safetec Burn; Safetec Sting Relief; Smartshield After Sun; Solarcaine Lidocaine; Soothing Gel; Stallion; Water-Jel; Xylocaine; Xylocard; *Chile*: Bebegesic; Dentaliv†; Dimecaina; Exido; Gelcain; Odongel; Prolong; Solin; Versatis; Xylocaina; *China*: Ke Ze Pu (克泽普); Li Shu Ka (利舒卡); Cz.: Trachisan; Versatis; Xylocaine; *Denm.*: Versatis; Xylocain; Xyloplyn; *Fin.*: Lidocard; Xylocain; *Fr.*: Biodicaine†; Dynexan; Dynexangival; Lidrian†; Mesocaine; Pressicaine N†; Pressicaine; Versatis; Xylocaine; Xylocard; Xylocontact; Xylonor; Xylorolland; Ziacaine; *Ger.*: Acoin; Gelicain†; Haemo-Exhirud Bufexamac†; Heweneural; Licain; Lidesthesin†; Lidocard; Lidoject†; LidoPosterine†; Posterisan akut; Trachilid; Trachisan Halsschmerztabletten†; Versatis; Xylocain (Kardiologie); Xylocain; Xylocitin cor; Xylocitin; Xyloneural; *Gr.*: Akten; Ecocain; Lidocosil; Lidoderm; Lidonet; Lignospan; Narcodon; Neo-Lidocaton; Osagel; Sensolid; Trachilid; Uriblack; Versatis; Xylestesin-A; Xylestesin-S Special; Xylestesin; Xylocaine; Xylol; Xylonor Noradrenaline; Xylozan; *Hong Kong*: Lidocaton†; Xylestesin-A; Xylocaine; *India*: Gesicain; Lignocad; Lignocip; Lignodent; Lignoloc; Lignosafe; Lignox; Lox; Loxicard; Nummit; Otidrop; Tivision†; Xylocaine; Xylocard; *Indon.*: Extracaine†; Garianes†; Lidodex; Lidonest†; Pehacain; Xylocaine; *Irl.*: Lignospan; Versatis; Xylocaine; *Israel*: After Burn; Betacaine†; Esracain; Lidocadren; Lignospan; Octocaine; Stud 100; Xylocaine; Xylonor Noradrenaline; *Ital.*: Basicaina; Ecocain; Lident Adrenalina; Lident Adrenor; Lidofast; Lidosen; Lidrian; Luan; Ortodermina; Xilo-Mynol; Xylocaina; Xylonor; Xyloplyina; *Jpn*: Penles; *Malaysia*: Denkan; Lakan; Xylocaine; *Mex.*: Betacaine†; Hipoden; Pharmacaine; Pisacaina†; Sensipharma; Sunicaine; Undorlan; Unicaine; Uvega; Xylocaina; *Neth.*: Dentinox; Lignospan; Nolaid; Otalgan; Trachisan; Unguentum contra haemorrhoides PCH†; Xylocaine; *Norw.*: Versatis; Xylocain; *NZ*: Virasolve; Xylestesin-A; Xylocaine; Xylocard; *Philipp.*: Dentocaine; Enducaine; Epicaine; Lygnonex; Nobucaine; Xepacaine; Xylocaine; Xylocard†; *Pol.*: Lidoposterin; Xylocaine; *Port.*: Lambdalina; Lidoject; Lidonostrum; Lincaina; Octocaine; Vessatis; Xilonibsa; Xylocaina; *Rus.*: Dynexan A (Динексан А); Gelicain (Гелицин); Licaine (Лицкаин); Lidochlor (Лидохлор); Luan (Луан); Versatis (Версатис); *S.Afr.*: Peterkaien†; Remicaine; Remicard; Xylocaine; Xylotox; *Singapore*: Gesicain; Lakan; Lignopad; Xylestesin-A; Xylocaine; Xylocard; *Spain*: Dermovagisil; Lambdalina; Octocaine; Versatis; Xilonibsa; Xylocaina†; Xylonor 2% Sin Vasoconst†; Xylonor Especial; *Swed.*: Versatis; Xylocain; Xylocard; *Switz.*: Dynexan; Kenergon; Neo-Sinedol; Neurodol Tissugel; Rapidocaine; Sedagul†; Solarcaine; Xylesine; Xylocain; Xylocard†; Xyloneural; *Thai.*: Docaine; Drocanil-A; LD-Caine†; Lidocation; Locana; Medicaine; Udocaine; Xylocaine; *Turk.*: Anestol; Aritmal; Jetmonal; Jetokain; Jetosel; Ksilidin; Laconest; Lidestol; Lidobag; Lidosel; Locanest-A; Lokalen; Monocain; Xylocain; *UAE*: Ecocain; *UK*: Dequaspray; Laryng-O-Jet; LMX4; Premjact; Stud; Vagisil; Versatis; Xylocaine; Xylocaine; *Ukr.*: Versatis (Версатис); *USA*: Akten; AneCream; Anestacon; Anestafoam†; Dentipatch†; Dilocaine; Dr Scholl's Cracked Heel Relief; Duo-Trach Kit; L-M-X; LC-4; LC-5; LidaMantle†; Lidoderm; LidoPen; Lidosite†; LTA; Nervocaine; Octocaine; RectiCare; Regenecare; Topicaine; Xolido; Xylocaine; Zingo†; *Venez.*: Cifarcaina; Farmacaina; Nenedent.

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

Used as an adjunct in: *Arg.*: Adaxil; Amplibenzatin Bronquial; Artrilase; Bago B1 B6 B12; Cefalomicina; Cefamezin; Mecanyl; Pen di Ben; Rivacefin; Tunik B12; Tunik; Vartalon Complemento; Zienam; *Austral.*: Zyderm†; Zyplast†; *Austria*: Rheumesser; Rocephin; Zienam; *Belg.*: Kefzol; Rocephine; *Braz.*: Butazolidina; Cefoxin†; Ceftriax; Cianotrat-Dexa; Gripsay; Injeflex; Neocefitriona; Olfen†; Rocefin; Terramicina; Tetrapulmo†; Vitatonus Dexa; Voltaflan; *Canad.*: Neo-Bex; *Chile*: Bioflex†; Cidoten Rapilento; Cronolevel; Depo-Medrol; Dolotol 12; Neurobionta; Prevepen Forte; Tol 12 Plus; *China*: Olfen (奥尔芬); Cz.: Dona; Olfen; *Fin.*: Rocephalin; *Fr.*: Cefaloject†; Claforan; Rocephine; Unacim; Zinnat; *Ger.*: Ambene; Keltican N†; Medivitan; Pendysin; Rocephin; *Gr.*: Apotel; *Hong Kong*: Olfen; Tapain; *Hung.*: Cefam†; Claforan; Dona; Milgamma N; Mydeton; Rocephin; *India*: Calcindon; Oxytetra; Terramycin; *Indon.*: Bioneuron; Neurobiovit; Neurophil; Neurotrat; *Ital.*: Acef; Aminomal; Ateroid; Aximad; Axobat; Batixim; Bethacil; Biotassina; Biotidic†; Bixon; Cefam; Cefamezin; Cefazil; Cefociclin; Cefodie; Cefomit; Cefoplus; Cefoprim†; Cefrag; Cemado†; Chefir; Cilpier; Clody; Coxanturenasi; Dardum; Davixon; Daycef; Daytrix; Deixim; Delius; Diaxone; Diezime; Dona; Ecosette; Eftry; Emidoxin; Eposerin; Eraxitron; Fareceft; Farecillin; Fidato; Ponicid; Posforilast; Prineg; Glicero-Valerovit; Imipem; Kocefan; Kruceft†; Lirgosin; Lisa; Loricin; Mancef; Maxid†; Mefoxin; Metafar; Metax; Mionevrast; Modiem; Modivid; Monobiotic; Monoxar; Necid; Nefazol; Neurol; Niklod; Nilson; Nokid; Panatrix; Pantoxon; Peracil; Picillin; Piperital; Pipersal; Pipertex; Praticef†; Ragex; Raikocef; Refotax; Repercillin; Rifocin; Rocefin; Roxiden; Salocef; Semipenil; Setriox; Sintocef; Sirtap; Sofarcid; Spectrocef; Supero; Surgamyl; Taxime; Tazobac; Tazocin; Tienam; Timecef; Tricortin; Trinevrina B6; Unasyn; Valecid†; Valexime; Zariviz; Zimanel; *Jpn*: Cefamezin; Cefmetazon; Cefoperazin; Pentcillin; *Mex.*: Benaxona; Bonadoxina; Butazolidina; Cefaxona; Ceftrex; Ceftrilem; Centrifal; Claforan; Dexabion; Porvin; Fosfocil; Fot-Amsa; Fotexina; Gadital; Kedacillin†; Limipro!; Megapenil Forte†; Megion; Rocephin; Terbac†; Terramicina; Tiaminal B_{12}; Tirotax; Triaken; Tribe 12; Viken†; *NZ*: Rocephin†; Zyderm; Zyplast; *Pol.*: Dicloratio; Milgamma N; Mydocalm; Neoton; Olfen; *Port.*: Monocid; Rocephin; *Rus.*: Ambene (Амбене); Combilipen (Комбилипен); CompligamV (КомплигамВ); Milgamma (Мильгамма); Mydocalm (Мидокалм); Trigamma (Тригамма); Vitagamma (Витагамма); *Singapore*: CosmoDerm; CosmoPlast; Juvederm; Olfen; *Spain*: Claforan; Fosfocina; Gobemicina Retard†; Inzitan; Kurgan; Monocid; Neurodavur Plus; Neuromade; Retarpen; Rocefalin†; Tecfazolina; *Swed.*: Rocephalin; *Switz.*: Ancopir; Butadion†; Olfen; Rocephin; *Thai.*: Fenacaine; Juvederm Ultra XC; Neo-Pyrazol†; Nivagin†; Olan-Gin†; Paramol TP; Paranal-L†; Umeda Para-J; Utofin; Vetamol; Viartril S; *Turk.*: Alfasid; Baktisef; Cefaks; Cefamezin; Cefizox; Cefozin; Cephaxon; Combicid; Desefin; Duobaktam; Duocid; Equiceft; Equizolin; Forsef; Iesef; Iespor; Maksiporin; Mefoxim; Neurogriseovit; Nevakson; Nobecid; Novosef; Rifocin; Rocephin; Sefamax; Sefazol; Sulcid; Sulperazon; Tienam; Triaxon; Unacefin; *Ukr.*: Diclocain (Диклокаин); Dona (Дона); Megafen Plus (Мегафен Плюс)†; Milgamma (Мильгамма); Olfen (Олфен); Tolperil (Толперил); Vitaxon (Витаксон); *USA*: Perlane; Restylane; *Venez.*: Briomet; Cefacidal; Complejo B Compositum; Deca-Lentermina Complex; Lentermina Complex; Mega-Neubion; Miovit; Neuribe; Rocephin; Rubrinal; Rubrinex.

Pharmacopoeial Preparations

BP 2014: Lidocaine and Adrenaline Injection; Lidocaine and Chlorhexidine Gel; Lidocaine Gel; Lidocaine Injection; Lidocaine Ointment; Sterile Lidocaine Solution;

USP 36: Lidocaine and Prilocaine Cream; Lidocaine Hydrochloride and Dextrose Injection; Lidocaine Hydrochloride and Epinephrine Injection; Lidocaine Hydrochloride Injection; Lidocaine Hydrochloride Jelly; Lidocaine Hydrochloride Oral Topical Solution; Lidocaine Hydrochloride Topical Solution; Lidocaine Ointment; Lidocaine Oral Topical Solution; Lidocaine Topical Aerosol; Neomycin and Polymyxin B Sulfates and Lidocaine Cream; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Lidocaine Ointment.

Mepivacaine Hydrochloride

(BANM, rINNM)

Hidrocloruro de mepivacaína; Mepivacaína, hidrocloruro de; Mépivacaïne, Chlorhydrate de; Mepivacainhydrochlorid; Mepivacaini Chloridum; Mepivacaini Hydrochloridum; Mepivakaiinihydrokloridi; Mepivakain-hidroklori d; Mepivakain-hydrochlorid; Mepivakainhydroklorid; Mepivakaino hidrochloridas; Мепивакаина Гидрохлорид.

(1-Methyl-2-piperidyl)formo-2',6'-xylidide hydrochloride.

$C_{15}H_{22}N_2O,HCl=282.8$

CAS — 96-88-8 (mepivacaine); 22801-44-1 ((±)-mepivacaine); 1722-62-9 (mepivacaine hydrochloride).

ATC — N01BB03.

ATC Vet — QN01BB03.

UNII — 4VFX2L7EMS.

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

Ph. Eur. 8: (Mepivacaine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in alcohol; very slightly soluble in dichloromethane. A 2% solution in water has a pH of 4.0 to 5.0.

USP 36: (Mepivacaine Hydrochloride). A white, odourless, crystalline solid. Freely soluble in water and in methyl alcohol; very slightly soluble in chloroform; practically insoluble in ether. A 2% solution in water has a pH of about 4.5.

pH of solutions. For a discussion of the effect that pH has on the stability of local anaesthetic solutions and the pain associated with their injection, see p. 1976.2.

Uses and Administration

Mepivacaine hydrochloride is a local anaesthetic of the amide type with actions and uses similar to those described on p. 1976.1. It is mainly used for infiltration anaesthesia, peripheral nerve block, and epidural block. (Local anaesthetic techniques are discussed on p. 1977.2.) Mepivacaine has a rapid onset and an intermediate duration of action. The speed of onset and duration of action are increased by the addition of a vasoconstrictor and absorption into the circulation from the site of injection is reduced.

The dosage of mepivacaine hydrochloride varies with the site of injection and the type of **local anaesthetic procedure.** In adults, the **maximum single dose** of mepivacaine hydrochloride should not generally exceed 400 mg and the total dose in 24 hours should not exceed 1 g. Doses should be reduced in the elderly, in debilitated patients, and in those with cardiac or hepatic impairment. Concentrations of less than 2% should be used in children under 3 years or weighing less than about 14 kg (30 pounds); the dose in children should not exceed 5 to 6 mg/kg.

- For *infiltration anaesthesia* up to 400 mg as a 1% (40 mL) or 0.5% (80 mL) solution is used. For *dental infiltration and nerve block* a 2% solution with a vasoconstrictor or a 3% plain solution is used. For anaesthesia at a single site in the jaw a dose of 36 mg (1.8 mL) as a 2% solution or 54 mg (1.8 mL) as a 3% solution is used. For anaesthesia of the entire oral cavity 180 mg (9 mL) as a 2% solution or 270 mg (9 mL) as a 3% solution is used. Some recommend that no more than 400 mg should be given at a single dental sitting.
- For *peripheral nerve blocks*, namely *cervical, brachial plexus, intercostal*, and *pudendal blocks*, 1 or 2% solutions may be used in doses of 50 to 400 mg (5 to 40 mL) as a 1% solution, or 100 to 400 mg (5 to 20 mL) as a 2% solution. For pudendal block half of the dose is injected on each side. For *paracervical block* a dose of up to 100 mg (10 mL) as a 1% solution on each side has been suggested allowing an interval of 5 minutes between sides. This may be repeated at an interval of not less than 30 minutes, and for a combined paracervical and pudendal block up to 150 mg (15 mL) as a 1% solution is injected on each side. For therapeutic nerve block in the management of pain 10 to 50 mg (1 to 5 mL) as a 1% solution or 20 to 100 mg (1 to 5 mL) as a 2% solution may be given.
- For *epidural block* usual doses are: 150 to 300 mg (15 to 30 mL) as a 1% solution, 150 to 375 mg (10 to 25 mL) as a 1.5% solution, or 200 to 400 mg (10 to 20 mL) as a 2% solution. Hyperbaric solutions of mepivacaine hydrochloride without adrenaline have also been used for *spinal block*.

Mepivacaine has been included in the intramuscular injections of other drugs to minimise the pain produced at the injection site.

Mepivacaine has also been used as a surface anaesthetic but other local anaesthetics such as lidocaine are more effective.

Action. For a comparison of the vasoactivity of mepivacaine and some other local anaesthetics, see p. 1976.2.

Administration in children. For uses and dosage of mepivacaine hydrochloride in children, see above.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p. 1978.1, p. 1979.1 and p. 1979.1, respectively.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mepivacaine 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 05/10/11)

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Local anaesthetics. Studies *in vitro* showed that *bupivacaine* dramatically reduced the binding of mepivacaine to α_1-acid glycoprotein.[1]

1. Hartrick CT, *et al.* Influence of bupivacaine on mepivacaine protein binding. *Clin Pharmacol Ther* 1984; 36: 546–50.

Pharmacokinetics

Mepivacaine is about 78% bound to plasma proteins. The plasma half-life has been reported to be about 2 to 3 hours in adults and about 9 hours in neonates. It is rapidly metabolised in the liver and less than 10% of a dose is reported to be excreted unchanged in the urine. Over 50% of a dose is excreted as metabolites into the bile but these probably undergo enterohepatic circulation as only small amounts appear in the faeces. Several metabolites are also excreted via the kidneys and include glucuronide conjugates of hydroxy compounds and an *N*-demethylated compound, 2',6'-pipecoloxylidide. Mepivacaine crosses the placenta.

See also under Local Anaesthetics, p. 1979.3.

Pregnancy. There is considerable transfer of mepivacaine across the placenta after maternal doses and the ratio of fetal to maternal concentrations[1] is about 0.7. Although neonates have a very limited capacity to metabolise mepivacaine it appears they are able to eliminate the drug.[2]

1. Lurie AO, Weiss JB. Blood concentration of mepivacaine and lidocaine in mother and baby after epidural anesthesia. *Am J Obstet Gynecol* 1970; 106: 850–6.
2. Meffin P, *et al.* Clearance and metabolism of mepivacaine in the human neonate. *Clin Pharmacol Ther* 1973; 14: 218–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Mepigobbi; *Austral.*: Carbocaine†; *Austria*: Mepinaest; Scandicain†; Scandonest; *Belg.*: Scandicaine; *Canad.*: Carbocaine; Isocaine; Polocaine; Scandonest; *China*: Scandonest (斯康杜尼); *Cz.*: Mepivastesin; Scandonest†; *Denm.*: Carbocain; Scandonest; *Fin.*: Scandonest; *Fr.*: Carbocaine; Scandicaine; *Ger.*: Meaverin; Mecain; Mepi-Welk; Mepihexal†; Mepivastesin; Scandicain; *Gr.*: Mepivakate; Mepivastesin; Optocain; Scandonest; Tevacaine; *Hong Kong*: Mepicaton†; Mepivastesin; *Irl.*: Scandonest; *Israel*: Isocaine; Mepicaton†; Mepivastesin; Scandicaine; *Ital.*: Carbocaina; Carboplyina; Carbosen; Mepi-Mynol; Mepibil; Mepicain; Mepident; Meptiforan; Mepisolver; Mepivamol; Mepivirgi; Optocain; Pericaina; Scandonest; *Neth.*: Scandicaine†; Scandonest; *Norw.*: Carbocain; Scandonest; *Port.*: Isogaine; Mepivastesin; Scandinibsa; Scandonest; *Rus.*: Mepivastesin (МЕПИВАСТЕЗИН); *S. Afr.*: Carbocaine; Scandonest; *Singapore*: Mepivastesin; *Spain*: Isogaine; Scandinibsa; Scandonest; *Swed.*: Carbocain; Scandonest; *Switz.*: Scandicain; Scandonest; *Thai.*: Mepicaton; *USA*: Carbocaine with Neo-Cobefrin; Carbocaine; Isocaine; Polocaine; Scandonest.

Multi-ingredient Preparations.

Used as an adjunct in:. *Austria*: Estradurin; *Belg.*: Estradurine†; *Denm.*: Estradurin; *Fin.*: Estradurin; *Jpn*: Amasulin; Bestcall; Pansporin; Takesulin†; *Norw.*: Estradurin†; *Singapore*: Nevramin; *Swed.*: Estradurin; *Switz.*: Estradurin; *Thai.*: Nevramin; *Ukr.*: Estradurin (Эстрадурин)†.

Pharmacopoeial Preparations
USP 36: Mepivacaine Hydrochloride and Levonordefrin Injection; Mepivacaine Hydrochloride Injection.

Myrtecaine *(rINN)*

Mirtecaína; Myrtécaïne; Myrtecainum; Nopoksamin; Nopoxamine; Миртекаин.

2-[2-(10-Norpin-2-en-2-yl)ethoxy]triethylamine.

$C_{17}H_{31}NO$=265.4

CAS — 7712-50-7.

UNII — 9902116282.

Profile

Myrtecaine is a local anaesthetic (p. 1976.1) used topically as the base or laurilsulfate in rubefacient preparations for the treatment of muscle and joint pain. Myrtecaine laurilsulfate is also used in preparations with antacids for the symptomatic relief of gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Algesal; *Austria*: Acidrine; Algesal; Latesyl; Rheugesal†; Traumasal; *Chile*: Sinacid†; *Cz.*: Algesal; *Fr.*: Acidrine; Algesal Suractive; *Ger.*: Algesal†; *Gr.*: Algesal Suractive; *Hung.*: Algesal; *Indon.*: Acidrine; Algesal Superactive; *Ital.*: Acidrine; *Neth.*: Algesal Forte†; *Port.*: Algesal; Latesil; *Spain*: Algesal; *Turk.*: Acidrine; Algesal Suractive; *Venez.*: Lemazol.

Oxetacaine *(BAN, rINN)*

Oksetakaiini; Oksetakain; Oxetacaína; Oxétacaïne; Oxetacainum; Oxetakain; Oxethazaine (USAN); Oxethazaine; Wy-806; Оксетакаин.

2,2′-(2-Hydroxyethylimino)bis[*N*-(α,α-dimethylphenethyl)-*N*-methylacetamide].

$C_{28}H_{41}N_3O_3$=467.7

CAS — 126-27-2 (oxetacaine); 13930-31-9 (oxetacaine hydrochloride).

ATC — C05AD06.

ATC Vet — QC05AD06.

UNII — IP8QT76V17.

Pharmacopoeias. In *Br.* and *Jpn.*

BP 2014: (Oxetacaine). A white or almost white powder. Practically insoluble in water; freely soluble in methyl alcohol; very soluble in chloroform; soluble in ethyl acetate.

Profile

Oxetacaine is an amide anaesthetic (p. 1976.1) that is stated to have a prolonged action. It is used orally with antacids for the symptomatic relief of gastro-oesophageal reflux disease (p. 1807.2). It has also been used as the hydrochloride in ointments and suppositories for the relief of pain associated with haemorrhoids.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Tricaine-MPS; *Ital.*: Emoren; *Jpn*: Strocain.

Multi-ingredient Preparations. *Arg.*: Mucaine; *Austral.*: Mucaine†; *Austria*: Tepilta; *Braz.*: Droxaine; *Canad.*: Mucaine; *Fr.*: Mutesa†; *Ger.*: Tepilta; *Gr.*: Oxaine-M; *Hong Kong*: Antacaine; Gastrocaine; Mucaine†; Oxema Improved; Strocain; *India*: Acicot-O; Acicral-O; Acinil-O; Acral-O; Alcaine; Alcocid; Belief; Bestocid-O; Bluegel-O; Coligon-O; Crasia-O; Daffocid-O; Depcid-O; Dicaine; Digiflux-A; Disocain; Erocot-O; Esfate-O; Focri-O; Gastromax-O; Graster; Greycid; Jevacain; Kaicid-O; Kulent-O; Kulfi; Lacrate-O; Lorcus-O; Maxicain; Merigel-A; Mucaine; Newcain; Nubase; OAM; Oshrid; Oxefate-O; Oxycane; Pepticaine; *Philipp.*: Geltazine; *S.Afr.*: Mucaine; *Singapore*: Strocain; *Spain*: Roberfarin; *Thai.*: Mucaine†; Strocain; *Turk.*: Mucaine.

Oxybuprocaine Hydrochloride

(BANM, rINNM)

Benoxinate Hydrochloride; Hidrocloruro de oxibuprocaína; Oksibuprokaiinihydrokloridi; Oksibuprokain Hidroklorür; Oksibuprokaino hidrochloridas; Oxibuprocaína, hidrocloruro de; Oxibuprokain-hidroklorid; Oxibuprokainhydroklorid; Oxybuprocaïne, Chlorhydrate d'; Oxybuprocainhydrochlorid; Oxybuprocaini Hydrochloridum; Oxybuprokain hydrochlorid; Оксибупрокаина Гидрохлорид.

2-Diethylaminoethyl 4-amino-3-butoxybenzoate hydrochloride.

$C_{17}H_{28}N_2O_3$,HCl=344.9

CAS — 99-43-4 (oxybuprocaine); 5987-82-6 (oxybuprocaine hydrochloride).

ATC — D04AB03; S01HA02.

ATC Vet — QD04AB03; QS01HA02.

UNII — 0VE4U49K15.

NOTE. OXB, formerly BNX, is a code approved by the BP 2014 for use on single unit doses of eye drops containing oxybuprocaine hydrochloride where the individual container may be too small to bear all the appropriate labelling information.

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

Ph. Eur. 8: (Oxybuprocaine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. It exhibits polymorphism. 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: (Benoxinate Hydrochloride). White or slightly off-white, crystals or crystalline powder, odourless or with a slight characteristic odour. Soluble 1 in 0.8 of water, 1 in 2.6 of alcohol, and 1 in 2.5 of chloroform; insoluble in ether. A 1% solution in water has a pH of 5.0 to 6.0.

Uses and Administration

Oxybuprocaine, a para-aminobenzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p. 1976.1. It is used for surface anaesthesia (p. 1977.3) and is reported to be less irritant than tetracaine when applied to the conjunctiva in therapeutic concentrations.

Oxybuprocaine is used as the hydrochloride in a 0.4% solution in short ophthalmological procedures. One drop instilled into the conjunctival sac anaesthetises the surface of the eye sufficiently to allow tonometry after 60 seconds and a further drop after 90 seconds provides adequate anaesthesia for the fitting of contact lenses. Three drops at 90-second intervals produces sufficient anaesthesia after 5 minutes for removal of a foreign body from the corneal epithelium, or for incision of a Meibomian cyst through the conjunctiva. The sensitivity of the cornea is normal again after about 1 hour.

A 1% solution of oxybuprocaine hydrochloride is used for surface anaesthesia of the ear, nose, and throat.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p. 1978.1, p. 1979.1, and p. 1979.1, respectively.

Effects on the eyes. Fibrinous iritis and moderate corneal swelling occurred in 2 patients after the use of a 0.4% or 1% solution of oxybuprocaine hydrochloride for topical anaesthesia of the eye for minor surgery.[1] The effects may have been due to inadvertent entry of the drug into the anterior chamber of the eye.

1. Haddad R. Fibrinous iritis due to oxybuprocaine. *Br J Ophthalmol* 1989; 73: 76–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxybuprocaine as not porphyrinogenic when used for surface anaesthesia in ophthalmological procedures; 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 05/10/11)

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Benoxinat; Novain; *Belg.*: Unicaine; *Braz.*: Oxinest; *China*: Benoxil (倍诺喜); *Cz.*: Benoxi; Novesin†; *Fin.*: Oftan Obucain; *Fr.*: Cebesine; *Ger.*: Conjuncain-EDO; Novesine; *Hung.*: Humacain; *India*: Bendzon†; *Israel*: Localin; *Ital.*: Novesina; *Philipp.*: Oxybent†; *Port.*: Anestocil; *Rus.*: Benoxi (Бенокси); Inokain (Инокаин); *S.Afr.*: Novesin; *Spain*: Prescaina; *Switz.*: Cebesin†; Novesin; *Thai.*: Novesin†; *Turk.*: Benoxinate; Novesin; *Ukr.*: Inokain (Инокаин).

Multi-ingredient Preparations. *Austral.*: Fluress†; *Austria*: Flurekain†; *Canad.*: Fluress; *Fin.*: Oftan Flurekain; *Fr.*: Collu-Blache†; Desomedine; *Ger.*: Thilorbin; *Gr.*: Collu-Blache; *Mex.*: Mentalgina; *Port.*: Fluotest; Mebocaina; *Rus.*: Grammidin with Anesthetic Neo (Граммидин с АнестетикОм Нео); *Spain*: Anestesico Doble; Fluotest; *Swed.*: Fluress; *Switz.*: Collu-Blache; Mebucaine; *UAE*: B-Cool; *Ukr.*: Grammidin with Anaesthetic Neo (Граммидин С Анестетиком Нео); *USA*: Fluorox; Flurate†; Fluress; Flurox.

Pharmacopoeial Preparations
BP 2014: Oxybuprocaine Eye Drops;
USP 36: Benoxinate Hydrochloride Ophthalmic Solution; Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution.

Pramocaine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de pramocaína; Pramocaína, hidrocloruro de; Pramocaïne, Chlorhydrate de; Pramocaini Hydrochloridum; Pramoksiinihydrokloridi; Pramoxine Hydrochloride; Pramoxinhydroklorid; Pramoxini Hydrochloridum; Pramoxinium Chloride; Прамокаина Гидрохлорид.

4-[3-(4-Butoxyphenoxy)propyl]morpholine hydrochloride.

$C_{17}H_{27}NO_3$,HCl=329.9

CAS — 140-65-8 (pramocaine); 637-58-1 (pramocaine hydrochloride).

ATC — C05AD07; D04AB07.

ATC Vet — QC05AD07; QD04AB07.

UNII — 88AY8867L5.

Pharmacopoeias. In *US*.

USP 36: (Pramoxine Hydrochloride). A white or almost white crystalline powder; it may have a faint aromatic odour. Freely soluble in water and in alcohol; soluble 1 in 35 of chloroform; very slightly soluble in ether. A 1% solution in water has a pH of about 4.5. Store in airtight containers.

Profile

Pramocaine hydrochloride is a local anaesthetic (p. 1976.1) used for surface anaesthesia. It is used alone or with corticosteroids and other drugs, usually in a concentration of 1%, in many formulations for the relief of pain and itching associated with minor skin conditions and anorectal disorders. Initial burning or stinging may occur following topical application. It should not be used for the nose or eyes. The base has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Dermoplast Poison Ivy Treatment; *Fr.*: Tronothane; *Israel*: Sarmed; *Ital.*: Tronotene; *S. Afr.*: Anugesic; *Spain*: Balsabit†; Denutraxan; *Thai.*: Primoly; *USA*: Campho-Phenique Cold Sore Treatment & Scab Relief; Fleet Pain Relief; Ivy Wash; Pramox; Prax; Proctofoam; Sarna Sensitive Anti-Itch; Tronothane; Vagisil.

Multi-ingredient Preparations. *Arg.*: Anusol Duo S; Anusol Duo; Anusol-A; Milorix†; Tocorectal; *Belg.*: Nestosyl; *Canad.*: Anugesic-HC; Anusol Plus; Anuzinc HC Plus; Anuzinc Plus; Aveeno Anti-Itch; Caladryl†; Gold Bond Anti-Itch; Gold Bond Medicated; Hemorrhoid Ointment; Hemorrhoidal Ointment; Onguent Hemorrhoidal†; Polysporin Itch Relief; Polysporin Lip Treatment; PrameGel; Pramox HC; Proctodan-HC; Proctofoam-HC; Sarna-P; *Chile*: Caladryl Clear; *Irl.*: Anugesic-HC; Anugesic-HC; Proctofoam-HC; *Israel*: Epifoam; Hemorid†; Proctofoam-HC; *Ital.*: Proctofoam-HC; *Mex.*: Caladryl Clear; Soyaloid Apruri; *Neth.*: Nestosyl; *S.Afr.*: Anugesic†; *Turk.*: Hipokort Arti; *UK*: Anugesic-HC†; Anugesic-HC; Proctofoam-HC; *USA*: 1 + 1-F; AmLactin AP†; Analpram E; Analpram-HC;

Anusol; Aveeno Anti-Itch†; Bacitraycin Plus; Bite & Itch Lotion; Caladear; Caladryl Clear; Caladryl; Calagesic; Callergy Clear; Cortamox†; Cortane-B; Cortic ND; Cyotic; EndaRoid; Enzone; Epifoam; Gold Bond Intensive Healing; HC Pram; HC Pramoxine; Hemorid For Women; Mediotic-HC; Neosporin + Pain Relief; Neosporin + Pain Relief; Novacort; Oticin HC; Otidin; Oto-End; Otomar-HC; Phicon-P; Phicon; Pram-HCA; PramCort; PrameGel; Pramosone; PramOtic; Preparation H; ProCort; Proctofoam-HC; Sarna Ultra†; Summer's Eve Anti-Itch; Tri-Biozene; Tronolane; Tucks; Zinotic†; Zone-A; Zoto-HC; ZyPram.

Pharmacopoeial Preparations
USP 36: Neomycin and Polymyxin B Sulfates and Pramoxine Hydrochloride Cream; Pramoxine Hydrochloride Cream; Pramoxine Hydrochloride Jelly.

Prilocaine *(BAN, USAN, rINN)*

Prilocain; Prilocaína; Prilocaine; Prilocainum; Prilokaiini; Prilokain; Prilokaínas; Прилокаин.

2-Propylaminopropiono-o-toluidide.

$C_{13}H_{20}N_2O$=220.3

CAS — 721-50-6.

ATC — N01BB04.

ATC Vet — QN01BB04.

UNII — 046O35D44R.

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

Ph. Eur. 8: (Prilocaine). A white or almost white, crystalline powder. M.p. 36 degrees to 39 degrees. Slightly soluble in water; very soluble in alcohol and in acetone.

USP 36: (Prilocaine). A white or almost white powder or crystal aggregates. M.p. 36 degrees to 39 degrees. Slightly soluble in water; very soluble in alcohol and in acetone. Store at a temperature below 25 degrees.

Eutectic mixture. Prilocaine forms a mixture with lidocaine that has a melting-point lower than that of either ingredient. This eutectic mixture is used in the preparation of topical dosage forms.

Prilocaine Hydrochloride *(BANM, USAN, rINNM)*

Astra-1512; Hidrocloruro de prilocaína; L-67; Prilocaína, hidrocloruro de; Prilocaine, Chlorhydrate de; Prilocainhydrochlorid; Prilocaini Hydrochloridum; Prilokaiinihydrokloridi; Prilokain Hidroklorür; Prilokain hydrochlorid; Prilokainhidroklorid; Prilokainhydroklorid; Prilokaino hidrochloridas; Propitocaine Hydrochloride; Прилокаина Гидрохлорид.

$C_{13}H_{20}N_2O.HCl$=256.8

CAS — 721-50-6 (prilocaine); 1786-81-8 (prilocaine hydrochloride).

ATC — N01BB04.

ATC Vet — QN01BB04.

UNII — MJW015BAPH.

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

Ph. Eur. 8: (Prilocaine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. M.p. 168 degrees to 171 degrees. Freely soluble in water and in alcohol; very slightly soluble in acetone.

USP 36: (Prilocaine Hydrochloride). A white odourless crystalline powder. Freely soluble in water and in alcohol; slightly soluble in chloroform; very slightly soluble in acetone; practically insoluble in ether.

pH of solutions. For a discussion of the effect that pH has on the stability of local anaesthetic solutions and the pain associated with their injection, see p. 1976.2.

Uses and Administration

Prilocaine is a local anaesthetic of the amide type with actions and uses similar to those described on p. 1976.1. It has a similar anaesthetic potency to lidocaine. However, it has a slower onset of action, less vasodilator activity, and a slightly longer duration of action; it is also less toxic. Prilocaine hydrochloride is used for infiltration anaesthesia and nerve blocks in solutions of 0.5%, 1%, and 2%. A 1% solution is also used for epidural analgesia and a 2% solution is used for epidural anaesthesia; for intravenous regional anaesthesia 0.5% solutions are used. A 3% solution with the vasoconstrictor felypressin (p. 2502.3) or a 4% solution without are used for dental procedures. A 4% solution with adrenaline 1 in 200 000 is also used for dentistry in some countries. Carbonated solutions of prilocaine have also been tried in some countries in epidural and brachial plexus nerve blocks (see under Administration, p. 1976.2). Prilocaine is used for surface anaesthesia in a eutectic mixture with lidocaine. (Local anaesthetic techniques are discussed on p. 1977.2.)

The dosage used in various **local anaesthetic procedures** varies with the site of injection and the procedure used. The recommended **maximum single dose** in adults for prilocaine hydrochloride is 400 mg if used alone, or 300 mg if used with felypressin. Doses should be reduced in elderly or debilitated patients. The dose for children over 6 months of age is up to 5 mg/kg. For *dental infiltration* or *dental nerve blocks*, the usual adult dose of prilocaine hydrochloride without felypressin is 40 to 80 mg (1 to 2 mL) as a 4% solution; children under 10 years generally require about 40 mg (1 mL). Similar doses of the 4% solution with adrenaline (1:200 000) may be used for most routine dental procedures. The usual adult dose of prilocaine hydrochloride with felypressin 0.03 international units/mL is 30 to 150 mg (1 to 5 mL) as a 3% solution; children under 10 years generally require 30 to 60 mg (1 to 2 mL).

A eutectic mixture of prilocaine base 2.5% and lidocaine base 2.5% (see Surface Anaesthesia, under Lidocaine, p. 1989.3) is applied as a cream under an occlusive dressing to produce *surface anaesthesia* of the skin before procedures requiring needle puncture, surgical treatment of localised lesions, and split skin grafting; it has been used similarly, but without an occlusive dressing, before removal of genital warts. It is also used as a eutectic gel for *anaesthesia of the periodontal pockets* during dental scaling and/or root planing. Typically, 1.7 g of gel, or less, will be sufficient for one quadrant of dentition; the maximum recommended quantity per treatment session is 8.5 g.

Action. For a comparison of the vasoactivity of prilocaine and some other local anaesthetics, see p. 1976.2.

Administration in children. The *BNFC* recommends that the dose of prilocaine in children should be adjusted according to physical status and the nature of the procedure.

For uses and dosage of prilocaine hydrochloride in children, see above.

Infiltration anaesthesia. Addition of felypressin at a concentration of 0.03 international units/mL to prilocaine 3% injection did not reduce plasma concentrations of prilocaine after infiltration of a 60-mg dose into the upper premolar region.[1]

1. Cannell H, Whelpton R. Systemic uptake of prilocaine after injection of various formulations of the drug. *Br Dent J* 1986; 160: 47–9.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p. 1978.1, p. 1979.1, and p. 1979.1, respectively.

Prilocaine has relatively modest toxicity compared with most amide-type local anaesthetics. However, dose-related methaemoglobinaemia and cyanosis, attributed to the metabolite *o*-toluidine, appear to occur more frequently with prilocaine than with other local anaesthetics (see Methaemoglobinaemia, p. 1978.3). Symptoms usually occur when doses of prilocaine hydrochloride exceed about 8 mg/kg but the very young may be more susceptible. Methaemoglobinaemia has been seen in neonates whose mothers received prilocaine shortly before delivery and it has also been reported after prolonged topical application of a prilocaine/lidocaine eutectic mixture in children. (See Surface Anaesthesia in Lidocaine, p. 1989.3 for precautions to be observed with such a eutectic mixture.) Methaemoglobinaemia may be treated by giving oxygen followed, if necessary, by an injection of methylthioninium chloride.

Prilocaine is contra-indicated for paracervical block in obstetrics.

Prilocaine should be avoided in patients with anaemia, congenital or acquired methaemoglobinaemia, cardiac or ventilatory failure, or hypoxia.

Effects on the CNS. For reference to the prilocaine serum concentrations associated with CNS toxicity, see Absorption under Pharmacokinetics, below.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies prilocaine 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 05/10/11)

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Methaemoglobinaemia may occur at lower doses of prilocaine in patients receiving therapy with other drugs known to cause such conditions (e.g. sulfonamides such as sulfamethoxazole in co-trimoxazole).

Neuromuscular blockers. For a possible interaction between *mivacurium* and prilocaine, see under Atracurium, p. 2033.1.

Pharmacokinetics

Prilocaine is reported to be 55% bound to plasma proteins. It is rapidly metabolised mainly in the liver and also in the kidneys and is excreted in the urine mainly as metabolites. One of the principal metabolites excreted in the urine is *o*-toluidine, which is believed to cause the methaemoglobinaemia seen after large doses. Prilocaine crosses the placenta and during prolonged epidural anaesthesia may produce methaemoglobinaemia in the fetus. It is distributed into breast milk.

See also under Local Anaesthetics, p. 1979.3.

Absorption. Peak serum concentrations of prilocaine hydrochloride attained after the use of 8.5 mL of a 1% solution for retrobulbar and facial nerve block were well below the concentration of 20 micrograms/mL associated with CNS toxicity due to prilocaine.[1]

1. Goggin M, *et al.* Serum concentrations of prilocaine following retrobulbar block. *Br J Anaesth* 1990; 64: 107–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Citanest; ***Belg.***: Citanest; ***Braz.***: Citanest com Octapressin; Citocaina; ***Canad.***: Citanest; ***Denm.***: Citanest Octapressin; ***Fin.***: Citanest Octapressin ***Ger.***: Takipril; Xylonest; ***Hong Kong***: Citanest Octapressin† ***Mex.***: Pristesin F; ***Neth.***: Citanest Octapressine; Citanest; ***Norw.*** Citanest Octapressin; ***NZ***: Citanest; ***Singapore***: Citanest Octapressin; ***Swed.***: Citanest Octapressin; Citanest; ***Switz.***: Xylonest ***Turk.***: Citanest Octapressin†; Citanest; ***UK***: Citanest with Octapressin; Citanest; Prilotekal; ***USA***: Citanest.

Multi-ingredient Preparations. ***Arg.***: Emla; ***Austral.***: Emla; ***Austria***: Emla; Oraqix; ***Belg.***: Emla; ***Braz.***: Emla; Medicaina ***Canad.***: Emla; ***Chile***: Eutecaina; ***China***: Emla (易维); ***Cz.***: Emla ***Denm.***: Emla; Oraqix; Tapin; ***Fin.***: Emla; Oraqix; Tapin; ***Fr.*** Anesderm; Emla; Emlapatch; Oraqix; ***Ger.***: Anesderm; Emla Oraqix; ***Gr.***: Emla; Funis; Opralix; Prinex; Xylocream; ***Hong Kong***: Emla; Lidiprine; ***India***: Asthesia; Emlap; ***Indon.***: Dolones Emla; Estesia; Topsy; ***Irl.***: Emla; Oraqix; ***Israel***: Duo-Caine Emla; ***Ital.***: Emla; Oraqix; ***Jpn***: EMLA; ***Malaysia***: Emla; Lipro ***Mex.***: Emla; ***Neth.***: Emla; Oraqix; ***Norw.***: Emla; Oraqix; Tapin ***NZ***: Emla; Oraqix; ***Philipp.***: Emla: Emlocaine; ***Pol.***: Emla; ***Port.*** Emla; Oraqix; ***Rus.***: Emla (Эмла); ***S.Afr.***: Emla; Topla; ***Singapore***: Emla; ***Spain***: Emla; Oraqix; ***Swed.***: Emla; Oraqix; Tapin ***Switz.***: Anesderm; Emla; Oraqix; ***Thai.***: Emla; Liprikaine ***Turk.***: Emla; ***UK***: Emla; Oraqix; ***Ukr.***: Emla (Эмла); ***USA***: Emla; Oraqix.

Pharmacopoeial Preparations
BP 2014: Prilocaine Injection;
USP 36: Lidocaine and Prilocaine Cream; Prilocaine and Epinephrine Injection; Prilocaine Hydrochloride Injection.

Procaine Hydrochloride *(BANM, rINNM)*

Allocaine; Ethocaine Hydrochloride; Hidrocloruro de procaína; Novocainum; Procaína, hidrocloruro de; Procaine, Chlorhydrate de; Procainhydrochlorid; Procaini Hydrochloridum; Procainii Chloridum; Procainium Chloride; Prokaiinihydrokloridi; Prokain Hidroklorür; Prokain-hidroklorid; Prokain-hydrochlorid; Prokainhydroklorid; Prokaino hidrochloridas; Prokainy chlorowodorek; Syncaine; Прокаина Гидрохлорид.

2-Diethylaminoethyl 4-aminobenzoate hydrochloride.

$C_{13}H_{20}N_2O_2.HCl$=272.8

CAS — 59-46-1 (procaine); 51-05-8 (procaine hydrochloride).

ATC — C05AD05; N01BA02; S01HA05.

ATC Vet — QC05AD05; QN01BA02; QS01HA05.

UNII — 95URV01IDQ.

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

Ph. Eur. 8: (Procaine Hydrochloride). A white or almost white crystalline powder or colourless crystals. Very soluble in water; soluble in alcohol. A 2% solution in water has a pH of 5.0 to 6.5. Protect from light.

USP 36: (Procaine Hydrochloride). Odourless, small, white crystals or white, crystalline powder. Soluble 1 in 1 of water and 1 in 15 of alcohol; slightly soluble in chloroform; practically insoluble in ether.

Incompatibility. Procaine hydrochloride has been reported to be incompatible with aminophylline, barbiturates, magnesium sulfate, phenytoin sodium, sodium bicarbonate, and amphotericin B.

Stability of solutions. Degradation of procaine in a cardioplegic solution containing magnesium, sodium, potassium, and calcium salts was found to be temperature dependent.[1] At a storage temperature of 6 degrees the shelf-life of the solution was 5 weeks and this was increased to 9 weeks when the storage temperature was -10 degrees.

Using carbon dioxide instead of nitrogen in the head space did not affect stability of procaine.

1. Synave R, *et al.* Stability of procaine hydrochloride in a cardioplegic solution containing bicarbonate. *J Clin Hosp Pharm* 1985; 10: 385–8.

Uses and Administration

Procaine hydrochloride, a para-aminobenzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p. 1976.1. Because of its poor penetration of intact mucous membranes, procaine is ineffective for surface application and has been chiefly used by injection, although in general it has been replaced by lidocaine and other local anaesthetics. It has a slow onset of action and a short duration of action. It has vasodilator activity and therefore a vasoconstrictor may be added to delay absorption and increase the duration of action. Procaine has mainly been used for infiltration anaesthesia, peripheral nerve blocks, and spinal block. (Local anaesthetic techniques are discussed on p. 1977.2.) It has also been used in cardioplegic solutions to protect the myocardium during cardiac surgery.

Procaine hydrochloride is given in concentrations of 0.5 to 2%. The dosage depends on the site of injection and the procedure used, as well as the status of the patient.

Procaine hydrochloride has been used with propoxycaine in dentistry.

Procaine forms poorly soluble salts or conjugates with some drugs, for example penicillin, and is used to prolong their action after injection. It may also reduce the pain of injection.

Procaine-*N*-glucoside hydrochloride has been included in a preparation for gastrointestinal disorders, and procaine ascorbate has been included in a multivitamin preparation.

Action. For a comparison of the vasoactivity of procaine and some other local anaesthetics, see p. 1976.2.

Dementia. Procaine hydrochloride has been used for many years for its anti-ageing effects including the prevention of dementia (p. 388.1) and cognitive impairment but its value is not established. A systematic review[1] found no evidence of its benefit; some serious adverse effects were associated with long-term use.

1. Szatmári S, Bereczki D. Procaine treatments for cognition and dementia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 23/12/09).

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p. 1978.1, p. 1979.1, and p. 1979.1, respectively.

Effects on the cardiovascular system. Severe hypotension leading to cardiac arrest and death developed in a patient after an infusion of 600 mg of procaine for malignant hyperthermia.[1]

1. MacLachlan D, Forrest AL. Procaine and malignant hyperthermia. *Lancet* 1974; i: 355.

Hypersensitivity. Of 600 persons with dermatitis or eczema submitted to patch testing with 2% aqueous solution of procaine hydrochloride, 4.8% gave a positive reaction.[1]

For reports of hypersensitivity including anaphylactic reactions associated with procaine and other local anaesthetics, see under Adverse Effects of Local Anaesthetics, p. 1978.2.

1. Rudzki E, Kleniewska D. The epidemiology of contact dermatitis in Poland. *Br J Dermatol* 1970; 83: 543–5.

Systemic lupus erythematosus. The limited theoretical risk from using procaine for local anaesthesia in patients who have had procainamide-induced SLE was aired some years ago.[1-3]

1. Dubois EL. Procaine anesthesia after procainamide-induced systemic erythematosus. *JAMA* 1977; 238: 2201.
2. Alarcón-Segovia D. Procaine anesthesia after procainamide-induced systemic erythematosus. *JAMA* 1977; 238: 2201.
3. Lee SL. Procaine anesthesia after procainamide-induced systemic erythematosus. *JAMA* 1977; 238: 2201.

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Diuretics. Use with *acetazolamide* extends the plasma half-life of procaine.[1]

1. Calvo R, *et al.* Effects of disease and acetazolamide on procaine hydrolysis by red blood cell enzymes. *Clin Pharmacol Ther* 1980; 27: 179–83.

Pharmacokinetics

Procaine is poorly absorbed from mucous membranes and is usually given parenterally. It is rapidly hydrolysed by plasma cholinesterase to para-aminobenzoic acid and diethylaminoethanol; some may also be metabolised in the liver. Only about 6% is bound to plasma proteins. About 80% of the para-aminobenzoic acid is excreted unchanged or conjugated in the urine. About 30% of the diethylaminoethanol is excreted in the urine, the remainder being metabolised in the liver.

See also under Local Anaesthetics, p. 1979.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Endocaina; Fadacaina; Procanest; *Austria*: Geroaslan H3†; Gerovital H3†; Novanaest; *Canad.*: Novocain†; *Ger.*: Hewedolor Procain; Lophakomp-Procain; Pasconeural-Injektopas; *Hong Kong*: Gerovital H3†; *Ital.*: Lenident; *Singapore*: Procanol; *USA*: Novocain†; *Venez.*: Artrocel; Bioquel; Genaplex.

Multi-ingredient Preparations. *Arg.*: 6-Copin; Dastonil; Gingeron; KH3†; Levantol Procaina; Longevital; Otalex G; Otonorthia; *Austral.*: Cardioplegia Concentrate; *Austria*: KH3; *Braz.*: Altine; Bismu-Jet; Claudemor; Colutoide; Dentisan†; Fonergin; Otoloide; Oturga; *Chile*: Biocord-E; Biocord; Diltotal; Infor; Pantiban†; *China*: Compound Anisodine (复方樟柳碱); Jinquan (金泉); Cz.: Solutio Thomas cum Procaino; *Denm.*: Kardioplex†; *Fr.*: Otylol; *Ger.*: Gero H3 Aslan†; Hewedolor plus Coffein†; Otalgan; *Gr.*: Cardioplegia; KH3; *Hong Kong*: Cardioplegia; KH3; *Hung.*: Hemorid; Hemorid; *India*: Cardiplegin; Florocid; KP-Plegia; *Indon.*: Cardioplegia; *Irl.*: Cardioplegia; *Ital.*: Dentosedina; Ginvapast; Neo-Ustiol; Otalgan; Otomidone; Otopax; Ustiosan; *Malaysia*: Cardioplegia; *NZ*: KH3; *Rus.*: Menovasin (Меновазин); Ottoslavin (Оттославин); Solutan (Солутан)†; *S. Afr.*: Universal Earache Drops†; *Singapore*: Cardioplegia; *Spain*: Anestesia Local Braun S/A; Co Bucal; Colliriocilina Adren Astr†; Eupnol; Kanafosal Predni†; Kanafosal†; Neocolan†; Nulacin Fermentos†; Oftalmol Ocular; Otosedol†; *Switz.*: Anaestalgin†; Ginvapast; Otalgan; Otosan; *Thai.*: Cardioplegia; KH3†; *Ukr.*: Menovasan (Меновазан).

Used as an adjunct in: *Arg.*: Betametasona B12; *Braz.*: Dexacobal; Dexador; Dexagil; Dexaneurin; *Ger.*: Eukallsan N†.

Homoeopathic Preparations. *Ger.*: NeyChon Nr 68; NeyGero Nr 64; NeyGeront Vitalkapsein A.

Pharmacopoeial Preparations

USP 36: Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection; Procaine Hydrochloride and Epinephrine Injection; Procaine Hydrochloride Injection; Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injection; Propoxycaine and Procaine Hydrochlorides and Norepinephrine Bitartrate Injection.

Propanocaine Hydrochloride *(rINNM)*

467D$_3$; Hidrocloruro de propanocaína; Propanocaína, hidrocloruro de; Propanocaine, Chlorhydrate de; Propanocaini Hydrochloridum; Пропаноканна Гидрохлорид.

3-Diethylamino-1-phenylpropyl benzoate hydrochloride.

$C_{20}H_{25}NO_2$,HCl=347.9

CAS — 493-76-5 (propanocaine); 1679-79-4 (propanocaine hydrochloride).

Profile

Propanocaine hydrochloride, a benzoic acid ester, is a local anaesthetic (p. 1976.1) that has been used topically for surface anaesthesia.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Spain*: Detraine†.

Propoxycaine Hydrochloride *(rINNM)*

Hidrocloruro de propoxicaína; Propoxicaína, hidrocloruro de; Propoxycaïne, Chlorhydrate de; Propoxycaini Hydrochloridum; Пропоксикаина Гидрохлорид.

2-Diethylaminoethyl 4-amino-2-propoxybenzoate hydrochloride.

$C_{16}H_{26}N_2O_3$,HCl=330.9

CAS — 86-43-1 (propoxycaine); 550-83-4 (propoxycaine hydrochloride).

UNII — K490D39G46.

Pharmacopoeias. In *US.*

USP 36: (Propoxycaine Hydrochloride). A white odourless crystalline solid. It discolours on prolonged exposure to light and air. Soluble 1 in 2 of water, 1 in 10 of alcohol, and 1 in 80 of ether; practically insoluble in acetone and in chloroform. A 2% solution in water has a pH of about 5.4. Protect from light.

Profile

Propoxycaine hydrochloride, a para-aminobenzoic acid ester, is a local anaesthetic (p. 1976.1). It has been used with procaine hydrochloride and a vasoconstrictor for infiltration anaesthesia and nerve block in dental procedures. Propoxycaine has a more rapid onset and a longer duration of action than that of procaine.

Preparations

Pharmacopoeial Preparations

USP 36: Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injection; Propoxycaine and Procaine Hydrochlorides and Norepinephrine Bitartrate Injection.

Proxymetacaine Hydrochloride

(BANM, rINNM)

Hidrocloruro de proximetacaína; Proksimetakain Hidroklorür; Proparacaine Hydrochloride; Proparakain Hidroklorür; Proximetacaína, hidrocloruro de; Proxymétacaïne, Chlorhydrate de; Proxymetacaini Hydrochloridum; Проксиметакаина Гидрохлорид.

2-Diethylaminoethyl 3-amino-4-propoxybenzoate hydrochloride.

$C_{16}H_{26}N_2O_3$,HCl=330.9

CAS — 499-67-2 (proxymetacaine); 5875-06-9 (proxymetacaine hydrochloride).

ATC — S01HA04.

ATC Vet — QS01HA04.

UNII — U96OL57GOY.

NOTE. PROX is a code approved by the BP 2014 for use on single unit doses of eye drops containing proxymetacaine hydrochloride where the individual container may be too small to bear all the appropriate labelling information. PROXFLN is a similar code approved for eye drops containing proxymetacaine hydrochloride and fluorescein sodium.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Proxymetacaine Hydrochloride). A white or almost white, odourless or almost odourless, crystalline powder. Soluble in water and in chloroform; very soluble in dehydrated alcohol; practically insoluble in ether. A 1% solution in water has a pH of 5.7 to 6.4. Protect from light.

USP 36: (Proparacaine Hydrochloride). A white to off-white, or faintly buff-coloured, odourless, crystalline powder. Soluble in water, in warm alcohol, and in methyl alcohol; insoluble in ether and in benzene.

Uses and Administration

Proxymetacaine hydrochloride, a meta-aminobenzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p. 1976.1. It is used for surface anaesthesia (p. 1977.3) in ophthalmology in a concentration of 0.5%. Proxymetacaine is of similar potency to tetracaine in equal concentrations and induces anaesthesia within about 20 seconds. The duration of action may be 15 minutes or longer. Instillation of 1 or 2 drops permits tonometry after 30 seconds. For removal of foreign bodies or sutures from the cornea 1 or 2 drops are instilled every 5 to 10 minutes for up to 3 applications, or 1 or 2 drops are instilled 2 to 3 minutes before the procedure. For deeper anaesthesia such as needed for cataract extraction 1 drop is instilled every 5 to 10 minutes to a total of 5 to 7 applications.

Trigeminal neuralgia. There have been anecdotal reports that proxymetacaine eye drops relieved trigeminal neuralgia (p. 11.2) refractory to carbamazepine.[1,2] However, a controlled study failed to show any benefit.[3]

1. Zavon MR, Fichte CM. Trigeminal neuralgia relieved by ophthalmic anesthetic. *JAMA* 1991; 265: 2807.
2. Zavon MR, Fichte CM. Trigeminal neuralgia relieved by optical anesthesia. *JAMA* 1991; 266: 1649.
3. Kondziolka D, *et al.* The effect of single-application topical ophthalmic anesthesia in patients with trigeminal neuralgia: a randomized double-blind placebo-controlled trial. *J Neurosurg* 1994; 80: 993–7.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p. 1978.1, p. 1979.1, and p. 1979.1, respectively.

A severe immediate-type corneal reaction to proxymetacaine may rarely occur. Allergic contact dermatitis has also been reported.

Effects on the skin. Exacerbation of Stevens-Johnson syndrome has been reported[1] in a woman after ophthalmic anaesthesia with proxymetacaine hydrochloride.

1. Ward B, *et al.* Dermatologic reaction in Stevens-Johnson syndrome after ophthalmic anesthesia with proparacaine hydrochloride. *Am J Ophthalmol* 1978; 86: 133–5.

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Pharmacokinetics

See under Local Anaesthetics, p. 1979.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Anestalcon; Poencaina; *Austral.*: Alcaine; *Belg.*: Alcaine; *Braz.*: Anestalcon; Visonest; *Canad.*: Ak-Taine; Alcaine; Diocaine; Ophthetic†; *Chile*: Anestalcon; *China*: Alcaine (爱尔凯因); *Ger.*: Proparakain-POS; *Gr.*: Alcaine; *Hong Kong*: Alcaine; *India*: Paracain; *Malaysia*: Alcaine; *Mex.*: Alcaine; *Norw.*: Alcaine; *NZ*: Ophthetic†; *Philipp.*: Alcaine; *Pol.*: Alcaine; *Rus.*: Alcaine (Алкаин)†; *Singapore*: Alcaine†; Primax; *Switz.*: Alcaine; *Turk.*: Alcaine; Opticaine†; *Ukr.*: Alcain (Алкаин); *USA*: Ak-Taine; Alcaine; Ocu-Caine; Ophthetic; Parcaine; *Venez.*: Alcaine; Poencaina.

Multi-ingredient Preparations. *Canad.*: Fluoracaine†; *USA*: Fluoracaine; Fluorocaine.

Pharmacopoeial Preparations
BP 2014: Proxymetacaine Eye Drops;
USP 36: Fluorescein Sodium and Proparacaine Hydrochloride Ophthalmic Solution; Proparacaine Hydrochloride Ophthalmic Solution.

Quinisocaine Hydrochloride *(BANM, rINNM)*

Chinisocainum Hydrochloride; Dimethisoquin Hydrochloride (USAN); Dimethisoquinium Chloride; Hidrocloruro de quinisocaína; Quinisocaína, hidrocloruro de; Quinisocaïne, Chlorhydrate de; Quinisocaini Hydrochloridum; Хинизокаина Гидрохлорид.

2-(3-Butyl-1-isoquinolyloxy)-*NN*-dimethylethylamine hydrochloride.

$C_{17}H_{24}N_2O,HCl=308.8$

CAS — 86-80-6 (quinisocaine); 2773-92-4 (quinisocaine hydrochloride).

ATC — D04AB05.

ATC Vet — QD04AB05.

UNII — SMP2689462.

Profile

Quinisocaine hydrochloride is a local anaesthetic (p. 1976.1) that has been used as a surface anaesthetic in the form of an ointment or cream in a concentration of 0.5% for the relief of pruritus, anogenital or anorectal irritation, and minor skin conditions. It has also been used as suppositories.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Quotane; *Ger.*: Haenal akut; *Switz.*: Isochinol.

Multi-ingredient Preparations. *Fr.*: Rectoquotane.

Ropivacaine Hydrochloride

(BANM, rINNM)

AL-281; Hidrocloruro de ropivacaína; Ropivacaína, hidrocloruro de; Ropivacaïne, Chlorhydrate de; Ropivacaini Hydrochloridum; Ropivakaiinihydrokloridi; Ropivakain Hidroklorür; Ropivakainhydroklorid; Ропивакаина Гидрохлорид.

(*S*)-2′,6′-Dimethyl-1-propylpiperidine-2-carboxanilide hydrochloride monohydrate.

$C_{17}H_{26}N_2O,HCl,H_2O=328.9$

CAS — 84057-95-4 (ropivacaine); 98717-15-8 (anhydrous ropivacaine hydrochloride); 132112-35-7 (ropivacaine hydrochloride monohydrate).

ATC — N01BB09.

ATC Vet — QN01BB09.

UNII — V910886109 (ropivacaine hydrochloride monohydrate); 3550ALBE21 (anhydrous ropivacaine hydrochloride).

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

Ph. Eur. 8: (Ropivacaine Hydrochloride Monohydrate). A white or almost white, crystalline powder. Soluble in water and in alcohol; slightly soluble in dichloromethane. pH of a 2% solution in water is 4.5 to 6.0.

USP 36: (Ropivacaine Hydrochloride). A white crystalline powder. Soluble in water. A 1% solution in water has a pH of 4.5 to 6.0.

Uses and Administration

Ropivacaine hydrochloride is a local anaesthetic of the amide type with actions and uses similar to those described on p. 1976.1. It is a long-acting local anaesthetic, although onset and duration of action are dependent upon the site of injection; the presence of a vasoconstrictor such as adrenaline has no effect. Ropivacaine is used for epidural block, peripheral nerve block, and infiltration anaesthesia and field block, but is contra-indicated for obstetric paracervical block and for use in intravenous regional anaesthesia (Bier's block). (Local anaesthetic techniques are discussed on p. 1977.2.) At high doses ropivacaine produces surgical anaesthesia, whereas at lower doses it is used for the management of acute pain such as labour pain (p. 8.3) and in postoperative analgesia (p. 6.1).

Like bupivacaine (p. 1980.3), ropivacaine has a differential blocking effect on nerve fibres and, at the lowest concentration used, there is good differentiation between sensory and motor block. The onset and duration of sensory block produced by ropivacaine is generally similar to that obtained with bupivacaine but the motor block is often slower in onset, shorter in duration, and less intense.

Ropivacaine hydrochloride is given in concentrations of 0.2 to 1%. The dosage depends on the site of injection and the procedure used, as well as the status of the patient. The dose of ropivacaine should be reduced in the elderly, and in acutely ill or debilitated patients. A test dose of lidocaine with adrenaline should be given before starting epidural block with ropivacaine to detect inadvertent intravascular administration.

- For **surgical anaesthesia**, doses of ropivacaine hydrochloride for *lumbar epidural block* are 75 to 150 mg (15 to 30 mL) as a 0.5% solution, or 112.5 to 187.5 mg (15 to 25 mL) as a 0.75% solution, or 150 to 200 mg (15 to 20 mL) as a 1% solution; for caesarean section, doses are 100 to 150 mg (20 to 30 mL) as a 0.5% solution or 112.5 to 150 mg (15 to 20 mL) as a 0.75% solution. Doses for *thoracic epidural block* to establish a block for postoperative pain relief are 25 to 75 mg (5 to 15 mL) as a 0.5% solution or 37.5 to 112.5 mg (5 to 15 mL) as a 0.75% solution; the actual dose used depends on the level of the injection.
- For *peripheral nerve block* of major nerves such as the brachial plexus, typical doses are 175 to 250 mg (35 to 50 mL) as a 0.5% solution; 225 to 300 mg (30 to 40 mL) as a 0.75% solution has also been recommended for brachial plexus block.
- For *infiltration anaesthesia* and *field block* up to 200 mg (40 mL) as a 0.5% solution or up to 225 mg (30 mL) as a 0.75% solution may be used.
- In the management of **acute pain** ropivacaine hydrochloride is used as a 0.2% solution for epidural block (0.5% solutions may be used for infiltration). Doses for *lumbar epidural block* are 20 to 40 mg (10 to 20 mL) as an initial bolus followed by 20 to 30 mg (10 to 15 mL) at intervals of not less than 30 minutes. Alternatively, 12 to 20 mg (6 to 10 mL) per hour may be given as a continuous epidural infusion; if additional pain relief is required, doses of up to 28 mg (14 mL) per hour may be given. Doses for *thoracic epidural block* are 12 to 28 mg (6 to 14 mL) per hour as a continuous infusion.
- For *infiltration anaesthesia* doses are 2 to 200 mg (1 to 100 mL) as a 0.2% solution or 5 to 200 mg (1 to 40 mL) as a 0.5% solution.
- In neonates, infants, and children aged up to 12 years, ropivacaine hydrochloride may be used for the management of peri- and postoperative pain. A 0.2% solution is given in a dose of 2 mg/kg (1 mL/kg) to achieve a *caudal epidural block*.

References.
1. Markham A, Faulds D. Ropivacaine: a review of its pharmacology and therapeutic use in regional anaesthesia. *Drugs* 1996; 52: 429–49.
2. McClure JH. Ropivacaine. *Br J Anaesth* 1996; 76: 300–307.
3. Morton C. Ropivacaine. *Br J Hosp Med* 1997; 58: 97–100.
4. Stienstra R. The place of ropivacaine in anesthesia. *Acta Anaesthesiol Belg* 2003; 54: 141–8.
5. Zink W, Graf BM. Benefit-risk assessment of ropivacaine in the management of postoperative pain. *Drug Safety* 2004; 27: 1093–1114.
6. Simpson D, *et al.* Ropivacaine: a review of its use in regional anaesthesia and acute pain management. *Drugs* 2005; 65: 2675–2717.

Administration in children. The *BNFC* recommends that the dose of ropivacaine in children should be adjusted according to physical status and the nature of the procedure.

For uses and dosage of ropivacaine hydrochloride in children, see above.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p. 1978.1, p. 1979.1, and p. 1979.1, respectively.

Ropivacaine is contra-indicated for use in intravenous regional anaesthesia (Bier's block) and for paracervical block in obstetrics.

Effects on the cardiovascular system. Ropivacaine is structurally related to bupivacaine, but data from extensive *animal* studies suggest that ropivacaine may be less cardiotoxic than bupivacaine.[1] Results from a study[2] in 12 healthy male subjects support these data; at doses producing CNS symptoms cardiovascular changes, such as depression of conduction and diastolic function, were less pronounced with ropivacaine than with bupivacaine.

1. Cederholm I. Preliminary risk-benefit analysis of ropivacaine in labour and following surgery. *Drug Safety* 1997; 16: 391–402.
2. Knudsen K, *et al.* Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997; 78: 507–14.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ropivacaine 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 05/10/11)

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Giving ropivacaine with general anaesthetics, opioid analgesics, or drugs structurally related to amide-type local anaesthetics (e.g. certain antiarrhythmics) may result in potentiation of adverse effects.

The metabolism of ropivacaine is mediated by the cytochrome P450 isoenzyme CYP1A2 and the potential exists for interactions between ropivacaine and other drugs that inhibit or act as a substrate for this isoenzyme. Prolonged use of ropivacaine should be avoided in patients treated with potent CYP1A2 inhibitors, such as fluvoxamine. Plasma concentrations of ropivacaine may be reduced by enzyme-inducing drugs such as rifampicin.

Pharmacokinetics

Ropivacaine is about 94% bound to plasma proteins. The terminal elimination half-life has been reported to be 1.8 hours. It is extensively metabolised in the liver, mainly by aromatic hydroxylation which is mediated by the cytochrome P450 isoenzyme CYP1A2; the isoenzyme CYP3A4 plays a minor role in the metabolism of ropivacaine. The metabolites are excreted mainly in the urine; about 1% of a dose is excreted as unchanged drug. Some metabolites also have a local anaesthetic effect but less than that of ropivacaine. Ropivacaine crosses the placenta.

See also under Local Anaesthetics, p. 1979.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Naropin; *Austral.*: Naropin; *Austria*: Naropin; *Belg.*: Naropin; *Braz.*: Naropin; Ropi; *Canad.*: Naropin; *Chile*: Naropin†; *China*: Heng Luo (恒洛); Naropin (耐乐品); Zhuo Tan (卓坦); *Cz.*: Naropin†; *Denm.*: Naropin; *Fin.*: Naropin; *Fr.*: Naropeine; *Ger.*: Naropin; *Gr.*: Naropeine; *Hong Kong*: Naropin; *Hung.*: Naropin; *Indon.*: Naropin; *Irl.*: Naropin; *Israel*: Naropin; *Ital.*: Naropina; *Malaysia*: Naropin; *Mex.*: Naropin; Ropiconest; *Neth.*: Naropin; *Norw.*: Naropin; *NZ*: Naropin; *Philipp.*: Naropin; *Pol.*: Naropin; Ropimol; *Port.*: Naropeine; *Rus.*: Naropin (Наропин); *S.Afr.*: Naropin; *Singapore*: Naropin; *Spain*: Naropin; *Swed.*: Narop; *Switz.*: Naropin; *Thai.*: Naropin; *Turk.*: Naropin; *UK*: Naropin; *Ukr.*: Naropin (Наропин); *USA*: Naropin.

Multi-ingredient Preparations. *Austral.*: Naropin with Fentanyl; *NZ*: Naropin with Fentanyl.

Pharmacopoeial Preparations
USP 36: Ropivacaine Hydrochloride Injection.

Tetracaine *(BAN, rINN)*

Amethocaine; Tetracaína; Tétracaïne; Tetracainum; Tetrakaiini; Tetrakain; Тетракаин.

2-Dimethylaminoethyl 4-butylaminobenzoate.

$C_{15}H_{24}N_2O_2=264.4$

CAS — 94-24-6.

ATC — C05AD02; D04AB06; N01BA03; S01HA03.

ATC Vet — QC05AD02; QD04AB06; QN01BA03; QS01HA03.

UNII — 0619F35CGV.

Pharmacopoeias. In *US*.

USP 36: (Tetracaine). A white or light yellow waxy solid. M. p. 41 degrees to 46 degrees. Very slightly soluble in water; soluble 1 in 5 of alcohol and 1 in 2 of chloroform or of ether; soluble in benzene. Store in airtight containers. Protect from light.

Tetracaine Hydrochloride *(BANM, rINNM)*

Amethocaine Hydrochloride; Dicainum; Hidrocloruro de tetracaína; Tetracaína, hidrocloruro de; Tétracaïne, Chlorhydrate de; Tetracainhydrochlorid; Tetracaini Hydrochloridum; Tetracainli Chloridum; Tetrakaiinihydrokloridi; Tetrakain Hidroklorür; Tetrakain hydrochlorid; Tetrakainhidroklorid; Tetrakainhydroklorid; Tetrakaino hidrochloridas; Tetrakainy chlorowodorek; Тетракаина Гидрохлорид.

$C_{15}H_{24}N_2O_2$,HCl=300.8
CAS — 136-47-0.
ATC — C05AD02; D04AB06; N01BA03; S01HA03.
ATC Vet — QC05AD02; QD04AB06; QN01BA03; QS01HA03.
UNII — 5NF5D4OPCI.

NOTE. TET is a code approved by the BP 2014 for use on single unit doses of eye drops containing tetracaine hydrochloride 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: (Tetracaine Hydrochloride). A white or almost white, slightly hygroscopic, polymorphic, crystalline powder. Freely soluble in water; soluble in alcohol. A 1% solution in water has a pH of 4.5 to 6.5. Store in airtight containers. Protect from light.

USP 36: (Tetracaine Hydrochloride). A fine, white, odourless, hygroscopic, polymorphic, crystalline powder. Very soluble in water; soluble in alcohol; insoluble in ether and in benzene. Its solutions are neutral to litmus. Store in airtight containers. Protect from light.

Uses and Administration

Tetracaine, a para-aminobenzoic acid ester, is a potent local anaesthetic with actions and uses similar to those described on p. 1976.1. It is used for surface anaesthesia and spinal block; its use in other local anaesthetic techniques is restricted by its systemic toxicity.

Tetracaine is generally used as the hydrochloride in solutions and creams, and as the base in gels or ointments.

For *anaesthesia of the eye*, solutions containing 0.5 to 1% tetracaine hydrochloride have been used; ointments have also been used. Instillation of a 0.5% solution produces anaesthesia within 25 seconds that lasts for 15 minutes or longer and is suitable for use before minor surgical procedures.

For *topical anaesthesia*, a 4% gel is used as a *percutaneous local anaesthetic* before *venepuncture or venous cannulation*. The gel is applied to the centre of the area to be anaesthetised and covered with an occlusive dressing. In some circumstances such as where cannulation is difficult anaesthesia of more than one site may be necessary. Children aged 5 years and over and adults may receive a maximum of 5 tubes (about 5 g) at a single time applied to separate sites; younger children should only receive the contents of one tube at a single time but this can be applied to separate sites. Gel and dressing are removed after 30 minutes for venepuncture and after 45 minutes for venous cannulation. A single application generally provides anaesthesia for 4 to 6 hours. Licensed product information states that this method is not suitable for premature infants or those less than 1 month of age; however, the *BNFC* recommends that such a method may be used in neonates. A transdermal patch containing tetracaine 70 mg with lidocaine 70 mg is available for surface anaesthesia of intact skin in connection with *needle puncture* and in cases of *superficial surgical procedures*. A cream or an ointment has been used for painful conditions of the *anus or rectum*.

Tetracaine hydrochloride has also been used in the *mouth* in sprays and lozenges.

Tetracaine hydrochloride has also been used for *spinal block* usually as a 0.5% solution.

Action. For a comparison of the vasoactivity of tetracaine with some other local anaesthetics, see p. 1976.2.

Administration in children. For the use of tetracaine hydrochloride as a percutaneous local anaesthetic in children, see above. See also Surface Anaesthesia, below

Spinal block. A study[1] in 40 patients indicated that for patients undergoing caesarean section with spinal anaesthesia (see Central Nerve Block, p. 1977.2) doses of 12 or 14 mg of tetracaine provided better intraoperative analgesia than doses of 8 or 10 mg without leading to excessive spread of the block.

1. Hirabayashi Y, *et al.* Visceral pain during Caesarean section: effect of varying dose of spinal amethocaine. *Br J Anaesth* 1995; 75: 266–8.

Surface anaesthesia. A topical gel formulation of tetracaine 4% appears to provide more rapid and prolonged surface anaesthesia (see p. 1977.3) than a eutectic mixture of lidocaine and prilocaine.[1,2] In a double-blind placebo-controlled study[3] the tetracaine gel formulation was significantly better than the eutectic mixture in reducing pain caused by laser treatment of portwine stains. Similar findings were also seen in a comparative study[4] and a systematic review[5] in children requiring venous cannulation, although others have questioned the efficacy of tetracaine gel in peripheral insertion of a central catheter.[6] The same formulation appears to be effective when incorporated into a transdermal patch.[7] Patches containing a mixture of lidocaine and tetracaine have also been tried[8,9] and are licensed in some countries for surface anaesthesia of intact skin in connection with needle puncture and in cases of superficial surgical procedures.

There have been reports of seizures and death in children after the use of a mixture of tetracaine, adrenaline, and cocaine on mucosal surfaces;[10] application of preparations of tetracaine to highly vascular surfaces is contra-indicated. A gel containing a mixture of lidocaine, adrenaline, and tetracaine has been found to be an effective alternative to the cocaine-containing preparation.[11]

Tetracaine has also been incorporated into a mucosa-adhesive polymer film to relieve the pain of oral lesions resulting from radiation and antineoplastic therapy.[12] Liposome-encapsulated tetracaine has also been shown to provide adequate surface anaesthesia.[13]

1. McCafferty DF, *et al.* In vivo assessment of percutaneous local anaesthetic preparations. *Br J Anaesth* 1989; 62: 17–21.
2. Rømsing J, *et al.* Tetracaine gel vs EMLA cream for percutaneous anaesthesia in children. *Br J Anaesth* 1999; 82: 637–8.
3. McCafferty DF, *et al.* Effect of percutaneous local anaesthetics on pain reduction during pulse dye laser treatment of portwine stains. *Br J Anaesth* 1997; 78: 286–9.
4. Arrowsmith J, Campbell C. A comparison of local anaesthetics for venepuncture. *Arch Dis Child* 2000; 82: 309–10.
5. Lander JA, *et al.* EMLA and amethocaine for reduction of children's pain associated with needle insertion. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 23/04/08).
6. Lemyre B, *et al.* How effective is tetracaine 4% gel, before a peripherally inserted central catheter, in reducing procedural pain in infants: a randomized double-blind placebo controlled trial. *BMC Med* 2006; 4: 11. Available at: http://www.biomedcentral.com/content/pdf/1741-7015-4-11.pdf (accessed 21/06/06)
7. McCafferty DF, Woolfson AD. New patch delivery system for percutaneous local anaesthesia. *Br J Anaesth* 1993; 71: 370–4.
8. Berman B, *et al.* Self-warming lidocaine/tetracaine patch effectively and safely induces local anesthesia during minor dermatologic procedures. *Dermatol Surg* 2005; 31: 133–8.
9. Schecter AK, *et al.* Randomized, double-blind, placebo-controlled study evaluating the lidocaine/tetracaine patch for induction of local anesthesia prior to minor dermatologic procedures in geriatric patients. *Dermatol Surg* 2005; 31: 287–91.
10. Wong S, Hart LL. Tetracaine/adrenaline/cocaine for local anesthesia. *DICP Ann Pharmacother* 1990; 24: 1181–3.
11. Ernst AA, *et al.* Lidocaine adrenaline tetracaine gel versus tetracaine adrenaline cocaine gel for topical anesthesia in linear scalp and facial lacerations in children aged 5 to 17 years. *Pediatrics* 1995; 95: 255–8.
12. Yotsuyanagi T, *et al.* Mucosa-adhesive film containing local analgesic. *Lancet* 1985; ii: 613.
13. Fisher R, *et al.* Topical anaesthesia of intact skin: liposome-encapsulated tetracaine vs EMLA. *Br J Anaesth* 1998; 81: 972–3.

Adverse Effects and Treatment

As for Local Anaesthetics in general, p. 1978.1 and p. 1979.1.

Tetracaine has high systemic toxicity. Absorption of tetracaine from mucous membranes is rapid and adverse reactions can occur abruptly without the appearance of prodromal signs or convulsions; fatalities have occurred.

A stinging sensation may occur when tetracaine is used in the eye. Mild erythema at the site of application is frequently seen with topical use; slight oedema or pruritus occur less commonly. Blistering of the skin may occur.

Urethral stricture. There has been a report[1] of a sudden increase in the incidence of urethral stricture after transurethral surgery, which may have been due to an increase in the concentration of tetracaine hydrochloride in the lubricant gel from 0.1 to 3%.

1. Pansadoro V. Role of local anaesthetics in urethral strictures after transurethral surgery. *Lancet* 1990; 336: 64.

Precautions

As for Local Anaesthetics in general, p. 1979.1.

Tetracaine should not be applied to inflamed, traumatised, or highly vascular surfaces. It should not be used to provide anaesthesia for bronchoscopy or cystoscopy, as lidocaine is a safer alternative.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tetracaine as not porphyrinogenic when used for surface anaesthesia in ophthalmological procedures; 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 05/10/11)

Interactions

For interactions associated with local anaesthetics, see p. 1979.3.

Pharmacokinetics

See under Local Anaesthetics, p. 1979.3. Tetracaine is reported to be about 15% bioavailable after application of a 4% gel to intact skin, with a mean absorption and elimination half-life of about 75 minutes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Tray-Te†; *Braz.*: Anestesico; *Canad.*: Ametop; Pontocaine; Viractin; *Fr.*: Solutricine Maux de Gorge; *Ger.*: Ophtocain N; *Gr.*: Tetravisc; *Irl.*: Ametop; *Mex.*: Ponti; *Philipp.*: Pontocaine; *Port.*: Lubrificante Anestesico; *S.Afr.*: Anethaine; Covostet; *Spain*: Anestesia Topi Braun C/A†; Anestesia Topi Braun S/A; Anestesico; Hemonet†; Lubricante Urologico; *Swed.*: Tetrakain; *UK*: Ametop; Anethaine; *USA*: Cepacol Viractin Cold Sore Treatment†; Pontocaine.

Multi-ingredient Preparations. *Arg.*: Bagociletas con Anestesia†; Clevosan; Drill; *Austria*: Dynexan; Herviros; *Belg.*: Hexomedine†; *Braz.*: Hexomedine; Oto-Betnovate; *Canad.*: Cetacaine; Denti-Care Denti-Freeze; Denti-Care Topical; One Touch; ZAP; *Cz.*: Drill; Rapyden; *Denm.*: Ralydan; *Fr.*: Aphtoral; Cantalene; Doli Mal de Gorge; Drill; Eludril; Ergix mal de gorge; Otylol; Rapydan†; Solutricine Maux de Gorge†; *Ger.*: Gingicain D; *Gr.*: Buccasept†; Rapydan; *Hung.*: Drill†; Faringopront; *Irl.*: Rapydan; *Israel*: Anaesthetic Ear Drops; Otidin; *Ital.*: Donalg; Odongi; Ralydan; Recto-Reparil; Ruscoroid; *Neth.*: Pliaglis; Rapydan; *Norw.*: Rapydan; *NZ*: Topicaine; *Pol.*: Ruskorex; *Port.*: Anucet; Drill; Hemofissural; Rapydan; *Rus.*: Anti-Angin (Анти-Ангин); Drill (Дрилл)†; Novosept (Новосепт Форте); *S.Afr.*: Dynexan; *Spain*: Anestesico Doble; Blastoestimulina†; Dentikrisos†; Otogen Calmante; Pliaglis; Resorborina; Vinciseptil Otico; *Swed.*: Rapydan; *Switz.*: Angidine†; Eludril†; Mucosan†; Tyrothricine + Gramicidine†; *Turk.*: Dervanol; Hemoralgine; Otimisin; *UK*: Eludril; Pliaglis; Rapydan†; *USA*: Cetacaine; Pliaglis; Stypto-Caine; Synera.

Pharmacopoeial Preparations
BP 2014: Tetracaine Eye Drops;
USP 36: Benzocaine, Butamben, and Tetracaine Hydrochloride Gel; Benzocaine, Butamben, and Tetracaine Hydrochloride Ointment; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Aerosol; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Solution; Cocaine and Tetracaine Hydrochlorides and Epinephrine Topical Solution; Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection; Tetracaine and Menthol Ointment; Tetracaine Hydrochloride Cream; Tetracaine Hydrochloride for Injection; Tetracaine Hydrochloride in Dextrose Injection; Tetracaine Hydrochloride Injection; Tetracaine Hydrochloride Ophthalmic Solution; Tetracaine Hydrochloride Topical Solution; Tetracaine Ointment; Tetracaine Ophthalmic Ointment.

Tolycaine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tolicaína; Tolicaína, hidrocloruro de; Tolycaine, Chlorhydrate de; Tolycaini Hydrochloridum; Толикаина Гидрохлорид.

Methyl 2-(2-diethylaminoacetamido)-*m*-toluate hydrochloride.

$C_{15}H_{22}N_2O_3$,HCl=314.8

CAS — 3686-58-6 (tolycaine); 7210-92-6 (tolycaine hydrochloride).

Profile

Tolycaine hydrochloride is an amide local anaesthetic (p. 1976.1) included in some preparations to reduce the pain of injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations.

Used as an adjunct in:. *Ger.*: Tardocillin.

Tricaine Mesilate

Metacaine Mesylate; Tricaína, mesilato de; Tricaine Mesylate; TS-222.

Ethyl 3-aminobenzoate methanesulphonate.

$C_{10}H_{15}NO_5S$=261.3

CAS — 886-86-2.

ATC Vet — QN01AX93.

UNII — 971ZM8IPK1.

Profile

Tricaine mesilate is a derivative of an isomer of benzocaine (see p. 1980.2) and although it has been used as a local anaesthetic in human medicine it is now mainly used as an anaesthetic and tranquilliser for fish and other cold-blooded animals.

Trimecaine Hydrochloride *(rINNM)*

Hidrocloruro de trimecaína; Trimecaína, hidrocloruro de; Trimécaïne, Chlorhydrate de; Trimecaini Hydrochloridum; Trimecainium Chloratum; Trimekain-hydrochlorid; Тримекаина Гидрохлорид.

2-Diethylamino-2',4',6'-trimethylacetanilide hydrochloride
$C_{15}H_{24}N_2O.HCl$=284.8
CAS — 616-68-2 (trimecaine); 1027-14-1 (trimecaine hydrochloride).
UNII — 5491FXS1NB.

Profile

Trimecaine hydrochloride is an amide local anaesthetic (p. 1976.1). It has been used topically and by injection and has been included in some preparations to reduce the pain of injection.

Preparations

Proprietary Preparations (details are given in Volume B)

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

Multi-ingredient Preparations. *Cz.*: Mesocain; Septonex Plus; *Rus.*: Levosin (Левосин); Simetrid (Симетрид).

Miotics Mydriatics and Antiglaucoma Drugs

Glaucoma and ocular hypertension, p. 1999
Mydriasis and cycloplegia, p. 2000
Reversal of mydriasis, p. 2000
Strabismus, p. 2000

Included in this chapter are a variety of drugs used in the eye to alter accommodation and produce mydriasis or cycloplegia, or in the treatment of glaucoma. Some drugs used for these purposes, or in other ocular disorders, but with other primary uses, may be found elsewhere in *Martindale*.

Glaucoma and ocular hypertension

Intra-ocular pressure rises when there is an imbalance between production and drainage of aqueous humour in the eye. Aqueous humour is secreted by the ciliary body and flows into the posterior chamber of the eye. It then passes through the pupil into the anterior chamber from where about 75% drains from the eye through the trabecular meshwork into Schlemm's canal and then into the episcleral veins. The remainder is removed by the uveoscleral route, passing through the ciliary muscle and finally into the episcleral tissues.

The term **ocular hypertension** is used to describe intra-ocular pressure above an upper normal value of 21 mmHg when there are no signs of optic nerve damage. The term **glaucoma** is used to describe a group of conditions characterised by cupping (excavation) of the optic disc and damage of the optic nerve leading to gradual but irreversible visual loss; glaucoma is one of the most common causes of blindness.

Raised intra-ocular pressure is an important risk factor for glaucoma, and as it is the only one that can be altered, current therapy for glaucoma is directed at lowering it. The aim is not just to reduce intra-ocular pressure to a normal value but to a level at which damage to the optic nerve ceases.[1-7] Some patients may have raised intra-ocular pressure for many years without evidence of glaucoma. Whether these patients would receive long-term benefit from a reduction in intra-ocular pressure has been a matter of debate. However, randomised studies[8,9] have shown that topical ocular hypotensive treatment was effective in preventing or delaying the onset of open-angle glaucoma in patients with raised intra-ocular pressure. In addition, another study[10,11] has found that lowering intra-ocular pressure slows the progression of glaucoma. A meta-analysis[12] has also confirmed that lowering intra-ocular pressure reduces the risk of visual field loss in the long term in patients with ocular hypertension or newly-diagnosed glaucoma. Similarly, a systematic review[13] concluded that topically lowering intra-ocular pressure had a protective effect on the visual field. Some,[14] including NICE[15] in the UK, consider that only high-risk patients with raised intra-ocular pressure should be treated; such risk factors include thin central corneal thickness measurement, large cup-to-disc ratio, older age, intra-ocular pressure fluctuation, and a family history of blindness. In practice, many ophthalmologists consider that therapy is indicated if the intra-ocular pressure is higher than 30 mmHg. Glaucoma can also occur and progress in patients with an intra-ocular pressure within the normal range (normal tension glaucoma).

Raised intra-ocular pressure associated with glaucoma is usually due to reduced outflow of aqueous humour from the eye. Glaucoma is described as open-angle or angle-closure depending on the mechanism of the obstruction of drainage and may be acute or chronic. Glaucoma may also be referred to as primary or secondary. **Primary glaucoma** is usually associated with a direct disturbance of outflow whereas **secondary glaucoma** develops as a consequence of some diseases or of trauma.

The most common form of glaucoma is **chronic open-angle glaucoma** (simple glaucoma; wide-angle glaucoma), which is due to blockage in drainage through the trabecular meshwork. Intra-ocular pressure increases gradually, and the condition is usually asymptomatic until well advanced and severe damage has occurred. Usually, both eyes are affected. Risk factors include old age, diabetes, Afro-Caribbean race, a family history of glaucoma, and myopia. A **'steroid glaucoma'** may be produced, after a few weeks of treatment with eye drops containing corticosteroids, in patients predisposed to open-angle glaucoma; the risk with systemic corticosteroids appears to be less.

In contrast, **angle-closure glaucoma** (closed-angle glaucoma; narrow-angle glaucoma) usually occurs as an acute emergency. Patients present with a painful red eye, sweating, and nausea and vomiting as a result of a rapid rise in intra-ocular pressure. This can result from blockage of the flow of aqueous humour into the anterior chamber. The resulting rise in intra-ocular pressure bows the iris against the trabecular meshwork, restricting outflow and thereby further raising intra-ocular pressure. It usually occurs in patients with hypermetropia who have a shallow anterior chamber and a narrow filtration angle. The use of mydriatics in such patients is generally considered to be contra-indicated on the grounds that dilatation of the pupil could precipitate an acute attack of angle-closure glaucoma, but see Glaucoma, under Tropicamide, p. 2012.3.

ANTIGLAUCOMA DRUGS.

Drugs used in the treatment of glaucoma[1,3-5,16-18] lower intra-ocular pressure by a variety of mechanisms and their effects are often additive. Most are used topically although a few are given by systemic routes.

- ***Beta blockers*** inhibit beta receptors in the ciliary epithelium and thereby reduce the secretion of aqueous humour. They have traditionally been the drugs of first choice for initial and maintenance treatment of open-angle and other chronic glaucomas and of ocular hypertension; other drugs are used with them when further reductions in intra-ocular pressure are required. Advantages over miotics (below) include a lack of effect on pupil size and accommodation; in addition they can be given once or twice daily which may improve compliance. They are also better tolerated than miotics but can produce systemic effects, and their safety, particularly in the elderly, has been questioned.[19,20] Cardioselective beta blockers may cause fewer pulmonary adverse effects, such as bronchoconstriction, than non-selective beta blockers. Studies suggest that individual topical beta blockers are probably equally effective in reducing intra-ocular pressure but if a non-selective beta blocker is used an additional reduction in pressure may not be obtained with adrenaline (see below). However, a meta-analysis has suggested that timolol may be more effective than betaxolol.[21]
- Topical ***prostaglandin analogues*** or ***prostamides***, such as bimatoprost, latanoprost, tafluprost, and travoprost, lower intra-ocular pressure by increasing uveoscleral outflow. They are increasingly a first choice, alone or as adjuncts, in the treatment of ocular hypertension or open-angle glaucoma. A meta-analysis of the efficacy of common antiglaucoma drugs found bimatoprost, travoprost, and latanoprost to be the most effective in lowering intra-ocular pressure.[21] They are given once daily and appear to be well-tolerated. They do not affect pupil size or accommodation, but may cause a potentially irreversible increase in brown pigmentation of the iris; the long-term significance of this effect is unknown. Unoprostone, which needs to be used twice daily, appears to be less effective than the other prostaglandin analogues.[22]
- ***Parasympathomimetic miotics*** help trabecular drainage by constricting the pupil and pulling open the trabecular meshwork. However, this can cause blurred vision and browache, especially in younger patients, and the small pupil may cause problems if central vision is already limited. Parasympathomimetic miotics also reduce uveoscleral outflow and this can cause a paradoxical increase in intra-ocular pressure in patients with a recessed anterior angle. They should not be used in the presence of inflammation as adhesions may form between the pupil and the lens (posterior synechiae). Topical miotics were once the mainstay of glaucoma treatment but their ocular adverse effects and multiple dosing regimens have limited their use. Pilocarpine is the most frequently used miotic and is indicated in the treatment of open-angle glaucoma and other chronic glaucomas. It is often added to treatment with other drugs when further reductions in intra-ocular pressure are required. Carbachol is sometimes used when resistance or intolerance to pilocarpine develops. Physostigmine is more potent than pilocarpine but is poorly tolerated and is rarely used now; it was used with pilocarpine but rarely alone. Stronger or longer-acting anticholinesterase miotics such as ecothiopate can cause pupillary block and induce angle-closure glaucoma. They are usually only used in patients refractory to other antiglaucoma treatment or in those in whom the lens of the eye has been removed (aphakic patients). Pilocarpine is also used in the emergency treatment of angle-closure glaucoma before surgery or laser therapy.
- ***Carbonic anhydrase inhibitors*** such as acetazolamide reduce production of aqueous humour by a mechanism independent of their diuretic action. They are used as part of the emergency treatment of angle-closure glaucoma to produce a rapid reduction in intra-ocular pressure before surgery or laser therapy. Systemic doses may also be added to treatment in open-angle glaucoma and other chronic glaucomas in patients refractory to standard treatment but many patients are unable to tolerate prolonged therapy. Topical carbonic anhydrase inhibitors, such as dorzolamide or brinzolamide, have a lower potential to produce adverse effects. They are used similarly to other topical drugs either alone or as an adjunct in patients resistant to or intolerant of first-line drugs.
- Topical ***alpha$_2$-adrenoceptor agonists*** such as apraclonidine and brimonidine lower intra-ocular pressure by reducing production of aqueous humour. Apraclonidine is used alone or as an adjunct to other drugs in the control of intra-ocular pressure associated with ocular surgery or in the short-term to delay laser treatment or surgery for patients with glaucoma not adequately controlled with other drugs; tachyphylaxis and ocular irritation limit its long-term use. Brimonidine is used similarly. Clonidine has also been used in some countries.
- Other topical ***sympathomimetics*** such as dipivefrine increase outflow of aqueous humour through the trabecular meshwork and the uveoscleral route and may also reduce its rate of production. They are used in open-angle glaucoma and other chronic glaucomas usually when further reductions in intra-ocular pressure are required in patients receiving beta blockers (but may not produce an additive effect if used with a non-selective beta blocker).[23] As they produce pupillary dilatation they can induce an acute attack if used in angle-closure glaucoma. Adrenaline can cause eye irritation and produce systemic effects; it is now rarely used. Dipivefrine is converted into adrenaline by corneal esterases and ocular adverse effects are usually less than with adrenaline itself although, again, it is rarely used. Guanethidine, an adrenergic neurone blocker, reduces aqueous humour secretion and is used either alone or in combination to enhance and prolong the effect of adrenaline; prolonged use can cause fibrosis and corneal changes.
- ***Osmotic diuretics*** reduce vitreous volume and can produce a marked reduction in intra-ocular pressure. They are used in the short-term management of glaucoma when a rapid reduction in intra-ocular pressure is required before surgery. Mannitol and urea are both given intravenously and have a faster onset than glycerol or isosorbide given orally.
- Several ***other drugs*** are used topically in glaucoma and ocular hypertension. The alpha-adrenergic antagonist dapiprazole is used in some countries.

DIAGNOSIS OF GLAUCOMA.

Open-angle glaucoma is asymptomatic in its early stages and the use of screening methods for detecting early disease is of great importance.[24] Measurement of intra-ocular pressure alone is a poor diagnostic tool and direct examination of the optic nerve together with visual field examination and intra-ocular pressure tonometry is considered to be more reliable.[1,3-5] Provocative tests such as placing the patient prone in a dark room are sometimes used to identify eyes suffering from or at risk of *angle-closure glaucoma*. Short-acting mydriatics have also been used but are not without risk. Long-term follow-up of patients whose treatment had been determined by the use of a provocative test using phenylephrine with pilocarpine has suggested that this test is neither sensitive nor specific.[25]

TREATMENT OF GLAUCOMA.

Open-angle glaucoma or *ocular hypertension* are frequently treated first with a topical beta blocker or, increasingly, a prostaglandin analogue. It may be necessary to combine

these drugs or add others such as a topical alpha$_2$-adrenoceptor agonist or a topical carbonic anhydrase inhibitor to control intra-ocular pressure. Miotics are usually reserved for third-line use. It has been suggested that each type of drug should be tried alone first before resorting to combination therapy.

If further reduction of intra-ocular pressure is required a systemic carbonic anhydrase inhibitor may be used but long-term treatment is poorly tolerated. If this is unsuccessful, surgery (trabeculectomy) or laser treatment (trabeculoplasty) is usually indicated. Laser treatment appears to be as effective as topical drug therapy[26] although its effects may be short-lived.[27] It has been suggested that it might be of use in the initial treatment of older patients who cannot use eye drops or when surgery needs to be postponed or is contra-indicated.[3] Some also recommend that laser treatment is tried before a miotic or an oral carbonic anhydrase inhibitor, because of the potential adverse effects associated with these drugs.[3] Surgery with fluorouracil or mitomycin augmentation (see below) should be offered to those who are at risk of progressing to vision loss despite topical treatment or those with advanced disease.[15] Initial studies in the UK also suggested that early surgery was superior to drug or laser treatment in reducing intra-ocular pressure and preserving vision;[27] however, a later study[28] showed no difference in the progression of visual field loss in patients with newly-diagnosed glaucoma after the initial use of surgery or drug treatment. A systematic review has also found that in early mild open-angle glaucoma progression of the disease over 5 years was no different if first treatment was with medication or trabeculectomy but trabeculectomy was associated with more eye discomfort, an increased risk of cataract, and reduction in visual acuity.[29] The early use of surgery was often advocated in Europe, especially in younger patients, although it is now rarely used as the primary form of treatment.[6]

It is essential to start treatment for an *acute attack of angle-closure glaucoma* within 24 to 48 hours. If treatment is delayed adhesions may form between the iris and the cornea (peripheral anterior synechiae) and the trabecular meshwork may be damaged. *Chronic angle-closure glaucoma* may then develop with permanently raised intra-ocular pressure which ultimately leads to total loss of vision (absolute glaucoma). The initial treatment aims to produce a rapid reduction in intra-ocular pressure. A miotic such as pilocarpine is used topically to constrict the pupil while a carbonic anhydrase inhibitor such as acetazolamide is given orally or by intravenous injection. Osmotic diuretics such as mannitol or urea given intravenously or glycerol or isosorbide given orally may also be used. When intra-ocular pressure has been reduced sufficiently, laser therapy or surgery is performed on both eyes to increase drainage of aqueous humour. If further topical treatment is required after surgery, treatment is usually as for open-angle glaucoma. Beta blockers, with or without adrenaline, are preferred to pilocarpine as there is a risk of posterior synechiae forming when pilocarpine is used.

Glaucoma filtering surgery such as trabeculectomy can be highly effective in reducing intra-ocular pressure, but in some groups of patients, such as children, Afro-Caribbeans, or those who have had previous ocular surgery, there is a high failure rate, usually due to formation of scar tissue.[30] The scar formation is associated with proliferation of fibroblasts; subconjunctival injection of antiproliferative drugs such as fluorouracil has been shown to reduce the failure rate of surgery but at a cost of increased epithelial toxicity and conjunctival wound leaks.[30] A study group[31] reporting on the long-term follow-up of patients treated with fluorouracil recommended that fluorouracil should still be used in the surgical management of glaucoma in patients with a history of ocular surgery, but in view of the increased incidence of late-onset conjunctival wound leaks at the dosage they employed, suggested caution in its use in eyes with good prognoses. Single intraoperative doses of mitomycin have been applied topically as an alternative to the regimen of multiple injections required with fluorouracil. Rates of success comparable with those for fluorouracil have been achieved but there is a risk of adverse effects that could affect vision;[32] long-term safety of antiproliferative drugs remains to be determined.

Postoperative ocular hypertension may occur after surgery on the anterior chamber of the eye or procedures such as trabeculoplasty. Acetylcholine or carbachol instilled directly into the anterior chamber of the eye (intracameral instillation) are used intra-operatively to reduce early postoperative rises in intra-ocular pressure in procedures such as cataract extraction. The short action of acetylcholine can be an advantage as prolonged miosis is associated with severe postoperative pain. However, some consider carbachol to be the more effective drug;[33,34] standard antiglaucoma drugs including beta blockers, pilocarpine, apraclonidine, and carbonic anhydrase inhibitors have also been used for prophylaxis of postoperative ocular hypertension.

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Mydriasis and cycloplegia

Drugs that dilate the pupil (mydriatics) and paralyse accommodation (cycloplegics) are used topically in the examination of the eye and other ophthalmic procedures. They are also used in the management of inflammatory conditions of the eye to treat or prevent the formation of adhesions between the lens and the iris (see Uveitis, p. 1615.1) and in strabismus (below).

Mydriasis requires either paralysis of the pupillary constrictor muscles, which can be achieved with antimuscarinics, or stimulation of the dilator muscles, as produced by sympathomimetics. Cycloplegia results from paralysis of the ciliary muscles (antimuscarinics, but not sympathomimetics, have this effect).

Antimuscarinics used in ophthalmology vary in onset and duration of action. *Atropine* can take up to 40 minutes or more to produce mydriasis, which persists for at least 7 days; it takes 1 to 3 hours to produce cycloplegia and 6 to 12 days for recovery of accommodation. *Hyoscine* has a shorter duration of action than atropine, although the effects may still persist for 3 to 7 days. For ophthalmic procedures, antimuscarinics such as *homatropine*, *cyclopentolate*, or *tropicamide*, with a more rapid onset and shorter duration of action than atropine, may be preferable. Recovery occurs up to 6 hours after tropicamide, and up to 24 hours after cyclopentolate; after homatropine it may take up to 3 days. Cycloplegia with homatropine may be incomplete, and particularly for young children (who are often resistant to the action of homatropine) cyclopentolate or atropine may be preferred.

The most common topical sympathomimetic is *phenylephrine*, but *hydroxyamfetamine* is also used in some countries. They are often used with an antimuscarinic to enhance mydriasis, especially in patients who might respond poorly to antimuscarinics alone, such as those with dark irides or diabetes, or those who are receiving prolonged miotic therapy. *Adrenaline* has been used for maintenance of mydriasis during ophthalmic surgery.

The local anaesthetic *cocaine* also has an independent mydriatic effect but because of concern over corneal toxicity it is now little used in ophthalmology.

Miosis (pupil constriction) resistant to conventional mydriatics often develops during ocular surgery, possibly due to the release of prostaglandins and other substances associated with trauma. *NSAIDs* are prostaglandin synthetase inhibitors and have been tried before ocular surgery to prevent or reduce intra-operative miosis. They do not possess intrinsic mydriatic properties.

Reversal of mydriasis

Topical miotics (mydriolytics) are sometimes used to reverse the effects of mydriatics after surgery or ophthalmoscopic examination but do not appear to be in routine clinical use. *Pilocarpine* can counteract the mydriatic effect of topical sympathomimetics, such as phenylephrine and hydroxyamfetamine, but is ineffective against mydriasis produced by antimuscarinics, such as homatropine, and may impair vision further when used with tropicamide. Furthermore, there is also the risk that pilocarpine might precipitate angle-closure glaucoma in susceptible patents. *Dapiprazole* appears to be safer than pilocarpine when used to reverse sympathomimetic-induced mydriasis and is effective to some degree against tropicamide-induced mydriasis. It also appears to enhance recovery of accommodation after the use of cycloplegics.

The rate of reversal of mydriasis is generally slower in patients with dark irides than in those with lighter irides.

Strabismus

Strabismus, sometimes referred to as a squint or cast, is a lack of coordination of the visual axes of the eyes so that the eyes are usually either turned towards (convergent strabismus; esotropia) or away (divergent strabismus; exotropia) from each other. It can arise from a physical defect of the attachment of the extra-ocular muscles to the eye or from paralysis, spasms, or overactivity affecting the extra-ocular muscles of one of the eyes. In young children strabismus or other conditions that prevent a clear image being formed on the retina can result in visual impairment (amblyopia) in the affected eye if not treated.

Treatment for strabismus often consists of eye exercises, and methods to force preferential use of the affected eye by restricting vision through the healthy eye. This is accomplished either by using an eye patch or by penalisation with glasses or the cycloplegic drug *atropine*. However, as prolonged use of atropine eye drops may be required there is a risk of systemic toxicity. Surgery may sometimes be necessary. Extra-ocular injection of *botulinum A toxin* has been used to weaken an overactive extra-ocular eye muscle as an aid to eye realignment; repeated injections may be required. Long-acting parasympathomimetic miotics such as *demecarium*, *dyflos*, and *ecothiopate* have been used in the diagnosis and management of convergent strabismus due to excessive accommodation. Centrally-acting drugs such as *levodopa* and *citicoline* have also been investigated. With any form of treatment care has to be taken not to induce amblyopia in the healthy eye.

References.

1. Chatzistefanou KI, Mills MD. The role of drug treatment in children with strabismus and amblyopia. *Paediatr Drugs* 2000; 2: 91–100.
2. Donahue SP. Pediatric strabismus. *N Engl J Med* 2007; 356: 1040–7.

Aceclidine *(USAN, rINN)*

Aceclidina; Acéclidine; Aceclidinum; Ацеклидин.

1-Azabicyclo[2.2.2]octan-3-ol acetate; 3-Quinuclidinol acetate; 3-Acetoxyquinuclidine.

$C_9H_{15}NO_2$=169.2

CAS — 827-61-2.

ATC — S01EB08.

ATC Vet — QS01EB08.

UNII — 0578K3EUO.

Aceclidine Hydrochloride (rINNM)

Acéclidine, Chlorhydrate d'; Aceclidini Hydrochloridum; Hidrocloruro de aceclidina; Ацеклидина Гидрохлорид.

$C_9H_{15}NO_2.HCl$=205.7.

CAS — 6109-70-2.

ATC — S01EB08.

ATC Vet — QS01EB08.

UNII — 3B22O325Q6.

Profile

Aceclidine hydrochloride is a parasympathomimetic miotic (see Pilocarpine, p. 2010.2) that is a cholinergic agonist. It has been used in eye drops to lower intra-ocular pressure in patients with glaucoma.

Use. Aceclidine has been tried for the management of disturbances of night vision after laser refractive surgery.[1]

1. Randazzo A, *et al.* Pharmacological management of night vision disturbances after refractive surgery: results of a randomized clinical trial. *J Cataract Refract Surg* 2005; 31: 1764–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Glaucostat†; Glaunorm; *Ital.*: Glaunorm.

Multi-ingredient Preparations. *Ital.*: Glautimol.

Acetazolamide (BAN, rINN) ⊗

Acetazolam; Acetazolamid; Acetazolamida; Acetazolamidas; Acétazolamide; Acetazolamidum; Asetatsoliamidi; Asetazolamid; Ацетазоламид.

5-Acetamido-1,3,4-thiadiazole-2-sulphonamide; *N*-(5-Sulphamoyl-1,3,4-thiadiazol-2-yl)acetamide.

$C_4H_6N_4O_3S_2$=222.2.

CAS — 59-66-5.

ATC — S01EC01.

ATC Vet — QS01EC01.

UNII — O3FX965V0I.

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

Ph. Eur. 8: (Acetazolamide). A white or almost white, crystalline powder. It exhibits polymorphism. Very slightly soluble in water; slightly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides.

USP 36: (Acetazolamide). A white to faintly yellowish-white, odourless, crystalline powder. Very slightly soluble in water; sparingly soluble in practically boiling water; slightly soluble in alcohol. Store in airtight containers.

Acetazolamide Sodium (BANM, rINNM) ⊗

Acetazolamida sódica; Acétazolamide Sodique; Natrii Acetazolamidum; Sodium Acetazolamide; Натрий Ацетазоламид.

$C_4H_5N_4NaO_3S_2$=244.2.

CAS — 1424-27-7.

ATC — S01EC01.

ATC Vet — QS01EC01.

UNII — 429ZT169UH.

Stability. Solutions of acetazolamide sodium in glucose 5% and sodium chloride 0.9% were stable for 5 days at 25 degrees with a loss of potency of less than 7.2%.[1] At 5 degrees the loss of potency in both solutions was less than 6% after 44 days of storage. Small reductions in pH were recorded, possibly due to the formation of acetic acid during the decomposition of acetazolamide. At -10 degrees the loss in potency after 44 days of storage was less than 3% in both solutions. Results were similar in samples thawed in tap water and in a microwave oven.

An oral suspension of acetazolamide 25 mg/mL prepared from tablets with the aid of sorbitol solution 70% was stable for at least 79 days at 5 degrees, 22 degrees, and 30 degrees. It was recommended that the formulation be maintained at pH 4 to 5 and stored in amber glass bottles.[2]

1. Parasrampuria J, *et al.* Stability of acetazolamide sodium in 5% dextrose or 0.9% sodium chloride injection. *Am J Hosp Pharm* 1987; 44: 358–60.
2. Alexander KS, *et al.* Stability of acetazolamide in suspension compounded from tablets. *Am J Hosp Pharm* 1991; 48: 1241–4.

Uses and Administration

Acetazolamide is an inhibitor of carbonic anhydrase with weak diuretic activity and is used mainly in the management of glaucoma (below). Other indications include epilepsy (below) and high-altitude disorders (below).

By inhibiting carbonic anhydrase in the eye acetazolamide decreases the formation of aqueous humour and so decreases intra-ocular pressure. It is used in the preoperative management of angle-closure **glaucoma**, or as an adjunct in the treatment of open-angle glaucoma. In the treatment of glaucoma the usual oral dose is 250 mg to 1 g daily; divided doses should be used for amounts greater than 250 mg daily. Modified-release preparations are also available.

Acetazolamide is also used, either alone or with other antiepileptics, for the treatment of various forms of **epilepsy** in oral doses of 250 mg to 1 g daily in divided doses.

When oral dosing is impracticable, acetazolamide may be given parenterally as the sodium salt; acetazolamide sodium 275 mg is equivalent to about 250 mg of acetazolamide. It may be given by intramuscular injection but the intravenous route is preferred due to the alkalinity of the solution. Doses are similar to those given orally.

Acetazolamide is also used to prevent or ameliorate the symptoms of **high-altitude disorders**. Prompt descent will still be necessary if severe symptoms such as cerebral oedema or pulmonary oedema occur. The usual oral dose is 500 mg to 1 g daily in divided doses, preferably starting 24 to 48 hours before ascent and continuing for at least 48 hours while at high altitude as necessary to control symptoms. It may also be given as a modified-release preparation.

For details of doses in children, see below.

Acetazolamide also increases the excretion of bicarbonate and of cations, chiefly sodium and potassium, by inhibiting the reaction catalysed by carbonic anhydrase in the renal tubules, and so promotes an alkaline diuresis. When given orally as an immediate-release preparation, its effect begins within 60 to 90 minutes and lasts for 8 to 12 hours. However, continuous use is associated with metabolic acidosis and an accompanying loss of diuretic activity. Therefore, although acetazolamide has been used as a diuretic, it has largely been superseded by drugs such as the thiazides or furosemide. For **diuresis** the usual oral dose is 250 to 375 mg and is given either once daily or on alternate days; intermittent therapy is required for a continued effect. Similar doses have also been given parenterally.

Administration in children. Acetazolamide is used, either alone or with other antiepileptics, for the treatment of various forms of **epilepsy** in children. UK licensed product information recommends giving 8 to 30 mg/kg (maximum of 750 mg) orally daily in divided doses. Alternatively, the *BNFC* suggests an initial dose of 2.5 mg/kg 2 or 3 times daily in neonates and children up to 12 years of age; this may then be increased to a maintenance dose of 5 to 7 mg/kg 2 or 3 times daily (maximum of 750 mg daily). Older children may be given the usual adult dose (see above).

Although unlicensed, the *BNFC* suggests that acetazolamide may be used in the management of open-angle and secondary **glaucoma**, or perioperatively in angle-closure glaucoma. Those aged 1 month to 12 years may be given oral doses of 5 mg/kg 2 to 4 times daily, adjusted according to response to a maximum of 750 mg daily; older children may be given the usual adult dose (see above).

The *BNFC* also suggests that acetazolamide may be used to reduce **raised intracranial pressure** in children aged 1 month to 12 years; an initial dose of 8 mg/kg may be given 3 times daily, increased as necessary to a maximum of 100 mg/kg daily.

When oral dosing is impractical, the aforementioned doses may be given by slow intravenous injection.

Administration in the elderly. For the suggestion that reduced doses may be required in elderly patients see under Precautions, p. 2002.3.

Epilepsy. Acetazolamide may be used in the treatment of epilepsy (p. 506.1) as an alternative or adjunct to first-line drugs for refractory partial seizures with or without secondary generalisation. It is also effective in some other refractory forms of epilepsy including atypical absence, tonic, atonic, myoclonic, and menstruation-related seizures (catamenial epilepsy).[1-5] It is believed to act by inhibition of carbonic anhydrase in glial cells in the CNS.[6] The major drawback to the chronic use of acetazolamide is the rapid development of tolerance,[6] but this may be delayed or prevented by using it as an adjunct to other antiepileptics. Acetazolamide has been successfully used in management of seizures in children from 1 year of age.[5]

1. Resor SR, Resor LD. Chronic acetazolamide monotherapy in the treatment of juvenile myoclonic epilepsy. *Neurology* 1990; 40: 1677–81.
2. Reiss WG, Oles KS. Acetazolamide in the treatment of seizures. *Ann Pharmacother* 1996; 30: 514–19.
3. Hoddevik GH. Acetazolamid—verdt en renessanse i epilepsibehandlingen? *Tidsskr Nor Laegeforen* 2000; 120: 1042–5.
4. Lim LL, *et al.* Acetazolamide in women with catamenial epilepsy. *Epilepsia* 2001; 42: 746–9.
5. Katayama F, *et al.* Long-term effectiveness and side effects of acetazolamide as an adjunct to other anticonvulsants in the treatment of refractory epilepsies. *Brain Dev* 2002; 24: 150–4.
6. Rogawski MA, Porter RJ. Antiepileptic drugs: pharmacological mechanisms and clinical efficacy with consideration of promising developmental stage compounds. *Pharmacol Rev* 1990; 42: 223–86.

Glaucoma. Acetazolamide may be given orally or parenterally in the acute management of angle-closure glaucoma (p. 1999.1) and to minimise rises in intra-ocular pressure associated with ocular surgery.[1,2] It may also be given orally in the long-term management of primary and secondary open-angle glaucoma but is usually used as a second-line drug and added to topical beta blockers. However, up to 50% of patients are unable to tolerate oral therapy because of adverse effects[3] although topical carbonic anhydrase inhibitors such as dorzolamide may be better tolerated. Attempts have been made to reduce the adverse effects of acetazolamide by modifying the dosage schedule. A single-dose study[4] showed that doses of acetazolamide greater than 63 mg produced no greater reductions in intra-ocular pressure in patients with ocular hypertension. Another study[5] reported that acetazolamide 250-mg tablets twice daily controlled intra-ocular pressure adequately while producing fewer adverse effects than 250 mg four times daily and it was suggested that there was no advantage in using the modified-release capsule formulation (500 mg twice daily). A study in patients with open-angle glaucoma[6] found that most patients were adequately controlled by a single night-time dose of acetazolamide 500 mg either as tablets or modified-release capsules. The night-time dose also reduced the severity of adverse effects compared with the same dose given in the morning, and could aid compliance.

1. Ladas ID, *et al.* Prophylactic use of acetazolamide to prevent intraocular pressure elevation following Nd-YAG laser posterior capsulotomy. *Br J Ophthalmol* 1993; 77: 136–8.
2. Edmunds B, Canning CR. The effect of prophylactic acetazolamide in patients undergoing extensive retinal detachment repair. *Eye* 1996; 10: 328–30.
3. Hurvitz LM, *et al.* New developments in the drug treatment of glaucoma. *Drugs* 1991; 41: 514–32.
4. Friedland BR, *et al.* Short-term dose response characteristics of acetazolamide in man. *Arch Ophthalmol* 1977; 95: 1809–12.
5. Ledger-Scott M, Hurst J. Comparison of the bioavailability of two acetazolamide formulations. *Pharm J* 1985; 235: 451.
6. Joyce PW, Mills KB. Comparison of the effect of acetazolamide tablets and sustets on diurnal intraocular pressure in patients with chronic simple glaucoma. *Br J Ophthalmol* 1990; 74: 413–16.

High-altitude disorders. Acetazolamide is the most frequently used drug for the prophylaxis of high-altitude disorders (p. 1276.2). It accelerates the process of acclimatisation, thus reducing the incidence of acute mountain sickness and associated symptoms such as headache, nausea, vomiting, and lethargy. The optimum dose is not clear. A systematic review[1] concluded that 750 mg daily effectively prevented acute mountain sickness, but that a dose of 500 mg daily was not effective. However, these conclusions have been criticised, and a subsequent controlled study[2] found that a dose of 125 mg twice daily reduced the incidence of acute mountain sickness by about 50%. Acetazolamide may also have some benefit in relieving symptoms once they have developed although experience is limited. It does not prevent or protect against pulmonary or cerebral oedema.

1. Dumont L, *et al.* Efficacy and harm of pharmacological prevention of acute mountain sickness: quantitative systematic review. *BMJ* 2000; 321: 267–72.
2. Basnyat B, *et al.* Efficacy of low-dose acetazolamide (125 mg BID) for the prophylaxis of acute mountain sickness: a prospective, double-blind, randomized, placebo-controlled trial. *High Alt Med Biol* 2003; 4: 45–52.

Macular oedema. For mention of the use of acetazolamide to treat macular oedema associated with uveitis, see Uveitis, p. 1615.1.

Ménière's disease. In Ménière's disease (p. 611.2) high concentrations of carbonic anhydrase are found in the labyrinth, and acetazolamide, a carbonic anhydrase inhibitor, has been tried for both diagnosis and treatment.[1] A dose of 500 mg by intravenous injection has been suggested for diagnosis of fluctuating Ménière's disease.[1] Oral treatment with the drug, however, has not been particularly effective and has been associated with a high incidence of adverse effects.[2]

1. Brookes GB. Ménière's disease: a practical approach to management. *Drugs* 1983; 25: 77–89.
2. Brookes GB, Booth JB. Oral acetazolamide in Ménière's disease. *J Laryngol Otol* 1984; 98: 1087–95.

Neuromuscular disorders. Acetazolamide may be of benefit in some neuromuscular disorders, including hypokalaemic periodic paralysis (p. 1777.3). Doses of 375 to 500 mg daily were effective in 2 patients with severe paralysis and were well tolerated.[1] Preliminary observations in 5 other patients showed a striking improvement in 3. In a further 12 patients,[2] doses of 125 mg were given three times daily to children and 250 mg two to six times daily to adults. There was dramatic improvement in 10 of the 12 and this lasted for up to 43 months. Chronic weakness between attacks in 10 patients was improved in 8.

Acetazolamide may reduce the frequency of attacks in patients with hyperkalaemic periodic paralysis (p. 1777.2). It has also been used in episodic ataxia.[3]

1. Resnick JS, *et al.* Acetazolamide prophylaxis in hypokalemic periodic paralysis. *N Engl J Med* 1968; 278: 582–6.

2. Griggs RC, *et al.* Acetazolamide treatment of hypokalemic periodic paralysis: prevention of attacks and improvement of persistent weakness. *Ann Intern Med* 1970; 73: 39–48.
3. Melberg A, *et al.* Loss of control after a cup of coffee. *Lancet* 1997; 350: 1220.

Raised intracranial pressure. Acetazolamide has been used to reduce raised intracranial pressure (p. 1271.3). It has a role in the management of idiopathic intracranial hypertension. It has also been tried in the treatment of immunocompromised patients with chronically raised intracranial pressure due to cryptococcal meningitis,[1] although a controlled study[2] was terminated early due to serious adverse events possibly due to additive toxicity with amphotericin. However, acetazolamide was used successfully for long-term treatment in 2 immunocompetent patients[3] with raised intracranial pressure following fungal meningitis.

1. Johnston SRD, *et al.* Raised intracranial pressure and visual complications in AIDS patients with cryptococcal meningitis. *J Infect* 1992; 24: 185–9.
2. Newton PN, *et al.* A randomized, double-blind, placebo-controlled trial of acetazolamide for the treatment of elevated intracranial pressure in cryptococcal meningitis. *Clin Infect Dis* 2002; 35: 769–72.
3. Patel S, *et al.* Acetazolamide therapy and intracranial pressure. *Clin Infect Dis* 2002; 36: 538.

Adverse Effects

Common adverse effects of acetazolamide are malaise, fatigue, depression, excitement, headache, weight loss, and gastrointestinal disturbances. Drowsiness and paraesthesia involving numbness and tingling of the face and extremities are also common with high doses in particular. Diuresis can be troublesome, but generally abates after a few days of continuous therapy. Acidosis may develop during treatment and is generally mild but severe metabolic acidosis has occasionally been reported, especially in elderly or diabetic patients or those with renal impairment. Electrolyte imbalances including hyponatraemia and hypokalaemia may occasionally occur; hypokalaemia is generally transient and rarely clinically significant.

Blood dyscrasias occur rarely and may include aplastic anaemia, agranulocytosis, leucopenia, thrombocytopenia, and thrombocytopenic purpura. Acetazolamide can give rise to crystalluria, renal calculi, and renal colic; renal lesions, possibly due to a hypersensitivity reaction, have also been reported.

Other adverse reactions include allergic skin reactions, fever, thirst, dizziness, ataxia, irritability, confusion, reduced libido, haematuria, glycosuria, renal failure, abnormal liver function tests, loss of appetite, alterations in taste, transient myopia, and tinnitus and hearing disturbances. Rare reactions include photosensitivity, hepatitis or cholestatic jaundice, flaccid paralysis, and convulsions.

Intramuscular injections are painful owing to the alkalinity of the solution.

Effects on the blood. Severe, often fatal, blood dyscrasias have been reported in patients taking acetazolamide. By 1989, the National Registry of Drug-Induced Ocular Side Effects in the USA[1] had received reports of haematological reactions possibly due to carbonic anhydrase inhibitors in 139 patients, of which 50 cases (36%) were fatal. Most deaths were due to aplastic anaemia. Over half the reactions occurred during the first 6 months of therapy. The value of periodic blood analysis in patients taking carbonic anhydrase inhibitors for prolonged periods has been debated[2-7] but is advised by licensed product information. The US National Registry has recommended[8] that initial and 6-monthly blood analysis should be undertaken.

1. Praunfelder FT, Bagby GC. Possible hematologic reactions associated with carbonic anhydrase inhibitors. *JAMA* 1989; 261: 2257.
2. Alm A, *et al.* Monitoring acetazolamide treatment. *Acta Ophthalmol (Copenh)* 1982; 60: 24–34.
3. Miller RD. Hematologic reactions to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1985; 100: 745–6.
4. Johnson T, Kass MA. Hematologic reactions to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1986; 101: 128–9.
5. Zimran A, Beutler E. Can the risk of acetazolamide-induced aplastic anemia be decreased by periodic monitoring of blood cell counts? *Am J Ophthalmol* 1987; 104: 654–8.
6. Lichter PR. Carbonic anhydrase inhibitors, blood dyscrasias, and standard-of-care. *Ophthalmology* 1988; 95: 711–12.
7. Mogk LG, Cyrlin MN. Blood dyscrasias and carbonic anhydrase inhibitors. *Ophthalmology* 1988; 95: 768–71.
8. Praunfelder FT, *et al.* Hematologic reactions to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1985; 100: 79–81.

Effects on electrolyte balance. Acetazolamide has been reported to cause symptomatic metabolic acidosis in the elderly, in diabetic patients, and in those with renal impairment.[1-4] Raised plasma-acetazolamide concentrations have been reported in elderly patients, probably attributable to reduced renal function, and in 6 of 9 glaucoma patients this was associated with hyperchloraemic metabolic acidosis.[7] A single-dose study[8] in 4 elderly patients found that reduced acetazolamide clearance correlated with renal function. Urea and electrolyte concentrations should be measured before and during treatment with acetazolamide, particularly in the elderly and in other patients, such as diabetics, who may have renal impairment.

1. Maisey DN, Brown RD. Acetazolamide and symptomatic metabolic acidosis in mild renal failure. *BMJ* 1981; 283: 1527–8.
2. Goodfield M, *et al.* Acetazolamide and symptomatic metabolic acidosis in mild renal failure. *BMJ* 1982; 284: 422.
3. Reid W, Harrower ADB. Acetazolamide and symptomatic metabolic acidosis in mild renal failure. *BMJ* 1982; 284: 1114.
4. Heller I, *et al.* Significant metabolic acidosis induced by acetazolamide: not a rare complication. *Arch Intern Med* 1985; 145: 1815–17.
5. Parker WA, Atkinson B. Acetazolamide therapy and acid-base disturbance. *Can J Hosp Pharm* 1987; 40: 31–4.
6. Zaidi FH, Kinnear PE. Acetazolamide, alternate carbonic anhydrase inhibitors and hypoglycaemic agents: comparing enzymatic with diuresis induced metabolic acidosis following intraocular surgery in diabetes. *Br J Ophthalmol* 2004; 88: 714–15.
7. Chapron DJ, *et al.* Acetazolamide blood concentrations are excessive in the elderly: propensity for acidosis and relationship to renal function. *J Clin Pharmacol* 1989; 29: 348–53.
8. Chapron DJ, *et al.* Influence of advanced age on the disposition of acetazolamide. *Br J Clin Pharmacol* 1985; 19: 363–71.

Effects on endocrine function. Hirsutism occurred in a 2½-year-old girl after treatment for 16 months with acetazolamide for congenital glaucoma.[1] There was no evidence of virilisation.

1. Weiss IS. Hirsutism after chronic administration of acetazolamide. *Am J Ophthalmol* 1974; 78: 327–8.

Effects on the kidneys. Large reductions in glomerular filtration rate occurred during treatment with carbonic anhydrase inhibitors in 3 type 1 diabetics with nephropathy and glaucoma.[1] Kidney function improved when the drug was withdrawn.

1. Skøtt P, *et al.* Effect of carbonic anhydrase inhibitors on glomerular filtration rate in diabetic nephropathy. *BMJ* 1987; 294: 549.

Effects on the liver. For a report of liver damage associated with use of acetazolamide, see Hypersensitivity, below.

Effects on the skin. Rashes, including severe skin reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported during acetazolamide therapy; the fact that acetazolamide is a sulfonamide-derivative has been suggested as a cause for these reactions. Photosensitivity has also been noted rarely.

Severe exacerbation of rosacea occurred in a patient taking acetazolamide for glaucoma; the rosacea improved on withdrawal of acetazolamide and relapsed again on its reintroduction.[1]

1. Shah P, *et al.* Severe exacerbation of rosacea by oral acetazolamide. *Br J Dermatol* 1993; 129: 647–8.

Extravasation. Extravasation was reported in a patient after intravenous acetazolamide and led to severe ulceration requiring surgery to repair the skin defect.[1] It was recommended that 1 to 2 mL of sodium citrate 3.8% should be injected subcutaneously near the site of extravasation in order to neutralise the alkaline effects of the acetazolamide injection.

1. Callear A, Kirkby G. Extravasation of acetazolamide. *Br J Ophthalmol* 1994; 78: 731.

Hypersensitivity. A 54-year-old man with glaucoma who was treated with acetazolamide 500 mg daily for 26 days developed a generalised erythematous rash and became delirious, dehydrated, markedly jaundiced, with peripheral circulatory failure, and died from cholestatic jaundice with hepatic coma and anuria.[1] Drug-induced hypersensitivity and hepatitis due to acetazolamide was suspected.

Anaphylaxis has also been reported[2] after a single oral dose in a patient who had not previously received acetazolamide. However, the patient was hypersensitive to sulfonamides and the reaction may have been caused by cross-sensitivity (see also Precautions, below).

1. Kristinsson A. Fatal reaction to acetazolamide. *Br J Ophthalmol* 1967; 51: 348–9.
2. Tzanakis N, *et al.* Anaphylactic shock after a single oral intake of acetazolamide. *Br J Ophthalmol* 1998; 82: 588.

Precautions

Acetazolamide is contra-indicated in the presence of sodium or potassium depletion, in hyperchloraemic acidosis, in conditions such as Addison's disease and adrenocortical insufficiency, and in marked hepatic or renal impairment. Encephalopathy may be precipitated in patients with hepatic dysfunction. It should not be used in chronic angle-closure glaucoma since it may mask deterioration of the condition. Since acetazolamide is a sulfonamide derivative, it should not be used in patients with a history of sulfonamide hypersensitivity, but see also further information on cross-reactivity between sulfonamides under Sulfamethoxazole, p. 365.3.

Acetazolamide should be given with care to patients likely to develop acidosis or with diabetes mellitus; severe metabolic acidosis may occur in the elderly, and in patients with renal impairment, pulmonary obstruction, or emphysema. Acetazolamide may increase the risk of hyperglycaemia in diabetic patients.

Periodic monitoring of plasma electrolytes and blood count is recommended during long-term therapy and patients should be cautioned to report any unusual rashes. Acetazolamide is teratogenic in *animals*.

Some adverse effects such as drowsiness and myopia may affect a patient's ability to perform skilled tasks including driving.

Breast feeding. Acetazolamide has been detected in breast milk.[1] However, there have been no reports of adverse effects in breast-fed infants whose mothers were receiving acetazolamide and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Söderman P, *et al.* Acetazolamide excretion into human breast milk. *Br J Clin Pharmacol* 1984; 17: 599–600.
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 17/03/06)

Diabetes mellitus. For a brief discussion of metabolic acidosis in patients with diabetes, see Effects on Electrolyte Balance, above.

For a report of deterioration in renal function in patients with diabetic nephropathy who were given carbonic anhydrase inhibitors, see Effects on the Kidneys, above.

The elderly. A retrospective review[1] of 222 patients with glaucoma reported that those aged 40 years or less tolerated treatment with carbonic anhydrase inhibitors much better than older patients. A single-dose study[2] of acetazolamide in 4 elderly subjects found that the capacity to clear acetazolamide from plasma correlated with creatinine clearance and was thus reduced in the elderly. They also had reduced plasma protein binding and the combination of these factors predisposed the elderly to enhanced accumulation of acetazolamide in erythrocytes.

Plasma-acetazolamide concentrations exceeded the **therapeutic range** (5 to 10 micrograms/mL) in 9 of 12 elderly patients receiving acetazolamide for glaucoma or metabolic alkalosis.[3] Hyperchloraemic metabolic acidosis was detected in 6 of 9 glaucoma patients. The excessive plasma concentrations were attributed to age-related reductions in renal function. It was suggested that elderly patients may require reduced doses of acetazolamide.

For reports of symptomatic metabolic acidosis associated with use of acetazolamide in the elderly, see Effects on Electrolyte Balance, above.

1. Shrader CE, *et al.* Relationship of patient age and tolerance to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1983; 96: 730–3.
2. Chapron DJ, *et al.* Influence of advanced age on the disposition of acetazolamide. *Br J Clin Pharmacol* 1985; 19: 363–71.
3. Chapron DJ, *et al.* Acetazolamide blood concentrations are excessive in the elderly: propensity for acidosis and relationship to renal function. *J Clin Pharmacol* 1989; 29: 348–53.

Interference with laboratory estimations. Acetazolamide interfered with an HPLC method of assay for theophylline[1] resulting in an unnecessary dose reduction and worsening apnoea in an infant. Other workers[2] pointed out that the interference depended on the solvent used in the extraction, and presented evidence to suggest that acetazolamide may not interfere with other assay methods for theophylline.

1. Mecrow IK, Goldie BP. Acetazolamide interferes with theophylline assay. *Lancet* 1987; i: 558.
2. Kelsey HC, *et al.* Interference by acetazolamide in theophylline assay depends on the method. *Lancet* 1987; ii: 403.

Renal impairment. For a brief discussion of metabolic acidosis in patients with renal impairment, see Effects on Electrolyte Balance, above.

Interactions

By rendering the urine alkaline acetazolamide reduces the urinary excretion, and so may enhance the effects, of drugs such as amfetamines, ephedrine, and quinidine; conversely, urinary alkalinisation can reduce the effects of methenamine and its compounds. Acetazolamide may enhance antiepileptic-induced osteomalacia. Use of acetazolamide with aspirin may result in severe acidosis and increase CNS toxicity. Acetazolamide may affect fluid and electrolyte balance leading to interactions similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1406.1). Unlike thiazides, however, acetazolamide may increase the excretion of lithium.

Antacids. *Sodium bicarbonate* therapy enhances the risk of renal calculus formation in patients taking acetazolamide.[1]

1. Rubenstein MA, Bucy JG. Acetazolamide-induced renal calculi. *J Urol (Baltimore)* 1975; 114: 610–12.

Antiepileptics. For severe osteomalacia in patients taking acetazolamide with *phenytoin* and other antiepileptics, see

Diuretics, p. 544.3. Acetazolamide may increase serum concentrations of *carbamazepine*, see Diuretics, p. 517.3.

Antineoplastics. Alkalinisation of the urine by acetazolamide increases the solubility of *methotrexate* in the urine and also increases its excretion. This effect has been exploited therapeutically to reduce the nephrotoxicity of methotrexate (see Effects on the Kidneys, p. 825.2).

Benzodiazepines. Ventilatory depression in a mountain climber with acute mountain sickness was considered to be due to the potentiation of *triazolam* by acetazolamide.[1]

1. Masuyama S, *et al.* Ondine's Curse': side effect of acetazolamide? *Am J Med* 1989; 86: 637.

Local anaesthetics. For the effect of acetazolamide on *procaine*, see p. 1995.1.

Salicylates. Salicylates displace acetazolamide from plasma protein binding sites and reduce its renal clearance,[1] leading to elevated plasma-acetazolamide concentrations. In addition acidosis produced by acetazolamide may increase salicylate toxicity by enhancing salicylate tissue penetration.[2] Severe metabolic acidosis has been reported[3] in patients with normal renal function given acetazolamide with salicylates.

Use of salicylates with acetazolamide should be avoided if possible, particularly if renal dysfunction is present. If the combination is used, patients should be carefully monitored for symptoms of CNS toxicity such as lethargy, confusion, somnolence, tinnitus, and anorexia.

1. Sweeney KR, *et al.* Toxic interaction between acetazolamide and salicylate: case report and a pharmacokinetic explanation. *Clin Pharmacol Ther* 1986; 40: 518–24.
2. Anderson CJ, *et al.* Toxicity of combined therapy with carbonic anhydrase inhibitors and aspirin. *Am J Ophthalmol* 1978; 86: 516–19.
3. Cowan RA, *et al.* Metabolic acidosis induced by carbonic anhydrase inhibitors and salicylates in patients with normal renal function. *BMJ* 1984; 289: 347–8.

Pharmacokinetics

Acetazolamide is fairly rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur about 2 hours after oral doses. It has been estimated to have a plasma half-life of about 3 to 6 hours. It is tightly bound to carbonic anhydrase and high concentrations are present in tissues containing this enzyme, particularly red blood cells and the renal cortex; it is highly bound to plasma proteins. It is excreted unchanged in the urine and has been detected in breast milk.

References.

1. Lehmann B, *et al.* The pharmacokinetics of acetazolamide in relation to its use in the treatment of glaucoma and to its effects as an inhibitor of carbonic anhydrases. *Adv Biosci* 1969; 5: 197–217.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Diamox; Hydroftal; Matro; *Austral.*: Diamox; *Austria*: Diamox; *Belg.*: Diamox; *Braz.*: Diamox; Zolamox; *Canad.*: Diamox†; *Cz.*: Diluran; *Denm.*: Diamox; *Fin.*: Diamox†; Odemin; *Fr.*: Defiltran; Diamox; *Ger.*: Acemit; Diamox; Glaupax; *Gr.*: Diamox; Edemox; *Hong Kong*: Diamox†; *Hung.*: Huma-Zolamide; *India*: Acetamide; Acetamin; Acetariv; Avva; Diamox; Iopar; *Indon.*: Diamox†; Glauseta; *Irl.*: Diamox; *Israel*: Uramox; *Ital.*: Diamox; *Mex.*: Aceta-Diazol†; Akezol; *Neth.*: Diamox; *Norw.*: Diamox; *NZ*: Diamox; Glaumox; *Philipp.*: Cetamid; Diamox†; Optamide; Zolmide; *Pol.*: Diuramid; *Port.*: Carbinib; *Rus.*: Diacarb (Диакарб); *S.Afr.*: Azomid; Diamox; *Singapore*: Diamox; *Spain*: Edemox; *Swed.*: Diamox; *Switz.*: Diamox; Glaupax; *Thai.*: Diamox; Medene; *Turk.*: Diazomid; *UK*: Diamox; *Ukr.*: Diacarb (Диакарб); Diuremid (Диуремид); *USA*: Diamox.

Pharmacopoeial Preparations

BP 2014: Acetazolamide Oral Suspension; Acetazolamide Tablets;
USP 36: Acetazolamide for Injection; Acetazolamide Tablets.

Acetylcholine Chloride *(BAN, rINN)*

Acetilcolino chloridas; Acetilcolina, cloruro de; Acetilkolinklorid; Acetylcholin chlorid; Acetylcholinchlorid; Acétylcholine, chlorure d'; Acetylcholini Chloridum; Acetylkolinklorid; Acetylocholiny chlorek; Asetilkolin Klorür; Asetyylikoliinikloridi; Cloruro de acetilcolina; Ацетилхолина Хлорид.

(2-Acetoxyethyl)trimethylammonium chloride.

$C_7H_{16}ClNO_2$=181.7.

CAS — 51-84-3 (acetylcholine); 60-31-1 (acetylcholine chloride).

ATC — S01EB09.

ATC Vet — QS01EB09.

UNII — AF73293C2R.

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

Jpn includes Acetylcholine Chloride for Injection.

Ph. Eur. 8: (Acetylcholine Chloride). A very hygroscopic, white or almost white crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol; slightly soluble in dichloromethane. Protect from light.

USP 36: (Acetylcholine Chloride). White or off-white crystals or crystalline powder. Very soluble in water; freely soluble in alcohol; insoluble in ether. It is decomposed by hot water and by alkalis. Store in airtight containers.

Uses and Administration

Acetylcholine is an endogenous chemical transmitter with a very wide range of actions in the body (see below). It is used as a miotic to reduce postoperative rises in intra-ocular pressure associated with cataract surgery, penetrating keratoplasty, iridectomy, and other anterior segment surgery (see p. 1999.1) but is ineffective when applied topically as it is hydrolysed more rapidly than it can penetrate the cornea. Doses of 0.5 to 2 mL of a freshly prepared 1% solution of acetylcholine chloride are therefore instilled directly into the anterior chamber of the eye (intracameral instillation). Miosis occurs within seconds and lasts for about 20 minutes. A second application may be made if prolonged miosis is required.

Action. Acetylcholine is a powerful quaternary ammonium parasympathomimetic but its action is transient as it is rapidly destroyed by cholinesterase. It is released from postganglionic parasympathetic nerves and also from some postganglionic sympathetic nerves to produce peripheral actions which correspond to those of muscarine. It is accordingly a vasodilator and cardiac depressant, a stimulant of the vagus and the parasympathetic nervous system, and it has a tonic action on smooth muscle. It also increases lachrymal, salivary, and other secretions. All the muscarinic actions of acetylcholine are abolished by atropine.

Acetylcholine also has actions that correspond to those of nicotine and is accordingly a stimulant of skeletal muscle, the autonomic ganglia, and the adrenal medulla. The nicotinic actions of acetylcholine on skeletal muscle are blocked by competitive neuromuscular blockers; they are also inhibited by massive doses or discharge of acetylcholine itself, which has clinical application in relation to the mode of action of suxamethonium (p. 2037.2).

Drugs that mimic or enhance the actions of acetylcholine in the body are known as **parasympathomimetics** and may be classified into 2 distinct pharmacological groups:

- **cholinergic agonists**, such as bethanechol, carbachol, methacholine, and pilocarpine which act directly on effector cells to mimic the effects of acetylcholine. They are sometimes referred to as cholinomimetics or true parasympathomimetics; some such as bethanechol, carbachol, and methacholine are choline esters
- **anticholinesterases** (cholinesterase inhibitors) which inhibit the enzymic hydrolysis of acetylcholine by acetylcholinesterase and other cholinesterases, thereby prolonging and enhancing its actions in the body. They may be classified by the length of time taken to restore active enzyme following binding of enzyme to drug. The 'reversible' anticholinesterases such as ambenonium, neostigmine, physostigmine, and pyridostigmine generally produce enzyme inhibition for a few hours, whereas 'irreversible' anticholinesterases such as dyflos and ecothiopate produce extremely prolonged inhibition, and return of cholinesterase activity depends on synthesis of new enzyme. Centrally acting reversible anticholinesterases include donepezil, galantamine, rivastigmine, and tacrine

Drugs such as fampridine and guanidine, which enhance the release of acetylcholine from nerve terminals, also have similar effects.

Diagnosis and testing. *AUTONOMIC FAILURE.* Acetylcholine has been used in a sweat-spot test for autonomic neuropathy in diabetic patients.[1] An area on the dorsum of the foot is painted with iodine and starch, followed by intradermal injection of acetylcholine into the centre of the area. Sweat produced in response to acetylcholine reacts with the iodine and starch to produce fine black dots corresponding to the pores of the sweat glands; a normal response is indicated by a uniform distribution of dark spots whereas in diabetic autonomic neuropathy this pattern is lost to a varying degree. A similar test has been carried out[2] to assess sympathetic nerve function and therefore predict the success of lumbar sympathectomy in patients with critical limb ischaemia.

1. Ryder REJ, *et al.* Acetylcholine sweatspot test for autonomic denervation. *Lancet* 1988; i: 1303–5.
2. Altomare DF. Acetylcholine sweat test: an effective way to select patients for lumbar sympathectomy. *Lancet* 1994; 344: 976–8.

Adverse Effects

Because it is rapidly hydrolysed in the body by cholinesterases the toxicity of acetylcholine is normally relatively low.

Systemic adverse effects of the choline esters include nausea and vomiting, abdominal pain, flushing, sweating, salivation, lachrymation, rhinorrhoea, eructation, diarrhoea, urinary frequency, headache, bradycardia, peripheral vasodilatation leading to hypotension, and bronchoconstriction.

Ocular adverse effects after local application of choline esters to the eye include corneal oedema, clouding, and decompensation, persistent bullous keratopathy, retinal detachment, and postoperative iritis.

Treatment of Adverse Effects

Atropine sulfate may be given intravenously, intramuscularly, or subcutaneously to control the muscarinic and most nicotinic effects of the choline esters. Supportive treatment may be required.

Precautions

Choline esters are generally contra-indicated for *systemic use* in intestinal or urinary obstruction or where increased muscular activity of the urinary or gastrointestinal tract is liable to be harmful. They are also contra-indicated in asthma and obstructive airways disease, in cardiovascular disorders including bradycardia or heart block and recent myocardial infarction, and in hypotension, vagotonia, epilepsy, parkinsonism, hyperthyroidism, peptic ulceration, and pregnancy. Choline esters should not be given by the intravenous or intramuscular routes as very severe muscarinic adverse effects are liable to occur, calling for emergency treatment with atropine.

Although acetylcholine is normally rapidly hydrolysed in the body, systemic effects have followed *topical application* of choline esters to the eye, albeit rarely, and caution is advisable in the above conditions.

Interactions

As for Neostigmine, p. 688.3. Acetylcholine is hydrolysed in the body by cholinesterase and its effects are markedly prolonged and enhanced if given after anticholinesterases.

Beta blockers. Severe bronchospasm with subsequent pulmonary oedema was reported[1] after intra-ocular injection of acetylcholine chloride in a patient also receiving oral *metoprolol*.

1. Rasch D, *et al.* Bronchospasm following intraocular injection of acetylcholine in a patient taking metoprolol. *Anesthesiology* 1983; 59: 583–5.

NSAIDs. According to licensed product information for acetylcholine chloride ophthalmic preparations, there have been reports that acetylcholine and carbachol were ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Miochol; *Belg.*: Miochole; *Canad.*: Miochol-E; Miogan†; *Fin.*: Miochol-E; *Fr.*: Miochole; *Ger.*: Miochol-E; *Gr.*: Miochol-E; *Hong Kong*: Miochol-E; *Indon.*: Miochol-E; *Irl.*: Miochol-E; *Israel*: Miochol; *Ital.*: Miochol-E†; Miovisin; *Mex.*: Iloc; *Neth.*: Miochol; *NZ*: Miochol; *Port.*: Miochol; *S.Afr.*: Covochol; Miochol; *Swed.*: Miochol-E; *Switz.*: Miochol; *Turk.*: Miochol-E; *UK*: Miochol; Miphtel; *USA*: Miochol.

Pharmacopoeial Preparations

USP 36: Acetylcholine Chloride for Ophthalmic Solution.

Apraclonidine Hydrochloride

(BANM, USAN, rINNM)

AL-02145 (apraclonidine); *p*-Aminoclonidine Hydrochloride; Aplonidine Hydrochloride; Apraclonidina, hidrocloruro de; Apraclonidine, chlorhydrate d'; Apraclonidini Hydrochloridum; Hidrocloruro de aminoclonidina; Hidrocloruro de aplonidina; Hidrocloruro de apraclonidina; NC-14; Апраклонидина Гидрохлорид.

2-[(4-Amino-2,6-dichlorophenyl)imino]imidazolidine hydrochloride; 2,6-Dichloro-N^1-imidazolidin-2-ylidene-*p*-phenylenediamine hydrochloride.

$C_9H_{10}Cl_2N_4$,HCl=281.6.

CAS — 66711-21-5 (apraclonidine); 73218-79-8 (apraclonidine hydrochloride).

ATC — S01EA03.

ATC Vet — QS01EA03.

UNII — D2VW67N38H.

NOTE. APR is a code approved by the BP 2014 for use on single unit doses of eye drops containing apraclonidine hydrochloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *US*.

USP 36: (Apraclonidine Hydrochloride). A white to off-white, odourless to practically odourless powder. Soluble 1 in 34 of water, 1 in 74 of alcohol, and 1 in 13 of methyl alcohol; insoluble in chloroform, in ethyl acetate, and in hexanes. pH of a 1% solution in water is between 5.0 and 6.6. Store in airtight containers. Protect from light.

Uses and Administration

Apraclonidine is an alpha$_2$-adrenoceptor agonist derived from clonidine (p. 1339.1). It reduces intra-ocular pressure when instilled into the eye and is used in patients undergoing eye surgery, and as an adjunct in the management of glaucoma (p. 1999.1). The reduction in intra-ocular pressure begins within an hour of instillation and is maximal after about 3 to 5 hours.

Apraclonidine is used as the hydrochloride, but the strength of an ophthalmic solution is usually expressed in terms of the base. Apraclonidine hydrochloride 11.5 mg is equivalent to about 10 mg of apraclonidine.

To control or prevent a postoperative increase in intra-ocular pressure in patients undergoing anterior segment laser surgery, a 1% solution is instilled into the eye one hour before surgery and again immediately upon completion of surgery.

For short-term adjunctive therapy in patients with raised intra-ocular pressure not controlled by conventional therapy, a 0.5% solution may be instilled three times daily.

There is a loss of effect over time (tachyphylaxis) with apraclonidine and the benefit in most patients lasts for less than a month.

Adverse Effects and Precautions

Adverse effects after perioperative instillation of apraclonidine into the eye include hyperaemia, lid retraction, and mydriasis. Some patients may develop an exaggerated reduction in intra-ocular pressure. On regular instillation an ocular intolerance reaction may occur, characterised by hyperaemia, ocular pruritus, increased lachrymation, ocular discomfort, and oedema of the lids and conjunctiva; treatment should be stopped if these symptoms occur. Other adverse effects reported include dry mouth and nose, conjunctivitis, conjunctival blanching, blurred vision, asthenia, headache, and taste disturbances.

Systemic absorption can occur after application to the eye and may result in adverse effects similar to those of clonidine (p. 1341.2). Cardiovascular effects have been reported; therefore apraclonidine should be used with caution in patients with severe cardiovascular disease, including hypertension, and in patients with a history of vasovagal attacks. Drowsiness may also occur; if affected, patients should not drive or operate machinery. Depression has rarely been associated with use of apraclonidine and it should be used with caution in depressed patients.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies apraclonidine 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 25/10/11)

Interactions

Systemic absorption may occur after topical application of apraclonidine to the eye and there is a theoretical possibility of interactions similar to those reported with clonidine (p. 1342.1). Since the effects of apraclonidine on circulating catecholamines are unknown, licensed product information recommends that MAOIs should not be given with apraclonidine; tricyclic and related antidepressants and systemic sympathomimetics should also be avoided or used with caution.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Iopidine; *Austria*: Iopidine; *Belg.*: Iopidine; *Canad.*: Iopidine; *China*: Chen Ze (辰泽); *Denm.*: Iopidine; *Fin.*: Iopidine; *Fr.*: Iopidine; *Ger.*: Iopidine; *Gr.*: Iopidine; *Hong Kong*: Iopidine; *India*: Alfadrops; *Irl.*: Iopidine; *Israel*: Iopidine; *Ital.*: Iopidine; *Jpn*: Iopidine; *Mex.*: Iopidine; *Neth.*: Iopidine; *Norw.*: Iopidine; *NZ*: Iopidine; *Port.*: Iopidine; *S.Afr.*: Iopidine; *Singapore*: Iopidine†; *Spain*: Iopimax; *Swed.*: Iopidine; *Switz.*: Iopidine; *Thai.*: Iopidine; *Turk.*: Iopidine; *UK*: Iopidine; *USA*: Iopidine.

Pharmacopoeial Preparations
USP 36: Apraclonidine Ophthalmic Solution.

Befunolol Hydrochloride *(rINNM)* ⊗

Befunolol, Chlorhydrate de; Befunolol, hidrocloruro de; Befunololi Hydrochloridum; BFE-60; Hidrocloruro de befunolol; Бефунолола Гидрохлорид.
7-[2-Hydroxy-3-(isopropylamino)propoxy]-2-benzofuranyl methyl ketone hydrochloride.
$C_{16}H_{21}NO_4$,HCl=327.8.
CAS — 39552-01-7 (befunolol); 39543-79-8 (befunolol hydrochloride).
ATC — S01ED06.
ATC Vet — QS01ED06.
UNII — B03Z2VY37I.

Profile

Befunolol is a beta blocker (p. 1316.3). It is used as the hydrochloride in the management of ocular hypertension and open-angle glaucoma (p. 1999.1). Eye drops containing befunolol hydrochloride 0.25%, 0.5%, or 1% are instilled twice daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Thilonium; *Ital.*: Betaclar†; *Jpn*: Bentos.

Bimatoprost *(BAN, USAN, rINN)*

AGN-192024; Bimatoprostum; Биматопрост.
(Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-N-ethyl-5-heptenamide.
$C_{25}H_{37}NO_4$=415.6.
CAS — 155206-00-1.
ATC — S01EE03.
ATC Vet — QS01EE03.
UNII — QXS94885MZ.

Uses and Administration

Bimatoprost is a synthetic prostamide, a fatty-acid amide that is structurally related to dinoprost (prostaglandin $F_{2\alpha}$). It is used to reduce intra-ocular pressure in the treatment of open-angle glaucoma and ocular hypertension (p. 1999.1). Reduction in pressure starts about 4 hours after instillation and is maximal within 8 to 12 hours; the effect lasts for at least 24 hours. It is given once daily in the evening as a 0.01% or 0.03% ophthalmic solution.

Bimatoprost is also used in the treatment of hypotrichosis of the eyelashes; one drop of a 0.03% ophthalmic solution is applied to each eye once nightly along the skin of the upper eyelid margin at the base of the eyelashes.

References.
1. Williams RD, *et al.* Bimatoprost Study Group. Long-term efficacy and safety of bimatoprost for intraocular pressure lowering in glaucoma and ocular hypertension: year 4. *Br J Ophthalmol* 2008; 92: 1387–92.
2. Patil AJ, *et al.* Bimatoprost - a review. *Expert Opin Pharmacother* 2009; 10: 2759–68.
3. Katz LJ, *et al.* Twelve-month, randomized, controlled trial of bimatoprost 0.01%, 0.0125%, and 0.03% in patients with glaucoma or ocular hypertension. *Am J Ophthalmol* 2010; 149: 661–671.

Adverse Effects and Precautions

As for Latanoprost, p. 2008.2. Ocular pruritus is common. Hypertension and headache also commonly occur. There have been reports of bradycardia or hypotension and bimatoprost should be used with caution in patients predisposed to a low heart rate or blood pressure. Reactivation of previous corneal infiltrates or ocular infections has also been reported rarely; it should be used with caution in those with a history of significant ocular viral infections, such as herpes simplex, or uveitis or iritis.

Pharmacokinetics

Small amounts of bimatoprost are absorbed from eye drops and peak blood concentrations occur within 10 minutes of dosing. Bimatoprost is metabolised by oxidation, de-ethylation, and glucuronidation, and is excreted mainly in the urine with about 25% appearing in the faeces. The elimination half-life is 45 minutes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lumigan; *Austral.*: Lumigan; *Austria*: Lumigan; *Belg.*: Lumigan; *Braz.*: Glamigan; Lumigan; *Canad.*: Latisse; Lumigan; *Chile*: Lumigan; *China*: Lumigan (卢美根); *Cz.*: Lumigan; *Denm.*: Lumigan; *Fin.*: Lumigan; *Fr.*: Lumigan; *Ger.*: Lumigan; *Gr.*: Lumigan; *Hong Kong*: Lumigan; *Hung.*: Lumigan; *India*: Careprost; Lumigan; *Irl.*: Lumigan; *Israel*: Latisse; Lumigan; *Ital.*: Lumigan; *Jpn*: Lumigan; *Malaysia*: Lumigan; *Mex.*: Lumigan; *Neth.*: Lumigan; *Norw.*: Lumigan; *NZ*: Lumigan; *Philipp.*: Lumigan; *Pol.*: Lumigan; *Port.*: Lumigan; *S.Afr.*: Lumigan; *Singapore*: Latisse; Lumigan; *Spain*: Lumigan; *Swed.*: Lumigan; *Switz.*: Lumigan; *Thai.*: Lumigan; *Turk.*: Lumigan; *UK*: Lumigan; *USA*: Latisse; Lumigan; *Venez.*: Lumigan.

Multi-ingredient Preparations. *Arg.*: Ganfort; *Austral.*: Ganfort; *Austria*: Ganfort; *Braz.*: Ganfort; *Chile*: Ganfort; *Cz.*: Ganfort; *Denm.*: Ganfort; *Fr.*: Ganfort; *Ger.*: Ganfort; *Gr.*: Ganfort; *Hong Kong*: Ganfort; *Hung.*: Ganfort; *India*: Careprost Plus; Ganfor; *Irl.*: Ganfort; *Israel*: Ganfort; *Ital.*: Ganfort; *Malaysia*: Ganfor; *Mex.*: Ganfort; *Neth.*: Ganfort; *Norw.*: Ganfort; *NZ*: Ganfor; *Philipp.*: Ganfort; *Pol.*: Ganfort; *Port.*: Ganfort; *Singapore*: Ganfort; *Spain*: Ganfort; *Swed.*: Ganfort; *Switz.*: Ganfort; *Thai*: Ganfort; *Turk.*: Ganfort; *UK*: Ganfort; *Ukr.*: Ganfort (Ганфорт)

Brimonidine Tartrate *(BANM, USAN, rINNM)*

AGN-190342-LF; Brimonidin Tartrat; Brimonidina, tartrato de; Brimonidine, Tartrate de; Brimonidini Tartras; Tartrato de brimonidina; UK-14304-18; Бримонидина Тартрат.
5-Bromo-6-(2-imidazolin-2-ylamino)quinoxaline D-tartrate.
$C_{11}H_{10}BrN_5.C_4H_6O_6$=442.2.
CAS — 59803-98-4 (brimonidine); 79570-19-7 (brimonidine tartrate).
ATC — S01EA05.
ATC Vet — QS01EA05.
UNII — 459CL2DY2H.

Uses and Administration

Brimonidine is an alpha$_2$-adrenoceptor agonist with actions and uses similar to those of apraclonidine (above). It is used to lower intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension (below), as an alternative or adjunct to topical beta blocker therapy. It may also be used as adjunctive therapy in patients with raised intra-ocular pressure not controlled by topical monotherapy with other drugs such as latanoprost and travoprost. The reduction in intra-ocular pressure is maximal about 2 hours after topical use.

In the management of glaucoma or ocular hypertension, eye drops containing brimonidine tartrate 0.1, 0.15, or 0.2% are instilled two or three times daily.

Glaucoma. References[1-4] to the use of brimonidine in glaucoma and ocular hypertension (p. 1999.1).

1. Prampton JE. Topical brimonidine 0.2%/timolol 0.5% ophthalmic solution: in glaucoma and ocular hypertension. *Drugs Aging* 2006; 23: 753–61.
2. Fung AT, *et al.* Meta-analysis of randomised controlled trials comparing latanoprost with brimonidine in the treatment of open-angle glaucoma, ocular hypertension or normal-tension glaucoma. *Br J Ophthalmol* 2007; 91: 62–8.
3. Katz LJ, *et al.* Efficacy and safety of brimonidine and dorzolamide for intraocular pressure lowering in glaucoma and ocular hypertension. *Curr Med Res Opin* 2007; 23: 2971–83.
4. Pudemberg SJ, *et al.* Efficacy, safety, and current applications of brimonidine. *Expert Opin Drug Safety* 2008; 7: 795–9.

Adverse Effects and Precautions

As for Apraclonidine Hydrochloride, above.

In children. Systemic adverse effects, occasionally severe,[1] have been reported in children treated with brimonidine eye drops. In one study[2] adverse effects were reported in 70 of 83 children given adjunctive brimonidine, the most common effects being lethargy and excessive sleepiness; other effects included ocular irritation and blurred vision. Hypothermia occurred in a few cases, mainly in older children. Effects suggesting CNS depression, such as cyanosis and breathing difficulty, were rare, and were most likely in children less than 6 years of age or weighing less than 20 kg. Alternative medication should be considered in this group. In the UK, licensed product information contra-indicates use in neonates and infants under 2 years of age; use in children under 12 years of age is not recommended.

1. Szajnbok J. Failure of naloxone to reverse brimonidine-induced coma in an infant. *J Pediatr* 2002; 140: 485–6.
2. Al-Shahwan S, *et al.* Side-effect profile of brimonidine tartrate in children. *Ophthalmology* 2005; 112: 2143–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies brimonidine 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 25/10/11)

Interactions

As for Apraclonidine Hydrochloride, above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alphagan; Brimo-Klonal; Brimopress; Oftalmotonil; *Austral.*: Alphagan; Enidin; *Austria*: Alphagan; *Belg.*: Alphagan; *Braz.*: Alphabrin; Alphagan; Bri-

moftal; Glaub; *Canad.*: Alphagan; *Chile*: Agglad Ofteno; Alphagan; Brimopress; *China*: Alphagan (阿法根); Brimocon (沐利汀); Mu Xin (沐欣); *Cz.*: Alphagan; *Luxfen*; *Denm.*: Alphagan; Alphastad; Brimoratio; Glaudin; *Fin.*: Alphagan; Glaudin†; *Fr.*: Alphagan; *Ger.*: Alphagan; Brimo Ophtal; Brimozept; *Gr.*: Alphagan; Benil; Brimodine; Brimogan; Brimontal; Brinal; Brinidin; Corneax; Glaucoval; Pharmexin; *Hong Kong*: Alphagan; *India*: Alphagan; Brimochek; Brimodin; Brimopress; Brimosun; Iobrim; *Irl.*: Alphagan; Brimon; *Israel*: Alphagan; *Ital.*: Alphagan; *Jpn*: Alphagan; *Malaysia*: Alphagan; *Mex.*: Agglad; Alphagan; Briop; Nor-Tenz; *Neth.*: Alphagan; Briglau; *Norw.*: Alphagan; Brimoratio; *NZ*: Alphagan; *Philipp.*: Alphagan; *Pol.*: Alphagan; Brimoteva; Luxfen; *Port.*: Alphagan; Bglau; *S.Afr.*: Alphagan; *Singapore*: Alphagan; *Spain*: Alfadina; Alphagan; *Swed.*: Alphagan; Brimoratio; Glaudin; *Switz.*: Alphagan; *Thai.*: Alphagan; *Turk.*: Alphagan; *UK*: Alphagan; Brymont; *Ukr.*: Alphagan (Альфаган); Luxfen (Люксфен); *USA*: Alphagan; Mirvaso; *Venez.*: Agglad Ofteno; Alphagan.

Multi-ingredient Preparations. *Arg.*: Combigan; Timobrim; *Austral.*: Combigan; *Austria*: Combigan; *Belg.*: Combigan; *Braz.*: Combigan; *Canad.*: Combigan; *Chile*: Combigan; *Cz.*: Combigan; *Denm.*: Combigan; *Fin.*: Combigan; *Fr.*: Combigan; *Ger.*: Combigan; *Gr.*: Combigan; *Hong Kong*: Combigan; *Hung.*: Combigan; *India*: Brimochek-T; Brimocom; Brimolol; Combigan; *Irl.*: Combigan; *Israel*: Combigan; *Ital.*: Combigan; *Malaysia*: Combigan; *Mex.*: Combigan-D; Krytantek; *Neth.*: Combigan; *Norw.*: Combigan; *NZ*: Combigan; *Philipp.*: Combigan; *Pol.*: Combigan; *Port.*: Combigan; *S.Afr.*: Combigan; *Singapore*: Combigan; *Spain*: Combigan; *Swed.*: Combigan; *Switz.*: Combigan; *Thai.*: Combigan; *Turk.*: Combigan; *UK*: Combigan; *Ukr.*: Combigan (Комбиган); *USA*: Combigan; Simbrinza.

Brinzolamide *(BAN, USAN, rINN)* ⊗

AL-4862; Brintsolamidi; Brinzolamid; Brinzolamida; Brinzolamidum; бринзоламид.

(*R*)-4-(Ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-2*H*-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide.

$C_{12}H_{21}N_3O_5S_3$=383.5

CAS — 138890-62-7.

ATC — S01EC04.

ATC Vet — QS01EC04.

UNII — 9451ZB9515.

Pharmacopoeias. In *US.*

USP 36: (Brinzolamide). A white or almost white powder. Insoluble in water; slightly soluble in alcohol and in methyl alcohol.

Uses and Administration

Brinzolamide is a carbonic anhydrase inhibitor with actions and uses similar to those of dorzolamide (p. 2006.3). It is used to reduce intra-ocular pressure in the management of open-angle glaucoma and ocular hypertension (p. 1999.1), either alone or as adjunctive therapy with a topical beta blocker or prostaglandin analogue. A 1% suspension is instilled into the eye two or three times daily.

Glaucoma. References.

1. Cvetkovic RS, Perry CM. Brinzolamide: a review of its use in the management of primary open-angle glaucoma and ocular hypertension. *Drugs Aging* 2003; 20: 919–47.
2. Iester M. Brinzolamide. *Expert Opin Pharmacother* 2008; 9: 653–62.

Adverse Effects and Precautions

As for Dorzolamide, p. 2007.1.

Effects on the eyes. Corneal oedema has been noted in the eyes of 2 patients after the long-term use of brinzolamide 1% eye drops;[1] both patients recovered after brinzolamide was stopped.

1. Zhao JC, Chen T. Brinzolamide induced reversible corneal decompensation. *Br J Ophthalmol* 2005; 89: 389–90.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies brinzolamide 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 25/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Azopt; *Austral.*: Azopt; *Austria*: Azopt; *Belg.*: Azopt; *Braz.*: Azopt; *Canad.*: Azopt; *Chile*: Azopt; *China*: Azopt (派立明); *Cz.*: Azopt; *Denm.*: Azopt; *Fin.*: Azopt; *Fr.*: Azopt; *Ger.*: Azopt; *Gr.*: Azopt; *Hong Kong*: Azopt; *Hung.*: Azopt; *Indon.*: Azopt; *Irl.*: Azopt; *Israel*: Azopt; *Ital.*: Azopt; *Malaysia*: Azopt; *Mex.*: Azopt; *Neth.*: Azopt; *Norw.*: Azopt; *NZ*: Azopt; *Philipp.*: Azopt; *Pol.*: Azopt; *Port.*: Azopt; *Rus.*: Azopt (Азопт); *S.Afr.*: Azoptic; *Singapore*: Azopt; *Spain*: Azopt; *Swed.*: Azopt; *Switz.*: Azopt; *Thai.*: Azopt; *Turk.*: Azopt; *UK*: Azopt; *Ukr.*: Azopt (Азопт); *USA*: Azopt; *Venez.*: Azopt.

Multi-ingredient Preparations. *Arg.*: Azarga; *Austral.*: Azarga; *Austria*: Azarga; *Belg.*: Azarga; *Canad.*: Azarga; *Chile*: Azarga; *Cz.*: Azarga; *Denm.*: Azarga; *Fr.*: Azarga; *Ger.*: Azarga; *Gr.*: Azarga; *Hung.*: Azarga; *Irl.*: Azarga; *Ital.*: Azarga; *Malaysia*: Azarga; *Neth.*: Azarga; *Norw.*: Azarga; *NZ*: Azarga; *Pol.*: Azarga; *Port.*: Azarga; *Rus.*: Azarga (Азарга); *Singapore*: Azarga; *Spain*: Azarga; *Swed.*: Azarga; *Switz.*: Azarga; *Thai.*: Azarga; *Turk.*: Azarga; *UK*: Azarga; *USA*: Simbrinza.

Pharmacopoeial Preparations

USP 36: Brinzolamide Ophthalmic Suspension.

Carbachol *(BAN, rINN)*

Carbach; Carbacholi Cloridum; Carbacholine; Carbacholum; Carbacholum Chloratum; Carbacol; Choline Chloride Carbamate; Karbachol; Karbacholis; Karbakol; Karbakoli; Karbaminocholiny chlorek; Карбахол.

O-Carbamoylcholine chloride; (2-Carbamoyloxyethyl)trimethylammonium chloride.

$C_6H_{15}ClN_2O_2$=182.6

CAS — 51-83-2.

ATC — N07AB01; S01EB02.

ATC Vet — QA03AB92; QN07AB01; QS01EB02.

UNII — 8Y164V895Y.

NOTE. CAR is a code approved by the BP 2014 for use on single unit doses of eye drops containing carbachol where the individual container may be too small to bear all the appropriate labelling information.

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

Ph. Eur. 8: (Carbachol). A white or almost white, crystalline, hygroscopic powder. Very slightly soluble in water; sparingly soluble in alcohol; practically insoluble in acetone. Store in airtight containers. Protect from light.

USP 36: (Carbachol). A white powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers.

Incompatibility. Chlorocresol (0.025 to 0.1%) and chlorobutanol (0.5%) were both found to be incompatible with a solution of carbachol (0.8%) and sodium chloride (0.69%), very slight precipitates forming on heating and increasing on standing.[1]

1. *PSGB Lab Report No.911* 1962.

Uses and Administration

Carbachol, a choline ester, is a quaternary ammonium parasympathomimetic with the muscarinic and nicotinic actions of acetylcholine (p. 2003.2). It is not inactivated by cholinesterases so its actions are more prolonged than those of acetylcholine.

Carbachol has a miotic action and is usually given intra-ocularly to produce miosis in ocular surgery and to reduce postoperative rises in intra-ocular pressure; up to 0.5 mL of a 0.01% solution is instilled into the anterior chamber of the eye (intracameral instillation). The maximum degree of miosis is usually obtained within 2 to 5 minutes of intra-ocular instillation and miosis lasts for 24 hours.

Eye drops containing up to 3% of carbachol have also been used to lower intra-ocular pressure in glaucoma, usually three times daily with other miotics (see below). Miosis occurs within 10 to 20 minutes of instillation and lasts for 4 to 8 hours; reduction in intra-ocular pressure lasts for 8 hours.

Carbachol has been used for the treatment of urinary retention including postoperative urinary retention. It has also been used in some countries for the treatment of decreased gastrointestinal motility.

Dry mouth. Carbachol has been used as an alternative to pilocarpine in the treatment of radiation-induced xerostomia.[1] The overall treatment of dry mouth is discussed on p. 2175.3.

1. Joensuu H. Treatment for post-irradiation xerostomia. *N Engl J Med* 1994; 330: 141–2.

Glaucoma and ocular hypertension. Carbachol is sometimes used as an alternative to pilocarpine in the management of glaucoma (p. 1999.1) when resistance or intolerance to pilocarpine develops. It is also instilled into the anterior chamber of the eye (intracameral instillation) to minimise postoperative rises in intra-ocular pressure associated with ocular surgery, and some[1,2] have found it to be more effective than acetylcholine.

1. Ruiz RS, *et al.* Effects of carbachol and acetylcholine on intramuscular pressure after cataract extraction. *Am J Ophthalmol* 1989; 107: 7–10.
2. Hollands RH, *et al.* Control of intraocular pressure after cataract extraction. *Can J Ophthalmol* 1990; 25: 128–32.

Adverse Effects, Treatment, and Precautions

As described for choline esters under Acetylcholine Chloride, p. 2003.2. Carbachol has substantial nicotinic activity which may be unmasked by the use of atropine to counteract muscarinic effects.

Carbachol also produces adverse effects and requires precautions similar to those of other miotics such as pilocarpine (p. 2011.2) when used in the eye, but may produce more ciliary spasm than pilocarpine.

Effects on the gastrointestinal tract. Fatal oesophageal rupture has been reported[1] after subcutaneous injection of carbachol to relieve urinary retention.

1. Cochrane P. Spontaneous oesophageal rupture after carbachol therapy. *BMJ* 1973; 1: 463–4.

Overdosage. Life-threatening attacks of profuse sweating, intestinal cramps, explosive defaecation, hypothermia, hypotension, and bradycardia occurred in a 36-year-old man after deliberate poisoning with 30 to 40 mg of carbachol.[1] The patient's 10-year-old son had died after poisoning with a similar dose of carbachol.

1. Sangster B, *et al.* Two cases of carbachol intoxication. *Neth J Med* 1979; 22: 27–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies carbachol for ophthalmic use 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 25/10/11)

Interactions

NSAIDs. Licensed UK product information for acetylcholine chloride ophthalmic preparations states that there have been reports that acetylcholine and carbachol were ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Miostat; *Austral.*: Miostat; *Belg.*: Miostat; *Canad.*: Miostat; *Cz.*: Miostat; *Fr.*: Miostat; *Ger.*: Carbamann†; *Hung.*: Miostat; *Israel*: Miostat; *Ital.*: Mioticol; *Malaysia*: Miostat; *Neth.*: Miostat; *NZ*: Miostat; *Philipp.*: Miostat; *Pol.*: Miostat; *Singapore*: Miostat; *Swed.*: Isopto Karbakolin†; Miostat; *Switz.*: Miostat; *Thai.*: Miostat; *Turk.*: Miostat; *USA*: Carbastat†; Miostat.

Pharmacopoeial Preparations

USP 36: Carbachol Intraocular Solution; Carbachol Ophthalmic Solution.

Cyclopentolate Hydrochloride

(BANM, rINNM)

Ciclopentolato, hidrocloruro de; Ciklopentolát-hidroklorid; Ciklopentolato hidroclorídas; Cloridrato de Ciclopentolato; Cyclopentolate, Chlorhydrate de; Cyclopentolathydrochlorid; Cyclopentolati Hydrochloridum; Cyklopentolát hydrochlorid; Cyklopentolathydroklorid; Hidrocloruro de ciclopentolato; Siklopentolat Hidroklorür; Syklopentolaattihydrokloridi; Циклопентолата гидрохлорид.

2-Dimethylaminoethyl 2-(1-hydroxycyclopentyl)-2-phenylacetate hydrochloride.

$C_{17}H_{25}NO_3$,HCl=327.8

CAS — 512-15-2 (cyclopentolate); 5870-29-1 (cyclopentolate hydrochloride).

ATC — S01FA04.

ATC Vet — QS01FA04.

UNII — 736I69717E.

NOTE. CYC is a code approved by the BP 2014 for single unit doses of eye drops containing cyclopentolate hydrochloride where the individual container may be too small to bear all the appropriate labelling information. PHNCYC is a similar code approved for eye drops containing phenylephrine hydrochloride and cyclopentolate hydrochloride.

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

Ph. Eur. 8: (Cyclopentolate Hydrochloride). A white or almost white, crystalline powder. It exhibits polymorphism. Very soluble in water; freely soluble in alcohol. A 1% solution in water has a pH of 4.5 to 5.5.

USP 36: (Cyclopentolate Hydrochloride). A white crystalline powder, which develops a characteristic odour on standing. Very soluble in water; freely soluble in alcohol; insoluble in ether. pH of a 1% solution in water is between 4.5 and 5.5. Store at a temperature not exceeding 8 degrees in airtight containers.

Uses and Administration

Cyclopentolate hydrochloride is a tertiary amine antimuscarinic with actions similar to those of atropine (p. 1310.3). It is used to produce mydriasis and cycloplegia (p. 2000.2) for ophthalmic diagnostic procedures and also in the treatment of uveitis and iritis (p. 1615.1). It acts more quickly than atropine and has a shorter duration of action; the maximum mydriatic effect is produced 30 to 60 minutes after instillation, and may persist for up to 24 hours or longer in some patients; the maximum cycloplegic effect is produced within 25 to 75 minutes and accommodation recovers within 6 to 24 hours.

For diagnostic procedures, instillation of a 0.5% ophthalmic solution of cyclopentolate hydrochloride, repeated after about 5 to 15 minutes if necessary, is usually sufficient. Higher strengths have been used.

In the treatment of uveitis and iritis, a 0.5% ophthalmic solution of cyclopentolate hydrochloride is instilled into the eye up to four times daily.

Deeply pigmented eyes are more resistant to pupillary dilatation and may require the use of a 1% solution.

For details of doses in children, see below.

Administration in children. For diagnostic procedures in children, instillation of a 1% ophthalmic solution of cyclopentolate hydrochloride, repeated after about 5 to 15 minutes if necessary, is usually sufficient. Higher strengths have been used. However, some recommend that strengths greater than 0.5% should not be used in infants and that cyclopentolate should not be used at all during the first 3 months of life.

In the treatment of uveitis, the *BNFC* suggests that a 0.5% ophthalmic solution of cyclopentolate hydrochloride may be instilled into the eye 2 to 4 times daily; a 1% solution should be used for deeply pigmented eyes.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1.

Eye drops of cyclopentolate hydrochloride may cause temporary irritation.

Abuse. Cyclopentolate eye drops have been abused.[1] One of 2 patients who did so had been instilling 200 to 400 drops of cyclopentolate into both eyes daily for about 4 months, presumably for its CNS effects, and had intense nausea, vomiting, weakness, and tremors on withdrawal.

1. Sato EH, *et al.* Abuse of cyclopentolate hydrochloride (Cyclogyl) drops. *N Engl J Med* 1992; 326: 1363–4.

Hypersensitivity. Two children developed hypersensitivity reactions shortly after the instillation of 1% cyclopentolate hydrochloride eye drops into each eye.[1] Both children initially had a facial rash but in one of them the rash later spread to include the arms and legs and was accompanied by mild breathlessness.

1. Jones LWJ, Hodes DT. Possible allergic reactions to cyclopentolate hydrochloride: case reports with literature review of uses and adverse reactions. *Ophthalmic Physiol Opt* 1991; 11: 16–21.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cyclopentolate 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 25/10/11)

Systemic toxicity. Ten of 66 patients (29 males and 37 females) who received one drop of 2% cyclopentolate in each eye developed mild to moderate systemic toxicity; 9 of the 10 were female.[1] Toxic signs included physical weakness, nausea, lightheadedness, changes in emotional attitude, unprovoked weeping, and loss of equilibrium; tachycardia was always present but changes in blood pressure were insignificant. Spontaneous recovery occurred within 1 hour to several days.

As with atropine, it has been recommended that cyclopentolate eye drops should not be used during the first 3 months of life because of the possible association with development of amblyopia. Systemic toxicity has also been reported in neonates given ocular cyclopentolate.[2]

A 4-year-old boy with cerebral palsy and paraplegia suffered tonic-clonic seizures, facial flushing, and tachycardia 70 minutes after one drop of a 1% cyclopentolate solution was instilled into each eye to dilate his pupils.[3] The child had no history of convulsions and had received 1% cyclopentolate eye drops on 2 previous occasions without incident. In a more recent case,[4] a 23-month-old boy had a tonic-clonic seizure lasting 30 minutes after the use of cyclopentolate 1% and phenylephrine 10% eye drops. One drop of each was instilled into both eyes every 5 minutes for 3 doses; the seizure occurred 45 minutes after the last dose. The child was found to have low pseudocholinesterase activity, an enzyme likely to be involved in the metabolism of cyclopentolate.

1. Awan KJ. Adverse systemic reactions of topical cyclopentolate hydrochloride. *Ann Ophthalmol* 1976; 8: 695–8.
2. Bauer CR, *et al.* Systemic cyclopentolate (Cyclogyl) toxicity in the newborn infant. *J Pediatr* 1973; 92: 501–5.
3. Fitzgerald DA, *et al.* Seizures associated with 1% cyclopentolate eyedrops. *J Paediatr Child Health* 1990; 26: 106–7.
4. Demayo AP, Reidenberg MM. Grand mal seizure in a child 30 minutes after Cyclogyl (cyclopentolate hydrochloride) and 10% Neo-Synephrine (phenylephrine hydrochloride) eye drops were instilled. Abstract: *Pediatrics* 2004; 113: 1390–1. Full version: http://pedatrics.aappublications.org/cgi/reprint/113/5/e499 (accessed 24/11/05)

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ciclopenal; *Austral.*: Cyclogyl; *Belg.*: Cyclogyl; *Braz.*: Ciclolato; Ciclopegico; *Canad.*: Ak-Pentolate; Cyclogyl; Diopentolate; *Chile*: Cyclogyl; *China*: Cyclogyl (赛飞杰); *Denm.*: Cyclogyl; *Fin.*: Oftan Syklo; *Fr.*: Skiacol; *Ger.*: Zykolat-EDO; *Gr.*: Cyclogyl; *Hong Kong*: Cyclogyl; *Hung.*: Humapent; *India*: Bell Pentolate†; Cyclate; Cyclogik; Cyclogyl; Cyclopent; Dilate; *Irl.*: Mydrilate; *Ital.*: Ciclolux; *Malaysia*: Colircusi Cicloplejico; Cyclogyl; *Mex.*: Refractyl; *Neth.*: Cyclogyl; *NZ*: Cyclogyl; *Port.*: Ciclopegicedol; Midriodavi; *Rus.*: Cyclomed (Цикломед); Cycloptic (Циклоптик); *S.Afr.*: Cyclogyl; *Singapore*: Cyclogyl†; *Spain*: Ciclopegic; Ciclopleijico; *Swed.*: Cyclogyl; *Switz.*: Cyclogyl; *Thai.*: Cyclogyl; *Turk.*: Siklomid; Sikloplejin; *UK*: Mydrilate; *Ukr.*: Cyclomed (Цикломед); *USA*: Ak-Pentolate; Cyclogyl; Ocu-Pentolate; Pentolair†; *Venez.*: Cyclogyl.

Multi-ingredient Preparations. *India*: Cycdex; Cyclogyl-D; Cyclopent Plus; Cyclopent-DM; *Malaysia*: Cyclomydril; *S.Afr.*: Cyclomydril; *Singapore*: Cyclomydril†; *USA*: Cyclomydril.

Pharmacopoeial Preparations
BP 2014: Cyclopentolate Eye Drops;
USP 36: Cyclopentolate Hydrochloride Ophthalmic Solution.

Dapiprazole Hydrochloride *(USAN, rINNM)*

AF-2139; Dapiprazol, hidrocloruro de; Dapiprazole, Chlorhydrate de; Dapiprazoli Hydrochloridum; Hidrocloruro de dapiprazol; Дапипразола Гидрохлорид.

5,6,7,8-Tetrahydro-3-[2-(4-*o*-tolyl-1-piperazinyl)ethyl]-*s*-triazolo[4,3-*a*]pyridine monohydrochloride.

$C_{19}H_{27}N_5$,HCl=361.9

CAS — 72822-12-9 (dapiprazole); 72822-13-0 (dapiprazole hydrochloride).

ATC — S01EX02.

ATC Vet — QS01EX02.

UNII — DS9UJN110X.

Profile

Dapiprazole hydrochloride is an alpha blocker given as eye drops to reverse mydriasis; it is also used in some countries in the management of glaucoma.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Benglau†; *Gr.*: Glamidolo; *Ital.*: Glamidolo; *USA*: Rev-Eyes†.

Demecarium Bromide *(BAN, rINN)*

BC-48; Bromuro de demecario; Demecarii Bromidum; Demecario, bromuro de; Démécarium, Bromure de; Demekariumbromid; Demekariumbromidi; Демекария бромид.

N,N'-Decamethylenebis(*N,N,N*-trimethyl-3-methylcarbamoyloxyanilinium) dibromide.

$C_{32}H_{52}Br_2N_4O_4$=716.6

CAS — 16505-84-3 (demecarium); 56-94-0 (demecarium bromide).

ATC — S01EB04.

ATC Vet — QS01EB04.

UNII — 61D5V4OKTP.

Pharmacopoeias. In *US.*

USP 36: (Demecarium Bromide). A white or slightly yellow, slightly hygroscopic, crystalline powder. Freely soluble in water and in alcohol; sparingly soluble in acetone; soluble in ether. pH of a 1% solution in water is between 5.0 and 7.0. Store in airtight containers. Protect from light.

Profile

Demecarium is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase with a long duration of action similar to that of ecothiopate iodide (p. 2007.2). It has been used as a 0.125 or 0.25% ophthalmic solution in the treatment of open-angle glaucoma and in the diagnosis and management of accommodative convergent strabismus.

Preparations

Pharmacopoeial Preparations
USP 36: Demecarium Bromide Ophthalmic Solution.

Diclofenamide *(BAN, rINN)* ⊗

Dichlorphenamide; Diclofenamida; Diclofénamide; Diclofenamidum; Diklofenamid; Diklofenamidi; Диклофенамид.

4,5-Dichlorobenzene-1,3-disulphonamide.

$C_6H_6Cl_2N_2O_4S_2$=305.1

CAS — 120-97-8.

ATC — S01EC02.

ATC Vet — QS01EC02.

UNII — VVJ6673MHY.

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

Profile

Diclofenamide is an inhibitor of carbonic anhydrase with properties similar to those of acetazolamide (p. 2001.1). When given orally its effect begins within 1 hour and lasts for 6 to 12 hours.

Diclofenamide is used to reduce intra-ocular pressure in glaucoma (p. 1999.1). The usual initial oral dose is 100 mg every 6 to 12 hours until the desired response is obtained, followed by a maintenance dose of 50 mg every 8 hours. Diclofenamide sodium has been given by injection.

Diclofenamide may be of benefit in hyper- and hypokalaemic periodic paralysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Oratrol; *Ital.*: Antidrasi†; Penamide; *Spain*: Glauconide†.

Pharmacopoeial Preparations
USP 36: Dichlorphenamide Tablets.

Dorzolamide Hydrochloride

(BANM, USAN, rINNM) ⊗

Dorzolamid Hidroklorür; Dorzolamida, hidrocloruro de; Dorzolamide, Chlorhydrate de; Dorzolamidhydrochlorid; Dorzolamidi hydrochloridum; Hidrocloruro de dorzolamida; L-671152 (dorzolamide); MK-0507; MK-507; Дорзоламида Гидрохлорид.

(4*S*,6*S*)-4-(Ethylamino)-5,6-dihydro-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulphonamide 7,7-dioxide hydrochloride.

$C_{10}H_{16}N_2O_4S_3$,HCl=360.9

CAS — 120279-96-1 (dorzolamide); 130693-82-2 (dorzolamide hydrochloride).

ATC — S01EC03.

ATC Vet — QS01EC03.

UNII — QZO5366EW7.

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

Ph. Eur. 8: (Dorzolamide Hydrochloride). A white or almost white, crystalline powder. Soluble in water; very slightly soluble in anhydrous alcohol; slightly soluble in methyl alcohol. It exhibits polymorphism.

USP 36: (Dorzolamide Hydrochloride). A white to off-white crystalline powder. Soluble in water. Store at 15 degrees to 30 degrees. Protect from light.

Uses and Administration

Dorzolamide is a carbonic anhydrase inhibitor with actions similar to those of acetazolamide (p. 2001.1). It is used in the management of open-angle glaucoma, pseudo-exfoliative glaucoma, and ocular hypertension (p. 1999.1), either alone or as an adjunct to a topical beta blocker.

Dorzolamide is given as eye drops containing dorzolamide hydrochloride equivalent to 2% of the base. For monotherapy it is usually given three times daily; a twice-daily regimen is recommended when used with a beta blocker.

References.

1. Lesk MR, *et al.* Effectiveness and safety of dorzolamide-timolol alone or combined with latanoprost in open-angle glaucoma or ocular hypertension. *Ann Pharmacother* 2008; 42: 498–504.
2. Katz LJ, *et al.* Efficacy and safety of brimonidine and dorzolamide for intraocular pressure lowering in glaucoma and ocular hypertension. *Curr Med Res Opin* 2007; 23: 2971–83.

Adverse Effects and Precautions

Local ocular adverse effects may occur with dorzolamide eye drops and include conjunctivitis, keratitis, burning or stinging, eyelid inflammation or irritation, and blurred vision. Corneal oedema and irreversible corneal decompensation have been reported in patients with pre-existing chronic corneal defects and/or a history of intra-ocular surgery. There is also an increased potential for developing corneal oedema in those with low endothelial cell counts. Hence, dorzolamide eye drops should be used with caution in these patient groups. Dorzolamide may be absorbed systemically, resulting in adverse effects and precautions similar to those of acetazolamide (see p. 2002.1). Other adverse effects reported are headache, bitter taste, epistaxis, fatigue, and nausea.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dorzolamide 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 25/10/11)

Interactions

Systemic absorption may occur after topical application of dorzolamide to the eye and there is a theoretical possibility of interactions similar to those reported with acetazolamide (see p. 2002.3).

Pharmacokinetics

Systemic absorption occurs after topical application of dorzolamide to the eye. It accumulates in red blood cells during chronic dosing due to binding to carbonic anhydrase and is about 33% bound to plasma proteins. Dorzolamide forms a single *N*-desethyl metabolite that is less active and also accumulates in red blood cells where it binds mainly to the less active isoenzyme of carbonic anhydrase. Although dorzolamide is mainly excreted unchanged in the urine, its metabolite is also excreted in the urine.

References.

1. Martens-Lobenhoffer J, Banditt P. Clinical pharmacokinetics of dorzolamide. *Clin Pharmacokinet* 2002; 41: 197–205.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dorlamida; Trusopt; ***Austral.***: Trusopt; ***Austria***: Trusopt; ***Belg.***: Trusopt; ***Braz.***: Glaifital; Ocupress; Trusopt; ***Canad.***: Trusopt; ***Chile***: Glaucotensil; Trusopt; ***Cz.***: Oftidor; Trusopt; ***Denm.***: Trusopt; ***Fin.***: Trusopt; ***Fr.***: Trusopt; ***Ger.***: Dorzo-Vision; Trusopt; ***Gr.***: Dorolad; Optodrop; Trusopt; ***Hong Kong***: Trusopt; ***Hung.***: Trusopt; ***India***: Dortas; Dorzox; Ocudor; ***Irl.***: Trusopt; ***Israel***: Trusopt; ***Ital.***: Trusopt; ***Malaysia***: Trusopt; ***Mex.***: Ploba]; Trusopt; ***Neth.***: Dorzostill; Trusopt; ***Norw.***: Trusopt; ***NZ***: Trusopt; ***Philipp.***: Trusopt; ***Pol.***: Dorzostill; Rozallin; Trusopt; ***Port.***: Proglau; Trusopt; ***Rus.***: Trusopt (Трусопт); ***S.Afr.***: Trusopt; ***Singapore***: Trusopt; ***Spain***: Trusopt; ***Swed.***: Trusopt; ***Switz.***: Dorzo-Vision; Trusopt; ***Thai.***: Trusopt; ***Turk.***: Trusopt; ***UK***: Trusopt; ***Ukr.***: Dorsamed (Дорзамед); ***USA***: Trusopt; ***Venez.***: Dorzol; Glaucotensil D; Trusopt.

Multi-ingredient Preparations. ***Arg.***: Aliviapres; Cosopt; Dor-Timolol; Dorlamida T; Glaucotensil TD; Timed D; Zopirol DM; ***Austral.***: Cosopt; ***Austria***: Cosopt; ***Belg.***: Cosopt; ***Braz.***: Cosopt; Glaucoftal; ***Canad.***: Cosopt; ***Chile***: Cosopt; Dorsof T; Dorzine; Glaucotensil T; Glausolets Plus; Tiof Plus; ***Cz.***: Cosopt; ***Denm.***: Cosopt; Timosopt†; ***Fin.***: Cosopt; Glaukostad; ***Fr.***: Cosopt; ***Ger.***: Cosopt; Dorzo Plus T; Dorzolamid comp; ***Gr.***: Cosopt; Dorzoptic Plus; Dorzotim; Dotiz; Optodrop-Co; Tesol; ***Hong Kong***: Cosopt; ***Hung.***: Cosopt; Glamzolid; ***India***: Misopt; Ocudor-T; ***Irl.***: Clar-opt; Cosopt; Dortim; ***Israel***: Cosopt; ***Ital.***: Cosopt; ***Malaysia***: Cosopt; ***Mex.***: Anhigot; Cosopt; Krytantek; Trovost; ***Neth.***: Cosopt; Dortim; ***Norw.***: Cosopt; ***NZ***: Cosopt; ***Philipp.***: Cosopt; ***Pol.***: Cosopt; Dotiteva; Rozacom; ***Port.***: Cosopt; Timosopt†; ***Rus.***: Cosopt (Косопт); Dorzopt (Дорзопт); ***S.Afr.***: Cosopt; ***Singapore***: Cosopt; ***Spain***: Cosopt; ***Swed.***: Cosopt; Costad; ***Switz.***: Co-Dorzolamid; Cosopt; ***Thai.***: Cosopt; ***Turk.***: Cosopt; ***UK***: Cosopt; ***USA***: Cosopt; ***Venez.***: Cosopt; Dobet; Glaucotensil T.

Pharmacopoeial Preparations
BP 2014: Dorzolamide and Timolol Eye Drops; Dorzolamide Eye Drops;
USP 36: Dorzolamide Hydrochloride Ophthalmic Solution.

Dyflos *(BAN)*

DFP; Diflos; Difluorophate; Di-isopropil fluorofosfato; Di-isopropyl Fluorophosphate; Di-isopropylfluorophosphonate; Fluostigmina; Fluostigmine; Isoflurofato; Isoflurophate.
Di-isopropyl phosphorofluoridate.
$C_6H_{14}FO_3P$=184.1
CAS — 55-91-4.
ATC — S01EB07.
ATC Vet — QS01EB07.
UNII — 12UHW9R67N.

Pharmacopoeias. In *US*.

USP 36: (Isoflurophate). A clear, colourless, or faintly yellow liquid. Specific gravity about 1.05. Sparingly soluble in water; soluble in alcohol and in vegetable oils. It is decomposed by moisture with the evolution of hydrogen fluoride. Store at 8 degrees to 15 degrees in sealed containers.

Profile

Dyflos is an irreversible inhibitor of cholinesterases with actions similar to those of ecothiopate iodide (below). It has been used mainly in the treatment of open-angle glaucoma, particularly in aphakic patients and when other drugs have proved inadequate; it has usually been given as a 0.025% ophthalmic ointment. It was also used in the diagnosis and management of accommodative convergent strabismus.

Handling. The vapour of dyflos is very toxic. The eyes, nose, and mouth should be protected when handling dyflos, and contact with the skin should be avoided. Dyflos can be removed from the skin by washing with soap and water. Contaminated material should be immersed in a 2% aqueous solution of sodium hydroxide for several hours.

Preparations

Pharmacopoeial Preparations
USP 36: Isoflurophate Ophthalmic Ointment.

Ecothiopate Iodide *(BAN, rINN)*

Echothiophate Iodide; Ecostigmine Iodide; Écothiopate, Iodure d'; Ecothiopati Iodidum; Ecotiopato, Ioduro de; Ekotiopaattijodidi; Ekotiopatjodid; Ioduro de ecotiopato; MI-217; Экотиопата Йодид.
(2-Diethoxyphosphinylthioethyl)trimethylammonium iodide.
$C_9H_{23}INO_3PS$=383.2
CAS — 6736-03-4 (ecothiopate); 513-10-0 (ecothiopate iodide).
ATC — S01EB03.
ATC Vet — QS01EB03.
UNII — BA9QH3P00T.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Echothiophate Iodide). A white, crystalline, hygroscopic solid having a slight mercaptan-like odour. Soluble 1 in 1 of water, 1 in 25 of dehydrated alcohol, and 1 in 3 of methyl alcohol; practically insoluble in other organic solvents. Its solutions in water have a pH of about 4. Store in airtight containers preferably at a temperature below 0 degrees. Protect from light.

Uses and Administration

Ecothiopate is an irreversible inhibitor of cholinesterase; its actions are similar to those of neostigmine (p. 687.2) but much more prolonged. Its miotic action begins within 1 hour of its application and may persist for 1 to 4 weeks; it causes a reduction in intra-ocular pressure, which is maximal after 24 hours and may persist for days or weeks.

Ecothiopate iodide is used mainly in the treatment of open-angle glaucoma (p. 1999.1), particularly in aphakic patients and when other drugs have proved inadequate. It is usually given as drops of a 0.125% ophthalmic solution. Licensed product information states that 2 daily doses are preferred to allow for diurnal variations in intra-ocular pressure, although it has also been given once daily or on alternate days. It is advisable to give the single dose or one of the 2 daily doses at bedtime.

Ecothiopate iodide eye drops are also used in the diagnosis and management of accommodative convergent strabismus.

Adverse Effects

As for Neostigmine, p. 688.2. For adverse effects of miotics, see also Pilocarpine, p. 2011.2.

Ecothiopate is an irreversible cholinesterase inhibitor; its action, and hence its adverse effects, may be prolonged.

Plasma and erythrocyte cholinesterases may be reduced by treatment with eye drops of ecothiopate or other long-acting anticholinesterases, and systemic toxicity occurs more frequently than with shorter-acting miotics. Acute iritis, retinal detachment, or precipitation of acute glaucoma may occasionally occur, and iris cysts (especially in children) or lens opacities may develop on prolonged treatment.

Treatment of Adverse Effects

To treat the systemic effects of poisoning, atropine sulfate may be given parenterally with pralidoxime chloride as for intoxication with organophosphorus insecticides (see p. 1571.2); subconjunctival injection of pralidoxime has been used to reverse severe ocular adverse effects. Supportive treatment, including assisted ventilation, should be given as necessary.

To prevent or reduce development of iris cysts in patients receiving ecothiopate eye drops, phenylephrine eye drops may be given simultaneously.

Precautions

As for Neostigmine, p. 688.3. For precautions of miotics, see also under Pilocarpine, p. 2011.2. In general, as with other long-acting anticholinesterases, ecothiopate should be used only where therapy with other drugs has proved ineffective. Ecothiopate iodide should not be used in patients with iodine hypersensitivity.

Interactions

As for Neostigmine, p. 688.3. The possibility of an interaction remains for a considerable time after stopping long-acting anticholinesterases such as ecothiopate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Phospholine Iodide.

Pharmacopoeial Preparations
USP 36: Echothiophate Iodide for Ophthalmic Solution.

Homatropine *(BAN)*

Homatropiini; Homatropin; Homatropina; Homatropinum.
(1*R*,3*r*,5*S*)-Tropan-3-yl (*RS*)-mandelate.
$C_{16}H_{21}NO_3$=275.3
CAS — 87-00-3.
ATC — S01FA05.
ATC Vet — QS01FA05.
UNII — 8OS6WCL55Z.

Homatropine Hydrobromide *(BANM)*

Homatr. Hydrobrom.; Homatropiinihydrobromidi; Homatropina, hidrobromuro de; Homatropine, bromhydrate d'; Homatropin-hidrobromid; Homatropin-hydrobromid; Homatropinhydrobromid; Homatropini hydrobromidum; Homatropinium Bromide; Homatropino hidrobromidas; Homatropinum Bromatum; Homatropiny bromowodorek; Omatropina Bromidrato; Oxtolyltropine Hydrobromide; Tropyl Mandelate Hydrobromide.
$C_{16}H_{21}NO_3$,HBr=356.3
CAS — 51-56-9.
ATC — S01FA05.
ATC Vet — QS01FA05.
UNII — BEW7469QZ0.

NOTE. HOM is a code approved by the BP 2014 for use on single unit doses of eye drops containing homatropine hydrobromide where the individual container may be too small to bear all the appropriate labelling information.

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

Ph. Eur. 8: (Homatropine Hydrobromide). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; sparingly soluble in alcohol. A 5% solution in water has a pH of 5.0 to 6.5. Protect from light.

USP 36: (Homatropine Hydrobromide). White crystals or a white crystalline powder. Soluble 1 in 6 of water, 1 in 40 of alcohol, and 1 in 420 of chloroform; insoluble in ether. pH of a 2% solution in water is between 5.7 and 7.0. Store in airtight containers. Protect from light.

Homatropine Methylbromide *(BANM, rINN)*

Homatropiinimetyylibromidi; Homatropina, metilbromuro de; Homatropine Methobromide; Homatropine, Méthylbromure d'; Homatropini Methylbromidum; Homatropinmethylbromid; Homatropin-methylbromid; Homatropinmetilbromid; Homatropinmetylbromid; Homatropino metilbromidas; Methylhomatropinium Bromatum; Methylhomatropinium Bromide; Metilbromuro de homatropina; Гоматропина Метилбромид.
(1*R*,3*r*,5*S*)-3-[(±)-Mandeloyloxy]-8-methyltropanium bromide.
$C_{16}H_{21}NO_3.CH_3Br$=370.3
CAS — 80-49-9.
UNII — 68JRS2HC1C.

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

Ph. Eur. 8: (Homatropine Methylbromide). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol. A 5% solution in water has a pH of 4.5 to 6.5. Protect from light.

USP 36: (Homatropine Methylbromide). A white, odourless, powder that slowly darkens on exposure to light. Very soluble in water; freely soluble in alcohol and in acetone containing about 20% of water; practically insoluble in acetone and in ether. pH of a 5% solution in water is between 4.5 and 6.5. Store in airtight containers. Protect from light.

Uses and Administration

Homatropine is a tertiary amine antimuscarinic with effects similar to those of atropine (p. 1310.3). It is used as the hydrobromide, also a tertiary amine, to produce mydriasis and cycloplegia (p. 2000.2); its actions are more rapid and of shorter duration than those of atropine, but it is less potent and has a relatively weak cycloplegic effect. In general, onset of action is between 30 and 60 minutes, and recovery within 1 to 3 days. Homatropine hydrobromide is generally used as a 1, 2, or 5% ophthalmic solution. For the determination of refraction, instillation may be repeated if necessary 5 to 10 minutes later. In the treatment of uveitis (p. 1615.1), the eye drops should be instilled two or three times daily, or up to every 3 to 4 hours if required.

For details of doses in children, see below.

Homatropine has also been used as the quaternary ammonium methobromide derivative in the treatment of gastrointestinal spasm and as an adjunct in peptic ulcer disease; the methobromide has also been included in preparations used for the treatment of coughs.

Administration in children. The *BNFC* suggests that eye drops containing 0.5% homatropine hydrobromide may be instilled once daily or on alternate days, adjusted according to response, for uveitis in children aged 3 months to 2 years; older children may use 0.5 or 1% eye drops instilled twice daily, adjusted according to response.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1.

Ophthalmic use. Antimuscarinic toxicity (including ataxia, restlessness, excitement, hallucinations) has been reported in children[1] and the elderly[2,3] given homatropine eye drops.

1. Hoefnagel D. Toxic effects of atropine and homatropine eyedrops in children. *N Engl J Med* 1961; **264:** 168–71.
2. Reid D, Fulton JD. Tachycardia precipitated by topical homatropine. *BMJ* 1989; **299:** 795–6.
3. Tune LE, *et al.* Anticholinergic delirium caused by topical homatropine ophthalmologic solution: confirmation by anticholinergic radioreceptor assay in two cases. *J Neuropsychiatr Clin Neurosci* 1992; **4:** 195–7.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Antiespasmodico; Dallapasmo; Espasmotropin; Paratropina; ***Braz.***: Espasmo Flatol; Novatropina; ***Gr.***: Nopar; ***India***: Homarin; Homide; ***Mex.***: Homogrin; Infafren Simple†; Pasmolit†; ***Philipp.***: Lesopen; ***Singapore***: Hemasol; ***Spain***: Homatrop†; ***Venez.***: Litropina.

Multi-ingredient Preparations. ***Arg.***: Antispasmina; Asestor; Bellatotal; Bibol Leloup; Carbon Tabs; Colistop; Dimaval; Espasmo Ibuprofeno; Espasmofin; Factor AG Antiespasmodico; Hepatodirectol; Ibufem; Ibupirac Fem; Opoenterol; Paratropina Antigas; Paratropina Compuesta; Sumal; Teprix Fem; Zimerol; ***Braz.***: Espasmo Dimetiliv; Espasmo Luftal; Flagass Baby; Migrane; Sedalene; Sedalin†; Spasmotropin; Tropinal; ***Chile***: Codelasa; ***Gr.***: Colik; ***Hung.***: Neo-Bilagit; Troparinum; ***Mex.***: Bontal; Coralzul; Dialgin†; Facetin-D; Neopecsul; Neoxil; Threchop†; Yodozona; ***Philipp.***: Creamalin HM; ***Thai.***: Diaropect; Polyenzyme-I†; ***USA***: Hycodan†; Hydromet; Hydropane; Tussigon.

Pharmacopoeial Preparations
BP 2014: Homatropine Eye Drops;
USP 36: Homatropine Hydrobromide Ophthalmic Solution; Homatropine Methylbromide Tablets; Hydrocodone Bitartrate and Homatropine Methylbromide Tablets.

Latanoprost *(BAN, USAN, rINN)*

Latanoprost; Latanoprostum; PhXA-41; XA-41; Латанопрост.
Isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate.
$C_{26}H_{40}O_5$=432.6
CAS — 130209-82-4.
ATC — S01EE01.
ATC Vet — QS01EE01.
UNII — 6Z5B6HVF6O.

Pharmacopoeias. In *US.*

USP 36: (Latanoprost). A colourless to slightly yellow oil. Practically insoluble in water; freely soluble in acetone, in alcohol, in ethyl acetate, in isopropyl alcohol, in methyl alcohol, and in octanol; very soluble in acetonitrile. Store at a temperature of -25 degrees to 8 degrees. Protect from light.

Uses and Administration

Latanoprost is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$) that is used to reduce intra-ocular pressure in patients with open-angle glaucoma and ocular hypertension (p. 1999.1). Reduction of intra-ocular pressure starts about 3 to 4 hours after instillation and is maximal after 8 to 12 hours; pressure reduction lasts for at least 24 hours. A 0.005% ophthalmic solution is instilled once daily, preferably in the evening.

References.

1. Patel SS, Spencer CM. Latanoprost: a review of its pharmacological properties, clinical efficacy and tolerability in the management of primary open-angle glaucoma and ocular hypertension. *Drugs Aging* 1996; **9:** 363–78.
2. Einarson TR, *et al.* Meta-analysis of the effect of latanoprost and brimonidine on intraocular pressure in the treatment of glaucoma. *Clin Ther* 2000; **22:** 1502–15.
3. Zhang WY, *et al.* Meta-analysis of randomised controlled trials comparing latanoprost with timolol in the treatment of patients with open angle glaucoma or ocular hypertension. *Br J Ophthalmol* 2001; **85:** 983–90.
4. Feldman RM. An evaluation of the fixed-combination of latanoprost and timolol for use in open-angle glaucoma and ocular hypertension. *Expert Opin Pharmacother* 2004; **5:** 909–21.
5. Bayer A, *et al.* Clinical predictors of latanoprost treatment effect. *J Glaucoma* 2005; **14:** 260–3.
6. Nagar M, *et al.* A randomised, prospective study comparing selective laser trabeculoplasty with latanoprost for the control of intraocular pressure in ocular hypertension and open angle glaucoma. *Br J Ophthalmol* 2005; **89:** 1413–17.
7. Diestelhorst M, Larsson LI. European-Canadian Latanoprost Fixed Combination Study Group. A 12-week, randomized, double-masked, multicenter study of the fixed combination of latanoprost and timolol in the evening versus the individual components. *Ophthalmology* 2006; **113:** 70–6.
8. Pung AT, *et al.* Meta-analysis of randomised controlled trials comparing latanoprost with brimonidine in the treatment of open-angle glaucoma, ocular hypertension or normal-tension glaucoma. *Br J Ophthalmol* 2007; **91:** 62–8.
9. Varma R, *et al.* Using diurnal intraocular pressure fluctuation to assess the efficacy of fixed-combination latanoprost/timolol versus latanoprost or timolol monotherapy. *Br J Ophthalmol* 2010; **94:** 80–4.

Adverse Effects and Precautions

Latanoprost eye drops may produce a gradual increase in the amount of brown pigment in the iris, due to increased melanin content of melanocytes. This change in eye colour is most evident in patients with mixed colour irises, and may be permanent in some patients. The onset of iris pigmentation is usually within the first 8 months of treatment, rarely during the second or third year, and has not been seen after the fourth year of treatment. Darkening, thickening, and lengthening of eyelashes may occur and are reversible upon stopping treatment. Darkening of the palpebral skin has been reported rarely. Ocular irritation, conjunctival hyperaemia, transient punctate epithelial erosions and eyelid oedema may occur; there have also been rare reports of iritis and/or uveitis, and macular oedema. Systemic effects may also occur, see below for further details. Dizziness, headache, arthralgia, and myalgia have also been reported.

Effects on the eyes. Latanoprost has been associated with various adverse effects on the eyes, including case reports of cystoid macular oedema[1] and bilateral optic disc oedema.[2] Licensed product information states that reports of macular oedema have mainly occurred in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with risk factors for cystoid macular oedema such as those with diabetic retinopathy or retinal vein occlusion.

Herpes simplex dendritic keratitis developed in 2 patients during latanoprost therapy.[3] The author suggested that the biochemical changes in the cornea caused by latanoprost may predispose to herpes keratitis.

1. Wardrop DRA, Wishart PK. Latanoprost and cystoid macular oedema in a pseudophake. *Br J Ophthalmol* 1998; **82:** 843–4.
2. Stewart O, *et al.* Bilateral optic disc oedema associated with latanoprost. *Br J Ophthalmol* 1999; **83:** 1092–3.
3. Ekatomatis P. Herpes simplex dendritic keratitis after treatment with latanoprost for primary open angle glaucoma. *Br J Ophthalmol* 2001; **85:** 1008–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies latanoprost 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 25/10/11)

Systemic effects. The use of latanoprost eye drops has been associated with systemic adverse reactions. In a case report[1] of 2 patients with latanoprost-associated hypertension the authors mentioned that other events including peripheral and facial oedema, dyspnoea, exacerbation of asthma, tachycardia, and chest pain or angina pectoris had been reported. Another case report[2] also referred to exacerbation of angina. Although a study[3] involving 24 stable asthmatics found that latanoprost eye drops had no effect on pulmonary function or asthma symptoms, UK licensed product information recommends caution in patients with asthma.

1. Peak AS, Sutton BM. Systemic adverse effects associated with topically applied latanoprost. *Ann Pharmacother* 1998; **32:** 504–5.
2. Mitra M, *et al.* Exacerbation of angina associated with latanoprost. *BMJ* 2001; **323:** 783.
3. Hedner J, *et al.* Latanoprost and respiratory function in asthmatic patients: randomized, double-masked, placebo-controlled crossover evaluation. *Arch Ophthalmol* 1999; **117:** 1305–9.

Interactions

Paradoxical increases in intra-ocular pressure have been reported after the concomitant ophthalmic use of 2 prostaglandin analogues. UK licensed product information states that the use of 2 or more prostaglandin analogues or derivatives is not recommended.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Glaucogesic; Glaucostat; Klonaprost; Latanoflax†; Louten; Ocuprost; Oftal-Mix; Paraiop†; Tanamof; Xalatan; ***Austral.***: Xalatan; ***Austria***: Xalatan; ***Belg.***: Xalatan; ***Braz.***: Drenatan; Xalatan; ***Canad.***: Xalatan; ***Chile***: Gaap Ofteno; Gaax; Latof; Louten; Para Iop; Xalatan; ***China***: Latoprost (拉坦前列素); Xalatan (适利达); ***Cz.***: Arulatan; Glaucotens; Latalux; Solusin; Unilat; Xalatan; Xaloptic; ***Denm.***: Xalatan; ***Fin.***: Monoprost; Oftastad; Xalatan; ***Fr.***: Xalatan; ***Ger.***: Xalatan; ***Gr.***: Joxar; Latandrops; Lataneau; Lataz; X-lop; Xalaprost; Xalatan; ***Hong Kong***: Xalatan; ***Hung.***: Lanotan; Latapres; Xalatan; ***India***: 9PM; Ioprost; Ioptame; Latochek; Latodrops; Latoprost; ***Indon.***: Xalatan; ***Irl.***: Latacris; Latop; Proxal; Xalatan; Zanopro Plus; Zanopro; ***Israel***: Glautan; Xalatan; ***Ital.***: Xalatan; ***Malaysia***: Xalatan; ***Mex.***: Algun; Gaap Ofteno; Kevixkeni; Latsol; Pioprost; Xalatan; ***Neth.***: Arulatan†; Exprosol; Exsolut; Eylasol; Latusol; Monoprost; Optopress; Prolasol†; Soleye†; Sollat; Solusin; Xalatan; ***Norw.***: Glauprost; Xalatan; ***NZ***: Eyeprost; Hysite; Xalatan†; ***Philipp.***: Xalatan; ***Pol.***: Ocumer; Xalatan; Xaloptic; ***Port.***: Xalatan; ***Rus.***: Glauprost (Глаупрост); Xalatan (Ксалатан); ***S.Afr.***: Ocuprost; Xalatan; ***Singapore***: Xalatan; ***Spain***: Arulatan; Tonlit; Xalatan; Xalavista; Xelor; ***Swed.***: Xalatan; ***Switz.***: Latano-Vision; Latanomed; Monoprost; Xalatan; Xalos; ***Thai.***: Xalatan; ***Turk.***: Oftagen; Xalatan; ***UK***: Monopost; Xalatan; ***Ukr.***: Lanotan (Ланотан); Latanox (Латанокс); Xalatan (Ксалатан); ***USA***: Xalatan; ***Venez.***: Gaap Ofteno; Laprost; Latanopress; Xalatan.

Multi-ingredient Preparations. ***Arg.***: Glaucostat T; Latimodorf; Louten T; Ocuprostim; Xalacom; ***Austral.***: Xalacom; ***Austria***: Xalacom; ***Belg.***: Xalacom; ***Braz.***: Xalacom; ***Canad.***: Xalacom; ***Chile***: Gaax T; Latof-T; Xalacom; ***China***: Xalacom (适利加); ***Cz.***: Xalacom; ***Denm.***: Alatopran; Latanostad Comp; Latiotim; Xalacom†; Xalcom; ***Fin.***: Latiotim; Oftastad Comp; Xalcom; ***Fr.***: Xalacom; ***Ger.***: Xalacom; ***Gr.***: Tinoprost; Xalacom; ***Hong Kong***: Xalacom; ***Hung.***: Xalacom; ***India***: Laprost Plus; Latim; Latochek-T; Latocom; ***Indon.***: Xalacom; ***Irl.***: Codalux; Glaucotima; Lataneau Plus; Timlatan; Xalacom; Xaloptic Combi; ***Israel***: Xalacom; ***Ital.***: Tavu; Xalacom†; ***Malaysia***: Xalacom; ***Mex.***: Xalacom; ***Neth.***: Latim-POS; Xalacom; ***Norw.***: Latiotim; Xalcom; ***NZ***: Xalacom; ***Philipp.***: Xalacom; ***Pol.***: Xalacom; ***Port.***: Tavu; Xalacom; ***Rus.***: Xalacom (Ксалаком); ***S.Afr.***: Xalacom; ***Singapore***: Xalacom; ***Spain***: Latimvista; Xalacom; ***Swed.***: Latiotim; Xalcom; ***Switz.***: Co-Latanoprost; Xalacom; ***Thai.***: Xalacom; ***Turk.***: Xalacom; ***UK***: Xalacom; ***Ukr.***: Lanotan T (Ланотан T); Xalacom (Ксалаком); ***Venez.***: Xalacom.

Levobunolol Hydrochloride

(BANM, USAN, rINNM) ⊗

(−)-Bunolol Hydrochloride; *l*-Bunolol Hydrochloride; Hidrocloruro de levobunolol; Lévobunolol, Chlorhydrate de; Levobunolol, hidrocloruro de; Levobunolol Hidroklorür; Levobunololhydroklorid; Levobunololi Hydrochloridum; Levobunololihydrokloridi; W-7000A; Левобунолола Гидрохлорид.
(−)-5-(3-*tert*-Butylamino-2-hydroxypropoxy)-1,2,3,4-tetrahydronaphthalen-1-one hydrochloride.
$C_{17}H_{25}NO_3$,HCl=327.8
CAS — 47141-42-4 (levobunolol); 27912-14-7 (levobunolol hydrochloride).
ATC — S01ED03.
ATC Vet — QS01ED03.
UNII — O90S49LDHH.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Levobunolol Hydrochloride). A white or pinkish-white crystalline powder. Freely soluble in water; sparingly

soluble in alcohol. A 5% solution in water has a pH of between 4.5 and 6.5. Protect from light.

USP 36: (Levobunolol Hydrochloride). A white odourless crystalline powder. Soluble in water and in methyl alcohol; slightly soluble in alcohol and in chloroform. A 5% solution in water has a pH between 4.5 and 6.5.

Uses and Administration

Levobunolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to lack intrinsic sympathomimetic activity and membrane-stabilising properties.

Levobunolol is used as the hydrochloride to reduce raised intra-ocular pressure in open-angle glaucoma and ocular hypertension (p. 1999.1). It begins to act 1 hour after instillation with maximal effect seen between 2 and 6 hours; the effect may be maintained for up to 24 hours. Levobunolol hydrochloride is usually used as a 0.5% ophthalmic solution instilled once or twice daily; alternatively a 0.25% solution may be instilled twice daily.

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

Some systemic absorption is reported to occur after topical application to the eye. After oral doses levobunolol is rapidly and almost completely absorbed from the gastrointestinal tract. It is extensively metabolised in the liver; the principal metabolite, dihydrolevobunolol, is reported to possess beta-blocking activity. The metabolites and some unchanged drug are excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Betagan; Levunolol; *Austral.*: Betagan†; *Austria*: Vistagan; *Belg.*: Betagan; *Braz.*: B-Tablock; Betagan; *Canad.*: Betagan; *Chile*: Betagen; *China*: Betagan (贝他根); *Cz.*: Vistagan; *Fr.*: Betagan; *Ger.*: Vistagan; *Gr.*: Bunolol; Pentila; Vistagan; *Hong Kong*: Betagan; *Hung.*: Vistagan; *India*: Betagan; *Irl.*: Betagan; *Ital.*: Vistagan; *Malaysia*: Betagan; *Mex.*: Betagan; *Neth.*: Betagan; *NZ*: Betagan; *Port.*: Betagan; *S.Afr.*: Betagan; *Singapore*: Betagan; *Spain*: Betagan; *Switz.*: Vistagan; *Thai.*: Betagan; *Turk.*: Betagan; *UK*: Betagan; *USA*: Ak-Beta; Betagan†; *Venez.*: Vistagan.

Multi-ingredient Preparations. *Canad.*: Probeta†.

Pharmacopoeial Preparations
BP 2014: Levobunolol Eye Drops;
USP 36: Levobunolol Hydrochloride Ophthalmic Solution.

Methazolamide *(BAN, rINN)* ⊗

Metazolamida; Méthazolamide; Methazolamidum; Метазоламид.

N-(4-Methyl-2-sulphamoyl-Δ^2-1,3,4-thiadiazolin-5-ylidene) acetamide.

$C_5H_8N_4O_3S_2$=236.3

CAS — 554-57-4.

ATC — S01EC05.

ATC Vet — QS01EC05.

UNII — W733B0S9SD.

Pharmacopoeias. In *US.*

USP 36: (Methazolamide). A white or faintly yellow crystalline powder with a slight odour. Very slightly soluble in water and in alcohol; slightly soluble in acetone; soluble in dimethylformamide. Protect from light.

Uses and Administration

Methazolamide is an inhibitor of carbonic anhydrase with actions similar to those of acetazolamide (p. 2001.1). It is used in the treatment of glaucoma (p. 1999.1) in oral doses of 50 to 100 mg two or three times daily. Its action is less prompt but of longer duration than that of acetazolamide, lasting for 10 to 18 hours.

The diuretic activity of methazolamide is less pronounced than that of acetazolamide.

Adverse Effects and Precautions

As for Acetazolamide, p. 2002.1.

Hypersensitivity. Cholestatic hepatitis with jaundice, rash, and subsequent pure red cell aplasia was associated with methazolamide in a patient.[1] Drug-induced hypersensitivity was suspected as the cause of the reaction.

1. **Krivoy N, *et al.* Methazolamide-induced hepatitis and pure RBC aplasia.** *Arch Intern Med* **1981; 141: 1229–30.**

Pharmacokinetics

Methazolamide is absorbed from the gastrointestinal tract more slowly than acetazolamide. It has been reported not to be extensively bound to plasma proteins, and to have a half-life of about 14 hours. About 15 to 30% of the dose is excreted in the urine; the fate of the remainder is unknown.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ni Mu Ke Si (尼目克司); *Thai.*: Neptazane; *USA*: Neptazane.

Pharmacopoeial Preparations
USP 36: Methazolamide Tablets.

Metipranolol *(BAN, USAN, rINN)* ⊗

BMOI-004; Methypranolol; Métipranolol; Metipranololum; VUAB-6453 (SPOFA); VUFB-6453; Метипранолол.

1-(4-Acetoxy-2,3,5-trimethylphenoxy)-3-isopropylaminopropan-2-ol; 4-(2-Hydroxy-3-isopropylaminopropoxy)-2,3,6-trimethylphenyl acetate.

$C_{17}H_{27}NO_4$=309.4

CAS — 22664-55-7.

ATC — S01ED04.

ATC Vet — QS01ED04.

UNII — X39AL81KEB.

NOTE. MPR is a code approved by the BP 2014 for use on single unit doses of eye drops containing metipranolol where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Br.*

BP 2014: (Metipranolol). A white crystalline powder. Practically insoluble in water; soluble in alcohol, in acetone, and in methyl alcohol; dissolves in dilute mineral acids. The filtrate of a 2.5% suspension in water has a pH of 9.0 to 10.0. Protect from light.

Uses and Administration

Metipranolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to be largely lacking in intrinsic sympathomimetic activity and membrane-stabilising properties.

Metipranolol is used to reduce raised intra-ocular pressure in the management of open-angle glaucoma and ocular hypertension (p. 1999.1). Eye drops usually containing metipranolol 0.1 or 0.3% are used twice daily.

Metipranolol has also been given orally in the management of cardiovascular disorders.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Conjunctivitis, conjunctival leucoplakia, transient stinging, as well as other ocular adverse effects have been reported with metipranolol eye drops. Granulomatous anterior uveitis has been reported rarely; a high incidence reported in the UK may have been associated with changes induced by radiation sterilisation of metipranolol eye drops in their final container, but this preparation is no longer available.

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Beta-Ophtiole; *Belg.*: Beta-Ophtiole; *Braz.*: Beta-Ophtiole; *Cz.*: Trimepranol; *Ger.*: Betamann; *Ital.*: Turoptin; *Mon.*: Betanol; *Neth.*: Beta-Ophtiole; *Philipp.*: Beta-Ophtiole; *Pol.*: Betamann; *Port.*: Beta-Ophtiole†; *S.Afr.*: Beta-Ophtiole; *Singapore*: Beta-Ophtiole; *Turk.*: Turoptin; *USA*: OptiPranolol.

Multi-ingredient Preparations. *Austria*: Betacarpin; *Belg.*: Normoglucon†; *China*: Normoglucon (喏高康); *Ger.*: Normoglucon; *Gr.*: Beta Opthiole; Ripix; *Neth.*: Normoglucon†; *Pol.*: Normoglucon; *Port.*: Normoglucon†.

Pharmacopoeial Preparations
BP 2014: Metipranolol Eye Drops.

Nipradilol *(rINN)* ⊗

K-351; Nipradilolum; Нипрадилол.

8-[2-Hydroxy-3-(isopropylamino)propoxy]-3-chromanol 3-nitrate.

$C_{15}H_{22}N_2O_6$=326.3

CAS — 81486-22-8.

UNII — FVM336I71Y.

Profile

Nipradilol is a non-cardioselective beta blocker (p. 1316.3). It is also reported to have direct vasodilating activity. It is used in the management of glaucoma and ocular hypertension (p. 1999.1); eye drops containing nipradilol 0.05% are instilled twice daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Hypadil.

Physostigmine *(BAN)*

Eserina; Eserine; Fisostigmina; Fysostigmiini; Fysostigmin; Physostigminum.

(3a*S*,8a*R*)-1,2,3,3a,8,8a-Hexahydro-1,3a,8-trimethylpyrrolo[2,3-*b*]indol-5-yl methylcarbamate.

$C_{15}H_{21}N_3O_2$=275.4

CAS — 57-47-6.

ATC — S01EB05; V03AB19.

ATC Vet — QA03AX90; QA03FA90; QS01EB05; QV03AB19.

UNII — 9U1VM840SP.

Description. An alkaloid obtained from the calabar bean (ordeal bean; chopnut), the seed of *Physostigma venenosum* (Leguminosae).

Pharmacopoeias. In *US.*

USP 36: (Physostigmine). An alkaloid usually obtained from the dried ripe seed of *Physostigma venenosum* (Leguminosae). It is a white, odourless, microcrystalline powder which acquires a red tint on exposure to heat, light, or air, or on contact with traces of metals. M.p. not lower than 103 degrees. Slightly soluble in water; freely soluble in alcohol; very soluble in chloroform and in dichloromethane; soluble in fixed oils and in benzene. Store in airtight containers. Protect from light.

Physostigmine Salicylate *(BANM)*

Eserine Salicylate; Ésérine, salicylate d'; Eserini Salicylas; Ezerino salicilatas; Fisostigmina, salicilato de; Fizostigmino salicilatas; Fizostygminy salicylan; Fizosztigmin-szalicilát; Fysostigmiinisalisylaatti; Fysostigminsalicylat; Fysostigmin-salicylát; Physostig. Sal.; Physostigmine Monosalicylate; Physostigmini Salicylas; Physostigminsalicylat.

$C_{15}H_{21}N_3O_2.C_7H_6O_3$=413.5

CAS — 57-64-7.

ATC — S01EB05; V03AB19.

ATC Vet — QS01EB05; QV03AB19.

UNII — 2046ZRO9VU.

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

Ph. Eur. 8: (Physostigmine Salicylate). Colourless or almost colourless crystals. It becomes red on exposure to air and light; the colour develops more quickly in the presence of moisture. Sparingly soluble in water; soluble in alcohol. A 0.9% solution in water has a pH of 5.1 to 5.9. Store in airtight containers. Protect from light. Aqueous solutions are unstable.

USP 36: (Physostigmine Salicylate). White, shining, odourless, crystals or white powder. It acquires a red tint on exposure to heat, light, or air, or on contact with traces of metals for long periods. Soluble 1 in 75 of water, 1 in 16 of alcohol, 1 in 6 of chloroform, and 1 in 250 of ether. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Stability. See p. 2010.1.

Physostigmine Sulfate *(BANM)*

Ésérine, sulfate d'; Eserine Sulphate; Eserini Sulfas; Ezerino sulfatas; Fisostigmina, sulfato de; Fizostigmino sulfatas; Fizosztigmin-szulfát; Fysostigmiinisulfaatti; Fysostigminsulfat; Fysostigmin-sulfát; Physostig. Sulph.; Physostigmine Sulphate; Physostigmini Sulfas; Physostigminsulfat; Sulfato de eserina.

$(C_{15}H_{21}N_3O_2)_2.H_2SO_4$=648.8

CAS — 64-47-1.

ATC — S01EB05; V03AB19.

ATC Vet — QS01EB05; QM03AB19.
UNII — G63V2J2N7I.

Pharmacopoeias. In *US.*

USP 36: (Physostigmine Sulfate). A white, odourless, microcrystalline powder. It is deliquescent in moist air, and acquires a red tint on exposure to heat, light, or air, or on contact with traces of metals for long periods. Soluble 1 in 4 of water, 1 in 0.4 of alcohol, and 1 in 1200 of ether. Store in airtight containers. Protect from light.

Stability. In aqueous solutions physostigmine is hydrolysed to eseroline and subsequently oxidised to the red compound rubreserine and other coloured products. Solutions for injection or ophthalmic use should not be used if more than slightly discoloured.

Uses and Administration

Physostigmine is a reversible tertiary amine inhibitor of cholinesterase activity with actions similar to those of neostigmine (p. 687.2). Physostigmine has been used, alone or more usually with other miotics such as pilocarpine, to decrease intra-ocular pressure in glaucoma; it has been given as eye drops containing the salicylate or as an ophthalmic ointment containing the sulfate. Physostigmine is a more potent miotic than pilocarpine but is rarely tolerated for prolonged periods.

Physostigmine crosses the blood-brain barrier and has been used parenterally to reverse the central as well as the peripheral effects of agents with antimuscarinic actions after overdosage but such treatment is not usually recommended.

Antimuscarinic poisoning. As physostigmine penetrates the blood-brain barrier it has been used to reverse the central effects of poisoning with agents that have antimuscarinic actions including tricyclic antidepressants, antihistamines, some antiemetics, some antiparkinsonian drugs, and phenothiazines. However, reviewers agree that in general such use is inappropriate and hazardous. Physostigmine does not appear to affect the mortality rate in tricyclic antidepressant poisoning[1] and its use can lead to severe cardiac[2,3] and respiratory effects[2,3] and to convulsions.[2,4]

1. Aquilonius S-M, Hedstrand U. The use of physostigmine as an antidote in tricyclic anti-depressant intoxication. *Acta Anaesthesiol Scand* 1978; 22: 40–5.
2. Newton RW. Physostigmine salicylate in the treatment of tricyclic antidepressant overdosage. *JAMA* 1975; 231: 941–3.
3. Caine ED. Anticholinergic toxicity. *N Engl J Med* 1979; 300: 1278.
4. Knudsen K, Heath A. Effects of self poisoning with maprotiline. *BMJ* 1984; 288: 601–3.

Baclofen overdosage. For references to the use of physostigmine in the treatment of baclofen overdosage, see p. 2016.1.

Cerebellar ataxias. Double-blind controlled studies indicate that physostigmine[1,2] can produce symptomatic improvement in some patients with cerebellar ataxia including those with hereditary forms of spinocerebellar degeneration such as Friedreich's ataxia. However, another study did not show any significant improvement in patients given physostigmine for cerebellar ataxia.[3]

1. Rodriguez-Budelli MM, *et al.* Action of physostigmine on inherited ataxias. *Adv Neurol* 1978; 21: 195–202.
2. Aschoff JC, *et al.* Physostigmin in der Behandlung von Kleinhirnataxien. *Nervenarzt* 1996; 67: 311–18.
3. Wessel K, *et al.* Double-blind crossover study with physostigmine in patients with degenerative cerebellar diseases. *Arch Neurol* 1997; 54: 397–400.

Dementia. Physostigmine has been studied in the symptomatic management of Alzheimer's disease (see Dementia, p. 388.1). However, a systematic review concluded that the evidence of its efficacy was limited and the benefits shown were not convincing.[1] Small early studies with oral physostigmine in Alzheimer's disease were inconclusive; a larger multicentre study[2] using controlled-release physostigmine found that it produced some improvement in cognitive and global function, but gastrointestinal adverse effects were common and led to a high drop-out rate.

1. Coelho Filho JM, Birks J. Physostigmine for dementia due to Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 17/03/06).
2. Thal LJ, *et al.* A 24-week randomized trial of controlled-release physostigmine in patients with Alzheimer's disease. *Neurology* 1999; 52: 1146–52.

Adverse Effects, Treatment, and Precautions

Systemic effects as for Neostigmine, p. 688.2, although usually more severe. Physostigmine crosses the blood-brain barrier and may therefore produce CNS effects.

For adverse effects and precautions for topical miotics see also under Pilocarpine, p. 2011.2. Physostigmine is not well tolerated when used in the eyes for long periods and may produce follicles in the conjunctiva; hypersensitivity reactions are also common. Prolonged use of ophthalmic ointments containing physostigmine may cause depigmentation of the lid margins in dark-skinned patients.

Overdosage. Symptomatic and supportive treatment, including the use of diazepam and atropine where necessary, is generally recommended for systemic toxicity due to physostigmine. However, in an early report, the use of atropine in a patient who had taken 1 g of physostigmine had to be abandoned after it produced tachycardia and multifocal ventricular ectopic beats.[1] In a similar case of severe poisoning a slow intravenous injection of propranolol 5 mg reduced the high pulse rate and controlled pulse irregularities permitting frequent intravenous doses of atropine.[2]

1. Cumming G, *et al.* Treatment and recovery after massive overdosage of physostigmine. *Lancet* 1968; ii: 147–9.
2. Valero A. Treatment of severe physostigmine poisoning. *Lancet* 1968; ii: 459–60.

Interactions

As for Neostigmine, p. 688.3.

Pharmacokinetics

Physostigmine is readily absorbed from the gastrointestinal tract, subcutaneous tissues, and mucous membranes. It is largely destroyed in the body by hydrolysis of the ester linkage by cholinesterases; a parenteral dose is claimed to be destroyed within 2 hours. It crosses the blood-brain barrier. Little is excreted in the urine.

Small studies suggest marked interindividual differences in the absorption and metabolism of physostigmine salicylate after oral doses of up to 4 mg, perhaps because of saturable presystemic metabolism.[1-3] Oral bioavailability ranged from 5.2 to 11.7% in 3 of 5 subjects.[3]

In a study[4] of a single application of a physostigmine (base) transdermal system in 6 subjects, the mean absolute bioavailability was 36% (range 12.6 to 53.2%); the interindividual variability in absolute bioavailability was decreased by about 30% in comparison with an oral solution of physostigmine salicylate. There was continued absorption of physostigmine after removal of the transdermal system, indicating a drug reservoir in the skin.

In a study[5] of 9 patients with Alzheimer's disease, a mean elimination half-life for physostigmine of 16.4 minutes was reported with intravenous physostigmine salicylate. Cholinesterase inhibition was more prolonged than suggested by its elimination half-life.

1. Gibson M, *et al.* Physostigmine concentrations after oral doses. *Lancet* 1985; i: 695–6.
2. Sharpless NS, Thal LJ. Plasma physostigmine concentrations after oral administration. *Lancet* 1985; i: 1397–8.
3. Whelpton R, Hurst P. Bioavailability of oral physostigmine. *N Engl J Med* 1985; 313: 1293–4.
4. Walker K, *et al.* Pharmacokinetics of physostigmine in man following a single application of a transdermal system. *Br J Clin Pharmacol* 1995; 39: 59–63.
5. Asthana S, *et al.* Clinical pharmacokinetics of physostigmine in patients with Alzheimer's disease. *Clin Pharmacol Ther* 1995; 58: 299–309.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria:* Anticholium; *Cz.:* Anticholium; *Ger.:* Anticholium; *Gr.:* Anticholium; *Singapore:* Antilirium.

Multi-ingredient Preparations. *India:* Bi-Miotic†.

Pharmacopoeial Preparations
USP 36: Physostigmine Salicylate Injection; Physostigmine Salicylate Ophthalmic Solution; Physostigmine Sulfate Ophthalmic Ointment.

Pilocarpine *(BAN)*

Pilocarpina; Pilocarpinum; Pilokarpiini; Pilokarpin.
(3*S*,4*R*)-3-Ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl) methyl]furan-2(3*H*)-one.
$C_{11}H_{16}N_2O_2$=208.3
CAS — 92-13-7.
ATC — N07AX01; S01EB01.
ATC Vet — QN07AX01; QS01EB01.
UNII — 01MI4Q9DI3.

Description. An alkaloid obtained from the leaves of jaborandi, *Pilocarpus microphyllus* (Rutaceae) and other species of *Pilocarpus.*

Pharmacopoeias. In *US.*

USP 36: (Pilocarpine). A viscous, exceedingly hygroscopic, oily liquid or crystals. M.p. about 34 degrees. Soluble in water, in alcohol, and in chloroform; sparingly soluble in ether and in benzene; practically insoluble in petroleum spirit. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Pilocarpine Borate

Pilocarpina, borato de.
$C_{11}H_{16}N_2O_2xBH_3O_3$
CAS — 16509-56-1.
ATC — N07AX01; S01EB01.
ATC Vet — QN07AX01; QS01EB01.

Pilocarpine Hydrochloride *(BANM)*

Pilocarp. Hydrochlor.; Pilocarpina, hidrocloruro de; Pilocarpine, chlorhydrate de; Pilocarpine Monohydrochloride; Pilocarpinhydrochlorid; Pilocarpini Chloridum; Pilocarpini hydrochloridum; Pilocarpinium Chloratum; Pilokarpilnihydrokloridi; Pilokarpin Hidroklorür; Pilokarpin-hidroklorid; Pilokarpin-hydrochlorid; Pilokarpinhydroklorid; Pilokarpino hidrochloridas; Pilokarpiny chlorowodorek.
$C_{11}H_{16}N_2O_2$,HCl=244.7
CAS — 54-71-7.
ATC — N07AX01; S01EB01.
ATC Vet — QN07AX01; QS01EB01.
UNII — 0WW6D218XJ.

NOTE. PIL is a code approved by the BP 2014 for use on single unit doses of eye drops containing pilocarpine hydrochloride where the individual container may be too small to bear all the appropriate labelling information.

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

Ph. Eur. 8: (Pilocarpine Hydrochloride). Hygroscopic, colourless crystals or white or almost white crystalline powder. M.p. about 203 degrees. Very soluble in water; freely soluble in alcohol. A 5% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

USP 36: (Pilocarpine Hydrochloride). Colourless, translucent, odourless, hygroscopic crystals. Soluble 1 in 0.3 of water, 1 in 3 of alcohol, and 1 in 360 of chloroform; insoluble in ether. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Stability. Pilocarpine hydrochloride oral solution, prepared from powder or eye drops and buffered at pH 5.5, was found[1] to be stable for 60 days at 25 degrees and for 90 days at 4 degrees.

1. Fawcett JP, *et al.* Formulation and stability of pilocarpine oral solution. *Int J Pharm Pract* 1994; 3: 14–18.

Pilocarpine Nitrate *(BANM)*

Pilocarp. Nit.; Pilocarpina, nitrato de; Pilocarpine Mononitrate; Pilocarpine, nitrate de; Pilocarpini Nitras; Pilocarpinii Nitras; Pilocarpinium Nitricum; Pilocarpinnitrat; Pilokarpiininitraatti; Pilokarpinnitrat; Pilokarpin-nitrát; Pilokarpino nitratas.
$C_{11}H_{16}N_2O_2$,HNO_3=271.3
CAS — 148-72-1.
ATC — N07AX01; S01EB01.
ATC Vet — QN07AX01; QS01EB01.
UNII — M20T465H6J.

NOTE. PIL is a code approved by the BP 2014 for use on single unit doses of eye drops containing pilocarpine nitrate where the individual container may be too small to bear all the appropriate labelling information.

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

Ph. Eur. 8: (Pilocarpine Nitrate). Colourless crystals, or white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol. A 5% solution in water has a pH of 3.5 to 4.5. Protect from light.

USP 36: (Pilocarpine Nitrate). Shining white crystals. Soluble 1 in 4 of water and 1 in 75 of alcohol; insoluble in chloroform and in ether. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Uses and Administration

Pilocarpine is a direct-acting tertiary amine parasympathomimetic that has the muscarinic effects of acetylcholine (p. 2003.2). It is used mainly in the treatment of glaucoma (p. 1999.1) and in the treatment of dry eye (p. 2190.1) or dry mouth (p. 2011.1); it has also been used as a diaphoretic in diagnostic tests for cystic fibrosis and leprosy (p. 2011.1). Topical application of pilocarpine to the eye produces miosis (pupil constriction) by contraction of the iris sphincter muscle; contraction of the ciliary muscle results in increased accommodation. Constriction of the pupil also pulls open the trabecular meshwork in the eye and this in turn facilitates drainage of aqueous humour and reduction of intra-ocular pressure. After the use of eye drops, miosis occurs in about 10 to 30 minutes and lasts 4 to 8 hours while peak reduction in intra-ocular pressure occurs within 75 minutes and the reduction usually persists for 4 to 14 hours.

Pilocarpine is used in the treatment of open-angle **glaucoma** (but see also Glaucoma, under Adverse Effects, p. 2011.2) and is commonly given with topical beta blockers

or sympathomimetics. It is used as the hydrochloride or the nitrate, usually as 0.5 to 4% eye drops instilled up to 4 times daily, adjusted according to response. Solutions containing up to 6% of the hydrochloride may also be available and the higher strengths may sometimes be required in patients with heavily pigmented irides. A 4% ophthalmic gel has also been used. Pilocarpine may be used before surgery as part of the emergency treatment of acute attacks of angle-closure glaucoma.

The miotic action of pilocarpine has been used to antagonise the effects of sympathomimetic mydriatics on the eye and in surgical procedures on the eye. Pilocarpine borate has been used similarly in ophthalmology to the hydrochloride and nitrate.

Pilocarpine hydrochloride is used in the treatment of **dry mouth** following radiotherapy for malignant neoplasms of the head and neck. It increases salivary flow only in patients with residual salivary gland function. The initial oral dose is 5 mg three times daily with or immediately after meals, increased gradually if necessary after 4 weeks until an adequate response is obtained, up to a maximum of 10 mg three times daily. Oral doses of 5 mg four times daily are used to treat **dry eye** or mouth in patients with Sjögren's syndrome; this dose may be increased to a maximum of 30 mg daily. Treatment should be stopped if no improvement occurs after 3 months of use. For doses in patients with hepatic impairment, see below.

Administration in hepatic impairment. UK licensed product information recommends that daily doses of *oral* pilocarpine should be reduced in patients with moderate to severe cirrhosis. The dose may gradually be increased to 5 mg three times daily if tolerated.

In the USA, licensed information suggests that the starting oral dose of pilocarpine should be 5 mg twice daily in patients with moderate hepatic impairment (Child-Pugh category B); it is not recommended in those with severe impairment (Child-Pugh category C) because of a lack of pharmacokinetic studies in these patients.

Diagnosis and testing. *CYSTIC FIBROSIS.* The fact that individuals with cystic fibrosis have abnormally high concentrations of sodium and chloride in their sweat has been used in the diagnosis of this condition and pilocarpine iontophoresis has been used to promote sweating as part of that test.[1] Despite the fact that neonatal genetic screening for cystic fibrosis-causing mutations is now possible, sweat testing using pilocarpine iontophoresis remains the gold standard for diagnosis, and can help avoid the small likelihood of diagnostic error.[2,3] US guidelines[3] note that sweat electrolytes may be transiently elevated during the first 24 hours of life, but sweat testing may be performed from 48 hours onward if an adequate sample can be obtained.

1. Gibson LE, Cooke RR. A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis. *Pediatrics* 1959; 23: 545–9.
2. Parad RB, *et al.* Sweat testing infants detected by cystic fibrosis newborn screening. *J Pediatr* 2005; 147 (suppl): S69–S72.
3. LeGrys VA, *et al.* Diagnostic sweat testing: the Cystic Fibrosis Foundation guidelines. *J Pediatr* 2007; 151: 85–9.

LEPROSY. The induction of sweat secretion by intradermal injection of pilocarpine nitrate has been used to assess the functional status of dermal nerves in patients with leprotic skin lesions.[1]

1. Joshi PB. Pilocarpine test in assesment of therapeutic efficacy in maculoanaesthetic leprosy. *Lepr India* 1976; 48: 55–60.

Dry mouth. Pilocarpine is used as a sialogogue in the treatment of dry mouth (p. 2175.3) after radiotherapy of the head and neck,[1,2] although benefit may not be entirely related to preservation of salivation.[3,4] A systematic review[5] based on 3 studies found limited evidence to support such use; although about half of the patients responded to pilocarpine, response did not occur in some for up to 12 weeks and adverse effects were common. Pilocarpine may also be of use in the management of drug-induced oral dryness,[6,7] and is used as a treatment for dry mouth and dry eye in the auto-immune disease, Sjögren's syndrome.[1,8–11]

1. Wiseman LR, Faulds D. Oral pilocarpine: a review of its pharmacological properties and clinical potential in xerostomia. *Drugs* 1995; 49: 143–55.
2. Taylor SE. Efficacy and economic evaluation of pilocarpine in treating radiation-induced xerostomia. *Expert Opin Pharmacother* 2003; 4: 1489–97.
3. Gorsky M, *et al.* The efficacy of pilocarpine and bethanechol upon saliva production in cancer patients with hyposalivation following radiation therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; 97: 190–5.
4. Gornitsky M, *et al.* Double-blind randomized, placebo-controlled study of pilocarpine to salvage salivary gland function during radiotherapy of patients with head and neck cancer. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; 98: 45–52.
5. Davies AN, Shorthose K. Parasympathomimetic drugs for the treatment of salivary gland dysfunction due to radiotherapy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 10/06/08).
6. Götrick B, *et al.* Oral pilocarpine for treatment of opioid-induced oral dryness in healthy adults. *J Dent Res* 2004; 83: 393–7.
7. Masters KJ. Pilocarpine treatment of xerostomia induced by psychoactive medications. *Am J Psychiatry* 2005; 162: 1023.
8. Nelson JD, *et al.* Oral pilocarpine for symptomatic relief of keratoconjunctivitis sicca in patients with Sjögren's syndrome. *Adv Exp Med Biol* 1998; 438: 979–83.
9. Vivino FB, *et al.* Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren syndrome: a randomized, placebo-controlled, fixed-dose, multicenter trial. *Arch Intern Med* 1999; 159: 174–81.
10. Tzifetaki N, *et al.* Oral pilocarpine for the treatment of ocular symptoms in patients with Sjögren's syndrome: a randomised 12 week controlled study. *Ann Rheum Dis* 2003; 62: 1204–7.
11. Baudouin C, *et al.* Traitements actuels de la xérophtalmie dans le syndrome de Gougerot-Sjögren. *Rev Med Interne* 2004; 25: 376–82.

Reversal of mydriasis. Pilocarpine has been used to reverse the effects of mydriatics after surgery or ophthalmoscopic examination but other miotics may be preferred (see p. 2000.3). It counteracts the mydriatic effects of sympathomimetics, such as phenylephrine and hydroxyamfetamine,[1] but is ineffective against mydriasis produced by antimuscarinics, such as homatropine,[1] and may impair vision further when used with tropicamide.[2] Furthermore, there is also the risk of pilocarpine precipitating angle-closure glaucoma in susceptible patients (see Glaucoma, under Precautions, below and also Glaucoma, in Tropicamide, p. 2012.3).

1. Anastasi LM, *et al.* Effect of pilocarpine in counteracting mydriasis. *Arch Ophthalmol* 1968; 79: 710–15.
2. Nelson ME, Orton HP. Counteracting the effects of mydriatics: does it benefit the patient? *Arch Ophthalmol* 1987; 105: 486–9.

Adverse Effects, Treatment, and Precautions

Systemic effects and cautions are as for Neostigmine, p. 688.2.

With the *oral* use of pilocarpine, sweating is a common problem; caution is needed to avoid dehydration in patients who may sweat excessively and who cannot maintain an adequate fluid intake. Paradoxical hypertension and constipation, confusion, and increased urinary frequency have also been reported. Licensed product information states that it should not be given when miosis is undesirable such as in patients with acute iritis or angle-closure glaucoma. Blurred vision or dizziness may affect the performance of skilled tasks including driving. In addition pilocarpine should be given with care to those with cognitive or psychiatric disturbances, with renal calculi or renal impairment, or with biliary-tract disorders. Dosage should be reduced in patients with hepatic impairment (see Administration in Hepatic Impairment, above).

After *ocular* use pilocarpine is usually better tolerated than the anticholinesterases, but in common with other miotics may produce ciliary spasm, ocular pain and irritation, blurred vision, lachrymation, myopia, and browache. Conjunctival vascular congestion, superficial keratitis, vitreous haemorrhage, and increased pupillary block have been reported. Lens opacities have occurred after prolonged use. Treatment with miotics should be stopped if symptoms of systemic toxicity develop.

Miotics are contra-indicated in conditions where pupillary constriction is undesirable such as acute iritis, acute uveitis, anterior uveitis, and some forms of secondary glaucoma. They should be avoided in acute inflammatory disease of the anterior segment of the eye. If possible, treatment with long-acting miotics should be stopped before surgery on the eye as there is an increased risk of hyphaema. Miotics should be used with extreme caution in patients with a history of retinal detachment and in young patients with myopia. Care is also needed in patients with corneal or conjunctival damage. Miosis may cause blurred vision and difficulty with dark adaptation and caution is necessary with night driving or when hazardous tasks are undertaken in poor illumination. Miotics should not be used by patients wearing soft contact lenses.

Asthma. A reminder that topical miotics can precipitate bronchospasm in susceptible patients.[1] However, the severity of the reaction induced by carbachol has been reported to be less than that produced by timolol. Bronchospastic complications are much less likely to occur with pilocarpine but have nevertheless been reported. As inhalations of methacholine are used to induce bronchospasm in the diagnosis of latent asthma, the risk of exacerbating asthma should be considered before methacholine is used in the eye.

1. Prakash UBS, *et al.* Pulmonary complications from ophthalmic preparations. *Mayo Clin Proc* 1990; 65: 521–9.

Dementia. In patients with dementia of Alzheimer type, CNS symptoms may be induced or exacerbated by the use of pilocarpine eye drops.[1,2]

1. Reyes PF, *et al.* Mental status changes induced by eye drops in dementia of the Alzheimer type. *J Neurol Neurosurg Psychiatry* 1987; 50: 113–15.
2. Praunfelder FT, Morgan R. The aggravation of dementia by pilocarpine. *JAMA* 1994; 271: 1742–3.

Glaucoma. Miotics usually lower intra-ocular pressure by decreasing the resistance to outflow of aqueous humour from the anterior chamber through the trabecular network. However, they appear to reduce uveoscleral outflow and this may cause a paradoxical rise in intra-ocular pressure in patients with severely compromised trabecular outflow as was reported in a patient with post-traumatic angle-recession glaucoma.[1] It has been recommended that pilocarpine should be avoided after drainage operations for glaucoma because its miotic effect can increase the occurrence of posterior pupillary synechiae; a topical beta blocker is usually adequate if control of intra-ocular pressure is required.[2] Pilocarpine-induced miosis was shown to cause a significant deterioration in visual field in patients with chronic open-angle glaucoma.[3] It was suggested that this should be an important consideration when choosing therapy for glaucoma, particularly in cases where field loss approaches the permitted legal minimum for driving. Of 53 patients receiving long-term therapy with pilocarpine gel, 15 developed a corneal haze, which persisted for at least 2 years in 13; although the patients remained asymptomatic the long-term effects were unknown.[4] Many patients using the gel also developed superficial punctate keratitis which usually cleared spontaneously during treatment.

1. Bietman BS, Schwartz AL. Paradoxical intraocular pressure response to pilocarpine: a proposed mechanism and treatment. *Arch Ophthalmol* 1979; 97: 1305–6.
2. Phillips CI, *et al.* Posterior synechiae after glaucoma operations: aggravation by shallow anterior chamber and pilocarpine. *Br J Ophthalmol* 1987; 71: 428–32.
3. Webster AR, *et al.* The effect of pilocarpine on the glaucomatous visual field. *Br J Ophthalmol* 1993; 77: 721–5.
4. Johnson DH, *et al.* Corneal changes during pilocarpine gel therapy. *Am J Ophthalmol* 1986; 101: 13–15.

Hypersensitivity. Contact urticaria involving the eyelids has been reported[1] in a patient after treatment with pilocarpine eye drops for glaucoma.

1. O'Donnell BF, Foulds IS. Contact allergic dermatitis and contact urticaria due to topical ophthalmic preparations. *Br J Ophthalmol* 1993; 77: 740–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pilocarpine 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 25/10/11)

Retinal detachment. The use of miotics has been implicated in many reports as a cause of retinal detachment but reviews of the subject have concluded that there is little factual evidence to support the association.[1,2] However, there is circumstantial evidence that retinal detachment is more likely to occur with strong miotics. Furthermore, patients with myopia or pre-existing retinal damage appear to be at greater risk and there is the possibility that even low concentrations of relatively mild miotics such as 1% pilocarpine might precipitate retinal detachment.

1. Alpar JJ. Miotics and retinal detachment: a survey and case report. *Ann Ophthalmol* 1979; 11: 395–401.
2. Beasley H, Praunfelder FT. Retinal detachments and topical ocular miotics. *Ophthalmology* 1979; 86: 95–8.

Systemic absorption. Systemic adverse effects after the ophthalmic use of pilocarpine are thought to be rare and reports of toxicity mainly involve elderly patients treated for acute angle-closure glaucoma before surgery and given relatively high doses.[1,2] It may not be feasible to stop the miotic in these circumstances. In a report of psychotic reaction in such a patient,[2] pilocarpine was continued but the patient was instructed on how to minimise absorption by closing the lachrymal canal; an atypical antipsychotic with minimal antimuscarinic effects (risperidone) was also given.

1. Everitt DE, Avorn J. Systemic effects of medications used to treat glaucoma. *Ann Intern Med* 1990; 112: 120–5.
2. Sirois FJ. Pilocarpine psychosis. *Psychosomatics* 2005; 46: 88.

Interactions

As for Neostigmine, p. 688.3.

Pharmacokinetics

Mean elimination half-lives for pilocarpine have been reported to be 0.76 and 1.35 hours after repeated oral doses of 5 and 10 mg of the hydrochloride, respectively. Inactivation of pilocarpine is thought to occur at neuronal synapses and probably in plasma. About 30% of an oral dose is excreted in the urine as pilocarpine and its inactive metabolites, including pilocarpic acid; the fate of the remaining 70% is unknown. Data from *animal* studies indicate that pilocarpine is distributed into breast milk at concentrations similar to those in the plasma.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Isopto Carpina; Klonocarpina; Omadopil; Pilocarpol†; Pilomed†; Sonadryl; Tensiocap†; Wetol; Xao Pil†; *Austral.*: Isopto Carpine; Pilopt†; PV Carpine†;

Austria: Pilorcarpin Puroptal; Salagen; ***Belg.***: Isopto Carpine; Pilo; Salagen; ***Braz.***: Isopto Carpine; Pilocan; Pilosol; ***Canad.***: Akarpine; Diocarpine; Isopto Carpine; Pilopine HS; Salagen; ***Chile***: Pilogel; ***China***: Rui Er Xin (瑞尔欣); Zhenrui (真瑞); ***Cz.***: Pilogel; Pilopos†; ***Fin.***: Isopto Carpine; Salagen; ***Fr.***: Pilo; Salagen; ***Ger.***: Pilomann-Ol; Pilomann; Pilopos†; Salagen; Spersacarpin; ***Gr.***: Cidren; Dispercarpine; Isopto Carpine; Pilocollyre; Pilofar; Pilogel; Pilotina; Prothenol; Saglion; Salagen; Salivoral; Sumario; Ugetin; Xerocarp; ***Hong Kong***: Isopto Carpine; Salagen; ***Hung.***: Humacarpin; Salagen; ***India***: Andre Carpine; Carpine; Carpinol; Carpo-Miotic†; Carporen; Locarp; Pilocar; ***Indon.***: Miokar; ***Irl.***: Pilogel†; Salagen†; ***Israel***: Mi-Pilo; Salagen; ***Ital.***: Dropilton; Salagen; ***Malaysia***: Isopto Carpine; ***Mex.***: Calipreneț; Pil; Pilo; ***Neth.***: Pilogel†; Salagen; ***Norw.***: Isopto Carpine†; ***NZ***: Ocusert†; Pilopt; ***Philipp.***: Isopto Carpine; ***Port.***: Salagen; ***Rus.***: Oftan Pilocarpin (Офтан Пилокарпин); ***S.Afr.***: Isopto Carpine; Pilogel; ***Singapore***: Isopto Carpine†; Opticar; Pilogel†; Salagen; ***Spain***: Isopto Carpina; Salagen; ***Swed.***: Salagen; ***Switz.***: Salagen; Spersacarpine; ***Thai.***: Isopto Carpine; Salagen†; ***Turk.***: Pilogel; Pilokarsol; Pilosed; Salagen; ***UK***: Pilogel†; Salagen; ***USA***: Adsorbocarpine†; Akarpine†; Isopto Carpine; Ocu-Carpine†; Pilocar†; Pilopine HS; Piloptic†; Pilopto-Carpine†; Pilostat†; Salagen; ***Venez.***: Pilocar.

Multi-ingredient Preparations. ***Arg.***: Amplus; Glaucotensil; Pilotim; ***Austral.***: Timpilo†; ***Austria***: Betacarpin; Fotil; Normastigmin mit Pilocarpin; Thiloadren†; ***Belg.***: Carteopil†; Normoglaucon†; ***China***: Normoglaucon (哌高康); ***Cz.***: Fotil; ***Denm.***: Fotil; ***Fin.***: Fotil; ***Fr.***: Carpilo†; Pilobloq†; ***Ger.***: Fotil; Glauko Biciron; Normoglaucon; TP-Ophtal; ***Gr.***: Dropiltim; Fotil; Ripix; Ryvina; T+P; Thilocombin; Timpilo; Yvano; ***Hong Kong***: Timpilo†; ***Hung.***: Fotil; ***India***: Bi-Miotic†; Iotim-Plus; ***Israel***: Timpilo†; ***Ital.***: Equiton; Pilobloc; Timicon; ***Neth.***: Fotil†; Normoglaucon†; ***Norw.***: Fotil; ***NZ***: Timpilo; ***Philipp.***: Fotil; ***Pol.***: Fotil†; Normoglaucon; ***Port.***: Normoglaucon†; Timoglau Plus†; ***Rus.***: Fotil (Фотил); Pilotimol (Пилотимол); Proxocarpine (Проксокарпин); ***Swed.***: Fotil; ***Switz.***: Arteopilo†.

Pharmacopoeial Preparations
BP 2014: Pilocarpine Hydrochloride Eye Drops; Pilocarpine Nitrate Eye Drops;
USP 36: Pilocarpine Hydrochloride Ophthalmic Solution; Pilocarpine Hydrochloride Tablets; Pilocarpine Nitrate Ophthalmic Solution; Pilocarpine Ocular System.

Tafluprost *(BAN, USAN, rINN)*

AFP-168; DE-085; MK-2452; Tafluprostum; Тафлупрост.
Isopropyl (5*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-2-[(1*E*)-3,3-difluoro-4-phenoxybut-1-enyl]-3,5-dihydroxycyclopentyl}hept-5-enoate.
$C_{25}H_{34}F_2O_5$=452.5
CAS — 209860-87-7.
ATC — S01EE05.
ATC Vet — QS01EE05.
UNII — 1O6WQ6T7G3.

Profile

Tafluprost is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$) that is used to reduce intra-ocular pressure in the treatment of open-angle glaucoma and ocular hypertension (p. 1999.1), either alone or as adjunctive therapy with a topical beta blocker. Reduction of intra-ocular pressure starts about 2 to 4 hours after instillation and is maximal after 12 hours; pressure reduction lasts for at least 24 hours. A 0.0015% ophthalmic solution is instilled once daily, preferably in the evening.

References.

1. Hamacher T, *et al.* Efficacy and safety levels of preserved and preservative-free tafluprost are equivalent in patients with glaucoma or ocular hypertension: results from a pharmacodynamics analysis. *Acta Ophthalmol Suppl (Oxf)* 2008; 242: 14–19.
2. Egorov E, *et al.* Adjunctive use of tafluprost with timolol provides additive effects for reduction of intraocular pressure in patients with glaucoma. *Eur J Ophthalmol* 2009; 19: 214–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Saflutan; ***Belg.***: Saflutan; ***Braz.***: Saflutan; ***Cz.***: Taflotan; ***Denm.***: Taflotan; ***Fin.***: Taflotan; ***Fr.***: Saflutan; ***Ger.***: Taflotan; ***Hong Kong***: Taflotan; ***Irl.***: Saflutan; ***Israel***: Saflutan; ***Neth.***: Saflutan; ***Norw.***: Taflotan; ***Pol.***: Taflotan; ***Singapore***: Taflotan; ***Spain***: Saflutan; ***Swed.***: Taflotan; ***Switz.***: Saflutan; ***Thai.***: Taflotan; ***UK***: Saflutan; ***USA***: Zioptan.

Travoprost *(BAN, USAN, rINN)*

AL-6221; Travoprosti; Travoprostum; Травопрост.
Isopropyl (*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(1*E*,3*R*)-3-hydroxy-4-[(α,α,α-trifluoro-*m*-tolyl)oxy]-1-butenyl]cyclopentyl}-5-heptenoate
$C_{26}H_{35}F_3O_6$=500.6
CAS — 157283-68-6.
ATC — S01EE04.
ATC Vet — QS01EE04.
UNII — WJ68R08KX9.

Pharmacopoeias. In *US*.

USP 36: (Travoprost). A clear, colourless, viscous oil. Insoluble in water. Store at -25 degrees to -15 degrees under nitrogen in airtight containers. Protect from light.

Uses and Administration

Travoprost is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$). It is used in the treatment of open-angle glaucoma and ocular hypertension (p. 1999.1), as a 0.004% ophthalmic solution instilled once daily, preferably in the evening. The reduction in pressure starts about 2 hours after instillation and is maximal after 12 hours; the effect is maintained for at least 24 hours.

References.

1. Ang GS, *et al.* The effect of travoprost on daytime intraocular pressure in normal tension glaucoma: a randomised controlled trial. *Br J Ophthalmol* 2008; 92: 1129–33.
2. Kammer JA, *et al.* Efficacy and tolerability of bimatoprost versus travoprost in patients previously on latanoprost: a 3-month, randomised, masked-evaluator, multicentre study. *Br J Ophthalmol* 2010; 94: 74–9.

Adverse Effects and Precautions

As for Latanoprost, p. 2008.2.

Effects on the eyes. Severe iritis and corneal oedema developed in an elderly woman 3 weeks after restarting travoprost after eye surgery;[1] rechallenge was positive. The authors commented that the UK MHRA was aware of one other case of uveitis associated with travoprost.

1. Kumarasamy M, Desai SP. Anterior uveitis is associated with travoprost. *BMJ* 2004; 329: 205.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies travoprost 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 25/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Arvo; Glaucoprost; Glaunot; Travatan; ***Austral.***: Travatan; ***Austria***: Travatan; ***Belg.***: Travatan; ***Braz.***: Travamed; Travatan; ***Canad.***: Travatan; ***Chile***: Travatan; ***China***: Travatan (苏为坦); ***Cz.***: Travatan; ***Denm.***: Travatan; ***Fin.***: Travatan; ***Fr.***: Travatan; ***Ger.***: Travatan; ***Gr.***: Travatan; ***Hong Kong***: Travatan; ***Hung.***: Travatan; ***India***: Lupitros; ***Indon.***: Travatan; ***Irl.***: Travatan; ***Israel***: Travatan; ***Ital.***: Travatan; ***Malaysia***: Travatan; ***Mex.***: Travatan; ***Neth.***: Travatan; ***Norw.***: Travatan; ***NZ***: Travatan; ***Philipp.***: Travatan; ***Pol.***: Travatan; ***Port.***: Travatan; ***Rus.***: Travatan (Травatан); ***S.Afr.***: Travatan; ***Singapore***: Travatan; ***Spain***: Travatan; ***Swed.***: Travatan; ***Switz.***: Travatan; ***Thai.***: Travatan; ***Turk.***: Travatan; ***UK***: Travatan; ***Ukr.***: Travatan (Травatан); ***USA***: Travatan; ***Venez.***: Travatan.

Multi-ingredient Preparations. ***Arg.***: DuoTrav; Neoprost; ***Austria***: DuoTrav; ***Belg.***: DuoTrav; ***Canad.***: DuoTrav; ***Chile***: DuoTrav; ***Cz.***: DuoTrav; ***Denm.***: DuoTrav; ***Fr.***: DuoTrav; ***Ger.***: DuoTrav; ***Gr.***: DuoTrav; ***Hong Kong***: DuoTrav; ***Hung.***: DuoTrav; ***Irl.***: DuoTrav; ***Israel***: DuoTrav; ***Ital.***: DuoTrav; ***Malaysia***: DuoTrav; ***Neth.***: DuoTrav; ***Norw.***: DuoTrav; ***NZ***: DuoTrav; ***Philipp.***: DuoTrav; ***Pol.***: DuoTrav; ***Port.***: DuoTrav; ***S.Afr.***: DuoTrav; ***Singapore***: DuoTrav; ***Spain***: DuoTrav; ***Swed.***: DuoTrav; ***Switz.***: DuoTrav; ***Thai.***: DuoTrav; ***Turk.***: DuoTrav; ***UK***: DuoTrav.

Pharmacopoeial Preparations
USP 36: Travoprost Ophthalmic Solution.

Tropicamide *(BAN, USAN, rINN)*

Bistropamide; Ro-1-7683; Tropicamid; Tropicamida; Tropicamidum; Tropikamid; Tropikamidas; Tropikamidi; Тропикамид.
N-Ethyl-*N*-(4-pyridylmethyl)tropamide; (2*RS*)-*N*-Ethyl-3-hydroxy-2-phenyl-*N*-(pyridin-4-ylmethyl)propanamide.
$C_{17}H_{20}N_2O_2$=284.4
CAS — 1508-75-4.
ATC — S01FA06.
ATC Vet — QS01FA06.
UNII — N0A3Z5XTC6.

NOTE. TRO is a code approved by the BP 2014 for use on single unit doses of eye drops containing tropicamide where the individual container may be too small to bear all the appropriate labelling information.

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

Ph. Eur. 8: (Tropicamide). A white or almost white, crystalline powder. M.p. 95 degrees to 98 degrees. Slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Tropicamide). A white or practically white crystalline powder, odourless or having not more than a slight odour. M.p. 96 degrees to 100 degrees. Slightly soluble in water; freely soluble in chloroform and in solutions of strong acids. Store in airtight containers. Protect from light.

Uses and Administration

Tropicamide is a tertiary amine antimuscarinic with actions similar to those of atropine (p. 1310.3). It is used as eye drops to produce mydriasis and cycloplegia (p. 2000.2). It has a more rapid onset and a shorter duration of effect than atropine: mydriasis is produced within 20 to 40 minutes of use and usually lasts for about 6 hours; cycloplegia is maximal within about 30 minutes and is short-lasting, with complete recovery of accommodation normally within 6 hours. Tropicamide has been reported to be inadequate for cycloplegia in children.

To produce **mydriasis**, a 0.5% ophthalmic solution is instilled 15 to 20 minutes before examination of the eye. To produce **cycloplegia** a 1% solution is used and repeated after 5 minutes; a further instillation may be necessary to prolong the effect after 20 to 30 minutes.

Dementia. Tropicamide has been studied for use in the differential diagnosis of Alzheimer's disease (see Dementia, p. 388.1). Excessive pupil dilatation in response to tropicamide eye drops occurred in patients with signs and symptoms of Alzheimer's disease.[1] However, a double-blind placebo-controlled study[2] in similar patients and healthy subjects indicated that this was not a reliable diagnostic test for Alzheimer's disease.

1. Gómez-Tortosa E, *et al.* Pupil response to tropicamide in Alzheimer's disease and other neurodegenerative disorders. *Acta Neurol Scand* 1996; 94: 104–9.
2. Graff-Radford NR, *et al.* Tropicamide eyedrops cannot be used for reliable diagnosis of Alzheimer's disease. *Mayo Clin Proc* 1997; 72: 495–504.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1.

References.
1. Vuori M-L, *et al.* Systemic absorption and anticholinergic activity of topically applied tropicamide. *J Ocul Pharmacol* 1994; 10: 431–7.

Glaucoma. The use of mydriatics is considered liable to provoke an acute attack in patients with glaucoma or a tendency to glaucoma; licensed product information generally contra-indicates their use in such patients. However, a systematic review concluded that in fact a history of open-angle glaucoma did not predispose to acute angle closure under mydriasis, and that mydriasis with tropicamide in particular appeared to be safe and should be recommended in all patients when thorough retinal examination was indicated.[1] In contrast, the use of pilocarpine to reverse mydriatics was potentially harmful.

1. Pandit RJ, Taylor R. Mydriasis and glaucoma: exploding the myth. A systematic review. *Diabet Med* 2000; 17: 693–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tropicamide 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 25/10/11)

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Mydril; ***Austral.***: Mydriacyl; ***Austria***: Mydriaticum; ***Belg.***: Mydriacyl; Tropicol; ***Braz.***: Ciclomidrin; Mydriacyl; Tropinom; ***Canad.***: Diotrope; Mydriacyl; Tropicacyl; ***Chile***: Mydriacyl; ***China***: Mydrin-M (美多丽灵); Runzheng (润正); ***Cz.***: Mydrum†; Unitropic; ***Denm.***: Mydriacyl; ***Fr.***: Mydriaticum; ***Ger.***: Mydriaticum; Mydrum; ***Gr.***: Tropixal; ***Hong Kong***: Mydriacyl; ***Hung.***: Mydrum†; ***India***: Meptrop; Optimide; Tmide; Tropico†; ***Indon.***: Midric; ***Irl.***: Mydriacil†; ***Israel***: Mydramide; ***Ital.***: Tropimil; Visumidriatic; ***Malaysia***: Mydriacyl; ***Mex.***: Myriacyl; ***NZ***: Mydriacyl; ***Philipp.***: Mydriacyl; ***Port.***: Tropicil Top; ***Rus.***: Mydriacyl (Мидриацил); Mydrum (Мидрум); ***S.Afr.***: Mydriacyl; Mydriaticum; ***Singapore***: Mydriacyl†; Triacyl; ***Swed.***: Mydriacyl; ***Switz.***: Mydriaticum; ***Thai.***: Mydriacyl; ***Turk.***: Tropamid; ***UK***: Mydriacyl; ***Ukr.***: Mydriacil (Мидриацил); ***USA***: Mydral; Mydriacyl; Ocu-Tropic; Opticyl; Tropicacyl; ***Venez.***: Mydriacyl.

Multi-ingredient Preparations. ***Arg.***: Fotorretin; Midria Phoenix; Midriax-T; Sensu; Tropioftal P; ***Belg.***: Mydriasert; ***Canad.***: Diophenyl-T; Phenyltrope; ***China***: Mydrin-P (美多丽); ***Denm.***: Mydriasert; ***Fin.***: Mydriasert; ***Fr.***: Mydriasert; ***Ger.***: Mydriasert; ***Hong Kong***: Mydrin-P; ***India***: Drosyn-T; Itrop Plus; Meptrop-P; Optimide Plus; Tropico Plus†; ***Ital.***: Mydriasert; Visumidriatic Fenilefrina; ***Mex.***: Augex; ***Neth.***: Mydriasert; ***Philipp.***: Sanmyd-P;

Port.: Mydriasert; *Spain*: Mydriasert; *Swed.*: Mydriasert; *Switz.*: Mydriasert; *UK*: Mydriasert; *USA*: Paremyd; *Venez.*: Fotorretin.

Pharmacopoeial Preparations
BP 2014: Tropicamide Eye Drops;
USP 36: Tropicamide Ophthalmic Solution.

Unoprostone Isopropyl *(rINNM)*

Isopropyl Lunoprostone; Isopropyl Unoprostone; UF-021; Unoprostona de isopropilo; Unoprostone, Isopropyle d'; Unoprostoni Isopropylas; Унопростона Изопропил.

Isopropyl (+)-(*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-(3-oxodecyl)cyclopentyl]-5-heptenoate.

$C_{25}H_{44}O_5$=424.6

CAS — 120373-36-6 (unoprostone); 120373-24-2 (unoprostone isopropyl).

ATC — S01EE02.

ATC Vet — QS01EE02.

UNII — 5M161S5O5P.

Profile

Unoprostone, like latanoprost (p. 2008.1), is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$). It is used as the isopropyl ester for the treatment of glaucoma and ocular hypertension (p. 1999.1). Ophthalmic solutions containing unoprostone isopropyl 0.12 or 0.15% may be instilled twice daily.

References.
1. de Arruda Mello PA, *et al.* Safety of unoprostone isopropyl as mono- or adjunctive therapy in patients with primary open-angle glaucoma or ocular hypertension. *Drug Safety* 2002; **25**: 583–97.
2. Chiba T, *et al.* Comparison of iridial pigmentation between latanoprost and isopropyl unoprostone: a long term prospective comparative study. *Br J Ophthalmol* 2003; **87**: 956–9.
3. Stewart WC, *et al.* The safety and efficacy of unoprostone 0.15% versus brimonidine 0.2%. *Acta Ophthalmol Scand* 2004; **82**: 161–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Rescula; *Braz.*: Rescula; *Chile*: Rescula†; Cz.: Rescula†; *Hung.*: Rescula†; *Jpn*: Rescula; *Mex.*: Rescula; *Philipp.*: Rescula; *Rus.*: Rescula (Рескула); *Thai.*: Rescula†; *USA*: Rescula; *Venez.*: Rescula.

Muscle Relaxants

The muscle relaxants included in this chapter are used in the management of musculoskeletal and neuromuscular disorders. There are 2 main types:

- **centrally acting relaxants**—these generally have a selective action on the CNS and are principally used for relieving painful muscle spasms or spasticity occurring in musculoskeletal and neuromuscular disorders. Their mechanism of action may be due to their CNS-depressant activity. Baclofen and tizanidine are two examples.
- **directly acting relaxants**—dantrolene is a drug that has a direct action on skeletal muscle and is used for the relief of spasticity associated with a variety of conditions.

Also included in this chapter are **botulinum toxins A and B**, which inhibit the release of acetylcholine at the motor nerve terminals.

Some benzodiazepines are also used in the treatment of muscle spasms; further details may be found under Diazepam, p. 1063.2.

Other drugs that block transmission at the neuromuscular junction and are used as adjuncts to general anaesthesia are discussed in the chapter on Neuromuscular Blockers, p. 2028.1.

Drugs used to relax *smooth muscle* include the various antispasmodics (p. 1803.3) used for their antimuscarinic or direct smooth-muscle relaxant effects in the management of gastrointestinal disorders, as well as some other drugs such as papaverine (p. 2362.2).

Muscle spasm

Spasm is a painful involuntary contraction of muscle that can cause involuntary movement, interfere with function, and cause distortion. It is a symptom of many muscular and other types of disorders and treatment should mainly be aimed at the underlying cause. Centrally acting muscle relaxants and benzodiazepines are used to treat muscle spasms such as *splinting* that occur in response to local trauma or musculoskeletal and joint disorders. Splinting is a reflex muscular spasm that produces muscular rigidity and acts as a protective mechanism to prevent movement and further damage of the affected part. Short courses of muscle relaxants may be considered in the management of acute low back pain (p. 9.2).

Cramps are muscle spasms of abrupt onset that occur at rest and usually last for a few seconds or minutes. They are often precipitated by dehydration and hyponatraemia produced by vigorous exercise, excessive sweating, diarrhoea, and vomiting, or may be associated with drug therapy or haemodialysis (see Haemodialysis-induced Cramp, p. 1779.3). Pregnant women, the elderly, and those with peripheral vascular disease, appear to be particularly susceptible to night cramps of the feet or legs, the cause of which is not well understood.

The management of muscle cramps has been reviewed.[1-4] Quinine has traditionally been used for *nocturnal cramps* but there has been concern over its efficacy and potential for adverse effects, especially in the elderly. Meta-analyses[5,6] have indicated that although quinine was modestly effective in the treatment of nocturnal cramps in ambulatory patients the risk of serious adverse effects should be borne in mind; patients should be closely monitored over a period of at least 4 weeks while the efficacy of quinine was assessed. In the UK, it is recommended that treatment should be stopped every 3 months to see whether it is still needed.[7] In the USA, the FDA has ruled that quinine products should no longer be used for the management of nocturnal cramps.[8,9] There is little convincing evidence to support the use of other drugs.[1-4,8]

A systematic review[10] concluded that magnesium (as the lactate and citrate) is modestly effective in the treatment of *leg cramps in pregnancy*; calcium salts were ineffective, and although early evidence suggested benefit with sodium chloride, high doses were required with their attendant cardiovascular risks.

1. McGee SR. Muscle cramps. *Arch Intern Med* 1990; 150: 511–18.
2. Butler JV, *et al.* Nocturnal leg cramps in older people. *Postgrad Med J* 2002; 78: 596–8.
3. Katzberg HD, *et al.* Assessment: symptomatic treatment for muscle cramps (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2010; 74: 691–6. Also available at: http://www.neurology.org/cgi/reprint/74/8/691.pdf (accessed 09/07/10)
4. Guay DR. Are there alternatives to the use of quinine to treat nocturnal leg cramps? *Consult Pharm* 2008; 23: 141–56.
5. Man-Son-Hing M, Wells G. Meta-analysis of efficacy of quinine for treatment of nocturnal leg cramps in elderly people. *BMJ* 1995; 310: 13–17.
6. Man-Son-Hing M, *et al.* Quinine for nocturnal leg cramps: a meta-analysis including unpublished data. *J Gen Intern Med* 1998; 13: 600–606.
7. Anonymous. Quinine for nocturnal leg cramps? *Drug Ther Bull* 1996; 34: 7–8.
8. FDA. Drug products for the treatment and/or prevention of nocturnal leg muscle cramps for over-the-counter human use. *Fed Regist* 1994; 59: 43234–52.
9. Nightingale SL. Quinine for nocturnal leg cramps. *ACP J Club* 1995; 123: 86.
10. Young GL, Jewell D. Interventions for leg cramps in pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 16/06/05).

Spasticity

The term spasticity has been loosely applied to various disorders of motor control resulting from CNS disease and marked by effects such as increased muscle tone, exaggerated stretch reflexes, impaired voluntary movement, weakness, loss of dexterity, abnormal posture, and often disturbed gait. In some patients muscle spasm and pain may be more distressing than impaired movement. Other complications may include contractures, pressure sores, and infection. Spasticity is a feature of neurological conditions such as multiple sclerosis, cerebral palsy, head injury, and stroke, particularly if there are spinal lesions.

Spasticity is disabling and difficult to treat when severe, but mild or moderate forms may be effectively managed by conservative treatment. Some patients may even rely on spasticity to provide a means of posture control and care should be taken that treatment does not lead to increased disability.

Various discussions on the management of spasticity have been published.[1-11] The mainstay of management is physiotherapy and antispastic drugs, although the evidence for the latter is rather scanty.[9,12,13] Baclofen, dantrolene, diazepam, and tizanidine are the drugs most often used. These 4 drugs act via different mechanisms, which are not fully understood.

Baclofen is thought to act at the spinal cord level but may also have supraspinal sites of action. It is a powerful neuronal depressant and may exert its inhibitory effects by acting as an agonist at GABA (gamma aminobutyric acid) receptors. *Diazepam* is also thought to act centrally by enhancing the response to GABA. In contrast, *dantrolene* acts directly on muscles, possibly by interfering with the release of calcium from muscular sarcoplasmic reticulum needed for contraction. *Tizanidine* is a centrally acting relaxant and α-adrenergic agonist; it is thought to act at spinal and supraspinal levels by inhibiting the presynaptic activity of excitatory interneurones.[7] It can produce additive effects with baclofen, allowing a reduction in the dosage of both drugs; use with benzodiazepines is not recommended because of the potential for interactions. All these are usually given orally but baclofen may also be given intrathecally in severe chronic spasticity.[10,14,15] Injection directly into the spinal subarachnoid space allows immediate delivery to the site of action in the spinal cord and the use of considerably lower doses than those given orally. It has been reported[16] that some patients receiving long-term intrathecal baclofen treatment have been able to stop their therapy without symptoms of spasticity reappearing, and that others have been able to reduce the dosage required.

Other drugs that may produce some benefit or are being studied in spasticity include *other benzodiazepines, clonidine, gabapentin,* and *memantine.*

Alternative approaches to treatment include nerve blocks using *local anaesthetics*; they should generally only be used when further muscle relaxation would not increase disability. *Chemical neurolysis* using alcohol or phenol is only considered when there is intractable continuous pain. Local injections of *botulinum A toxin* have produced some encouraging results in the management of limb spasticity in post-stroke or spinal injury patients and in children with cerebral palsy;[17-19] its temporary effect may be an advantage over chemical neurolysis but the need for regular injections may limit acceptability in children.[17] In children with cerebral palsy, a systematic review[20] has found insufficient evidence to support or refute such use in those with lower limb spasticity; however, another systematic review[21] has found the use of botulinum A toxin as an adjunct to occupational therapy to be effective in the management of upper limb spasticity.

Nondrug treatments have included electrical stimulation techniques such as transcutaneous nerve stimulation and dorsal column stimulation; vibration applied to agonist spastic muscles to improve voluntary movement; cooling to decrease afferent inputs from peripheral receptors; and orthopaedic surgery or neurosurgery.

1. Young RR. Spasticity: a review. *Neurology* 1994; 44 (suppl 9): S12–S20.
2. Ko CK, Ward AB. Management of spasticity. *Br J Hosp Med* 1997; 58: 400–5.
3. Kita M, Goodkin DE. Drugs used to treat spasticity. *Drugs* 2000; 59: 487–95.
4. Anonymous. The management of spasticity. *Drug Ther Bull* 2000; 38: 44–6.
5. Bhakta BB. Management of spasticity in stroke. *Br Med Bull* 2000; 56: 476–85.
6. Burchiel KJ, Hsu FPK. Pain and spasticity after spinal cord injury: mechanisms and treatment. *Spine* 2001; 26 (suppl): S146–S160.
7. Ward AB. A summary of spasticity management – a treatment algorithm. *Eur J Neurol* 2002; 9 (suppl 1): 48–52.
8. Abbruzzese G. The medical management of spasticity. *Eur J Neurol* 2002; 9 (suppl 1): 30–4.
9. Montané E, *et al.* Oral antispastic drugs in nonprogressive neurologic diseases: a systematic review. *Neurology* 2004; 63: 1357–63.
10. Verrotti A, *et al.* Pharmacotherapy of spasticity in children with cerebral palsy. *Pediatr Neurol* 2006; 34: 1–6.
11. Delgado MR, *et al.* Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2010; 74: 336–43. Also available at: http://www.neurology.org/cgi/reprint/74/4/336.pdf (accessed 09/07/10)
12. Tarkka M, *et al.* Pharmacological interventions for spasticity following spinal cord injury. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 16/06/05).
13. Shakespeare DT, *et al.* Anti-spasticity agents for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 16/06/05).
14. McLean BN. Intrathecal baclofen in severe spasticity. *Br J Hosp Med* 1993; 49: 262–7.
15. Anonymous. Intrathecal baclofen for spasticity. *Med Lett Drugs Ther* 1994; 36: 21–2.
16. Dressnandt J, Conrad B. Lasting reduction of severe spasticity after ending chronic treatment with intrathecal baclofen. *J Neurol Neurosurg Psychiatry* 1996; 60: 168–73.
17. Neville B. Botulinum toxin in the cerebral palsies. *BMJ* 1994; 309: 1526–7.
18. Fried GW, Fried KM. Spinal cord injury and use of botulinum toxin in reducing spasticity. *Phys Med Rehabil Clin N Am* 2003; 14: 901–10.
19. Preiss RA, *et al.* The effects of botulinum toxin (BTX-A) on spasticity of the lower limb and on gait in cerebral palsy. *J Bone Joint Surg Br* 2003; 85: 943–8.
20. Ade-Hall RA, Moore AP. Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 07/05/08).
21. Hoare BJ, *et al.* Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy (UPDATE). Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 28/01/10).

Afloqualone *(rINN)*

Aflocualona; Afloqualonum; HQ-495; Афлоквалон.

6-Amino-2-fluoromethyl-3-o-tolylquinazolin-4(3*H*)-one.

$C_{16}H_{14}FN_3O$=283.3

CAS — 56287-74-2.

UNII — CO4U2C8ORZ.

NOTE. The names Aflozon, Airomate, Anapolet, Anmetolon, Arostowa, and Ohsiat have been used as trade marks for afloqualone.

Pharmacopoeias. In *Jpn*.

Profile

Afloqualone is a centrally acting skeletal muscle relaxant that has been given orally for the treatment of muscle spasm associated with musculoskeletal conditions. Photosensitivity reactions have been reported.

References.

1. Ishikawa T, *et al.* Photoleukomelanodermatitis (Kobori) induced by afloqualone. *J Dermatol* 1994; 21: 430–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Arofuto.

Baclofen *(BAN, USAN, rINN)*

Aminomethyl Chlorohydrocinnamic Acid; Ba-34647; Baclofène; Baclofeno; Baclofenum; Baklofeeni; Baklofen; Baklofén; Baklofenas; Баклофен.

β-Aminomethyl-*p*-chlorohydrocinnamic acid; (*RS*)-Amino-3-(4-chlorophenyl)butyric acid.

$C_{10}H_{12}ClNO_2$=213.7

CAS — 1134-47-0.

ATC — M03BX01.

ATC Vet — QM03BX01.

UNII — H789N3FKE8 (baclofen); NYU6UTW25B (R-baclofen); 3OHN4989XM (S-baclofen).

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

Ph. Eur. 8: (Baclofen). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water; very slightly soluble in alcohol; practically insoluble in acetone; dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

USP 36: (Baclofen). A white to off-white, odourless or practically odourless, crystalline powder. Slightly soluble in water; very slightly soluble in methyl alcohol; insoluble in chloroform. Store in airtight containers.

Uses and Administration

Baclofen, an analogue of gamma-aminobutyric acid (p. 2509.2), is a centrally acting skeletal muscle relaxant. It interferes with the release of excitatory neurotransmitters and inhibits monosynaptic and polysynaptic transmission at the spinal cord level. It may also act at supraspinal sites producing CNS depression. Baclofen is one of the drugs commonly used for the symptomatic relief of severe chronic spasticity associated with a variety of conditions.

Baclofen is given *orally* in divided doses, preferably with or after food or milk. The initial dose of baclofen is 15 mg daily, increased gradually according to response. A suggested regimen is 5 mg three times daily for 3 days, increased to 10 mg three times daily for 3 days, then in similar increments and intervals until either a dose of 20 mg three times daily is reached or until the desired therapeutic effect is obtained. Higher doses have been used: doses of more than 80 to 100 mg daily are not generally recommended although doses of up to 150 mg daily have been given to carefully supervised patients.

Elderly patients should receive lower initial doses, although final maintenance doses may be in the same range as younger adults. For dosage in renal impairment, see below.

If no benefit is apparent within 6 weeks of achieving the maximum dosage, therapy should probably be gradually withdrawn.

Baclofen is also given *by continuous intrathecal infusion* in the treatment of spasticity in patients intolerant of, or unresponsive to, oral antispastic therapy including baclofen. Before beginning the intrathecal regimen any existing antispastic therapy should be gradually withdrawn to avoid overdosage or drug interactions. Intrathecal test doses are given initially to determine if there is going to be any benefit before implanting a controlled infusion pump. It is important that patients are monitored closely in experienced centres during screening and immediately after implantation of the infusion pump and that resuscitation equipment is available for immediate use.

Test doses start at 25 or 50 micrograms given over at least 1 minute and are increased by 25 micrograms at intervals of not less than 24 hours until a dose of 100 micrograms is reached or a positive response of about 4 to 8 hours is obtained. Patients who fail to respond to a test dose of 100 micrograms are considered to be unsuitable for intrathecal treatment.

For patients showing a positive response lasting for longer than 8 to 12 hours, the test dose that was required to produce the response can then be given as a 24-hour infusion; if the response to the test dose lasted 8 to 12 hours or less, then a dose equivalent to twice the test dose is given. Daily dosage can then be adjusted as required. Maintenance doses range from about 12 micrograms to 2 mg daily in those with spasticity of spinal origin, with most patients being adequately maintained on 300 to 800 micrograms daily. In those with spasticity of cerebral origin, maintenance doses range from about 22 micrograms to 1.4 mg daily, with a mean of 276 micrograms daily at 12 months and 307 micrograms daily at 24 months.

For details of dosage in children, see below.

Administration in children. Baclofen is one of the drugs commonly used for the symptomatic relief of severe chronic spasticity associated with a variety of conditions in children. UK licensed product information recommends, in children from birth to 18 years of age, an initial *oral* dose of 300 micrograms/kg daily, preferably in 4 divided doses, increased gradually at intervals of about 1 week until the desired therapeutic effect is obtained; maintenance doses range from 750 micrograms/kg to 2 mg/kg daily. The total daily dose should not exceed 40 mg in children under 8 years of age and 60 mg in those aged from 8 to 18 years.

Baclofen is also given *by continuous intrathecal infusion* in the treatment of severe chronic spasticity of spinal or cerebral origin in children intolerant of, or unresponsive to, oral antispastic therapy including baclofen. An initial test dose of 25 to 50 micrograms is recommended in children aged 4 to 18 years (see above for further dosing details); initial maintenance doses range from 25 to 200 micrograms daily (median daily dose 100 micrograms).

Administration in renal impairment. Doses of baclofen should be reduced in renal impairment or in patients undergoing chronic haemodialysis; oral doses of 5 mg daily have been suggested in UK licensed product information (but see also under Precautions, p. 2016.3).

Alcohol withdrawal and abstinence. Reviews[1-3] of baclofen in both the treatment of alcohol withdrawal syndrome and maintenance of abstinence (p. 1734.1) have shown promising results and that it was well tolerated; however, the optimal dose and duration have yet to be established. Increased sedation may occur when baclofen is used in patients likely to ingest alcohol (see Interactions, p. 2016.3), however, a study[4] found that performance was not impaired to a greater extent with concomitant use than with the use of baclofen or alcohol alone.

1. Leggio L, *et al.* Effectiveness and safety of baclofen in the treatment of alcohol dependent patients. *CNS Neurol Disord Drug Targets* 2010; 9: 33–44.
2. Liu J, Wang L. Baclofen for alcohol withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2011 (accessed 03/04/12).
3. Muzyk AJ, *et al.* Defining the role of baclofen for the treatment of alcohol dependence: a systematic review of the evidence. *CNS Drugs* 2012; 26: 69–78.
4. Evans SM, Bisaga A. Acute interaction of baclofen in combination with alcohol in heavy social drinkers. *Alcohol Clin Exp Res* 2009; 33: 19–30.

Dystonias. There have been reports of improvement in patients with various forms of dystonia (p. 903.3) treated with baclofen[1-5] although there has also been a report[6] of a patient whose condition deteriorated during baclofen therapy.

1. Narayan RK, *et al.* Intrathecal baclofen for intractable axial dystonia. *Neurology* 1991; 41: 1141–2.
2. Greene PE, Fahn S. Baclofen in the treatment of idiopathic dystonia in children. *Mov Disord* 1992; 7: 48–52.
3. van Hilten BJ, *et al.* Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. *N Engl J Med* 2000; 343: 625–30.
4. Albright AL, *et al.* Intrathecal baclofen for generalized dystonia. *Dev Med Child Neurol* 2001; 43: 652–7.
5. Jaffe MS, Nienstedt LJ. Intrathecal baclofen for generalized dystonia: a case report. *Arch Phys Med Rehabil* 2001; 82: 853–5.
6. Silbert PL, Stewart-Wynne EG. Increased dystonia after intrathecal baclofen. *Neurology* 1992; 42: 1639–40.

Gastro-oesophageal reflux disease. Baclofen has been tried in the treatment of gastro-oesophageal reflux disease (p. 1807.2) in adults[1,2] and children.[3] It may control gastro-oesophageal reflux by inhibiting transient sphincter relaxation. Although a reduction in the number of reflux episodes was reported,[1-3] there was no effect on acid reflux symptoms.[1,2] However, another study[4] has shown a positive effect on the symptoms of acid reflux. It has been suggested that although baclofen may be of benefit, its adverse CNS effects mean that new oral selective GABA-B agonists should be developed for this indication.[5]

1. Van Herwaarden MA, *et al.* The effect of baclofen on gastro-oesophageal reflux, lower oesophageal sphincter function and reflux symptoms in patients with reflux disease. *Aliment Pharmacol Ther* 2002; 16: 1655–62.
2. Zhang Q, *et al.* Control of transient lower oesophageal sphincter relaxations and reflux by the $GABA_B$ agonist baclofen in patients with gastro-oesophageal reflux disease. *Gut* 2002; 50: 19–24.
3. Omari TI, *et al.* Effect of baclofen on esophagogastric motility and gastroesophageal reflux in children with gastroesophageal reflux disease: a randomized controlled trial. *J Pediatr* 2006; 149: 468–74.
4. Ciccaglione AF, Marzio L. Effect of acute and chronic administration of the $GABA_B$ agonist baclofen on 24 hour pH metry and symptoms in control subjects and in patients with gastro-oesophageal reflux disease. *Gut* 2003; 52: 464–70.
5. Tonini M, *et al.* Progress with novel pharmacological strategies for gastro-oesophageal reflux disease. *Drugs* 2004; 64: 347–61.

Hiccup. Baclofen has been given orally in doses ranging from 10 to 80 mg daily for the management of intractable hiccup (p. 1046.3) poorly controlled by other drugs. It has also been combined with gabapentin.

References.

1. Burke AM, *et al.* Baclofen for intractable hiccups. *N Engl J Med* 1988; 319: 1354.
2. Lance JW, Bassil GT. Familial intractable hiccup relieved by baclofen. *Lancet* 1989; ii: 276–7.
3. Yaqoob M, *et al.* Baclofen for intractable hiccups. *Lancet* 1989; ii: 562–3.
4. Ramirez FC, Graham DY. Treatment of intractable hiccup with baclofen: results of a double-blind randomized, controlled, cross-over study. *Am J Gastroenterol* 1992; 87: 1789–91.
5. Ramirez FC, Graham DY. Hiccups, compulsive water drinking, and hyponatremia. *Ann Intern Med* 1993; 118: 649.
6. Walker P, *et al.* Baclofen, a treatment for chronic hiccup. *J Pain Symptom Manage* 1998; 16: 125–32.
7. Hernández JL, *et al.* Gabapentin for intractable hiccup. *Am J Med* 2004; 117: 279–81.

Migraine and cluster headache. The efficacy of baclofen in conditions such as trigeminal neuralgia or various types of neuropathic pain suggested that it may be useful in migraine or cluster headache. Pilot studies confirmed these hypotheses with baclofen proving useful for prophylaxis[1] in migraine (p. 670.3) and for treatment[2] in cluster headache (p. 670.1).

1. Hering-Hanit R. Baclofen for prevention of migraine. *Cephalalgia* 1999; 19: 589–91.
2. Hering-Hanit R, Gadoth N. The use of baclofen in cluster headache. *Curr Pain Headache Rep* 2001; 5: 79–82.

Pain. Like some other muscle relaxants baclofen is used in the management of painful conditions associated with muscle spasm or spasticity (see below). The use of muscle relaxants for conditions such as acute low back pain is referred to on p. 9.2. Baclofen does not appear to possess conventional analgesic activity[1] but may potentiate the analgesia produced by opioid analgesics,[2] and has been used as an adjuvant in neuropathic pain,[3,4] notably trigeminal neuralgia[5] (p. 11.2).

1. Terrence CF, *et al.* Is baclofen an analgesic? *Clin Neuropharmacol* 1983; 6: 241–5.
2. Panerai AE, *et al.* Baclofen prolongs the analgesic effect of fentanyl in man. *Br J Anaesth* 1985; 57: 954–5.
3. Fromm GH. Baclofen as an adjuvant analgesic. *J Pain Symptom Manage* 1994; 9: 500–9.
4. Slonimski M, *et al.* Intrathecal baclofen in pain management. *Reg Anesth Pain Med* 2004; 29: 269–76.
5. Fromm GH, *et al.* Baclofen in the treatment of trigeminal neuralgia: double-blind study and long-term follow-up. *Ann Neurol* 1984; 15: 240–4.

Spasticity. Baclofen is one of the main drugs used in the management of spasticity (see p. 2014.2). It is used to reduce muscle spasm and pain especially in spinal cord lesions in conditions such as multiple sclerosis or paraplegia. Baclofen is also used for spasticity of cerebral origin. However, some consider that there are insufficient data to refute or support the use of oral or continuous intrathecal baclofen in the management of spasticity in children or adolescents with cerebral palsy.[1]

Oral doses of 30 to 80 mg daily are usually quite well tolerated,[2] but patients with severe spasticity often require high doses of baclofen before a response occurs and, consequently, some may fail to respond because adverse effects limit increases in dosage. Intrathecal baclofen is therefore sometimes tried as this produces much higher concentrations in the CNS than oral doses.[2-4] It may be given intrathecally by bolus injection or by continuous infusion; infusion is probably preferred[5] to minimise the risk of overdosage. Because patients are screened for response before beginning continuous infusion, results have generally been good.[2] There is a large interindividual variation in the intrathecal dose required to produce improvement in spasticity (see Uses and Administration, above). An increased dose of baclofen may be given at night to prevent spasms that interfere with sleep.

Although reports of tolerance to the effect of intrathecal baclofen have raised doubt[6] over whether long-term benefit can be maintained, long-term efficacy has been achieved.[7-10] Furthermore, some patients receiving long-term intrathecal baclofen treatment have been able to stop their therapy without symptoms of spasticity re-appearing and others have been able to reduce the dosage required.[11]

1. Delgado MR, *et al.* Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2010; 74: 336–43. Also available at: http://www.neurology.org/cgi/reprint/74/4/336.pdf (accessed 09/07/10)
2. Dario A, Tomei G. A benefit-risk assessment of baclofen in severe spinal spasticity. *Drug Safety* 2004; 27: 799–818.
3. McLean BN. Intrathecal baclofen in severe spasticity. *Br J Hosp Med* 1993; 49: 262–7.
4. Anonymous. Intrathecal baclofen for spasticity. *Med Lett Drugs Ther* 1994; 36: 21–2.
5. Penn RD, Kroin JS. Intrathecal baclofen. *N Engl J Med* 1989; 321: 1414–15.
6. Lewis KS, Mueller WM. Intrathecal baclofen for severe spasticity secondary to spinal cord injury. *Ann Pharmacother* 1993; 27: 767–74.
7. Penn RD, *et al.* Intrathecal baclofen for severe spinal spasticity. *N Engl J Med* 1989; 320: 1517–21.
8. Azouvi P, *et al.* Intrathecal baclofen administration for control of severe spinal spasticity: functional improvement and long-term follow-up. *Arch Phys Med Rehabil* 1996; 77: 35–9.
9. Dario A, *et al.* Long-term intrathecal baclofen infusion in supraspinal spasticity of adulthood. *Acta Neurol Scand* 2002; 105: 83–7.
10. Campbell WM, *et al.* Long-term safety and efficacy of continuous intrathecal baclofen. *Dev Med Child Neurol* 2002; 44: 660–5.
11. Dressnandt J, Conrad B. Lasting reduction of severe spasticity after ending chronic treatment with intrathecal baclofen. *J Neurol Neurosurg Psychiatry* 1996; 60: 168–73.

Stiff-man syndrome. There have been anecdotal case reports[1] of benefit with intrathecal baclofen in a patient with stiff-man syndrome (see under Muscle Spasm, p. 1064.3) inadequately controlled with other drugs or oral baclofen. However, in a double-blind placebo-controlled study[2] clinical improvement was evident in only 1 of 3 patients given intrathecal baclofen.

1. Stayer C, *et al.* Intrathecal baclofen therapy for stiff-man syndrome and progressive encephalomyelopathy with rigidity and myoclonus. *Neurology* 1997; 49: 1591–7.
2. Silbert PL, *et al.* Intrathecal baclofen therapy in stiff-man syndrome: a double-blind, placebo-controlled trial. *Neurology* 1995; 45: 1893–7.

Tardive dyskinesia. Baclofen is one of many drugs that have been tried in antipsychotic-induced tardive dyskinesia (see Extrapyramidal Disorders, p. 1049.2) but its efficacy is unclear. A systematic review[1] found the effects of baclofen, and other gamma-aminobutyric acid agonists to be inconclusive and unconvincing in the management of antipsychotic-induced tardive dyskinesia. The review also pointed out that the adverse effects caused by use of these drugs might outweigh any benefits.

1. Rathbone J, *et al.* Gamma-aminobutyric acid agonists for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 20/10/05).

Tetanus. The management of tetanus is described on p. 2029.2 and p. 209.2. Beneficial responses have been seen with baclofen by continuous intrathecal infusion,[1-5] usually in doses of 1 to 2 mg daily.[1,5] However, the therapeutic range of intrathecal baclofen in severe tetanus may be very narrow and deep coma with loss of spontaneous respiration and reflexes has been reported[6] after an increase in dosage from 1.2 mg to 2 mg daily. This adverse effect could be fatal in the absence of ventilatory support. To avoid the risk of secondary infection from an indwelling intraspinal catheter intermittent intrathecal baclofen has also been used.[7,8]

1. Müller H, *et al.* Intrathecal baclofen in tetanus. *Lancet* 1986; i: 317–18.
2. Dressnandt J, *et al.* Intrathecal baclofen in tetanus: four cases and a review of reported cases. *Intensive Care Med* 1997; 23: 896–902.
3. Engrand N, *et al.* The efficacy of intrathecal baclofen in severe tetanus. *Anesthesiology* 1999; 90: 1773–6.
4. Boots RJ, *et al.* The treatment of tetanus with intrathecal baclofen. *Anaesth Intensive Care* 2000; 28: 438–42.
5. Santos ML, *et al.* Intrathecal baclofen for the treatment of tetanus. *Clin Infect Dis* 2004; 38: 321–8.
6. Romijn JA, *et al.* Reversible coma due to intrathecal baclofen. *Lancet* 1986; ii: 696.
7. Demaziere J, *et al.* Intermittent intrathecal baclofen for severe tetanus. *Lancet* 1991; 337: 427.
8. Saissy JM, *et al.* Treatment of severe tetanus by intrathecal injections of baclofen without artificial ventilation. *Intensive Care Med* 1992; 18: 241–4.

Tourette's syndrome. Improvement was noted in children with Tourette's syndrome (see Tics, p. 1030.1) treated with baclofen compared with placebo in a small study.[1]

1. Singer HS, *et al.* Baclofen treatment in Tourette syndrome: a double-blind, placebo-controlled, crossover trial. *Neurology* 2001; 56: 599–604.

Urinary incontinence. Baclofen has been used with some benefit in the management of urinary incontinence and retention (p. 2349.2) secondary to lesions of the spinal cord.

References.

1. Hachen HJ, Krucker V. Clinical and laboratory assessment of the efficacy of baclofen (Lioresal) on urethral sphincter spasticity in patients with traumatic paraplegia. *Eur Urol* 1977; 3: 237–40.
2. Leyson JFJ, *et al.* Baclofen in the treatment of detrusor-sphincter dyssynergia in spinal cord injury patients. *J Urol (Baltimore)* 1980; 124: 82–4.
3. Kums JJM, Delhaas EM. Intrathecal baclofen infusion in patients with spasticity and neurogenic bladder disease. *World J Urol* 1991; 9: 153–6.

Adverse Effects

Adverse effects associated with baclofen such as sedation, somnolence, and nausea are often transient and dose-related. They may be minimised by increasing doses gradually or controlled by a reduction in dosage.

Other common adverse effects include dizziness, lassitude, lightheadedness, confusion, fatigue, muscular pain and weakness, and hypotension. Other adverse effects include euphoria, hallucinations, depression, headache, tinnitus, convulsions, paraesthesias, slurred speech, dry mouth, taste alterations, vomiting, diarrhoea or constipation, ataxia, nystagmus, tremors, insomnia, visual disturbances, rashes, pruritus, increased sweating, urinary disturbances, respiratory or cardiovascular depression, blood sugar changes, alterations in liver function values, and a paradoxical increase in spasticity. Hypothermia has been reported rarely. Problems with erection and ejaculation have also been reported with intrathecal baclofen; these are usually reversible on withdrawal of therapy.

Overdosage may lead to muscular hypotonia, hypothermia, drowsiness, respiratory depression, coma, and convulsions (see also below).

Stopping baclofen abruptly may result in a withdrawal syndrome (see under Precautions, below).

Effects on the nervous system. Epilepsy, progressing to status epilepticus, has been associated with the use of baclofen in a patient who had had no history of seizures.[1] Baclofen had been given in a dose of 80 mg daily and symptoms had resolved after gradual withdrawal and the use of antiepileptics.

1. Rush JM, Gibberd FB. Baclofen-induced epilepsy. *J R Soc Med* 1990; 83: 115–16.

Treatment of Adverse Effects

Treatment of baclofen overdosage is symptomatic. The value of gastric decontamination in the management of overdosage with baclofen is unclear but oral activated charcoal may be considered if given within 1 hour of ingesting more than 3 mg/kg. Haemodialysis or haemofiltration should be considered in severe cases. Observation should continue for at least 6 hours after ingestion. For the use of physostigmine salicylate in the treatment of intrathecal baclofen overdosage, see below.

Overdosage. Atropine sulfate 600 micrograms intravenously[1] was used to treat a patient who had ingested 420 mg of baclofen and had failed to improve after gastric lavage and induced diuresis. Bradycardia, hypotension, hypothermia, and respiratory depression all improved and no further treatment was needed. The clinical course and management of acute intoxication in 8 adolescents, who ingested estimated amounts of baclofen ranging from 60 to more than 600 mg, has also been described.[2]

Accidental *intrathecal* overdosage has caused respiratory depression, decreased alertness, coma, muscle weakness, and vomiting.[3] Mild intrathecal bolus overdoses of baclofen in patients without cardiac compromise have been treated using physostigmine although the use of physostigmine in poisoning is now generally considered hazardous (see Antimuscarinic Poisoning, p. 2010.1). Physostigmine salicylate was given intravenously in a dose of 1 to 2 mg over 5 minutes and repeated if necessary at intervals of 30 to 60 minutes.[3,4] Physostigmine was ineffective in a patient who accidentally received 10 mg of baclofen intrathecally;[5] in such severe overdosage, respiratory support and time to recover is needed.[4] A lumbar tap to remove about 30 to 50 mL of CSF may help to reduce the intrathecal concentration of baclofen if implemented soon after the overdose.

1. Ferner RE. Atropine treatment for baclofen overdose. *Postgrad Med J* 1981; 57: 580–1.
2. Perry HE, *et al.* Baclofen overdose: drug experimentation in a group of adolescents. *Pediatrics* 1998; 101: 1045–8.
3. Müller-Schwefe G, Penn RD. Physostigmine in the treatment of intrathecal baclofen overdose. *J Neurosurg* 1989; 71: 273–5.
4. Penn RD, Kroin JS. Failure of physostigmine in treatment of acute severe intrathecal baclofen intoxication. *N Engl J Med* 1990; 322: 1533–4.
5. Saltuari L, *et al.* Failure of physostigmine in treatment of acute severe intrathecal baclofen intoxication. *N Engl J Med* 1990; 322: 1533.

Precautions

Baclofen stimulates gastric acid secretion and should be used with caution in patients with a history of peptic ulcer and avoided in those with active peptic ulcer disease. It should also be used with caution in patients with severe psychiatric disorders or epilepsy or convulsive disorders since these disorders may be exacerbated by baclofen. Liver function should be monitored in patients with liver disease. Baclofen should be used with caution in patients with renal impairment; a reduced dose should be given (see also Renal Impairment, below). Baclofen should also be used with caution in patients with respiratory impairment. Observations of increased blood sugar concentrations suggest caution in patients with diabetes mellitus. Care is also required in the elderly, in whom adverse effects may be more common, and in patients with cerebrovascular disease (who tolerate baclofen poorly). It should be used with caution in patients who use their spasticity to maintain posture or to increase function. Urine retention may be exacerbated in patients with hypertonic bladder sphincters. Baclofen may cause drowsiness; patients affected should not drive or operate machinery.

Abrupt withdrawal of baclofen may result in a withdrawal syndrome and exacerbation of spasticity; dosage should be reduced gradually over at least 1 to 2 weeks, or longer if symptoms occur.

Anaesthesia. Acute bradycardia and hypotension occurred after rib retraction in 3 patients given baclofen 30 mg orally 90 minutes before thoracic surgery under general anaesthesia, but not in a further 3 patients given placebo.[1] Giving atropine and ephedrine relieved bradycardia and hypotension in 2 patients, but a brief cardiac arrest occurred in 1. Baclofen may disturb autonomic control of the circulation during general anaesthesia and surgery.

1. Sill JC, *et al.* Bradycardia and hypotension associated with baclofen used during general anaesthesia. *Anesthesiology* 1986; 64: 255–8.

Breast feeding. The concentrations of baclofen found in breast milk are small[1] and UK licensed product information states that no undesirable effects are to be expected in breast-fed infants. The American Academy of Pediatrics also considers that baclofen is usually compatible with breast feeding; no adverse effects have been seen in breast-feeding infants whose mothers were receiving baclofen.[2]

1. Eriksson G, Swahn C-G. Concentrations of baclofen in serum and breast milk from a lactating woman. *Scand J Clin Lab Invest* 1981; 41: 185–7.
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 23/06/04)

Peptic ulcer. Results of a study of baclofen-stimulated gastric acid secretion in 10 healthy subjects given 600 micrograms/kg intravenously suggested that patients on baclofen might be at risk from baclofen-induced hyperacidity.[1]

1. Pugh S, *et al.* Clinical and experimental significance of the newly discovered activity of baclofen (PCP-GABA) as a stimulant of gastric acid secretion. *Gut* 1985; 26: A545.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies baclofen 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 24/10/11)

Pregnancy and the neonate. Two successful pregnancies have been reported[1] in a woman receiving intrathecal baclofen; there was no evidence of teratogenicity, and neurodevelopmental outcome in the children seemed normal. However, convulsions were seen in a week-old infant whose mother had taken oral baclofen during pregnancy.[2] The convulsions, which were refractory to antiepileptics, lidocaine, and pyridoxine, ceased within 30 minutes of giving baclofen to the infant.

1. Calderón Muñoz F, *et al.* Pregnancy outcome in a woman exposed to continuous intrathecal baclofen infusion. *Ann Pharmacother* 2000; 34: 956.
2. Ratnayaka BDM, *et al.* Neonatal convulsions after withdrawal of baclofen. *BMJ* 2001; 323: 85.

Renal impairment. There have been reports of baclofen toxicity in patients with severe renal impairment.[1] Most patients had received oral doses of 15 mg or more of baclofen daily although some dialysis patients still developed toxic symptoms after having received the manufacturer's suggested dose of 5 mg daily for only 4 days or after a cumulative dose of only 15 mg. The most common symptom of toxicity was impaired consciousness which often occurred within 12 hours of ingestion.

1. Su W, *et al.* Reduced level of consciousness from baclofen in people with low kidney function. *BMJ* 2009; 339: b4559. Available at: http://www.bmj.com/content/339/bmj.b4559?view=long&pmid=20044395 (accessed 29/03/12)

Respiratory disorders. Baclofen might precipitate bronchoconstriction in susceptible individuals. A patient with asthma developed symptomatic bronchoconstriction after taking baclofen on two separate occasions.[1] Another patient who had a history of exercise-induced dyspnoea and wheezing was found to have bronchial hyperresponsiveness to methacholine only after taking baclofen.

1. Dicpinigaitis PV, *et al.* Baclofen-induced bronchoconstriction. *Ann Pharmacother* 1993; 27: 883–4.

Withdrawal. Psychiatric reactions including hallucinations, paranoia, delusions, psychosis, anxiety, confusion, and agitation have been reported[1-5] on abrupt withdrawal of oral baclofen; symptoms generally resolved on restarting. Convulsions have also been reported.[6] The abrupt withdrawal of intrathecal baclofen may also result in high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity which in rare cases has advanced to rhabdomyolysis, multiple organ failure, and death.[7-9]

Except for serious adverse reactions, the dose of oral baclofen should be gradually reduced: the UK CSM recommends reduction over at least 1 to 2 weeks or longer if symptoms occur. Similarly, the FDA has advised against the abrupt withdrawal of intrathecal baclofen.[9]

1. Lees AJ, *et al.* Hallucinations after withdrawal of baclofen. *Lancet* 1977; i: 858.
2. Stein R. Hallucinations after sudden withdrawal of baclofen. *Lancet* 1977; ii: 44–5.
3. Harrison SA, Wood CA. Hallucinations after preoperative baclofen discontinuation in spinal cord injury patients. *Drug Intell Clin Pharm* 1985; 19: 747–9.
4. CSM/MCA. Severe withdrawal reactions with baclofen. *Current Problems* 1997; 23: 3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015623&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
5. Leo RJ, Baer D. Delirium associated with baclofen withdrawal: a review of common presentations and management strategies. *Psychosomatics* 2003; 44: 503–7.
6. Barker L, Grant IS. Convulsions after abrupt withdrawal of baclofen. *Lancet* 1982; ii: 556–7.
7. Grenier B, *et al.* Hyperthermie grave liée à un sevrage brutal de baclofène administré de façon continue par voie intrathécale. *Ann Fr Anesth Reanim* 1996; 15: 659–62.
8. Green LB, Nelson VS. Death after acute withdrawal of intrathecal baclofen: case report and literature review. *Arch Phys Med Rehabil* 1999; 80: 1600–4.
9. Coffey RJ [Medtronic]. Important drug warning (issued April 2002). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM170907.pdf (accessed 22/01/10)

Interactions

Alcohol and other CNS depressants may exacerbate the CNS effects of baclofen and should be avoided; severe aggravation of hyperkinetic symptoms may possibly occur in patients taking lithium. There may be increased weakness if baclofen is given to patients taking a tricyclic antidepressant and there may be an increased hypotensive effect if it is given to patients receiving antihypertensive therapy. Ibuprofen (see NSAIDs, p. 2017.1) and other drugs that produce renal insufficiency may reduce baclofen excretion leading to toxicity.

Dopaminergics. For reports of patients with Parkinson's disease taking *levodopa* who have had adverse effects when given baclofen, see under Levodopa, on p. 907.3.

NSAIDs. There has been a report of an elderly patient who developed baclofen toxicity after *ibuprofen* therapy was also started.[1] It appeared that acute renal insufficiency caused by ibuprofen had impaired baclofen excretion.

1. Dahlin PA, George J. Baclofen toxicity associated with declining renal clearance after ibuprofen. *Drug Intell Clin Pharm* 1984; 18: 805–8.

Pharmacokinetics

Baclofen is rapidly and almost completely absorbed from the gastrointestinal tract after an oral dose. Peak plasma concentrations occur about 0.5 to 3 hours after ingestion, but the rate and extent of absorption vary between patients, and may vary inversely with the dose. After oral doses some baclofen crosses the blood-brain barrier, with concentrations in CSF about 12% of those in the plasma. About 30% of baclofen is bound to plasma proteins. About 70 to 80% of a dose is excreted in the urine mainly as unchanged drug; about 15% is metabolised in the liver. The elimination half-life of baclofen is about 3 to 4 hours in plasma and about 1 to 5 hours in the CSF. Baclofen crosses the placenta and is distributed into breast milk.

Absorption. A crossover study in 5 healthy subjects given baclofen 20 mg orally after an overnight fast or a standardised breakfast showed that baclofen was rapidly absorbed in both cases, and the rate and extent of absorption were not significantly altered by the presence of food.[1] There is no need to modify the current practice of giving baclofen with food to minimise gastrointestinal adverse effects.

1. Peterson GM, *et al.* Food does not affect the bioavailability of baclofen. *Med J Aust* 1985; 142: 689–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Baclodox†; Bafen; Lioresal; *Austral.*: Baclo†; Clofen; Lioresal; Stelax; *Austria*: Lioresal; *Belg.*: Lioresal; *Braz.*: Baclon; Lioresal; *Canad.*: Lioresal; Nu-Baclo; *Chile*: Cetril; Lioresyl; *China*: Lioresal (力奥来素); Spinax (棘智); Zufen (枢芬); *Denm.*: Lioresal; *Fin.*: Lioresal; *Fr.*: Lioresal; *Ger.*: Lebic†; Lioresal; *Gr.*: Glasbor; Jofen; Lioresal; Miorel; Vioridon; *Hong Kong*: Clofen†; Lioresal; Stelax; *Hung.*: Lioresal; *India*: Baclan; Bacmax; Chinofen; Liofen; Lioresal; Parafon DSC; *Indon.*: Lioresal; *Irl.*: Baclopar; Lioresal; *Israel*: Baclosal; Lioresal; *Ital.*: Lioresal; *Malaysia*: Clofen†; Lioresal; *Neth.*: Lioresal; *Norw.*: Lioresal; *NZ*: Lioresal; Pacifen; *Philipp.*: Lioresal; Onelaxant-R; *Pol.*: Lioresal; *Port.*: Lioresal; *Rus.*: Baclosan (Баклосан); *S.Afr.*: Lioresal; *Singapore*: Colmifen; Lioresal; *Spain*: Lioresal; *Swed.*: Lioresal; *Switz.*: Lioresal; *Thai.*: Baclosal; Fenisal; Liobac; Lioresal; *Turk.*: Lioresal; *UK*: Lioresal; Lyflex; *USA*: Gablofen; Kemstro†; Lioresal; *Venez.*: Lioresal.

Pharmacopoeial Preparations
BP 2014: Baclofen Oral Solution; Baclofen Tablets;
USP 36: Baclofen Oral Suspension; Baclofen Tablets.

Botulinum Toxins

Toxinas botulínicas.
ATC — M03AX01.
ATC Vet — QM03AX01.

Description. Botulinum toxins A and B are neurotoxins produced by *Clostridium botulinum*. They are proteins comprising a heavy chain thought to be responsible for binding to the target cells and translocation of the toxin across the cell membrane, linked by a disulfide bond to a light chain responsible for the toxic activity.

Botulinum A Toxin

Botulinitoksiini tyyppi A; Botulinum A Toksini; Toxin typ A mot botulism; Toxina botulínica A; Toxine botulinique type A; Toxinum botulinicum typum A.
UNII — E2J1KPY694.

Pharmacopoeias. *Eur.* (see p. vii) includes the injection.

Ph. Eur. 8: (Botulinum Toxin Type A for Injection; Toxinum Botulinicum Typum A ad Iniectabile). A dried preparation containing purified botulinum neurotoxin type A, which may be present in the form of a complex with haemagglutinins and non-toxic proteins, prepared from a suitable strain of *Clostridium botulinum* type A.

Botulinum B Toxin

Botulinum B Toksini; Botulinum Toxin Type B; Toxina botulínica B.
UNII — 0Y70T9M1F.

Pharmacopoeias. *Eur.* (see p. vii) includes the injection.

Ph. Eur. 8: (Botulinum Toxin Type B for Injection; Toxinum Botulinicum B ad Iniectabile). A liquid preparation containing purified botulinum neurotoxin type B, which may be present in the form of a complex with haemagglutinins and non-toxic proteins, prepared from a suitable strain of *Clostridium botulinum* type B.

Units

The dose of preparations containing botulinum toxins A or B is expressed in terms of units, but the available preparations are used at different doses for the same indications, and the units of one preparation cannot be considered to apply to another.

Uses and Administration

Botulinum toxins cause neuromuscular blockade by inhibiting the calcium-ion mediated release of acetylcholine at the motor nerve terminals, resulting in a diminished endplate potential and subsequent flaccid paralysis of the affected muscles. The paralysis persists until new nerve terminals form, usually within 2 to 4 months.

Botulinum A toxin is given by local injection in the treatment of hemifacial spasm, blepharospasm, spasmodic torticollis, lower limb spasticity in children with cerebral palsy, and upper limb spasticity associated with stroke in adults. Botulinum A toxin is also used for the management of strabismus and hyperhidrosis, and has also been approved for the treatment of glabellar (frown) lines in adults up to 65 years of age. It is being investigated for use in the management of several other disorders. The following preparations of botulinum A toxin are available in the UK and the USA:

- *Azzalure* (*Galderma, UK*): described as botulinum A toxin-haemagglutinin complex
- *Botox* (*Allergan, UK*): described as botulinum A toxin protein complex
- *Botox/Botox Cosmetic* (*Allergan, USA*): described as onabotulinumtoxinA
- *Dysport* (*Ipsen, UK*): described as botulinum A toxin-haemagglutinin complex
- *Dysport* (*Ipsen, USA*): described as abobotulinumtoxinA
- *Vistabel* (*Allergan, UK*): described as botulinum A toxin
- *Xeomin* (*Merz, UK*): described as botulinum A toxin
- *Xeomin* (*Merz, USA*): described as incobotulinumtoxinA

Botulinum B toxin is used in the management of spasmodic torticollis and, being antigenically distinct, it has the potential for use in patients who develop resistance to treatment due to the development of antibodies to type A toxin. The following preparations of botulinum B toxin are available in the UK and the USA:

- *Myobloc* (*Solstice, USA*): described as rimabotulinumtoxinB
- *NeuroBloc* (*Eisai, UK*): described as botulinum B toxin

Doses of botulinum toxins A and B are expressed in terms of units, which have not been standardised between preparations (see under Units, above). Doses are therefore specific to each individual preparation; details are given under each indication, below, where relevant.

Botulinum F toxin is under investigation for the treatment of similar neuromuscular disorders.

Reviews.
1. Borodic GE, Pearce LB. New concepts in botulinum toxin therapy. *Drug Safety* 1994; 11: 145–52.
2. Hughes AJ. Botulinum toxin in clinical practice. *Drugs* 1994; 48: 888–93.
3. Cheng CM, *et al.* Unlabeled uses of botulinum toxins: a review, part 1. *Am J Health-Syst Pharm* 2006; 63: 145–52.
4. Cheng CM, *et al.* Unlabeled uses of botulinum toxins: a review, part 2. *Am J Health-Syst Pharm* 2006; 63: 225–32.
5. Simpson DM, *et al.* Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review)—report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008; 70: 1699–1706.
6. Naumann M, *et al.* Assessment: botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008; 70: 1707–14.

Achalasia. The treatment of choice for achalasia (see Oesophageal Motility Disorders, p. 1813.2) is mechanical dilatation of the lower oesophageal sphincter, or if necessary surgery, but more recently injection of botulinum A toxin[1-3] has been found to be effective. However, a systematic review[4] found that one year after treatment only 11 of 43 (26%) patients who received botulinum A toxin were in symptomatic remission compared with 33 of 47 (70%) patients treated with mechanical dilatation. It has been recommended that its use would be better reserved for patients thought to be at risk from mechanical dilatation or surgery.[3,5] Another study[6] showed that intrasphincteric injection of botulinum toxin A was safe and effective for the treatment of achalasia in the short and medium term, although only a weak correlation with dose emerged.

1. Pasricha PJ, *et al.* Intrasphincteric botulinum toxin for the treatment of achalasia. *N Engl J Med* 1995; 332: 774–8. Correction. *ibid.*; 333: 75.
2. Cuilliére C, *et al.* Achalasia: outcome of patients treated with intrasphincteric injection of botulinum toxin. *Gut* 1997; 41: 87–92.
3. da Silveira EBV, Rogers AI. Treatment of achalasia with botulinum A toxin. *Am J Ther* 2002; 9: 157–61.
4. Leyden JE, *et al.* Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 27/01/10).
5. Spiess AE, Kahrilas PJ. Treating achalasia: from whalebone to laparoscope. *JAMA* 1998; 280: 638–42.
6. Annese V, *et al.* A multicentre randomised study of intrasphincteric botulinum toxin in patients with oesophageal achalasia. *Gut* 2000; 46: 597–600.

Anal fissure. Anal fissure is a superficial tear in the mucosa of the distal anal canal characterised by pain on defaecation, rectal bleeding, and spasm of the anal sphincter. Healing, which is usually uneventful, may be helped by conservative management with bran and bulk laxatives and topical local anaesthetics for pain relief. Surgical treatment has been used for patients who develop a chronic condition but has been associated with high rates of long-term incontinence and recurrence. Although systematic reviews considered that surgery was more effective than alternative medical therapies,[1,2] some of these have been investigated.[3-6] As hypertonicity of the internal anal sphincter may be involved in the pathophysiology of chronic anal fissure, local injections of botulinum A toxin have been used to produce paresis of this sphincter.[7-9] The duration of the effect appears to be long enough to allow complete healing of the fissure in most patients although some may relapse; a long-term, follow-up study[10] involving 57 completely healed patients, noted a high recurrence rate (41.5%) once the effects of botulinum toxin disappeared. Temporary incontinence had been the only adverse effect reported during treatment.

Topical application of nitrates can relax the anal sphincter; benefit from topical application of glyceryl trinitrate has been reported,[11-13] although a high rate of spontaneous resolution with placebo has cast doubt over the degree of advantage in some studies.[1,12] Follow-up[14] of patients treated with glyceryl trinitrate indicated that after 24 to 38 months most had not had further problems or had had occasional recurrences which in the majority of cases had responded to further topical treatment. Isosorbide dinitrate ointment has also been tried, and may be of benefit with botulinum A toxin.[15]

Topical calcium antagonists also seem to be effective. Both diltiazem[16-18] and nifedipine[19,20] seem to be of benefit and there is evidence that they may be a better choice than topical glyceryl trinitrate.[19,20] Nifedipine has been combined with botulinum toxin;[20] it has also been given orally.[21]

1. Nelson R. A systematic review of medical therapy for anal fissure. *Dis Colon Rectum* 2004; 47: 422–31.
2. Nelson R. Non surgical therapy for anal fissure. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 08/05/08).
3. Cook TA, *et al.* The pharmacology of the internal anal sphincter and new treatments of ano-rectal disorders. *Aliment Pharmacol Ther* 2001; 15: 887–98.
4. American Gastroenterological Association. American Gastroenterological Association medical position statement: diagnosis and care of patients with anal fissure. *Gastroenterology* 2003; 124: 233–4.
5. Madoff RD, Fleshman JW. AGA technical review on the diagnosis and care of patients with anal fissure. *Gastroenterology* 2003; 124: 235–45.
6. Wray D, *et al.* Anal fissure: a review. *Br J Hosp Med* 2008; 69: 455–8.
7. Jost WH, Schimrigk K. Botulinum toxin in therapy of anal fissure. *Lancet* 1993; 345: 188–9.
8. Maria G, *et al.* A comparison of botulinum toxin and saline for the treatment of chronic anal fissure. *N Engl J Med* 1998; 338: 217–20.
9. Jost WH. Ten years' experience with botulin toxin in anal fissure. *Int J Colorectal Dis* 2002; 17: 298–302.
10. Minguez M, *et al.* Long-term follow-up (42 months) of chronic anal fissure after healing with botulinum toxin. *Gastroenterology* 2002; 123: 112–17.
11. 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.
12. Bailey HR, *et al.* Fissure Study Group. A study to determine the nitroglycerin ointment dose and dosing interval that best promote the healing of chronic anal fissures. *Dis Colon Rectum* 2002; 45: 1192–9.
13. Scholefield JH, *et al.* A dose finding study with 0.1%, 0.2%, and 0.4% glyceryl trinitrate ointment in patients with chronic anal fissures. *Gut* 2003; 52: 264–9.
14. Lund JN, Scholefield JH. Follow-up of patients with chronic anal fissure treated with topical glyceryl trinitrate. *Lancet* 1998; 352: 1681.
15. Lysy J, *et al.* Topical nitrates potentiate the effect of botulinum toxin in the treatment of patients with refractory anal fissure. *Gut* 2001; 48: 221–4.
16. Jonas M, *et al.* A randomized trial of oral vs topical diltiazem for chronic anal fissures. *Dis Colon Rectum* 2001; 44: 1074–8.
17. Jonas M, *et al.* Diltiazem heals glyceryl trinitrate-resistant chronic anal fissures: a prospective study. *Dis Colon Rectum* 2002; 45: 1091–5.
18. Bielecki K, Kolodziejczak M. A prospective randomized trial of diltiazem and glyceryltrinitrate ointment in the treatment of chronic anal fissure. *Colorectal Dis* 2003; 5: 256–7.
19. Ezri T, Susmallian S. Topical nifedipine vs. topical glyceryl trinitrate for treatment of chronic anal fissure. *Dis Colon Rectum* 2003; 46: 805–8.
20. Tranqui P, *et al.* Nonsurgical treatment of chronic anal fissure: nitroglycerin and dilatation versus nifedipine and botulinum toxin. *Can J Surg* 2006; 49: 41–5.
21. Cook TA, *et al.* Oral nifedipine reduces resting anal pressure and heals chronic anal fissure. *Br J Surg* 1999; 86: 1269–73.

Anismus. Anismus is a condition in which inappropriate contraction of the anal sphincters occurs when bowel evacuation is attempted; it seems to be a form of dystonia.

Treatment with botulinum A toxin was investigated in 7 patients with intractable constipation due mainly to anismus.[1] The toxin was injected bilaterally into the puborectalis muscle using an electromyographically guided needle; patients were allowed to continue with their laxatives throughout the study if required. Symptoms improved in all but one of the patients, although two patients could not be regarded as treatment successes

because they developed faecal incontinence; four patients had an excellent clinical outcome. However, another study involving 24 patients found the clinical efficacy of botulinum A toxin to be limited.[2]

1. Hallan RI, *et al.* Treatment of anismus in intractable constipation with botulinum A toxin. *Lancet* 1988; ii: 714–17.
2. Ron Y, *et al.* Botulinum toxin type-A in therapy of patients with anismus. *Dis Colon Rectum* 2001; 44: 1821–6.

Blepharospasm. Blepharospasm is a focal dystonia characterised by repeated involuntary blinking caused by spasms of the orbicularis oculi muscle of the eye, and can result in functional blindness. Blepharospasm is often associated with other dystonias of the head and neck, such as Meige syndrome, in which patients also suffer from involuntary contractures of the muscles around the mouth. Oral drug treatment as used for dystonias in general (see p. 903.3) is usually ineffective, and surgery (facial nerve avulsion) is often followed by recurrent spasm.[1] Local injections of botulinum A toxin into the orbicularis oculi muscle mimic the effect of surgical denervation of the muscle and are reported[2–6] to have been effective in over 70% of patients; they are now generally considered[7] to be the treatment of choice. Symptomatic improvement has been reported to last from about 9 to 15 weeks; no increase in duration of effect is apparent after multiple injections. In one retrospective study in patients with blepharospasm and Meige syndrome, treatment with botulinum A toxin was still effective in most patients 11 years after the start of therapy.[4]

For blepharospasm botulinum A toxin is injected into the orbicularis oculi of the upper and lower lids; injection into additional sites in the brow area and upper facial area may be indicated if the spasms interfere with vision. Doses of botulinum A toxin are expressed in terms of units, which have not been standardised between preparations. Doses are therefore *specific to each individual preparation*:

- The preparation *Botox* (*Allergan, UK*) is injected intramuscularly in an initial dose of 1.25 to 2.5 units at each site to a total of up to 25 units per eye. An effect is usually obtained within 3 days and reaches a peak after 1 to 2 weeks; each treatment lasts for about 3 months. If the response lasts less than 2 months the dose may be increased up to 5 units at each site but the total dose given in a 12-week period should not exceed 100 units. Giving more often than every 3 months confers no additional benefit. *Botox* (*Allergan*) is also available in the USA and given in similar doses, although higher cumulative doses of up to 200 units are allowed in a 30-day period.
- The preparation *Xeomin (Merz, UK)* is injected intramuscularly in an initial dose of 1.25 to 2.5 units at each site to a total of up to 25 units per eye. An effect is usually obtained within 4 days; each treatment lasts for about 3 to 4 months. If the response lasts less than 2 months the dose may be increased up to 5 units at each site but the total dose given in a 12-week period should not exceed 100 units. Giving more often than every 3 months confers no additional benefit. *Xeomin* (*Merz*) is also available in the USA for use in patients who have previously been treated with *Botox*; the total initial dose in both eyes should not exceed 70 units.
- For the preparation *Dysport* (*Ipsen, UK*) the initial dose is a total of 120 units per eye given as subcutaneous injections of 20 and 40 units per site. Subsequently the total dose may need to be reduced to 60 to 80 units per eye. With this preparation the relief of symptoms may begin within 2 to 4 days with a maximum effect being obtained within 2 weeks. Injections of *Dysport* should be repeated every 12 weeks or as required.

1. Kennedy RH, *et al.* Treatment of blepharospasm with botulinum toxin. *Mayo Clin Proc* 1989; 64: 1085–90.
2. Grandas F. Blepharospasm: a review of 264 patients. *J Neurol Neurosurg Psychiatry* 1988; 51: 767–72.
3. Elston JS. The management of blepharospasm and hemifacial spasm. *J Neurol* 1992; 239: 5–8.
4. Mauriello JA, *et al.* Treatment selections of 239 patients with blepharospasm and Meige syndrome over 11 years. *Br J Ophthalmol* 1996; 80: 1073–6.
5. Defazio G, Livrea P. Primary blepharospasm: diagnosis and management. *Drugs* 2004; 64: 237–44.
6. Costa J, *et al.* Botulinum toxin type A therapy for blepharospasm. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 28/03/06).
7. Hallett M, *et al.* Update on blepharospasm: report from the BEBRF International Workshop. *Neurology* 2008; 71: 1275–82.

Cosmetic use. Botulinum A toxin has been used for the cosmetic treatment of facial lines and wrinkles and age-related neck degeneration.[1–5]

For the temporary improvement in appearance of moderate to severe glabellar (frown) lines two doses of botulinum A toxin are injected into each of the corrugator muscles (not closer than 1 cm above the central eyebrow) and one dose into the procerus muscle. Doses of botulinum A toxin are expressed in terms of units, which have not been standardised between preparations. Doses are therefore *specific to each individual preparation*:

- The preparation *Botox Cosmetic* (*Allergan, USA*) is given in a dose of 4 units into each of 5 sites to a total dose of 20 units. An effect is obtained in 1 to 2 days which increases in intensity in the first week; each treatment lasts for about 3 to 4 months. More frequent dosing is not recommended as safety and efficacy have not been evaluated. A preparation with a similar dosage regimen (*Vistabel; Allergan, UK*) is available in the UK.
- The preparation *Dysport* (*Ipsen, USA*) is given in a dose of 10 units into each of 5 sites to a total dose of 50 units. Each treatment may last for up to 4 months and it should be given no more frequently than every 3 months.
- The preparation *Azzalure* (*Galderma, UK*) is also available for such use. A dose of 10 units is given into each of 5 sites to a total dose of 50 units. Each treatment lasts for up to 4, in some cases 5, months. The treatment interval should be no more frequent than every 3 months.

1. Oliver JM. Botulinum toxin A treatment of overactive corrugator supercilii in thyroid eye disease. *Br J Ophthalmol* 1998; 82: 528–33.
2. Song KH. Botulinum toxin type A injection for the treatment of frown lines. *Ann Pharmacother* 1998 32: 1365–7.
3. Anonymous. Cosmetic use of botulinum toxin. *Med Lett Drugs Ther* 1999; 41: 63–4.
4. Anonymous. Botulinum toxin (Botox Cosmetic) for frown lines. *Med Lett Drugs Ther* 2002; 44: 47–8.
5. Carruthers A. Botulinum toxin type A: history and current cosmetic use in the upper face. *Dis Mon* 2002; 48: 299–322.

Gastric motility disorders. Some benefit has been reported from the use of botulinum A toxin injection in gastric motility disorders (p. 1805.2). In an open-label study[1] 6 diabetic patients with gastroparesis had an improvement in gastric emptying after treatment with botulinum A toxin. A literature search[2] was only able to find case reports, case series, and open-label studies on the use of botulinum A toxin for gastroparesis.

1. Ezzeddine D, *et al.* Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. *Gastrointest Endosc* 2002; 55: 920–3.
2. DeSantis ERH, Huang S. Botulinum toxin type A for treatment of refractory gastroparesis. *Am J Health-Syst Pharm* 2007; 64: 2237–40.

Hand dystonia. Hand dystonia, or hand cramp, is a type of focal dystonia (p. 903.3). It is more commonly reported in people who perform repetitive movements with their hands, such as writers, keyboard operators, and musicians. Treatment was traditionally with antimuscarinics, although with limited success, but botulinum toxin has increasingly become the first-line option.[1] A double-blind study reported that 8 out of 10 patients had greater subjective improvement in focal hand dystonia, compared with placebo, after treatment with intramuscular botulinum A toxin; objective improvement in muscle strength was seen in 6 patients.[2] However, pain and severe weakness in the shoulder region resembling neuralgic amyotrophy has been reported[3] in 2 patients injected with botulinum A toxin for writer's cramp. It was considered that if unexplained pain occurred in the shoulder or upper arm after a first injection of botulinum A toxin further injections were contra-indicated.

1. Karp BI. Botulinum toxin treatment of occupational and focal hand dystonia. *Mov Disord* 2004; 19 (suppl 8): S116–S119.
2. Cole R, *et al.* Double-blind trial of botulinum toxin for treatment of focal hand dystonia. *Mov Disord* 1995; 10: 466–71.
3. Sheean GL, *et al.* Pain and remote weakness in limbs injected with botulinum toxin A for writer's cramp. *Lancet* 1995; 346: 154–6.

Headache. The therapeutic effect of botulinum A toxin in headache was first seen as a coincidental side effect in patients receiving the drug for hyperfunctional facial lines. A review[1] of subsequent studies concluded that efficacy could be shown for the prophylaxis of migraine (p. 670.3); a small number of patients who received treatment during the acute phase of a migraine attack also had pain relief. However, other reviews[2,3] have concluded that, despite promising initial results, there was limited evidence from controlled studies to support the use of botulinum toxins in the management of migraine. More recently, studies using stricter inclusion criteria have shown positive results with botulinum A toxin in patients with chronic migraine.[4] In the UK, botulinum A toxin as the preparation *Botox* (*Allergan, UK*) is licensed for the prophylaxis of headaches in adults with chronic migraine; this is defined as headaches on at least 15 days each month of which at least 8 days are with migraine. The recommended total dose, given intramuscularly, is 155 to 195 units which should be divided across 7 specific head and neck muscle areas: frontalis: total of 20 units over 4 sites; corrugator: total of 10 units over 2 sites; procerus: total of 5 units at one site; occipitalis: total of 30 to 40 units over 6 to 8 sites; temporalis: total of 40 to 50 units over 8 to 10 sites; trapezius: total of 30 to 50 units over 6 to 10 sites; cervical paraspinal muscle group: total of 20 units over 4 sites. Injections may be repeated every 12 weeks. *Botox* (*Allergan*) is also available in the USA for the management of chronic migraine; it is given in a similar manner.

Contradictory results had been reported in the studies evaluating tension-type headache (p. 671.3).[2,5–7] However, in the original review[1] it was emphasised that an important finding had been the need to inject botulinum A toxin at the site of the pain or trigger points and not on a standardised basis, and that this should be considered in future studies. Improvement had been noted in individual cases of cluster headache (p. 670.1) and in some patients with headache attributed to disorders of the neck.

Some benefit has also been seen with botulinum B toxin in the treatment of migraine and tension-type headaches.[8]

1. Göbel H, *et al.* Evidence-based medicine: botulinum toxin A in migraine and tension-type headache. *J Neurol* 2001; 248 (suppl 1): 34–8.
2. Schulte-Mattler WJ, Martinez-Castrillo JC. Botulinum toxin therapy of migraine and tension-type headache: comparing different botulinum toxin preparations. *Eur J Neurol* 2006; 13 (suppl 1): 31–4.
3. Gupta VK. Botulinum toxin a treatment for migraine? A systematic review. *Pain Med* 2006; 7: 386–94.
4. Ashkenazi A. Botulinum toxin type a for chronic migraine. *Curr Neurol Neurosci Rep* 2010; 10: 140–6.
5. Ondo WG, *et al.* Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study. *Cephalalgia* 2004; 24: 60–5.
6. Schulte-Mattler WJ, *et al.* Treatment of chronic tension-type headache with botulinum toxin A: a randomized, double-blind, placebo-controlled multicenter study. *Pain* 2004; 109: 110–14.
7. Rozen D, Sharma J. Treatment of tension-type headache with Botox: a review of the literature. *Mt Sinai J Med* 2006; 73: 493–8.
8. Fadeyi MO, Adams QM. Use of botulinum toxin type B for migraine and tension headaches. *Am J Health-Syst Pharm* 2002; 59: 1860–2.

Hemifacial spasm. Hemifacial spasm is characterised by involuntary unilateral synchronous contractions of muscles innervated by the facial nerve. The spasms usually begin with twitching of muscles around the eye or mouth but as the disease progresses their frequency increases and they spread to involve the rest of the facial muscles. Hemifacial spasm may be improved by surgery but there is a risk of irreversible paralysis. Few drugs are effective for hemifacial spasm but carbamazepine has been reported to have been of help on occasions. Reports suggest that injections of botulinum A toxin may be effective in relieving symptoms in at least 75% of patients but there do not appear to be any studies comparing it against other treatments. Repeat injections are required by most patients every 3 to 4 months but long-term efficacy appears to be maintained. Dosage regimens of botulinum A toxin used in hemifacial spasm are similar to those used for blepharospasm (see above) although an electromyographically guided needle may be required to identify small muscles around the mouth.

References.

1. Elston JS. The management of blepharospasm and hemifacial spasm. *J Neurol* 1992; 239: 5–8.
2. Chen R-S, *et al.* Botulinum toxin A injection in the treatment of hemifacial spasm. *Acta Neurol Scand* 1996; 94: 207–11.
3. Boghen DR, Lesser RL. Blepharospasm and hemifacial spasm. *Curr Treat Options Neurol* 2000; 2: 393–400.
4. Jost WH, Kohl A. Botulinum toxin: evidence-based medicine criteria in blepharospasm and hemifacial spasm. *J Neurol* 2001; 248 (suppl 1): 21–4.
5. Defazio G, *et al.* Botulinum toxin A treatment for primary hemifacial spasm: a 10-year multicenter study. *Arch Neurol* 2002; 59: 418–20.
6. Costa J, *et al.* Botulinum toxin type A therapy for hemifacial spasm. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 28/03/06).

Hyperhidrosis. Various drugs and surgical techniques have been used in the treatment of hyperhidrosis (p. 1685.1). Botulinum A toxin is used in the management of focal hyperhidrosis because of its ability to block cholinergic transmission at nerve terminals innervating the sweat glands. Encouraging results have been obtained in patients with severe resistant focal hyperhidrosis using intradermal[1,2] or subcutaneous[3,4] injections and results from two larger multicentre studies[5,6] confirm that intradermal injection of botulinum A is effective and well-tolerated for the treatment of axillary hyperhidrosis. In the UK, it is given for this purpose as the preparation *Botox* (*Allergan, UK*), by intradermal injection in doses of 50 units to each axilla, evenly distributed in multiple sites about 1 to 2 cm apart. Clinical improvement generally occurs within a week of injection, and may last for 4 to 7 months; repeat injections may be given once the effects of the previous injection have subsided. *Botox* (*Allergan*) is also available in the USA for the treatment of axillary hyperhidrosis; it is given in similar doses.

Some workers[7] prefer to use intradermal injections for palmar hyperhidrosis in order to minimise the risk of reversible weakness of the small muscles of the hand reported with subcutaneous injection.

1. Naumann M, *et al.* Focal hyperhidrosis: effective treatment with intracutaneous botulinum toxin. *Arch Dermatol* 1998; 134: 301–4.
2. Schnider P, *et al.* Treatment of focal hyperhidrosis with botulinum toxin type A: long-term follow-up in 61 patients. *Br J Dermatol* 2001; 145: 289–93.
3. Schnider P, *et al.* Double-blind trial of botulinum A toxin for the treatment of focal hyperhidrosis of the palms. *Br J Dermatol* 1997; 136: 548–52.
4. Schnider P, *et al.* Uses of botulinum toxin. *Lancet* 1997; 349: 953.
5. Heckmann M, *et al.* Botulinum toxin A for axillary hyperhidrosis (excessive sweating). *N Engl J Med* 2001; 344: 488–93.
6. Naumann M, *et al.* Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double blind, placebo controlled trial. *BMJ* 2001; 323: 596–9.
7. Heckmann M, *et al.* Optimizing botulinum toxin therapy for hyperhidrosis. *Br J Dermatol* 1998; 138: 553–4.

Hyperlachrymation. Botulinum A toxin may be of benefit[1,2] in the management of hyperlachrymation ('crocodile tears').

1. Riemann R, *et al.* Successful treatment of crocodile tears by injection of botulinum toxin into the lacrimal gland: a case report. *Ophthalmology* 1999; 106: 2322–4.
2. Keegan DJ, *et al.* Botulinum toxin treatment for hyperlacrimation secondary to aberrant regenerated seventh nerve palsy or salivary gland transplantation. *Br J Ophthalmol* 2002; 86: 43–6.

Laryngeal dystonias. Botulinum A toxin has been tried in the treatment of spasmodic dysphonia,[1-3] focal laryngeal dystonia,[4] and dysfunctional spasm after total laryngectomy.[5] Botulinum B toxin has also been used.[6]

1. Whurr R, *et al.* Meta-analysis of botulinum toxin treatment of spasmodic dysphonia: a review of 22 studies. *Int J Lang Commun Disord* 1998; 33 (suppl): 327–9.
2. Gibbs SR, Blitzer A. Botulinum toxin for the treatment of spasmodic dysphonia. *Otolaryngol Clin North Am* 2000; 33: 879–94.
3. Watts C, *et al.* Botulinum toxin injections for the treatment of spasmodic dysphonia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 07/05/08).
4. Marion M-H, *et al.* Stridor and focal laryngeal dystonia. *Lancet* 1992; 339: 457–8.
5. Crary MA, *et al.* Using botulinum toxin A to improve speech and swallowing function following total laryngectomy. *Arch Otolaryngol Head Neck Surg* 1996; 122: 760–3.
6. Sataloff RT, *et al.* Botulinum toxin type B for treatment of spasmodic dysphonia: a case report. *J Voice* 2002; 16: 422–4.

Micturition disorders. Preliminary results[1] suggest that injection of botulinum A toxin into the detrusor muscle can increase functional bladder capacity and restore continence in patients with urinary incontinence (p. 2349.2) after spinal cord injury who are resistant to antimuscarinics. Similar results[2] have been found in children with detrusor hyperreflexia caused by myelomeningocele.

Botulinum A toxin has also been tried in other bladder dysfunctions.[3,4] Reviews[5,6] have concluded that although there is some evidence that injection of botulinum toxins into the detrusor wall can improve symptoms of overactive bladder syndrome, further studies are warranted.

In a few small studies[7,8] the injection of botulinum A toxin into the prostate gland has been reported to relieve the symptoms of urinary retention associated with benign prostatic hyperplasia (p. 2347.1).

1. Schurch B, *et al.* Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. *J Urol (Baltimore)* 2000; 164: 692–7.
2. Schulte-Baukloh H, *et al.* Efficacy of botulinum-A toxin in children with detrusor hyperreflexia due to myelomeningocele: preliminary results. *Urology* 2002; 59: 325–7.
3. Phelan MW, *et al.* Botulinum toxin urethral sphincter injection to restore bladder emptying in men and women with voiding dysfunction. *J Urol (Baltimore)* 2001; 165: 1107–10.
4. Smith CP, *et al.* Botulinum toxin in urology: evaluation using an evidence-based medicine approach. *Nat Clin Pract Urol* 2004; 1: 31–7.
5. Schurch B. Botulinum toxin for the management of bladder dysfunction. *Drugs* 2006; 66: 1301–18.
6. Duthie J, *et al.* Botulinum toxin injections for adults with overactive bladder syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 07/05/08).
7. Maria G, *et al.* Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: results of a randomized, placebo-controlled study. *Urology* 2003; 62: 259–65.
8. Kuo H-C. Prostate botulinum A toxin injection—an alternative treatment for benign prostatic obstruction in poor surgical candidates. *Urology* 2005; 65: 670–4.

Nystagmus. Surgery, corrective spectacles, and drug therapy have all been tried for the treatment of nystagmus (rapid involuntary movement of the eyeball). Retrobulbar injection of botulinum A toxin has produced improvement in patients with acquired or congenital nystagmus.[1-4] In 6 patients with acquired nystagmus visual acuity was improved, and the amplitude of the nystagmus was reduced, but the frequency was generally unchanged and the need for repeated injections and adverse effects such as diplopia limited patient acceptability.[1]

1. Repka MX, *et al.* Treatment of acquired nystagmus with botulinum neurotoxin A. *Arch Ophthalmol* 1994; 112: 1320–4.
2. Carruthers J. The treatment of congenital nystagmus with Botox. *J Pediatr Ophthalmol Strabismus* 1995; 32: 306–8.
3. Lennerstrand G, *et al.* Treatment of strabismus and nystagmus with botulinum toxin type A: an evaluation of effects and complications. *Acta Ophthalmol Scand* 1998; 76: 27–37.
4. Stahl JS, *et al.* Medical treatment of nystagmus and its visual consequences. *J R Soc Med* 2002; 95: 235–7.

Ocular surgery. Ptosis is a common adverse effect of botulinum A toxin but therapeutic ptosis induced with botulinum toxin has been described as a useful adjunct in the management of patients undergoing epikeratoplasty since it promoted stabilisation of the epithelium on the graft.[1]

1. Freegard T, *et al.* Therapeutic ptosis with botulinum toxin in epikeratoplasty. *Br J Ophthalmol* 1993; 77: 820–2.

Pain. There have been anecdotal reports of the use of botulinum A toxin in the treatment of painful disorders such as postcholecystectomy pain associated with sphincter of Oddi dysfunction,[1] and relief of orofacial pain associated with temporomandibular joint dysfunction[2] and facial arthromyalgia.[3] Promising results have been obtained from an open study[4] investigating botulinum toxin as a treatment for chronic refractory tennis elbow in 14 patients. Its efficacy in relieving pain in other chronic conditions such as low back pain, and myofascial pain, in addition to improving function, has also been shown in individual studies.[5] A small pilot study[6] found that botulinum A toxin reduced diabetic neuropathic pain in the feet. The general management of pain is discussed on p. 4.2 with separate sections on biliary and renal colic (p. 6.3), diabetic neuropathy (p. 8.2), low back pain (p. 9.2), orofacial pain (p. 10.2), and soft-tissue rheumatism (p. 14.2).

1. Pasricha PJ, *et al.* Intrasphincteric injection of botulinum toxin for suspected sphincter of Oddi dysfunction. *Gut* 1994; 35: 1319–21.
2. Girdler NM. Use of botulinum toxin to alleviate facial pain. *Br J Hosp Med* 1994; 52: 363.
3. Girdler NM. Uses of botulinum toxin. *Lancet* 1997; 349: 953.
4. Morré HHE, *et al.* Treatment of chronic tennis elbow with botulinum toxin. *Lancet* 1997; 349: 1746.
5. Lang AM. Botulinum toxin therapy for myofascial pain disorders. *Curr Pain Headache Rep* 2002; 6: 355–60.
6. Yuan R-Y, *et al.* Botulinum toxin for diabetic neuropathic pain: a randomized double-blind crossover trial. *Neurology* 2009; 72: 1473–8.

Sialorrhoea. Botulinum toxins may be effective in the treatment of sialorrhoea and drooling associated with conditions such as cerebral palsy[1] and Parkinson's disease.[2] A review[3] found botulinum toxin A to be safe and effective in the treatment of sialorrhoea; however, further studies are warranted.

1. Jongerius PH, *et al.* Effect of botulinum toxin in the treatment of drooling: a controlled clinical trial. *Pediatrics* 2004; 114: 620–7.
2. Ondo WG, *et al.* A double-blind placebo-controlled trial of botulinum toxin B for sialorrhea in Parkinson's disease. *Neurology* 2004; 62: 37–40.
3. Benson J, Daugherty KK. Botulinum toxin A in the treatment of sialorrhea. *Ann Pharmacother* 2007; 41: 79–85.

Spasmodic torticollis. Spasmodic torticollis (cervical dystonia) is a focal dystonia (p. 903.3) characterised by spasmodic rotation of the head as a result of dystonic spasm of the neck muscles. The head may turn to one side (torticollis), extend (retrocollis), or flex (antecollis). Spasms may be repetitive or sustained. Response of spasmodic torticollis to drug therapy is usually poor and surgery has been associated with potentially serious complications. Intramuscular injections of botulinum toxins can be effective but dysphagia, which can have severe consequences (see under Adverse Effects, p. 2021.1) occurs in a significant number of patients. Other adverse effects have included lethargy, local weakness, vertigo, and dysphonia.

When injecting botulinum toxins localisation of the involved muscles with electromyographic guidance may be useful. Multiple injection sites allow more uniform contact with the innervation areas of the dystonic muscle and are especially useful in larger muscles. Bilateral injection of the sternocleidomastoid muscle is not recommended as there is an increased risk of adverse effects, especially dysphagia. Reduced doses may be required for patients with reduced muscle mass.

Doses of botulinum toxins, which are expressed in terms of units, have not been standardised between preparations. Doses are therefore *specific to each individual preparation*.

In the UK the usual initial dose of botulinum A toxin as the preparation *Dysport* (*Ipsen, UK*) is 500 units injected in divided doses into the two or three most active neck muscles:

- for *rotational torticollis*, 350 units is given initially into the splenius capitis muscle (ipsilateral to the direction of the chin/head rotation) and 150 units into the sternocleidomastoid muscle (contralateral to rotation)
- for *laterocollis*, 350 units is given initially into the ipsilateral splenius capitis muscle and 150 units into the ipsilateral sternocleidomastoid muscle; if associated with *shoulder elevation*, ipsilateral trapezoid or levator scapulae muscles may also require treatment; if 3 muscles need treatment, 300 units are injected into the splenius capitis muscle, 100 units into the sternocleidomastoid muscle, and 100 units into the third muscle
- for *retrocollis*, 250 units is given into each of the splenius capitis muscles which may be followed after 6 weeks by bilateral trapezius injections in a dose of up to 250 units per muscle; bilateral splenii injections may increase the risk of neck muscle weakness

Subsequent doses may range from 250 to 1000 units, although the higher doses may be accompanied by an increase in adverse effects such as dysphagia; doses above 1000 units are not recommended. An initial effect is usually seen within 1 week; injections usually need to be repeated every 12 weeks or as required. A preparation with a similar dosage regimen (*Dysport; Ipsen, USA*) is also available in the USA.

In the UK, botulinum A toxin as the preparation *Xeomin (Merz, UK)* is indicated for spasmodic torticollis. Licensed product information recommends that doses should be tailored to meet individual patient requirements. In practice, the maximum total dose is usually not more than 200 units but up to 300 units may be given. No more than 50 units should be given at any one injection site; limiting the dose injected into the sternocleidomastoid muscle to less than 100 units may reduce the risk of dysphagia. An initial effect is usually observed within 1 week; each treatment lasts for about 3 to 4 months and injections may be repeated if necessary after at least 10 weeks. *Xeomin* (*Merz*) is also available in the USA for the treatment of spasmodic torticollis.

Recommended doses in the UK for botulinum A toxin as the preparation *Botox* (*Allergan, UK*) are listed below but licensed product information states that in practice the maximum total dose is not usually more than 200 units. No more than 50 units should be given at any one injection site; limiting the dose injected into the sternocleidomastoid muscle to less than 100 units may reduce the risk of dysphagia.

- *Type I* (head rotated toward side of shoulder elevation)—sternocleidomastoid muscle: total dosage of 50 to 100 units divided amongst at least 2 sites; levator scapulae: total of 50 units amongst 1 or 2 sites; scalene: total of 25 to 50 units amongst 1 or 2 sites; splenius capitis: total of 25 to 75 units amongst 1 to 3 sites; trapezius: total of 25 to 100 units amongst 1 to 8 sites
- *Type II* (head rotation only)—sternocleidomastoid muscle: total dosage of 25 to 100 units divided amongst at least 2 sites if more than 25 units is given
- *Type III* (head tilted toward side of shoulder elevation)—sternocleidomastoid muscle: total dosage of 25 to 100 units at posterior border divided amongst at least 2 sites if more than 25 units is given; levator scapulae: total of 25 to 100 units amongst at least 2 sites; scalene: total of 25 to 75 units amongst at least 2 sites; trapezius: total of 25 to 100 units amongst 1 to 8 sites
- *Type IV* (bilateral posterior cervical muscle spasm with elevation of the face)—splenius capitis and splenius cervicis: a total dosage of 50 to 200 units divided amongst 2 to 8 sites and which include both sides of the neck

Botulinum A toxin as the preparation *Botox* (*Allergan, USA*) is also available in the USA for the treatment of spasmodic torticollis. Licensed product information recommends that doses should be tailored to meet individual patient requirements.

In the UK the usual initial dose of botulinum B toxin as the preparation *NeuroBloc* (*Eisai, UK*) is 5000 to 10 000 units given by intramuscular injection in divided doses into the two to four most affected muscles.

Botulinum B toxin as the preparation *Myobloc* (*Solstice, USA*) is also available in the USA. The initial dose is 2500 to 5000 units given by intramuscular injection divided between the affected muscles. Licensed product information recommends that patients with no history of tolerating botulinum injections should be started on a lower initial dose.

References.

1. Blackie JD, Lees AJ. Botulinum toxin treatment in spasmodic torticollis. *J Neurol Neurosurg Psychiatry* 1990; 53: 640–3.
2. Greene P, *et al.* Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis. *Neurology* 1990; 40: 1213–18.
3. Anderson TJ, *et al.* Botulinum toxin treatment of spasmodic torticollis. *J R Soc Med* 1992; 85: 524–9.
4. Brans JWM, *et al.* Botulinum toxin versus trihexyphenidyl in cervical dystonia: a prospective, randomized, double-blind controlled trial. *Neurology* 1996; 46: 1066–72.
5. Brin MF, *et al.* Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia. *Neurology* 1999; 53: 1431–8.
6. Brashear A, *et al.* Safety and efficacy of NeuroBloc (botulinum toxin B) in type A-resistant cervical dystonia. *Neurology* 1999; 53: 1439–46.
7. Velickovic M, *et al.* Cervical dystonia: pathophysiology and treatment options. *Drugs* 2001; 61: 1921–43.
8. Figgitt DP, Noble S. Botulinum toxin B: a review of its therapeutic potential in the management of cervical dystonia. *Drugs* 2002; 62: 705–22.
9. Dressler D, *et al.* Botulinum toxin type B in antibody-induced botulinum toxin type A therapy failure. *J Neurol* 2003; 250: 967–9. Correction. *ibid.*; 1263–5.
10. Walker FO. Botulinum toxin therapy for cervical dystonia. *Phys Med Rehabil Clin N Am* 2003; 14: 749–66.
11. Lew MF. Duration of effectiveness of botulinum toxin type B in the treatment of cervical dystonia. *Adv Neurol* 2004; 94: 211–15.
12. Jankovic J. Treatment of cervical dystonia with botulinum toxin. *Mov Disord* 2004; 19 (suppl 8): S109–S115.
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14. Costa J, *et al.* Botulinum toxin type A therapy for cervical dystonia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 28/03/06).
15. Comella CL, *et al.* Comparison of botulinum toxin serotypes A and B for the treatment of cervical dystonia. *Neurology* 2005; 65: 1423–9.
16. Costa J, *et al.* Botulinum toxin type A versus anticholinergics for cervical dystonia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 07/05/08).

Spasticity. The mainstay of management of spasticity, as discussed on p. 2014.2, is physiotherapy and antispastic drugs. Chemical neurolysis should only be considered when there is intractable continuous pain. Local injections of botulinum A toxin, as an alternative to chemical neurolysis, have been used in the management of limb spasticity in multiple sclerosis,[1] and in post-stroke patients,[1-6] and children with cerebral palsy.[7-14] In children with cerebral palsy, a systematic review[15] has found insufficient evidence to support or refute such use in those with lower

limb spasticity; however, another systematic review[16] has found the use of botulinum A toxin as an adjunct to occupational therapy to be effective in the management of upper limb spasticity. Botulinum B toxin has also been tried.[12,17]

Doses of botulinum A toxin, which are expressed in terms of units, have not been standardised between preparations. Doses are therefore *specific to each individual preparation:* Botulinum A toxin is used in the management of dynamic equinus foot deformity associated with spasticity in children with cerebral palsy.

- For children over 2 years of age the recommended total dose of botulinum A toxin as the preparation *Botox* (*Allergan, UK*) is 4 units/kg injected into each of 2 sites in the medial and lateral heads of the gastrocnemius muscle. When both lower limbs are to be injected on the same occasion this total dose should be divided between the 2 limbs. Clinical improvement generally occurs within the first 2 weeks. Repeat doses should not be given more frequently than every 2 months.
- For children over 2 years of age the recommended total dose of botulinum A toxin as the preparation *Dysport* (*Ipsen, UK*) is 10 to 30 units/kg divided between both calf muscles, mainly targeted to the gastrocnemius muscle. The maximum dose administered should not exceed 1000 units per patient. Clinical improvement generally occurs within the first 2 weeks. Repeat doses should not be given more frequently than every 12 weeks.

Botulinum A toxin is also used in the treatment of upper limb spasticity in adults.

- In the treatment of upper limb spasticity associated with stroke, the exact dosage and number of injection sites of botulinum A toxin as the preparation *Botox* (*Allergan, UK*) should be tailored to the individual based on the muscles involved, the severity of the spasticity, and the presence of local weakness. The manufacturer recommends a total dose of 50 units into the flexor digitorum profundus, the flexor digitorum sublimis, the flexor carpi radialis, or the flexor carpi ulnaris, and a total dose of 20 units into the adductor pollicis or flexor pollicis longus. In clinical studies, cumulative doses did not exceed 360 units at any treatment session. Botulinum A toxin as the preparation *Botox* (*Allergan, USA*) is also available in the USA for the treatment of upper arm spasticity. Doses should be tailored to meet individual patient requirements.
- The preparation *Xeomin* (*Merz, UK*) is used in the treatment of post-stroke upper arm spasticity. Initial doses range from 10 to 80 units and should be tailored to the individual; a total dose of 400 units should not be exceeded at a given session. Clinical improvement is seen within 4 weeks. Treatment may be repeated after a minimum of 12 weeks.
- In the treatment of focal spasticity of the arm, the recommended total dose of botulinum A toxin as the preparation *Dysport* (*Ipsen, UK*) is 1000 units divided into: a dose of 150 units into the flexor digitorum profundus, the flexor carpi ulnaris, and the flexor carpi radialis; 150 to 250 units into the flexor digitorum superficialis; and 300 to 400 units into the biceps brachii. All muscles should be injected at one site except the biceps brachii which should be injected at 2 sites. Lower doses are recommended in patients whose target muscles are small, where the biceps brachii is not to be injected, or in patients receiving multi-level injections. Clinical improvement generally occurs within the first 2 weeks.

1. Sheean G. Botulinum toxin treatment of adult spasticity: a benefit-risk assessment. *Drug Safety* 2006; 29: 31–48.
2. Simpson DM, *et al.* Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. *Neurology* 1996; 46: 1306–10.
3. Bhakta BB, *et al.* Use of botulinum toxin in stroke patients with severe upper limb spasticity. *J Neurol Neurosurg Psychiatry* 1996; 61: 30–5.
4. Burbaud P, *et al.* A randomised, double blind, placebo controlled trial of botulinum toxin in the treatment of spastic foot in hemiparetic patients. *J Neurol Neurosurg Psychiatry* 1996; 61: 265–9.
5. Brashear A, *et al.* Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N Engl J Med* 2002; 347: 395–400.
6. Shaw L, Rodgers H. Botulinum toxin type A for upper limb spasticity after stroke. *Expert Rev Neurother* 2009; 9: 1713–25.
7. Zeinik N, *et al.* The role of botulinum toxin in the treatment of lower limb spasticity in children with cerebral palsy—a pilot study. *Isr J Med Sci* 1997; 33: 129–33.
8. Carr LJ, *et al.* Position paper on the use of botulinum toxin in cerebral palsy. *Arch Dis Child* 1998; 79: 271–3.
9. Fehlings D, *et al.* An evaluation of botulinum-A toxin injections to improve upper extremity function in children with hemiplegic cerebral palsy. *J Pediatr* 2000; 137: 331–7.
10. Ubhi T, *et al.* Randomised double blind placebo controlled trial of the effect of botulinum toxin on walking in cerebral palsy. *Arch Dis Child* 2000; 83: 481–7.
11. Koman LA, *et al.* Botulinum toxin type A neuromuscular blockade in the treatment of equinus foot deformity in cerebral palsy: a multicenter, open-label clinical trial. *Pediatrics* 2001; 108: 1062–71.
12. Berweck S, Heinen F. Use of botulinum toxin in pediatric spasticity (cerebral palsy). *Mov Disord* 2004; 19 (suppl 8): S162–S167.
13. Bjornson K, *et al.* Botulinum toxin for spasticity in children with cerebral palsy: a comprehensive evaluation. *Pediatrics* 2007; 120: 49–58.
14. Moore AP, *et al.* Two-year placebo-controlled trial of botulinum toxin A for leg spasticity in cerebral palsy. *Neurology* 2008; 71: 122–8.
15. Ade-Hall RA, Moore AP. Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 07/05/08).
16. Hoare BJ, *et al.* Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy (UPDATE). Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 27/01/10).
17. Brashear A, *et al.* Botulinum toxin type B in upper-limb poststroke spasticity: a double-blind, placebo-controlled trial. *Arch Phys Med Rehabil* 2004; 85: 705–9.

Stiff-man syndrome. A patient with stiff-man syndrome (see Muscle Spasm, p. 1064.3) had marked improvement of ambulation and cessation of pain after injection of botulinum A toxin into affected paraspinal muscles.[1] In another case report, improvement in rigidity and muscle spasm was reported[2] in 2 patients after botulinum treatment; muscle spasms reduced within 3 days of treatment. It was also found that there was an increase in the duration of effect of botulinum A toxin after each subsequent injection and only a gradual return of painful spasm.

1. Davis D, Jabbari B. Significant improvement of stiff-person syndrome after paraspinal injection of botulinum toxin A. *Mov Disord* 1993; 8: 371–3.
2. Liguori R, *et al.* Botulinum toxin A improves muscle spasms and rigidity in stiff-person syndrome. *Mov Disord* 1997; 12: 1060–3.

Strabismus. Botulinum A toxin has been used to weaken overactive extra-ocular muscles as an alternative or adjunct to surgery in the correction of strabismus (p. 2000.3). Not all patients respond to botulinum A toxin and many patients who do respond require more than one injection to maintain improvement. Botulinum A toxin does not appear to offer a better degree of correction than traditional surgery, and it has been suggested that it should be reserved for use in patients unresponsive to, or unsuitable for, surgery. In the USA botulinum A toxin as the preparation *Botox* (*Allergan, USA*) is indicated for the treatment of strabismus in patients 12 years of age or older. Depending on the direction and degree of deviation to be corrected the recommended initial dose of Botox to be injected into any one extra-ocular muscle ranges from 1.25 to 5 units. Paralysis is usually seen within the first 2 days and increases in intensity during the first week. The paralysis lasts for 2 to 6 weeks and gradually resolves over a further 2 to 6 weeks. It is recommended that patients are re-examined 7 to 14 days after injection to assess the effect of the dose given. If treatment is required for residual or recurrent strabismus, patients are either given treatment at the previous dosage if response was judged to have been adequate or up to twice the previous dose if paralysis had been incomplete; no more than 25 units should be injected into any one muscle. Repeat injections should not be given until the effects of the previous dose have dissipated. Injections should be diluted with unpreserved 0.9% sodium chloride solution so that the volume given per muscle is between 0.05 mL and 0.15 mL. Injections should also be made using an electromyographically guided needle to aid location of the target muscle.

References.

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3. Lyons CJ, *et al.* Botulinum toxin therapy in dysthyroid strabismus. *Eye* 1990; 4: 538–42.
4. McNeer KW. An investigation of the clinical use of botulinum toxin A as a postoperative adjustment procedure in the therapy of strabismus. *J Pediatr Ophthalmol Strabismus* 1990; 27: 3–9.
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6. Petitto VB, Buckley EG. Use of botulinum toxin in strabismus after retinal detachment surgery. *Ophthalmology* 1991; 98: 509–13.
7. Elston J. Is botulinum toxin helpful in squint management? *Br J Ophthalmol* 1998; 82: 105.
8. Tejedor J, Rodríguez JM. Early retreatment of infantile esotropia: comparison of reoperation and botulinum toxin. *Br J Ophthalmol* 1999; 83: 783–7.
9. Dawson EL, Lee JP. Does botulinum toxin have a role in the treatment of small-angle esotropia? *Strabismus* 2004; 12: 257–60.
10. Dawson EL, *et al.* Does botulinum toxin have a role in the treatment of secondary strabismus? *Strabismus* 2005; 13: 71–3.
11. Rowe FJ, Noonan CP. Botulinum toxin for the treatment of strabismus. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 27/01/10).

Stuttering. Botulinum toxin may be of benefit in the treatment of stuttering (p. 1078.1).[1,2]

1. Brin MF, *et al.* Laryngeal botulinum toxin injections for disabling stuttering in adults. *Neurology* 1994; 44: 2262–6.
2. Cordivari C, *et al.* New therapeutic indications for botulinum toxins. *Mov Disord* 2004; 19 (suppl 8): S157–S161.

Tourette's syndrome. Improvement in tics was noted in patients with Tourette's syndrome (see Tics, p. 1030.1) treated with botulinum A toxin.[1,2]

1. Kwak CH, *et al.* Botulinum toxin in the treatment of tics. *Arch Neurol* 2000; 57: 1190–3.
2. Marras C, *et al.* Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial. *Neurology* 2001; 56: 605–10.

Tremor. Local injection of botulinum A toxin[1–4] has been tried in patients with essential tremor (p. 1318.3) that fails to respond to conventional treatment. Botulinum A toxin injection has also been successfully used to treat essential palatal tremor[5–7] and associated symptoms such as uncomfortable ear clicking.

1. Henderson JM, *et al.* Botulinum toxin A in non-dystonic tremors. *Eur Neurol* 1996; 36: 29–35.
2. Jankovic J, *et al.* A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. *Mov Disord* 1996; 11: 250–6.
3. Pacchetti C, *et al.* Botulinum toxin treatment for functional disability induced by essential tremor. *Neurol Sci* 2000; 21: 349–53.
4. Brin MF, *et al.* A randomized, double masked, controlled trial of botulinum toxin type A in essential hand tremor. *Neurology* 2001; 56: 1523–8.
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7. Cho JW, *et al.* Case of essential palatal tremor: atypical features and remarkable benefit from botulinum toxin injection. *Mov Disord* 2001; 16: 779–82.

Vaginismus. Report[1] of one patient who had relief of vaginismus (painful involuntary spasm of the vaginal or perianal muscles severe enough to prevent intercourse) for more than 24 months after injection of botulinum toxin into the vaginal wall muscles.

1. Brin MF, Vapnek JM. Treatment of vaginismus with botulinum toxin injections. *Lancet* 1997; 349: 252–3.

Adverse Effects

Injections of botulinum toxins have been associated with a transient burning sensation, bruising at the injection site, and local weakness. Adverse reactions related to the spread of botulinum toxins distant to the site of injection have been reported and sometimes this was associated with significant debility or a fatal outcome in very rare cases. Exaggerated muscle weakness may occur with therapeutic doses. Deep or misplaced injections may paralyse nearby muscle groups and excessive doses may paralyse distant muscles. Overdosage can produce a widespread paralysis.

There have been occasional reports of hypersensitivity reactions such as rashes and flu-like symptoms. There have also been rare reports of cardiovascular adverse effects, including arrhythmia and myocardial infarction, and of seizures or convulsions, particularly in predisposed patients.

- The most common adverse effects after injection into muscles around the eye, such as in the management of blepharospasm, hemifacial spasm, or strabismus, are ptosis, lachrymation, photophobia, ocular irritation, and facial swelling. Some patients may be unable to close the eyelid completely. Other adverse effects that have been reported include ectropion and entropion, and diplopia. Blinking may be reduced and this can lead to dry eye, keratitis, and corneal damage. Angle-closure glaucoma has been reported. Vertical deviation has also occurred in patients treated for horizontal strabismus. Needle penetrations of the eye during treatment of strabismus have resulted in vitreous and retrobulbar haemorrhages.
- Dysphagia is the most common adverse effect after injection into neck muscles in the treatment of spasmodic torticollis and there may be pooling of saliva with risk of aspiration in severely affected patients (*important*, see also Precautions, p. 2021.2). Dry mouth, paralysis of the vocal cords, and weakness of the neck muscles may also occur. Generalised weakness, malaise, nausea, and visual disturbances have occasionally been reported. Other effects which have occurred rarely include drowsiness, numbness, stiffness, ptosis, and headache. Respiratory difficulties, associated with the use of large doses, have occurred on rare occasions.
- Adverse effects most frequently associated with injection into the lower limbs in the treatment of cerebral palsy include falling, leg pain, and local and general weakness; lethargy and leg cramps have also been reported.
- Common adverse effects after injection into the upper limb in the treatment of spasticity associated with stroke are arm pain, dysphagia, muscle weakness, and hypertonia. A perceived increase in non-axillary sweating, within one month of the injection, has been reported after treatment for hyperhidrosis of the axillae; rarely, mild transient weakness of the arms has also occurred.
- Headache is the most frequent adverse effect after injection into the muscles around the forehead in the treatment of glabellar (frown) lines. Other adverse effects frequently reported include ptosis, facial pain, muscle weakness, and nausea.

Reviews.

1. Klein AW. Complications and adverse reactions with the use of botulinum toxin. *Dis Mon* 2002; 48: 336–56.

Incidence of adverse effects. It has been suggested that the difference between botulinum A toxin preparations may not be confined to just a numerical dosage adjust-

ment.[1] Reviews of the literature have suggested that there may also be a difference in the incidence of adverse effects. The reported frequency of dysphagia for *Dysport* (28% and 44%) in patients with spasmodic torticollis was greater than that for *Botox* (9.5 to 17%). This variation might relate to differences in bioactivity not recognised by the mouse lethality bioassay that is used to determine the potency of preparations.

In February 2009, the Australian Adverse Drug Reactions Advisory Committee[2] reported that since mid-1994 it had received 45 reports of adverse effects associated with botulinum A toxin in 36 females and 9 males, whose age ranged from 2 to 79 years (median: 45 years); none were fatal. The most common reaction (16 cases) was muscle weakness at sites adjacent to, or distant from, the injected area; of these, there were 8 reports of dysphagia, 3 of respiratory failure or dyspnoea, and 7 of generalised muscle weakness. Other reactions included rash or other allergic reaction (10 reports), diplopia (6 reports), and fatigue (4 reports).

1. Borodic G. Therapeutic botulinum toxin. *Lancet* 1994; 344: 1370.
2. Adverse Drug Reactions Advisory Committee (ADRAC). Adverse reactions with botulinum toxin A (Botox, Dysport). *Aust Adverse Drug React Bull* 2009; 28: 2. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0902.pdf (accessed 27/01/10)

Angiosarcoma. It has been suggested[1] that botulinum A toxin injection might have acted as a triggering factor for angiosarcoma in a 66-year-old patient being treated for blepharospasm.

1. Kárpáti S, *et al.* Human herpesvirus type 8-positive facial angiosarcoma developing at the site of botulinum toxin injection for blepharospasm. *Br J Dermatol* 2000; 143: 660–2.

Antibody formation. Neutralising antibodies that reduce or abolish the beneficial effects of treatment have been found after prolonged treatment with botulinum A toxin.[1] A review[2] in 1994 considered that there was growing concern over the development of antibodies after repeated injections, as many of the conditions for which botulinum toxin is indicated require indefinite treatment. Antibody formation was reported to be more common with high doses (as in spasmodic torticollis) than after low doses (as for blepharospasm). The occurrence of antibodies appeared to correlate with the dose per injection, the quantity of botulinum protein given per injection, the number of injections given, and the frequency of injections.

Antibodies have also developed after the use of botulinum B toxin. However, botulinum toxin B is antigenically distinct from botulinum A toxin, and may be of value in patients who develop resistance to treatment associated with antibody formation to type A toxin.[3] Botulinum F toxin is also antigenically distinct and is being studied in a similar way.

1. Hambleton P, *et al.* Antitoxins and botulinum toxin treatment. *BMJ* 1992; 304: 959–60.
2. Borodic GE, Pearce LB. New concepts in botulinum toxin therapy. *Drug Safety* 1994; 11: 145–52.
3. Brin MF, *et al.* Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia. *Neurology* 1999; 53: 1431–8.

Biliary colic. A 43-year-old woman with no history of gallbladder disease had single episodes of biliary colic after each of 3 sessions of treatment with botulinum A toxin for blepharospasm.[1] Botulinum A toxin might have exerted a systemic effect to block acetylcholine release leading to gallbladder hypomotility with delayed emptying and stasis.

1. Schnider P, *et al.* Gallbladder dysfunction induced by botulinum A toxin. *Lancet* 1993; 342: 811–12.

Dysphagia. By November 1993, the UK CSM had received 4 reports of severe dysphagia with choking in patients given injections of botulinum A toxin into the neck muscles as a treatment for torticollis.[1] The dysphagia developed 5 to 7 days after the injection and in one patient it was persisting 6 weeks after the injection. The dysphagia led to aspiration of the stomach contents into the lungs and one patient with a history of poor lung function died from bronchopneumonia. Dysphagia is also reported to be a common adverse effect in patients with spasmodic torticollis being treated with botulinum B toxin.[2]

See also Incidence of Adverse Effects and Systemic Effects, p. 2020.3 and below, respectively, for further reference to dysphagia as an adverse effect.

1. CSM/MCA. Reminder: botulinum type A toxin (Dysport)—severe dysphagia with unlicensed route of administration. *Current Problems* 1993; 19: 11. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Lew MF, *et al.* The safety and efficacy of botulinum toxin type B in the treatment of patients with cervical dystonia: summary of three controlled clinical trials. *Neurology* 2000; 55 (suppl 5): S29–S35.

Effects on the eyes. Acute angle-closure glaucoma has been reported[1] in an 83-year-old woman after a series of injections of botulinum A toxin for the treatment of blepharospasm. Permanent extra-ocular muscle damage after botulinum A toxin injection into the left inferior rectus muscle has been reported[2] in a 70-year-old man.

1. Corridan P, *et al.* Acute angle-closure glaucoma following botulinum toxin injection for blepharospasm. *Br J Ophthalmol* 1990; 74: 309–10.
2. Mohan M, *et al.* Permanent extraocular muscle damage following botulinum toxin injection. *Br J Ophthalmol* 1999; 83: 1309–10.

Systemic effects. In February 2008, the FDA[1] reported that it had received reports of systemic adverse reactions associated with the spread of botulinum toxin from the injected area. Symptoms described include dysphagia, ptosis, weakness and numbness of the lower extremities, and respiratory insufficiency. The most serious cases, resulting in hospitalisation and death, occurred mostly in children with cerebral palsy who were being treated for limb spasticity; doses used ranged from 6.25 to 32 units/kg of a botulinum A toxin preparation *Botox*, and 388 to 625 units/kg of a botulinum B toxin preparation *Myobloc*. No deaths had been reported in adults; doses used ranged from 100 to 700 units of *Botox*, and 10 000 to 20 000 units of *Myobloc*.

In April 2009, a follow-up report[2] from the FDA added that the majority of such case reports in adults occurred in those being treated for spasticity or spasmodic torticollis. The FDA was aware of several deaths in adults; however, causality to botulinum toxin use could not be established due to the patients' pre-existing conditions. No definitive reports of serious adverse reactions associated with the spread of botulinum toxin had been identified with the use of *Botox* in the treatment of glabellar (frown) lines or severe primary axillary hyperhidrosis.

Similar cases have also been reported in other countries.[3] See also Incidence of Adverse Effects and Dysphagia, p. 2020.3 and above, respectively.

1. FDA. Early communication about an ongoing safety review of Botox and Botox Cosmetic (botulinum toxin type A) and Myobloc (botulinum toxin type B) (issued 8th February, 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm070366.htm (accessed 28/01/10)
2. FDA. Follow-up to the February 8, 2008, early communication about an ongoing safety review of Botox and Botox Cosmetic (botulinum toxin type A) and Myobloc (botulinum toxin type B) (issued April 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm143819.htm (accessed 28/01/10)
3. Health Canada. Botulinum toxin type A (Botox) and distant toxin spread. *Can Adverse React News* 2008; 18(4): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v18n4-eng.pdf (accessed 28/01/10)

Treatment of Adverse Effects

The use of artificial tears may relieve keratitis and dry eye. In the event of overdosage general supportive care is required. The patient should be monitored for several days for signs of paralysis and artificial respiration may be necessary. Since the effects of botulinum toxins are irreversible once bound to nerve terminals, it is doubtful that specific botulinum antitoxin (p. 2380.2) will be of value unless given very rapidly after overdosage.

Precautions

Botulinum toxin is contra-indicated in generalised disorders of muscle activity such as myasthenia gravis. As with other biological products, the potential for botulinum toxin to cause anaphylaxis should be considered. Botulinum toxins should be given with extreme caution to patients with neurological disorders or a history of dysphagia or aspiration. Patients or their carers should be advised to seek immediate medical attention if problems with swallowing or speech, or respiratory disorders develop.

Botulinum toxins should only be used by appropriately qualified and trained specialists. Injections must be made with great care, especially those into the neck, to avoid unintended paralysis; the relevant anatomy, and any alterations due to previous surgery, must be understood before injection. Botulinum toxins should not be given if there is any infection at the proposed injection site.

The effects of botulinum toxins in pregnancy are unknown; fetal malformations and abortion have been reported in *rabbits*, and licensed product information recommends that botulinum toxins should not be given to pregnant women. Breast feeding is also considered a contra-indication: it is not clear whether the toxin is distributed into breast milk.

When **injected into the muscles around the eyes**, as for the treatment of blepharospasm, hemifacial spasm, or strabismus, reduced blinking can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with seventh cranial nerve disorders. Corneal sensation should be carefully tested in previously treated eyes, injection into the lower eyelid area avoided, and any resulting epithelial defect vigorously treated.

Handling. Residual botulinum A toxin or spillages should be inactivated by autoclaving or use of a dilute hypochlorite solution (0.5%). Botulinum B toxin may be decontaminated in a similar manner; a strong caustic solution may also be used.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies botulinum toxins 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 27/10/11)

Interactions

The effect of botulinum toxins may theoretically be potentiated by aminoglycosides or spectinomycin. Interactions may also occur with other drugs that have neuromuscular blocking activity, including lincosamides, polymyxins, tetracyclines, and muscle relaxants.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Botox; Dysport; Xeomin; *Austral.*: Botox; Dysport; *Austria*: Azzalure; Botox; Dysport; NeuroBloc; Xeomin; *Belg.*: Azzalure; Botox; Dysport; Vistabel; *Braz.*: Botox; Botulift; Dysport; Prosigne; Xeomin; *Canad.*: Botox; Xeomin; *Chile*: Dysloт†; *China*: Botox (保妥适); *Cz.*: Botox; Dysport; NeuroBloc; Vistabel; *Denm.*: Azzalure; Botox; Dysport; NeuroBloc; Vistabel; Xeomin; *Fin.*: Azzalure; Bocouture; Botox; Dysport; Vistabel; Xeomin; *Fr.*: Azzalure; Botox; Dysport; NeuroBloc; Vistabel; Xeomin; *Ger.*: Azzalure; Bocouture; Botox; Dysport; NeuroBloc; Vistabel; Xeomin; *Gr.*: Botox; Dysport; NeuroBloc; Vistabel; *Hong Kong*: Botox; BTXA; Dysport; *Hung.*: Botox; Dysport; NeuroBloc; Vistabel; *India*: Botox; *Indon.*: Botox; Lanzox; *Irl.*: Azzalure; Botox; Dysport; NeuroBloc; Vistabel; *Israel*: Botox; Dysport; *Ital.*: Botox; Dysport; NeuroBloc; Vistabex; Xeomin; *Jpn*: Botox; NerBloc; *Malaysia*: Botox; Dysport; *Mex.*: Antipar; Botox; Dysport; Xeomeen; *Neth.*: Azzalure; Bocouture; Botox; Dysport; NeuroBloc; Vistabel; Xeomin; *Norw.*: Azzalure; Botox; Dysport; NeuroBloc; Vistabel; Xeomin; *NZ*: Botox; Dysport; *Philipp.*: Botox; Dysport; *Pol.*: Botox; Dysport; NeuroBloc; Vistabel; Xeomin; *Port.*: Azzalure; Botox; Dysport; NeuroBloc; Vistabel; Xeomin; *Rus.*: Botox (Ботокс); Dysport (Диспорт); Lantox (Лантокс); Xeomin (Ксеомин); *S.Afr.*: Botox; Dysport; *Singapore*: Botox; Dysport; *Spain*: Azzalure; Bocouture; Botox; Dysport; NeuroBloc; Vistabel; Xeomin; *Swed.*: Azzalure; Bocouture; Botox; Dysport; NeuroBloc; Vistabel; Xeomin; *Switz.*: Botox; Dysport; Vistabel; *Thai.*: Botox; Botulax; Dysport; Zentox; *Turk.*: Botox; Dysport; *UK*: Azzalure; Bocouture; Botox; Dysport; NeuroBloc; Vistabel; Xeomin; *Ukr.*: Botox (Ботокс); Dysport (Диспорт); *USA*: Botox; Dysport; Myobloc; Xeomin; *Venez.*: Botox; Dysport.

Pharmacopoeial Preparations

Ph. Eur.: Botulinum Toxin Type A for Injection; Botulinum Toxin Type B for Injection.

Carisoprodol *(BAN, rINN)*

Carisoprodolum; Isopropylmeprobamate; Karisoprodol; Karisoprodoli; Karizoprodol; Karizoprodolis; Каризопродол.

2-Methyl-2-propyltrimethylene carbamate isopropylcarbamate.

$C_{12}H_{24}N_2O_4$=260.3

CAS — 78-44-4.

ATC — M03BA02.

ATC Vet — QM03BA02.

UNII — 21925K482H.

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

Ph. Eur. 8: (Carisoprodol). A white or almost white fine powder. M.p. 92 degrees to 95 degrees. Very slightly soluble in water; freely soluble in alcohol, in acetone, and in dichloromethane.

USP 36: (Carisoprodol). A white crystalline powder having a mild characteristic odour. M.p. 91 degrees to 94 degrees. Soluble 1 in 2083 of water, 1 in 2.5 of alcohol and of acetone, and 1 in 2.3 of chloroform. Store in airtight containers.

Uses and Administration

Carisoprodol is a centrally acting skeletal muscle relaxant whose mechanism of action is not completely understood but may be related to its sedative actions. After oral doses its effects begin within about 30 minutes and last for 4 to 6 hours. It is used as an adjunct in the short-term symptomatic treatment of painful muscle spasm (p. 2014.1) associated with musculoskeletal conditions. A usual oral dose is 250 to 350 mg given three or four times daily for up to 2 to 3 weeks. Elderly patients may require half the usual dose or less. It is also given with analgesics in compound preparations.

The EMEA and some other authorities have recommended for carisoprodol to be suspended from the market due to the increased risk of abuse and addiction, as well as

the risk of altered mental state and psychomotor impairment.

Dependence and Withdrawal, Adverse Effects, Treatment, and Precautions

As for Meprobamate, p. 1084.1.

The most common adverse effects reported with carisoprodol are drowsiness, dizziness, and headache. Sedation may affect the performance of skilled tasks and affected patients should not drive or operate machinery. Poor metabolisers, deficient in the cytochrome P450 isoenzyme CYP2C19, may be at greater risk of drowsiness.

Idiosyncratic reactions may occur within minutes of a dose in patients who have not previously received carisoprodol. Such reactions have been reported rarely and include anaphylactic shock, syncope, tachycardia, confusion, transient quadriplegia, and bronchospasm. Cross-reactivity can occur with its metabolite meprobamate.

Overdosage may result in seizures, stupor, coma, shock, respiratory depression, and rarely death.

Carisoprodol should be used with caution in patients with impaired hepatic or renal function.

Cases of dependence and abuse have been reported with the prolonged use of carisoprodol, particularly in patients with a history of addiction; withdrawal reactions have also occurred when treatment is suddenly stopped after prolonged use or the use of high doses. The increased risk of abuse and addiction with carisoprodol, as well as the risk of altered mental state and psychomotor impairment, has led the EMEA and some other authorities to recommend that it is suspended from the market in the USA, however, it is recommended that use is limited to 2 to 3 weeks.

Abuse. Analysis[1] of data from the Norwegian Prescription Database found that carisoprodol was used in higher doses than recommended indicating its potential as a drug of abuse. Subsequently, the Norwegian Medicines Agency and the EMEA have recommended for its suspension (see above).

There have been isolated reports[2,3] of amnestic states associated with abuse of carisoprodol.

1. Bramness JG, *et al.* Carisoprodol use and abuse in Norway: a pharmacoepidemiological study. *Br J Clin Pharmacol* 2007; 64: 210–18.
2. Hussain EM, *et al.* Carisoprodol-induced amnestic state and nocturnal blackouts. *Aust N Z J Psychiatry* 2008; 42: 909–11.
3. Gupta A, *et al.* Carisoprodol-induced amnestic state. *Indian J Psychiatry* 2008; 50: 72–3.

Breast feeding. Carisoprodol is distributed into breast milk, achieving concentrations 2 to 4 times those in maternal plasma. In a case report,[1] except for mild sedation, no other adverse effects were seen in an infant whose mother received carisoprodol 2.8 g daily before and throughout gestation, and during 1 month of exclusive breast feeding; the maximum infant dose of carisoprodol and meprobamate was 6.9% of the mother's weight-adjusted dose during breast feeding.

US licensed product information states that carisoprodol should be used with caution in breast-feeding mothers.

1. Briggs GG, *et al.* High-dose carisoprodol during pregnancy and lactation. *Ann Pharmacother* 2008; 42: 898–901.

Dependence. There are reports[1,2] of carisoprodol dependence, probably due to its metabolism to meprobamate (see p. 1084.1). Symptoms of abrupt withdrawal have included chills, tremors, myalgia, muscle twitching, insomnia, irritability, anxiety, and hallucinations.[1,3] In one case[1] the patient had symptoms of meprobamate withdrawal that resolved with a dose-reducing schedule of meprobamate.

Dependence may occur more often when carisoprodol is given in high doses and for prolonged periods, especially in patients with a history of alcohol or drug dependence or in those with marked personality disorders. One group[2] found that patients with a history of substance abuse were twice as likely to use carisoprodol in larger doses to those prescribed than those with no such history.

The risk of dependence with carisoprodol has led the EMEA and some other authorities to recommend its suspension from the market (see above).

1. Luehr JG, *et al.* Mail-order (veterinary) drug dependence. *JAMA* 1990; 263: 657.
2. Reeves RR, *et al.* Carisoprodol (Soma): abuse potential and physician unawareness. *J Addict Dis* 1999; 18: 51–6.
3. Reeves RR, Burke RS. Carisoprodol: abuse potential and withdrawal syndrome. *Curr Drug Abuse Rev* 2010; 3: 33–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies carisoprodol 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 24/10/11)

Interactions

The CNS effects of carisoprodol may be potentiated by alcohol or other CNS depressants. Carisoprodol may cause hepatic enzyme induction and it may therefore affect the metabolism of some drugs. The metabolism of carisoprodol is mediated by the cytochrome P450 isoenzyme CYP2C19; use with other drugs that inhibit or induce this isoenzyme may result in changes in plasma concentration of carisoprodol, however, there is a lack of data.

Pharmacokinetics

Carisoprodol is absorbed from the gastrointestinal tract and peak plasma concentrations occur after 1.5 to 2 hours. It is metabolised in the liver mainly by the cytochrome P450 isoenzyme CYP2C19, which shows genetic polymorphism, and excreted in urine as metabolites, including meprobamate (p. 1083.3). The terminal elimination half-life of carisoprodol is about 2 hours. It is distributed in substantial amounts into breast milk.

References.

1. Olsen H, *et al.* Carisoprodol elimination in humans. *Ther Drug Monit* 1994; 16: 337–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Listaflex; *Gr.*: Artifar; Soma; *India*: Carisoma; *Mex.*: Somacid; *Thai.*: Somagin†; *USA*: Soma.

Multi-ingredient Preparations. *Arg.*: Algiseda Plus; Algiseda; Flexicamin A; Flexicamin B12; Flexicamin; Flogiatrin B12; Flogiatrin; Listaflex Forte; Naprontag Flex; Naprux Disten; Rumisedan Fuerte; Solocalm Plus; Solocalm-Flex; *Braz.*: Algi-Tanderil; Beserol; Diclofetamol; Dorilax; Flexalgin; Infralax; Mio-Citalgan; Mioflex A; Mioflex; Mionevrix; Sanilax; Sedilax; Tandene; Tanderalgin; Tandriflan; Tandrilax; Tandrotamol; Torsilax; Trilax; *Gr.*: Relacton; *India*: Carisoma Compound; Somaflam; *Indon.*: New Skelan; Somadril Compound; *Mex.*: Blocacid†; Caridoxen; Caxidol; Contraxen; Dolaren; Dorsal; Duoflex; Empatil; Naxodol†; Profenlax†; Somalgesic; *Thai.*: Alaxan†; Asialax†; Cariso-Co†; Caritasone; Cenpadol†; Muscelax†; Myophen†; Pasodol†; Polixan†; Raxsoma†; *USA*: Sodol Compound; *Venez.*: Praxona.

Pharmacopoeial Preparations

USP 36: Carisoprodol and Aspirin Tablets; Carisoprodol Tablets; Carisoprodol, Aspirin, and Codeine Phosphate Tablets.

Chlorphenesin Carbamate

(BANM, USAN, pINNM)

Carbamato de clorfenesina; Chlorphénésine, Carbamate de; Chlorphenesini Carbamatum; Clorfenesina, carbamato de; U-19646; Хлорфенезина Карбамат.

3-(4-Chlorophenoxy)propane-1,2-diol 1-carbamate.

$C_{10}H_{12}ClNO_4$=245.7

CAS — 104-29-0 (chlorphenesin); 886-74-8 (chlorphenesin carbamate).

UNII — 57USY11WP.

Pharmacopoeias. In *Jpn*.

Profile

Chlorphenesin carbamate is a centrally acting skeletal muscle relaxant related to mephenesin (p. 2025.2). Its mode of action may be related to general depressant effects on the CNS. It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p. 2014.1) associated with musculoskeletal conditions. The usual initial oral dose is 250 mg three times daily, adjusted according to response. It has been recommended that chlorphenesin carbamate should not be given for longer than 8 weeks.

Chlorphenesin base (p. 575.3) is used as an antifungal.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Rinlaxer.

Chlorzoxazone *(BAN, rINN)*

Chlorobenzoxazolinone; Chlorzoxazonum; Clorzoxazona; Klooritsoksatsoni; Klorzoksazon; Klorzoxazon; Хлорзоксазон.

5-Chlorobenzoxazol-2(3*H*)-one.

$C_7H_4ClNO_2$=169.6

CAS — 95-25-0.

ATC — M03BB03.

ATC Vet — QM03BB03.

UNII — H0DE420U8G.

Pharmacopoeias. In *US*.

USP 36: (Chlorzoxazone). A white or practically white, practically odourless, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol, in isopropyl alcohol, and in methyl alcohol; soluble in solutions of alkali hydroxides and ammonia. Store in airtight containers.

Uses and Administration

Chlorzoxazone is a centrally acting skeletal muscle relaxant with sedative properties. It is claimed to inhibit muscle spasm by exerting an effect mainly at the level of the spinal cord and subcortical areas of the brain. Its effects begin within an hour of an oral dose and last for 3 to 4 hours.

It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p. 2014.1) associated with musculoskeletal conditions. The usual oral dose is 250 mg three or four times daily. For severe muscle spasms, an initial dose of 500 mg three or four times daily may be given; the dose can often be reduced subsequently, although doses of up to 750 mg three or four times daily may be given if necessary. Chlorzoxazone is also given with analgesics in compound preparations.

Adverse Effects and Treatment

The most common adverse effects of chlorzoxazone are drowsiness and dizziness. There may occasionally also be gastrointestinal irritation and gastrointestinal bleeding has been reported rarely. Other effects that have occurred are headache, overstimulation, and rarely sensitivity reactions including rashes, petechiae, ecchymoses, urticaria and pruritus; very rarely, angioedema or anaphylactoid reactions may occur. Some patients taking chlorzoxazone have developed jaundice and liver damage suspected to be caused by the drug.

After overdosage there may be gastrointestinal disturbances, drowsiness, dizziness, headache, malaise, and sluggishness followed by marked loss of muscle tone, hypotension, and respiratory depression. Emptying the stomach by lavage should be considered, followed by activated charcoal and supportive therapy.

Effects on the liver. Hepatotoxicity, sometimes fatal, has been associated with chlorzoxazone treatment.[1]

1. Powers BJ, *et al.* Chlorzoxazone hepatotoxic reactions: an analysis of 21 identified or presumed cases. *Arch Intern Med* 1986; 146: 1183–6.

Overdosage. Overdosage and coma occurred on 2 occasions in a patient taking chlorzoxazone; on the second occasion, the patient responded to intravenous flumazenil.[1]

1. Roberge RJ, *et al.* Two chlorzoxazone (Parafon forte) overdoses and coma in one patient: reversal with flumazenil. *Am J Emerg Med* 1998; 16: 393–5.

Torticollis. There has been a report of a patient with a spasmodic torticollis-like syndrome, consisting of tonic deviation of the head to the right, clenching of the teeth, and dysarthria, which developed repeatedly within 2 hours of ingesting chlorzoxazone for low back pain.[1] Intravenous injection of benzatropine mesilate 1 mg gave rapid relief of symptoms.

1. Rosin MA. Chlorzoxazone-induced spasmodic torticollis. *JAMA* 1981; 246: 2575.

Precautions

Chlorzoxazone should not be given to patients with impaired liver function and should be stopped if signs of liver toxicity appear. Patients should be advised to report to their doctor any signs or symptoms of possible liver toxicity such as fever, rash, jaundice, dark urine, anorexia, nausea, vomiting, or right upper quadrant pain. Chlorzoxazone may cause drowsiness; patients affected should not drive or operate machinery.

The urine of patients taking chlorzoxazone may be coloured orange or reddish-purple by a phenolic metabolite.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies chlorzoxazone 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 24/10/11)

Interactions

The CNS effects of chlorzoxazone may be enhanced by alcohol and other CNS depressants.

Disulfiram. A study[1] of the efficacy of disulfiram as an inhibitor of the cytochrome P450 isoenzyme CYP2E1 (an enzyme involved in the metabolism of chlorzoxazone) found that a single 500-mg dose of disulfiram reduced plasma clearance of chlorzoxazone by 85%, resulting in a doubling of the latter's peak plasma concentrations and

prolongation of its elimination half-life from a mean of 0.92 to 5.1 hours.

1. Kharasch ED, *et al.* Single-dose disulfiram inhibition of chlorzoxazone metabolism: a clinical probe for P450 2E1. *Clin Pharmacol Ther* 1993; 53: 643–50.

Isoniazid. Isoniazid inhibited the clearance of chlorzoxazone by 56% when given to 10 slow acetylator subjects resulting in an increase in sedation, headache, and nausea.[1] Two days after stopping isoniazid there had been a rebound increase in the clearance of chlorzoxazone by 56% over the pre-isoniazid clearance value. Similar but less pronounced effects have also been reported[2] in rapid acetylators with chlorzoxazone's pharmacokinetic parameters returning to baseline values in 2 days.

1. Zand R, *et al.* Inhibition and induction of cytochrome P4502E1-catalyzed oxidation by isoniazid in humans. *Clin Pharmacol Ther* 1993; 54: 142–9.
2. O'Shea D, *et al.* Modulation of CYP2E1 activity by isoniazid in rapid and slow N-acetylators. *Br J Clin Pharmacol* 1997; 43: 99–103.

Pharmacokinetics

Chlorzoxazone is reported to be completely absorbed after oral doses and peak plasma concentrations occur after 1 to 2 hours. It is rapidly metabolised in the liver via the cytochrome P450 isoenzyme CYP2E1, mainly to 6-hydroxychlorzoxazone, and excreted in the urine mainly as the glucuronide metabolite. The elimination half-life of chlorzoxazone is about 1 hour.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hong Kong***: Solaxin; ***Hung.***: Myoflexin; ***India***: Bio Flexic; Divorel Plus; New Panazox; Ontac Plus; ***Indon.***: Solaxin; ***S.Afr.***: Paraflex†; ***Swed.***: Paraflex; ***Thai.***: Chlorzox; ***Turk.***: Paraflex; ***USA***: Lorzone; Paraflex; Parafon Forte DSC; Remular-S.

Multi-ingredient Preparations. ***Arg.***: Ibupirac Flex; Paraflex AN; Paraflex Plus; Rucaten Forte; Vefren Flex; ***Braz.***: Paralon; ***Canad.***: Acetazone Forte C8; Acetazone Forte; Back-Aid; ***Chile***: Beserol-S; Brevex; Desdol; Flectadol; Tonoflex; Winasorb Flex; ***China***: Lunan Beite (鲁南贝特); ***Gr.***: Parafon; ***India***: Abate-CZ; Aceclo-MR; Aceforce-MR; Acemiz-MR; Acemove-MR; Acent-MR; Acepar-MR; Acetuff-MR; Aci-MR; Aclog-CX; Aclozox; Actizox; Adenim-MR; Adnac-MR; Afesan-CZ; Agile-MR; Arflur-MR; Armdic MR; Artigesic-MR; Asonac Forte; Aspa Plus; Aspa; Avifem-MR; Avinim-MR; Balzox; Brenlax; Brufamol-M; Bufex-C; Bufex-CD; C-MR; Cadiflam; Cep-MR; Chlorizok; Cipzox; Clopar MR; Clopar Plus; Clopar-K; Combinac-MR; Cuzox-MR; Cynac-MR; Decizox; Delock-MR; Demo-MR; Diazox-MR; Dicloat-CZ; Diclofalm Forte; Diclofast-P; Dicloflam MR; Diclomove-MR; Diclonac-MR; Diclonet-Forte; Diclonij-KMR; Diclonij-Super; Diclonova MR; Dicloriz; Diclovar-CZ; Dicnac MR; Dicnac Plus; Dicnap-MR; Dicol-MR; Dicoliv-MR; Dicron-C; Dicyclozed; Diczone Plus; Diczone-MR; Difisal Relax; Diflac Plus; Dikul MR; Dilofen-CZ; Dion MR; Dipclo-MR; Diplofen-MR; Divexx-MR; Dizox; Dodo-MR; Doloban; Dolocide MR; Dolokind-MR; Dolomed-MR; Dolostat-MR; Dolowin-MR; Dolozox; Don-MR; DP Gesic MR; Dpazox; Dual Gesic Plus; Duodil; E-Fen-CZ; Elaxic; Elfenac-MR; Fenadec MR; Fenaplus-MR†; Fenbest MR; Fenzone Forte; Penzoxe Forte; Flamace-MR; Flamar-MX; Flamese-KR; Flexicam; Flexigesic-MR; Flexon-MR; Forgesic-MR; Fornac-CZ; Frenac-MR; Hifenac-MR; Icobit-Plus; Imflamol-ZX; Intagesic-MR; Intragesic-MR; KMR; Larigox; Lebec-MR; Lipcy-MR; Litonac-MR; Lobak; Lupisulide MR; Magadol-SP; Maxigesic-MR; Maxoflam-MR; Mezonac Micronac-MR; Minidolo; Mobifen; Mobiflam; Mobisox; Mobizox; Mofax; Morcet-MR; Mumo; Muscodac; Muskel; Muzox; Mydic-MR; Myofan; Myospaz Forte; Myospaz; Naclomol-MR; Nacpo; Namplus; Nelsid Fort; Neulab-MR; New Mezonac; Nicip MR; Nifen MR; Nile-CZ; Nim-MR; Nimkul-CZ; Nimkul-MR; Nimucet-MR; Nimuflex-MR; Nimuflex; Nimvista-MR; Niplonac-MR; Novil; Novozox; Numol-MR; Nusaid-MR; Onafen-CZ; Orthodac MR; Osdip-MR; Osteoflam-MR; Ostizox; Pacizox; Paclo-MR; Painkair-MR; Paradic-C; Paradic-MR; Paraflax; Parafon; Paratel-ACP; Parazox-D; ***Malaysia***; Paras; ***Mex.***: Parafon Forte; Reumophan Alka; Reumophan Vit; Tafirol Flex; ***Philipp.***: Parafon†; ***S.Afr.***: Parafon†; ***Thai.***: Cezox; Falfon†; MP Fon; Myora†; Neofon†; Parafon; Vorafon; ***Turk.***: Mepadol; Muskazon; Parafon; ***USA***: Flexaphen†.

Pharmacopoeial Preparations

USP 36: Chlorzoxazone Tablets.

Cyclobenzaprine Hydrochloride

(USAN, rINNM)

Ciclobenzaprina, hidrocloruro de; Cyclobenzaprine, Chlorhydrate de; Cyclobenzaprini Hydrochloridum; Hidrocloruro de ciclobenzaprina; MK-130 (cyclobenzaprine); Proheptatriene Hydrochloride; Ro-4-1557 (cyclobenzaprine); RP-9715 (cyclobenzaprine); Циклобензаприна Гидрохлорид.

3-(5*H*-Dibenzo[*a,d*]cyclohepten-5-ylidene)-*NN*-dimethylpropylamine hydrochloride.

$C_{20}H_{21}N,HCl=311.9$

CAS — 303-53-7 (cyclobenzaprine); 6202-23-9 (cyclobenzaprine hydrochloride).

ATC — M03BX08.

ATC Vet — QM03BX08.

UNII — 0VE05JYS2P.

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

Cyclo; Cyclone.

Pharmacopoeias. In *US*.

USP 36: (Cyclobenzaprine Hydrochloride). A white to off-white, odourless, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in isopropyl alcohol; slightly soluble in chloroform and in dichloromethane; insoluble in hydrocarbons.

Uses and Administration

Cyclobenzaprine hydrochloride is a centrally acting skeletal muscle relaxant, related to the tricyclic antidepressants. It acts mainly at the brain stem to decrease tonic somatic motor activity influencing both alpha and gamma motor systems. Additional activity at spinal cord sites may be involved. Effects begin within 1 hour of an oral dose; the effects of a single dose have been reported to last as long as 12 to 24 hours.

It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p. 2014.1) associated with musculoskeletal conditions. The usual oral dose is 5 mg three times daily, increased if necessary to 10 mg three times daily. Treatment for more than 2 or 3 weeks is not recommended. A starting dose of 5 mg with less frequent dosing is recommended for elderly patients. For doses in patients with hepatic impairment, see below. A modified-release preparation of cyclobenzaprine hydrochloride is also available for once-daily dosing.

Administration in hepatic impairment. A starting oral dose of 5 mg of cyclobenzaprine hydrochloride, and perhaps less frequent dosing than usual (see Uses and Administration, above), is recommended for those with mild hepatic impairment; use in moderate to severe hepatic impairment is not recommended.

Back pain. A meta-analysis[1] of 14 studies concluded that cyclobenzaprine hydrochloride, in the short term, improves low back pain (p. 9.2). Doses given to patients were titrated and ranged from 10 to 60 mg daily with a median dose of 30 mg daily. Patients improved moderately in the first 4 days of treatment, with the effects of cyclobenzaprine hydrochloride gradually declining with time although there was some evidence of continued improvement at 2 weeks. Further studies are needed to determine the optimal length of use in the management of acute back pain. Adverse effects were common, occurring in at least 53% of patients.

1. Browning R, *et al.* Cyclobenzaprine and back pain: a meta-analysis. *Arch Intern Med* 2001; 161: 1613–20.

Fibromyalgia. Studies of the efficacy of cyclobenzaprine in the management of fibromyalgia, a painful musculoskeletal disorder which usually responds poorly to analgesics (see Soft-tissue Rheumatism, p. 14.2), have produced conflicting results but a meta-analysis[1] of 5 such studies suggested that cyclobenzaprine had some modest benefit in the condition. Patients were more likely to report overall improvement and moderate reductions in individual symptoms, particularly sleep, while taking the drug.

1. Tofferi JK, *et al.* Treatmem of fibromyalgia with cyclobenzaprine: a meta-analysis. *Arthritis Rheum* 2004; 51: 9–13.

Adverse Effects, Treatment, and Precautions

Cyclobenzaprine is structurally related to the tricyclic antidepressants and shares their adverse effects and precautions (see Amitriptyline, p. 402.3). Cyclobenzaprine should be used with caution in the elderly and patients with hepatic impairment; use in moderate to severe hepatic impairment is not recommended.

It may cause drowsiness; patients affected should not drive or operate machinery.

The elderly. Symptoms of toxicity[1] (hallucinations, insomnia, and restlessness) were seen in a 76-year-old patient taking cyclobenzaprine at therapeutic doses. US licensed product information states that the elderly may be more likely to have adverse effects such as hallucinations and confusion..

In another study[2] the mean elimination half-life of cyclobenzaprine in the elderly was longer than in younger subjects and clearance was reduced. It was suggested that it should be used in a reduced dose or frequency in the elderly.

1. Douglass MA, Levine DP. Hallucinations in an elderly patient taking recommended doses of cyclobenzaprine. *Arch Intern Med* 2000; 160: 1373.
2. Winchell GA, *et al.* Cyclobenzaprine pharmacokinetics, including the effects of age, gender, and hepatic insufficiency. *J Clin Pharmacol* 2002; 42: 61–9.

Neuroleptic malignant syndrome. Report of a neuroleptic malignant-like syndrome associated with cyclobenzaprine in a 36-year-old man.[1] It was not clear whether the syndrome was due to an idiosyncratic reaction or to an overdose.

1. Theobarides TC, *et al.* Neuroleptic malignant-like syndrome due to cyclobenzaprine. *J Clin Psychopharmacol* 1995; 15: 79–81.

Overdosage. Treatment of cyclobenzaprine overdose is mainly symptomatic and supportive. A large retrospective study[1] found that cyclobenzaprine hydrochloride overdoses of up to 1 g rarely present with the serious cardiovascular and neurological effects seen with tricyclic antidepressant overdoses. There were no reports of seizures, life-threatening arrhythmias, or fatalities. However, 150 patients required treatment in the intensive care unit, 13 patients needed assisted ventilation, and 8 were unresponsive to stimuli. It was noted that observation may be sufficient for overdoses of under 50 mg in children.

Rhabdomyolysis, associated with cyclobenzaprine overdosage has been reported.[2]

1. Spiller HA, *et al.* Five-year multicentre retrospective review of cyclobenzaprine toxicity. *J Emerg Med* 1995; 13: 781–5.
2. Chabria SB. Rhabdomyolysis: a manifestation of cyclobenzaprine toxicity. *J Occup Med Toxicol* 2006; 1: 16.

Interactions

Cyclobenzaprine is structurally related to the tricyclic antidepressants and may be subject to similar interactions (see Amitriptyline, p. 406.1). The CNS effects of cyclobenzaprine may be enhanced by alcohol or other CNS depressants.

Antidepressants. A patient who already had QT prolongation associated with use of cyclobenzaprine and *fluoxetine*, developed torsade de pointes, progressing into ventricular fibrillation, when given *droperidol* as premedication before surgery.[1] QT abnormalities resolved on stopping cyclobenzaprine.

1. Michalets EL, *et al.* Torsade de pointes resulting from the addition of droperidol to an existing cytochrome P450 drug interaction. *Ann Pharmacother* 1998; 32: 761–5.

Antipsychotics. For a report of an interaction between cyclobenzaprine and *droperidol*, see Antidepressants above.

Pharmacokinetics

Cyclobenzaprine hydrochloride is readily and almost completely absorbed from the gastrointestinal tract, although plasma concentrations vary considerably among individuals given the same dose. About 93% is bound to plasma proteins and has a reported effective half-life of 8 to 37 hours. It is extensively metabolised, mainly to glucuronide conjugates, and excreted in the urine. Cytochrome P450 isoenzymes CYP3A4, CYP1A2, and to a lesser extent CYP2D6 mediate its demethylation. Some unchanged drug appears in the bile and is excreted in the faeces.

References.

1. Winchell GA, *et al.* Cyclobenzaprine pharmacokinetics, including the effects of age, gender, and hepatic insufficiency. *J Clin Pharmacol* 2002; 42: 61–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Cizax; Miofibrax; Miosan; Mirtax; Musculare; Muscuprina; ***Canad.***: Novo-Cycloprine; ***Chile***: Ciclamil; Fibrox; Flexin; Iphsaflex; Masterelax; Medarex; Mio-Relax; Nostaden; Reflexan; Relexil; Tensamon; Tensiomax; Tensodox; Tonalgen; Ziclob; ***India***: Mobrine-IR; ***Israel***: Amrixal; ***Ital.***: Flexiban; ***Port.***: Flexiban; ***Spain***: Yurelax; ***USA***: Amrix; Fexmid; Flexeril†.

Multi-ingredient Preparations. ***Arg.***: Dorixina Relax; ***Braz.***: Dolamin Flex; ***Mex.***: Dorixina Relax; Yuredol; ***Venez.***: Dorixina Flex.

Pharmacopoeial Preparations

USP 36: Cyclobenzaprine Hydrochloride Tablets.

Dantrolene Sodium *(BANM, USAN, rINNM)*

Dantrolène Sodique; Dantroleno sódico; F-368 (dantrolene); F-440; Natrii Dantrolenum; Sodyum Dantrolen; Натрий Дантролен.

The hemiheptahydrate of the sodium salt of 1-[5-(4-nitrophenyl)furfurylideneamino]imidazolidine-2,4-dione.

$C_{14}H_9N_4NaO_5.3½H_2O=399.3$

CAS — 7261-97-4 (dantrolene); 14663-23-1 (anhydrous dantrolene sodium); 24868-20-0 (dantrolene sodium, hemiheptahydrate).

ATC — M03CA01.

The symbol † denotes a preparation no longer actively marketed

ATC Vet — QM03CA01; UNII — 287M0347EV.

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

BP 2014: (Dantrolene Sodium). A yellowish-orange to orange crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; practically insoluble in acetone; sparingly soluble in methyl alcohol.

USP 36: (Dantrolene Sodium). A fine orange to orange-brown powder. Sparingly soluble in dimethylformamide and in glycerol; sparingly soluble to practically insoluble in acetone. Store in airtight containers. Protect from light.

Uses and Administration

Dantrolene sodium is a muscle relaxant with a direct action on skeletal muscle. It uncouples muscular contraction from excitation, probably by interfering with the release of calcium from the sarcoplasmic reticulum.

It is used orally, for the symptomatic relief of chronic, severe spasticity (p. 2014.2). It is also given, usually by intravenous injection, for the treatment of malignant hyperthermia.

For **spasticity**, the initial oral dose is 25 mg daily increased gradually as necessary, at 7-day intervals, over about 7 weeks to a maximum dose of 100 mg four times daily. If no response is achieved within 45 days treatment should be stopped.

In the treatment of **malignant hyperthermia**, dantrolene sodium is given, with supportive measures, in an initial dose of 1 mg/kg by rapid intravenous injection, repeated, if necessary, to a total dose of 10 mg/kg. An average dose of 2.5 mg/kg is usually effective. If a relapse or recurrence occurs, dantrolene should be given again at the last effective dose. In the USA, doses of 1 to 2 mg/kg orally four times daily have also been recommended for up to 3 days after the crisis to prevent recurrence, and similar doses have been given for 1 to 2 days before surgery in individuals thought to be at risk of developing the syndrome. Prophylactic doses may also be given intravenously; 2.5 mg/kg has been recommended, infused over about 60 minutes, starting about 75 minutes before anticipated anaesthesia, with further doses during anaesthesia and surgery if signs of malignant hyperthermia develop.

For details of doses in children, see below.

Administration in children. Dantrolene may be given orally for the symptomatic relief of chronic, severe spasticity in children. Although not licensed in the UK, the *BNFC* suggests that children aged 5 to 12 years may initially be given 500 micrograms/kg once daily, increased to 500 micrograms/kg 3 times daily after 7 days, and those aged 12 to 18 years may initially be given 25 mg once daily, increased to 3 times daily after 7 days. For all age groups, further increases may be made in steps of 500 micrograms/kg every 7 days until a satisfactory response is achieved, to a maximum dose of 2 mg/kg 3 or 4 times daily (400 mg daily). Similar doses have been given in US licensed product information.

Dantrolene may also be given for the treatment of malignant hyperthermia in children. In the UK, the *BNFC* suggests that those aged 1 month to 18 years may be given an initial dose of 2 to 3 mg/kg by rapid intravenous injection, then 1 mg/kg repeated as necessary to a total dose of 10 mg/kg. US licensed product information suggests that children may be given the usual adult doses (see Uses and Administration, above) for the prevention and treatment of malignant hyperthermia.

Hyperthermia. Dantrolene is used in the treatment of hyperthermia associated with muscle rigidity and fulminant hypermetabolism of skeletal muscle, which occurs in the neuroleptic malignant syndrome (see below and p. 1050.2) and in malignant hyperthermia (see below). There is also anecdotal evidence that dantrolene may produce beneficial effects for the treatment of similar symptoms resulting from poisoning with various agents such as carbon monoxide,[1] MAOIs,[2] and ethyltenamfetamine.[3] However, after suggestions that it might also be of use in cocaine intoxication, the manufacturers[4] warned physicians that they should not regard dantrolene as an effective treatment for all types of hyperthermia and rigidity accompanying poisoning.

Dantrolene has been tried as part of treatment for heat stroke (see under Fever and Hyperthermia, p. 11.3) but does not appear to affect outcome.[5]

1. Ten Holter JBM, Schellens RLLAM. Dantrolene sodium for treatment of carbon monoxide poisoning. *BMJ* 1988; **296:** 1772–3.
2. Kaplan RF, *et al.* Phenelzine overdose treatment with dantrolene sodium. *JAMA* 1986; **255:** 642–4.
3. Tehan B. Ecstasy and dantrolene. *BMJ* 1993; **306:** 146.
4. Fox AW. More on rhabdomyolysis associated with cocaine intoxication. *N Engl J Med* 1989; **321:** 1271.
5. Bouchama A, Knochel JP. Heat stroke. *N Engl J Med* 2002; **346:** 1978–88.

MALIGNANT HYPERTHERMIA. Malignant hyperthermia (malignant hyperpyrexia) is a rare but potentially fatal syndrome associated with general anaesthesia, in which a sudden increase in the concentration of calcium in muscle cytoplasm initiates a series of metabolic disturbances. The disorder appears to be genetically determined and is more common in males. In susceptible individuals a reaction may be induced by inhalation anaesthetics (mainly halogenated hydrocarbons), suxamethonium, prolonged anaesthesia, pre-operative exercise, muscle trauma, fever, or anxiety. However, many reactions occur in individuals who have had uneventful general anaesthesia previously. Early signs and symptoms of the syndrome include tachycardia, unstable blood pressure, hypercapnia, rising temperature, and hyperventilation followed by metabolic acidosis and hyperkalaemia. Muscle rigidity develops in many patients and later there may be evidence of muscle damage including raised serum concentrations of creatine phosphokinase and other enzymes, myoglobinaemia, and myoglobinuria. Hyperthermia develops relatively late. Other late complications may include renal failure, intravascular coagulopathy, and pulmonary oedema.

Treatment should be started as soon as possible after symptoms appear with dantrolene being given by rapid intravenous injection until symptoms disappear.[1-3] Supportive treatment must also be given including immediate withdrawal of anaesthesia, giving oxygen, correction of acidosis with sodium bicarbonate, control of hyperkalaemia with insulin, and cooling procedures (see p. 11.3).

The incidence of reactions in susceptible individuals can be reduced by avoiding triggering agents. Dantrolene has also been given prophylactically, but a high incidence of adverse effects has been reported,[4] and such use is not generally recommended.[3] Susceptibility to malignant hyperthermia can be detected by histological examination of muscle fibres obtained by biopsy and study of their response to caffeine and/or halothane *in vitro*. Although such testing remains the gold standard for determining susceptibility, genetic testing is also being developed as an alternative.[5]

Dantrolene has been suggested[6] for use as a secondary drug in the treatment of a related and potentially fatal syndrome that has developed in some children after induction of anaesthesia with halothane and suxamethonium (see also Children, under Precautions of Suxamethonium, p. 2039.1).

1. Britt BA. Dantrolene. *Can Anaesth Soc J* 1984; **31:** 61–75.
2. Ward A, *et al.* Dantrolene: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in malignant hyperthermia, the neuroleptic malignant syndrome and an update of its use in muscle spasticity. *Drugs* 1986; **32:** 130–68.
3. Krause T, *et al.* Dantrolene—a review of its pharmacology, therapeutic use and new developments. *Anaesthesia* 2004; **59:** 364–73.
4. Wedel DJ, *et al.* Clinical effects of intravenously administered dantrolene. *Mayo Clin Proc* 1995; **70:** 241–6.
5. Litman RS, Rosenberg H. Malignant hyperthermia: update on susceptibility testing. *JAMA* 2005; **293:** 2918–24.
6. Rosenberg H, Gronert GA. Intractable cardiac arrest in children given succinylcholine. *Anesthesiology* 1992; **77:** 1054.

Neuroleptic malignant syndrome. Dantrolene has been used, usually alone or with bromocriptine, in the treatment of neuroleptic malignant syndrome (p. 1050.2), although some workers have not found it to be of use,[1] and evidence from controlled studies is lacking.[2] Doses reported for dantrolene have varied greatly.[3,4] For those patients unable to swallow and when rapid control of symptoms is required, doses of 1 mg/kg or more have been given initially by intravenous injection. Oral doses of up to 600 mg daily have been given in divided doses.

1. Rosebush PI, *et al.* The treatment of neuroleptic malignant syndrome: are dantrolene and bromocriptine useful adjuncts to supportive care? *Br J Psychiatry* 1991; **159:** 709–12.
2. Krause T, *et al.* Dantrolene—a review of its pharmacology, therapeutic use and new developments. *Anaesthesia* 2004; **59:** 364–73.
3. Ward A, *et al.* Dantrolene: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in malignant hyperthermia, the neuroleptic malignant syndrome and an update of its use in muscle spasticity. *Drugs* 1986; **32:** 130–68.
4. Harpe C, Stoudemire A. Aetiology and treatment of neuroleptic malignant syndrome. *Med Toxicol* 1987; **2:** 166–76.

Tetanus. Dantrolene has effectively controlled muscle spasms in the treatment of tetanus (see p. 2029.2). It has also been used as an adjunct[1] to neuromuscular blockade; there are conflicting reports[2,3] of its value in avoiding mechanical ventilation.

1. Tidyman M, *et al.* Adjunctive use of dantrolene in severe tetanus. *Anesth Analg* 1985; **64:** 538–40.
2. Checketts MR, White RJ. Avoidance of intermittent positive pressure ventilation in tetanus with dantrolene therapy. *Anaesthesia* 1993; **48:** 969–71.
3. Possamai C, *et al.* Dantrolene infusion in severe tetanus. *Anaesthesia* 1997; **52:** 610.

Adverse Effects

Adverse effects associated with dantrolene sodium tend to occur at the start of treatment, but are often short lived and can be controlled by adjusting the dose. The most common adverse effects are drowsiness, dizziness, fatigue, weakness, and general malaise. Diarrhoea may be severe enough to require withdrawal. If diarrhoea recurs on restarting dantrolene, then treatment should probably be stopped permanently. Other adverse effects reported include nausea and vomiting, anorexia, constipation, abdominal cramps, gastrointestinal bleeding, tachycardia, unstable blood pressure, dyspnoea, rashes (often acneform), pruritus, chills and fever, headache, myalgia, nervousness, insomnia, confusion, visual disturbances, mental depression, dysphagia and speech disturbances, and seizures. Haematuria, crystalluria, urinary frequency and retention, and incontinence may occur. Rare but serious adverse effects include hepatotoxicity which may be fatal (see below) and pleural effusion with pericarditis.

Serious adverse effects do not appear to be a problem with the short-term use of intravenous dantrolene sodium in the treatment of malignant hyperthermia.

Effects on the liver. Dantrolene has caused hepatotoxicity with raised liver enzyme values, jaundice, and hepatitis;[1-3] fatalities have been reported.[1,3] Not all patients had symptoms such as anorexia, nausea, or abdominal discomfort before the onset of disease and the severity of hepatic injury was unrelated to clinical presentation. In the first report[1] the 14 fatalities occurred with doses in excess of 200 mg daily; a later review[3] found the mean dose associated with 27 fatalities to be 582 mg daily, while reports of non-fatal liver toxicity (95 cases) were associated with a mean dose of 263 mg daily. The onset of hepatic injury was usually between 1 and 6 months after starting treatment and fatalities were not reported in the first 2 months. Only rarely did injury develop before 45 days of treatment. Females appeared to be at greater risk of serious liver injury and the severity of reaction appeared to be age-related with most fatalities occurring in patients over 30 years of age. The liver injury was usually hepatocellular and might include ascending cholangitis; there was little evidence of hypersensitivity.

1. Utili R, *et al.* Dantrolene-associated hepatic injury: incidence and character. *Gastroenterology* 1977; **72:** 610–16.
2. Wilkinson SP, *et al.* Hepatitis from dantrolene sodium. *Gut* 1979; **20:** 33–6.
3. Chan CH. Dantrolene sodium and hepatic injury. *Neurology* 1990; **40:** 1427–32.

Effects on the lungs. Pulmonary oedema associated with heart failure,[1] and pleural effusions with eosinophilia[2-4] have been reported rarely in patients receiving dantrolene. These reactions generally resolve on withdrawal of the drug but resolution may take several months; corticosteroid therapy may be of benefit in dantrolene-related eosinophilic pleural effusion.[3]

1. Robillart A, *et al.* Insuffisance cardiaque par surdosage en dantrolène. *Ann Fr Anesth Reanim* 1986; **5:** 617–19.
2. Mahoney JM, Bachtel MD. Pleural effusion associated with chronic dantrolene administration. *Ann Pharmacother* 1994; **28:** 587–9.
3. Pelz MW, Haviland-Foley DJ. Eosinophilic pleural effusion due to dantrolene: resolution with steroid therapy. *South Med J* 2001; **94:** 502–4.
4. Le-Quang B, *et al.* Dantrolene and pleural effusion: case report and review of literature. *Spinal Cord* 2004; **42:** 317–20.

Lymphomas. A case of fatal lymphocytic lymphoma was associated with prolonged dantrolene therapy (600 mg daily) for progressive spastic paraplegia.[1]

1. Wan HH, Tucker JS. Dantrolene and lymphocytic lymphoma. *Postgrad Med J* 1980; **56:** 261–2.

Precautions

It is recommended that dantrolene sodium should not be given to patients with active liver disease. Liver-function tests should be performed in all patients before and during treatment; if abnormal values are found, treatment should generally be stopped. The risk of liver injury may be increased in patients over 30 years of age, in females (especially those taking oestrogens), in those with a history of liver disease, and with doses above 400 mg daily (see under Effects on the Liver, above). Dantrolene sodium should be used with caution in patients with cardiac or pulmonary disorders. It should not be given to patients who use their spasticity to maintain posture or function or to patients with acute muscle spasm.

Dantrolene sodium may cause drowsiness; patients affected should not drive or operate machinery.

Interactions

The CNS effects of dantrolene sodium may be enhanced by alcohol or other CNS depressants. Use with other potentially hepatotoxic drugs such as oestrogens may possibly increase the risk of liver damage and should be avoided.

Calcium-channel blockers. Severe hyperkalaemia and myocardial depression occurred with intravenous dantrolene for prophylaxis of malignant hyperthermia in a patient also taking *verapamil* for angina.[1] The peak serum-potassium concentration was 7.1 mmol/litre 2.5 hours after the dantrolene infusion. *Nifedipine* was substituted for verapamil in a subsequent operation and only a small

increase in serum potassium occurred after dantrolene. Ventricular fibrillation and cardiovascular collapse associated with hyperkalaemia have been seen with this combination in *animal* studies, and the manufacturers recommend that calcium-channel blockers and intravenous dantrolene should not be used together.

Severe hyperkalaemia has also been noted in a patient taking *diltiazem* after a dantrolene infusion was started.[2]

1. Rubin AS, Zablocki AD. Hyperkalaemia, verapamil, and dantrolene. *Anesthesiology* 1987; 66: 246–9.
2. Yoganathan T, *et al.* Dantrolene-induced hyperkalaemia in a patient treated with diltiazem and metoprolol. *J Cardiothorac Anesth* 1988; 2: 363–4.

Pharmacokinetics

Dantrolene sodium is slowly and almost completely absorbed from the gastrointestinal tract after oral doses. It is metabolised in the liver mainly to the hydroxylated metabolite, which is nearly as potent as dantrolene sodium, and the acetamide metabolite which has weak muscle relaxant activity. It is excreted in the urine, mainly as metabolites with a small amount of unchanged dantrolene; some is excreted in the bile. Dantrolene is bound extensively to plasma proteins. The elimination half-life of oral dantrolene is about 9 hours, although half-lives of up to 12 hours have been reported after intravenous use. Dantrolene crosses the placenta and has been detected in breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Dantrium; ***Belg.***: Dantrium; ***Braz.***: Dantrolen; ***Canad.***: Dantrium; ***Chile***: Dantrium; ***Denm.***: Dantrium; ***Fr.***: Dantrium; ***Ger.***: Dantamacrin; ***Gr.***: Dantrium; Dantrolen†; ***Irl.***: Dantrium; ***Israel***: Dantrium; ***Ital.***: Dantrium; ***Neth.***: Dantrium; ***NZ***: Dantrium; ***S. Afr.***: Dantrium; ***Switz.***: Dantamacrin; ***UK***: Dantrium; ***USA***: Dantrium; Revonto.

Pharmacopoeial Preparations
BP 2014: Dantrolene Oral Suspension;
USP 36: Dantrolene Sodium Capsules; Dantrolene Sodium for Injection.

Eperisone Hydrochloride *(rINNM)*

Eperisona, hidrocloruro de; Épérisone, Chlorhydrate d'; Eperisoni Hydrochloridum; Hidrocloruro de eperisona; Эперизона Гидрохлорид.

4′-Ethyl-2-methyl-3-piperidinopropiophenone hydrochloride.

$C_{17}H_{25}NO.HCl$=295.9

CAS — 64840-90-0 (eperisone); 56839-43-1 (eperisone hydrochloride).

ATC — M03BX09.

ATC Vet — QM03BX09.

UNII — U38O8U7P6X.

Pharmacopoeias. In *Jpn*.

Profile

Eperisone is a centrally acting skeletal muscle relaxant that has been used in the symptomatic treatment of muscle spasm (p. 2014.1) and spasticity (p. 2014.2). It may also have a vasodilator action. Eperisone hydrochloride has been given in usual oral doses of 50 mg three times daily after food.

Effects on the skin. A non-pigmenting fixed drug eruption developed in a 42-year-old woman after taking oral diclofenac sodium and eperisone hydrochloride.[1] There was no residual hyperpigmentation and the rash and accompanying itching and burning sensation resolved within 7 days after stopping both drugs. On rechallenge with eperisone, an erythematous plaque developed at the same site within a couple of hours. The lesion disappeared within 5 days with no sequelae.

1. Choonhakarn C. Non-pigmenting fixed drug eruption: a new case due to eperisone hydrochloride. *Br J Dermatol* 2001; 144: 1288–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bei Li Si (贝力斯); Beigesi (贝格斯); Myonal (妙纳); Yi Yu (宜宇); Zuo Ning (佐宁); ***Indon.***: Eprinoc; Epsonal; Estalex; Forelax; Porres; Lional; Myobat; Myoman; Myonal; Myonep; Myori; Permyo; Plexion; Rizonax; Zonal; ***Ital.***: Expose; Myonal; ***Jpn***: Myonal; ***Malaysia***: Myonal; ***Philipp.***: Myonal; Perispa; ***Singapore***: Myonal; ***Thai.***: Espenal; Musolax; Myonal; Ralexa.

Idrocilamide *(rINN)*

Idrociclamida; Idrociclamidum; LCB-29; Идроциламид.

N-(2-Hydroxyethyl)cinnamamide.

$C_{11}H_{13}NO_2$=191.2

CAS — 6961-46-2.

ATC — M02AX05.

ATC Vet — QM02AX05.

UNII — 6C816LUB1O.

Profile

Idrocilamide is a centrally acting muscle relaxant. It is reported to have local muscle relaxant and anti-inflammatory effects and is now mainly used topically.

Adverse effects. When given orally idrocilamide was reported to produce abdominal pain, nausea, and drowsiness. Excitement, euphoria and hallucinations, and depression may occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Srilane; ***Switz.***: Talval.

Mephenesin *(BAN, rINN)*

Cresoxydiol; Glykresin; Mefenesiini; Mefenesin; Mefenesina; Méphénésine; Mephenesinum; Мефенезин.

3-(*o*-Tolyloxy)propane-1,2-diol.

$C_{10}H_{14}O_3$=182.2

CAS — 59-47-2.

ATC — M03BX06.

ATC Vet — QM03BX06.

UNII — 7B8PIR2954.

NOTE. The name tolynol has been applied to both mephenesin and *p*,α-dimethylbenzyl alcohol (p. 2493.3).

Pharmacopoeias. In *It*.

Profile

Mephenesin is a centrally acting skeletal muscle relaxant used for the symptomatic treatment of painful muscle spasm (p. 2014.1) associated with musculoskeletal conditions. Its clinical usefulness is considered to be limited by its brief duration of action. It is given orally in doses of 1.5 to 3 g daily in divided doses. It is also applied topically, usually with rubefacients.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Decontractyl; ***Ger.***: DoloVisano M†.

Multi-ingredient Preparations. ***Belg.***: Algipan; ***Fr.***: Algipan†; Decontractyl; Traumalgyl†; ***India***: Acks†; Capsigyl-D; Capsigyl; Diclowin; Dolomed; Ethnorub; Flamar†; Inflazone; Medicreme; Neurophen; Relaxyl; Systaflam; ***Ital.***: Relaxar; ***S.Afr.***: Spasmend.

Mephenoxalone *(rINN)*

AHR-233; Mefenoksalon; Mefenoxalona; Méphénoxalone; Mephenoxalonum; Methoxadone; OM-518; Мефеноксалон.

5-(2-Methoxyphenoxymethyl)oxazolidin-2-one.

$C_{11}H_{13}NO_4$=223.2

CAS — 70-07-5.

ATC — N05BX01.

ATC Vet — QN05BX01.

UNII — CZB7T54W8W.

Profile

Mephenoxalone has actions similar to those of meprobamate (p. 1083.3). It has been given orally in a dose of 200 to 400 mg three times daily as a muscle relaxant in the treatment of muscle spasm (p. 2014.1). It has also been given for the treatment of anxiety.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Cz.***: Dimexol; Dorsiflex; ***Neth.***: Dorsiflex†; ***Turk.***: Dorsiflex.

Multi-ingredient Preparations. ***Turk.***: Dorsilon.

Metaxalone *(BAN, USAN, rINN)*

AHR-438; Metaxalona; Métaxalone; Metaxalonum; Метаксалон.

5-(3,5-Xylyloxymethyl)oxazolidin-2-one.

$C_{12}H_{15}NO_3$=221.3

CAS — 1665-48-1.

UNII — 1NMA9J598Y.

Uses and Administration

Metaxalone is a centrally acting skeletal muscle relaxant. Its mode of action may be related to its sedative properties.

It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p. 2014.1) associated with musculoskeletal conditions. The usual oral dose is 800 mg three or four times daily.

Adverse Effects, Treatment, and Precautions

As for Chlorzoxazone, p. 2022.3.

Metaxalone may cause drowsiness; patients affected should not drive or operate machinery.

Patients taking metaxalone excrete in the urine a metabolite which gives a false positive reaction to copper sulfate-based tests for glycosuria.

Overdosage. The most common symptoms in a series of 142 adults with metaxalone ingestion reported to Texas poison centres during 2000 to 2006 were drowsiness or lethargy, tachycardia, nausea, dizziness or vertigo, agitation, slurred speech, and tremor; doses of up to 44 g had been taken.[1] The severity of the final medical outcome was judged to be none (49.3% of patients), minor (35.2%), moderate (13.4%), and major (2.1%); no deaths were reported.

1. Forrester MB. Adult metaxalone ingestions reported to Texas poison control centers, 2000-2006. *Hum Exp Toxicol* 2010; 29: 55–62.

Interactions

The CNS effects of metaxalone may be enhanced by alcohol and other CNS depressants.

Pharmacokinetics

Metaxalone is absorbed from the gastrointestinal tract, metabolised in the liver, and excreted in urine as metabolites. The plasma elimination half-life is about 2 to 3 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Flexura; ***USA***: Skelaxin.

Multi-ingredient Preparations. ***India***: Fenaplus-RX; Flexura-D; Metadol; Mobiswift-D.

Methocarbamol *(BAN, rINN)*

Guaiphenesin Carbamate; Méthocarbamol; Methocarbamolum; Metocarbamol; Metokarbamol; Metokarbamoli; Метокарбамол.

2-Hydroxy-3-(2-methoxyphenoxy)propyl carbamate.

$C_{11}H_{15}NO_5$=241.2

CAS — 532-03-6.

ATC — M03BA03.

ATC Vet — QM03BA03.

UNII — 125OD7737X.

Pharmacopoeias. In *US*.

USP 36: (Methocarbamol). A white powder, odourless or having a slight characteristic odour. M.p. about 94 degrees or, if previously ground to a fine powder, about 90 degrees. Soluble 1 in 40 of water at 20 degrees; sparingly soluble in chloroform; soluble in alcohol only with heating; insoluble in *n*-hexane and in benzene. Store in airtight containers.

Uses and Administration

Methocarbamol is a centrally acting skeletal muscle relaxant whose action may be due to general depressant effects on the CNS.

Methocarbamol is used as an adjunct in the short-term symptomatic treatment of painful muscle spasm (p. 2014.1) associated with musculoskeletal conditions. It is sometimes given with analgesics in compound preparations for the treatment of musculoskeletal pain.

The usual initial oral dose for muscle spasm is 1.5 g four times daily, reduced to a maintenance dose of about 4 g daily after 2 to 3 days. A dose of 750 mg three times daily may be sufficient for a therapeutic effect. Half the maximum daily dose or less may be sufficient for elderly patients.

Methocarbamol has also been given intravenously at a rate of not more than 300 mg/minute, by slow injection or by infusion in sodium chloride 0.9% or glucose 5% injection. The parenteral route should not be used for more than 3 consecutive days and the dose should not exceed 3 g daily. The patient should remain lying down during, and for

10 to 15 minutes after, intravenous doses. The US manufacturers state that the injection is hypertonic and extravasation should be avoided. However, it may also be given by intramuscular injection in a dose of up to 500 mg into each gluteal region at intervals of 8 hours.

Adverse Effects

Adverse effects reported with methocarbamol include nausea, vomiting, anorexia, lightheadedness, dizziness, lassitude, drowsiness, restlessness, anxiety, confusion, tremor, vertigo, blurred vision, fever, headache, convulsions, and hypersensitivity reactions such as rashes, pruritus, urticaria, angioedema, and conjunctivitis with nasal congestion.

After injection patients may have flushing and a metallic taste; incoordination, diplopia, nystagmus, vertigo, syncope, hypotension, bradycardia, and anaphylaxis have been reported. There may be sloughing and thrombophlebitis at the site of injection.

Precautions

Methocarbamol is contra-indicated in coma or pre-coma states, brain damage, myasthenia gravis, or in patients with a history of epilepsy. Caution is advisable in renal or hepatic impairment. Methocarbamol may cause drowsiness; patients affected should not drive or operate machinery.

Preparations for injection may contain, as a solvent, a macrogol which could increase existing acidosis and urea retention in patients with renal impairment; such preparations should not be used in patients with known or suspected renal disease.

Abnormal coloration. Methocarbamol has been reported to cause brown to black or green discoloration of the urine on standing.[1]

1. Baran RB, Rowles B. Factors affecting coloration of urine and feces. *J Am Pharm Assoc* 1973; NS13: 139–42.

Interactions

The CNS effects of methocarbamol may be potentiated by alcohol or other CNS depressants. Methocarbamol has also been reported to potentiate the effects of anorectics and antimuscarinics, and to inhibit the effect of pyridostigmine.

Pharmacokinetics

Methocarbamol is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses. Its plasma half-life is reported to be about 1 to 2 hours. It is metabolised by dealkylation and hydroxylation and is excreted in urine mainly as the glucuronide and sulfate conjugates of its metabolites. A small amount is excreted in faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Robaxin; *Fr.*: Lumirelax; *Ger.*: DoloVisano Methocarbamol; Ortoton; *Gr.*: Robaxin; Trolar; *Hong Kong*: Myomethol; *India*: Robinax; *Mex.*: Remisol†; Rexlvin; *S.Afr.*: Robaxin; *Spain*: Robaxin; *Thai.*: Laxan; Mannix; Manobaxine; Mebaxin; Methamol; Musxan; Myomethol†; Polyxan; *UK*: Robaxin; *USA*: Robaxin.

Multi-ingredient Preparations. *Canad.*: Analgesic and Muscle Relaxant Caplets; Aspirin Night-Time†; Dodds Back Ease†; Extra Strength Muscle & Back Pain ASA; Extra Strength Muscle & Back Pain Relief; Methoxacet-C; Methoxacet; Methoxisal-C; Methoxisal; Midol Night-Time; Muscle & Back Pain Relief Extra Strength; Muscle & Back Pain Relief-8; Muscle & Back Pain Relief; Relaxophen; Robax Platinum; Robaxacet-8; Robaxacet; Robaxisal-C; Robaxisal; Spasmhalt-ASA; Spasmhalt; Summit Ultra; Tylenol Back Pain; *Gr.*: Robaxisal; *India*: Asolt-AT; Flexinol; Ibugesic-M; Neuromol-MR; Robiflam; Robinaxol; *Mex.*: Ardosons; Artridol; Carbafen; Carbager-Plus; Carbamox; Dolocam Plus; Flexamol†; Malival Compuesto; Morlan; Remisol-Plus; Retoflam P; Reupat; Robaxifen; Robaxisal; *S.Afr.*: Robaxisal†; *Spain*: Robaxisal Compuesto; *Thai.*: Sancago; *Turk.*: Miyorel; *Venez.*: Beseroldos; Robaxifen; Robaxisal.

Pharmacopoeial Preparations
USP 36: Methocarbamol Injection; Methocarbamol Tablets.

Pridinol Mesilate *(rINNM)*

C-238 (pridinol); Mesilato de pridinol; Pridinol, Mésilate de; Pridinol, mesilato de; Pridinol Mesylate; Pridinoli Mesilas; Придинола Мезилат.

1,1-Diphenyl-3-piperidinopropan-1-ol methanesulphonate.

$C_{20}H_{25}NO.CH_4SO_3H=391.5$

CAS — 511-45-5 (pridinol); 968-58-1 (pridinol hydrochloride); 6856-31-1 (pridinol mesilate).

ATC — M03BX03.

ATC Vet — QM03BX03.

Profile

Pridinol mesilate is a centrally acting muscle relaxant used in the symptomatic treatment of muscle spasm (p. 2014.1). The usual initial oral dose is 2 to 8 mg three times daily, reduced to 4 to 8 mg daily for maintenance treatment. It has also been given by intramuscular or intravenous injection or rectally, and has been applied in compound topical preparations.

Pridinol has been used as the hydrochloride for its antimuscarinic properties in the management of parkinsonism (p. 889.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Prinil; Relaxedan; *Ger.*: Myoson; *Ital.*: Lyseen; *Pol.*: Polmesilat.

Multi-ingredient Preparations. *Arg.*: Aldoron Flex; Blokium Flex; Bronax Flex; Curinflam Plus; Diclofenac Flex; Diclogesic Relax; Diclolabsa Relax; Diclomar Flex; Diclonex Flex; Diclonex R; Dioxaflex Plus; Dolvan Flex; Doxtran Flex; Flexidol Relax; Iglodine Flex; Metaflex Plus NF; Mextran Flex; Mio Aldoron NF; Mio-Virobron NF; Nalgiflex Relax; Oxa Sport; Oxadisten; Pancloflex; Prifec; Rodinac Flex; Silfox Flex; Tenaron Flex; Tomanil Flex; Valuca Flex; Vesalion Flex; Viartril Flex; Vimultisa Flex; Voltaren Flex; Xedenol Flex.

Thiocolchicoside *(rINN)*

Thiocolchicosidum; Tiocolchicósido; Tiyokolşikozid; Тиокольхикозид.

3,10-Di(demethoxy)-3-glucopyranosyloxy-10-methylthiocolchicine.

$C_{27}H_{33}NO_{10}S=563.6$

CAS — 602-41-5.

ATC — M03BX05.

ATC Vet — QM03BX05.

UNII — T1X8S697GT.

Pharmacopoeias. In *Fr.*

Profile

Thiocolchicoside is a muscle relaxant that has been claimed to possess GABA-mimetic and glycinergic actions. It is used in the symptomatic treatment of painful muscle spasm (p. 2014.1). The usual initial oral dose is 16 mg daily given in 2 divided doses. It has also been given intramuscularly in a usual dose of 8 mg daily given in 2 divided doses, or applied as cream or ointment. Photosensitivity reactions may occur.

References.

1. Tüzün F, *et al.* Multicenter, randomized, double-blinded, placebo-controlled trial of thiocolchicoside in acute low back pain. *Joint Bone Spine* 2003; 70: 356–61.
2. Guarneri C, *et al.* Embolia cutis medicamentosa following thiocolchicoside injection. *J Eur Acad Dermatol Venereol* 2008; 22: 1005–6.
3. Giavina-Bianchi P, *et al.* Epileptic seizure after treatment with thiocolchicoside. *Ther Clin Risk Manag* 2009; 5: 635–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Molagar; *Braz.*: Coltrax; Muscoril; *Cz.*: Muscoril; *Fr.*: Colthiozid; Coltramyl; Miorel; Myoplege; *Gr.*: Dirulan; Disintryl; Hallver; Izinor; Klesidren; Lamepon; Musclide; Musco-ril; Relief; Thiacomin; *India*: Colchico; Muscodol; Myoril; *Ital.*: Decontril; Miostart; Miotens; Muscoflex; Muscoril; Sciomir; Strialisin; Teraside; Tiorilene†; Tioside; *Pol.*: Muscoril†; *Port.*: Coltramyl; Relmus; *Turk.*: Adeleks; Dynaxon; Kenfix; Maxthio; Muscoflex; Muscoril; Myal; Myodin; Recoside; Thiospa; Tiorelax; Tyoflex; *Venez.*: Biocolchid; Coltrax; Colval; Busilen; Lampral; Tiochax.

Multi-ingredient Preparations. *India*: Lorchek-MR; Lupiflex; Nucoxia-MR; *Ital.*: Muscoril Trauma; *Mex.*: Neuroflax; *Port.*: Adalgur N; *Spain*: Adalgur; *Venez.*: Colfene.

Tizanidine Hydrochloride

(BANM, USAN, rINNM)

AN-021; DS-103-282; DS-103-282-ch; Hidrocloruro de tizanidina; Tizanidina, hidrocloruro de; Tizanidine, Chlorhydrate de; Tizanidini Hydrochloridum; Тизанидина Гидрохлорид.

5-Chloro-*N*-(2-imidazolin-2-yl)-2,1,3-benzothiadiazol-4-ylamine hydrochloride.

$C_9H_8ClN_5S.HCl=290.2$

CAS — 51322-75-9 (tizanidine); 64461-82-1 (tizanidine hydrochloride).

ATC — M03BX02.

ATC Vet — QM03BX02.

UNII — B53E3NMY5C.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Tizanidine Hydrochloride). Store in airtight containers.

Uses and Administration

Tizanidine hydrochloride is a centrally acting skeletal muscle relaxant. It is an α_2-adrenergic agonist structurally related to clonidine (p. 1339.1) and acts mainly at spinal and supraspinal levels to inhibit excitatory interneurones. It is used for the symptomatic relief of spasticity associated with multiple sclerosis or with spinal cord injury or disease. It is also used in the symptomatic treatment of painful muscle spasm (p. 2014.1) associated with musculoskeletal conditions.

Tizanidine hydrochloride is given orally, usually in divided doses; doses are expressed in terms of the base. Tizanidine hydrochloride 1.14 mg is equivalent to about 1 mg of tizanidine. The usual initial daily dose in the UK in the management of spasticity is the equivalent of 2 mg of the base given as a single dose. The dose may be increased thereafter according to response in steps of 2 mg at intervals of at least 3 to 4 days, usually up to 24 mg daily given in 3 or 4 divided doses. A similar schedule, with an initial daily dose of 4 mg, increased as required in steps of 2 to 4 mg, is used in the USA. The maximum recommended dose is 36 mg daily. Maintenance doses have been given in some countries in the form of modified-release preparations. For dosage in renal impairment, see below.

In the treatment of painful muscle spasm tizanidine hydrochloride is given in doses equivalent to 2 to 4 mg of the base three times daily.

Administration in renal impairment. UK licensed product information recommends that in patients with renal insufficiency, oral treatment with tizanidine hydrochloride should be started with the equivalent of 2 mg of the base once daily; thereafter it advises a slow increase in the once-daily dose before increasing the frequency of administration. Similar recommendations are made in US product information.

Headache. Results from an open-label study[1] and a later controlled study[2] suggested that tizanidine might be of value in the prophylaxis of chronic daily headache. However, an earlier controlled study[3] failed to show any significant advantage over placebo in the treatment of chronic tension-type headache. In another study[4] tizanidine was also effective when given with a long-acting NSAID as part of a detoxification regimen for patients with chronic daily headaches induced by analgesic overuse.

1. Saper JR, *et al.* An open-label dose-titration study of the efficacy and tolerability of tizanidine hydrochloride tablets in the prophylaxis of chronic daily headache. *Headache* 2001; 41: 357–68.
2. Saper JR, *et al.* Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. *Headache* 2002; 42: 470–82.
3. Murros K, *et al.* Modified-release formulation of tizanidine in chronic tension-type headache. *Headache* 2000; 40: 633–7.
4. Smith TR. Low-dose tizanidine with nonsteroidal anti-inflammatory drugs for detoxification from analgesic rebound headache. *Headache* 2002; 42: 175–7.

Premedication. The value of tizanidine as a premedicant has been studied.[1] An oral dose of tizanidine 12 mg appears to have sedative and sympatholytic effects comparable with oral clonidine 150 micrograms.

1. Meittinen TJ, *et al.* The sedative and sympatholytic effects of oral tizanidine in healthy volunteers. *Anesth Analg* 1996; 82: 817–20.

Spasticity. The efficacy of tizanidine for spasticity (p. 2014.2) associated with cerebral and spinal disorders[1,2] has been shown in several placebo-controlled studies and in comparative studies it has produced similar improvements in muscle tone to baclofen or diazepam. Carefully titrated doses of tizanidine and baclofen used together may have additive beneficial effects[1,2] but use with benzodiazepines is not recommended because of potential interactions.[1] It was considered that tizanidine might have the advantage of being better tolerated than baclofen.

1. Wagstaff AJ, Bryson HM. Tizanidine: a review of its pharmacology, clinical efficacy and tolerability in the management of spasticity associated with cerebral and spinal disorders. *Drugs* 1997; 53: 435–52.
2. Kamen L, *et al.* A practical overview of tizanidine use for spasticity secondary to multiple sclerosis, stroke, and spinal cord injury. *Curr Med Res Opin* 2008; 24: 425–39.

Adverse Effects and Precautions

Tizanidine hydrochloride may cause drowsiness; patients affected should not drive or operate machinery. Other adverse effects include dry mouth, fatigue, dizziness or vertigo, muscle pain and weakness, insomnia, anxiety, headache, bradycardia, nausea, and gastrointestinal disturbances. Hallucinations have occurred on rare occasions. Many adverse effects have been found to be dose related and slow titration of doses appears to reduce the frequency of occurrence. Hypotension may occur.

Increases in liver enzymes and rarely acute hepatitis have been associated with tizanidine and it is contra-indicated in patients with severe hepatic dysfunction. In the UK it is recommended that liver function should be monitored monthly in all patients for the first 4 months

and in those who develop symptoms suggestive of hepatic dysfunction; similarly, in the USA baseline assessment and monitoring at 1, 3, and 6 months is advised. Treatment should be stopped if liver enzymes are persistently raised.

Caution is required in the elderly and in patients with renal insufficiency.

Interactions

Tizanidine is metabolised by the cytochrome P450 isoenzyme CYP1A2 and use with ciprofloxacin or fluvoxamine, both potent inhibitors of this isoenzyme, is contra-indicated. Use with other more moderate inhibitors of CYP1A2 (such as other quinolone antibacterials, cimetidine, and antiarrhythmics such as amiodarone, mexiletine, propafenone, and verapamil) should be avoided unless clinically necessary. The CNS effects of tizanidine may be enhanced by alcohol or other CNS depressants. There may be an additive hypotensive effect when tizanidine is used in patients receiving antihypertensive therapy; bradycardia may also be enhanced if given with beta blockers or digoxin. Caution should be exercised when tizanidine is given with drugs known to increase the QT interval. The clearance of tizanidine has been reported to be lower in women receiving hormonal contraceptives.

Antibacterials. In a study of healthy subjects,[1] *ciprofloxacin*, an inhibitor of the cytochrome P450 isoenzyme CYP1A2, was reported to elevate the plasma concentrations of tizanidine thereby potentiating its hypotensive and sedative effects.

1. Granfors MT, *et al.* Ciprofloxacin greatly increases concentrations and hypotensive effect of tizanidine by inhibiting its cytochrome P450 1A2-mediated presystemic metabolism. *Clin Pharmacol Ther* 2004; 76: 598–606.

Antidepressants. In a study[1] in 10 healthy subjects, *fluvoxamine*, a potent inhibitor of the cytochrome P450 isoenzyme CYP1A2, was reported to increase tizanidine's peak plasma concentrations and elimination half-life twelvefold and threefold, respectively. An increased incidence of adverse effects associated with tizanidine such as hypotension, bradycardia, drowsiness, and dizziness was noted in these subjects.

A 70-year-old woman receiving fluvoxamine 150 mg daily and other medications developed bradycardia, dry mouth, urinary retention, and a low body temperature when given tizanidine 3 mg daily;[2] the patient improved when tizanidine was stopped. In a retrospective survey of medical records, the authors reported adverse effects associated with tizanidine in 6 of 23 patients also receiving fluvoxamine.

1. Granfors MT, *et al.* Fluvoxamine drastically increases concentrations and effects of tizanidine: a potentially hazardous interaction. *Clin Pharmacol Ther* 2004; 75: 331–41.
2. Momo K, *et al.* Drug interaction of tizanidine and fluvoxamine. *Clin Pharmacol Ther* 2004; 76: 509–10.

Antiepileptics. For reference to an interaction between tizanidine and *phenytoin*, see p. 545.1.

Cardiovascular drugs. Severe hypotension, occurring 2 hours after treatment with tizanidine, has been reported in a patient receiving antihypertensives, including *lisinopril*, and other medications.[1] The patient improved after tizanidine and antihypertensives were stopped; they were later resumed without lisinopril, and caused no problems.

1. Kao C-D, *et al.* Hypotension due to interaction between lisinopril and tizanidine. *Ann Pharmacother* 2004; 38: 1840–3.

Oral contraceptives. Mean peak plasma concentrations after a single 4-mg dose of tizanidine were 3 times greater in 15 women using an oral contraceptive containing *ethinylestradiol* and *gestodene* than in controls;[1] the elimination half-life was not, however, significantly different. The effect appeared to be due to inhibition of the cytochrome P450 isoenzyme CYP1A2 by the contraceptive, resulting in reduced presystemic metabolism of tizanidine. Because the therapeutic range of tizanidine is narrow, care should be exercised if it is given to patients taking oral contraceptives.

1. Granfors MT, *et al.* Oral contraceptives containing ethinyl estradiol and gestodene markedly increase plasma concentrations and effects of tizanidine by inhibiting cytochrome P450 1A2. *Clin Pharmacol Ther* 2005; 78: 400–11.

Pharmacokinetics

Tizanidine is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 2 hours after oral doses. It is about 30% bound to plasma proteins. Tizanidine undergoes extensive first-pass metabolism in the liver mainly via the cytochrome P450 isoenzyme CYP1A2 and is excreted mainly in the urine as inactive metabolites. Elimination half-lives of 2 to 4 hours have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sirdalud; Tizanidal; ***Austria***: Sirdalud; ***Belg.***: Sirdalud; ***Braz.***: Sirdalud; ***Canad.***: Zanaflex; ***Chile***: Sirdalud; ***China***: Chang Bang (畅邦); KaiLaiTong (凯莱通); ***Cz.***: Sirdalud; ***Denm.***: Sirdalud; Zanic; ***Fin.***: Sirdalud; ***Ger.***: Sirdalud; ***Gr.***: Sirdalud; ***Hong Kong***: Sirdalud†; ***Hung.***: Sirdalud; ***India***: DTN 52; Emsulide-MR; Nimcom; Nimeb-T; Nimuflex-T; Nixia; Sirdalud; ***Indon.***: Myores; Sirdalud; Tizacom; Zitanid; ***Irl.***: Tizaflex; Zanaflex; ***Ital.***: Navizan; Sirdalud; ***Jpn***: Ternelin; ***Mex.***: Sirdalud; ***Neth.***: Sirdalud; ***Philipp.***: Sirdalud; Ternelax; ***Pol.***: Sirdalud; TizaniTeva; Tizanor; ***Port.***: Sirdalud; ***Rus.***: Sirdalud (Сирдалуд); Tisalud (Тизалуд); ***Spain***: Sirdalud; ***Switz.***: Sirdalud; ***Thai.***: Sirdalud; Tidar; Tizan; ***Turk.***: Devalud; Sirdalud; ***UK***: Zanaflex; ***Ukr.***: Sirdalud (Сирдалуд); Tizalud (Тизалуд); ***USA***: Zanaflex; ***Venez.***: Sirdalud.

Multi-ingredient Preparations. ***India***: Accetiz-P; Acent-TZ; Acicloflex-MR; Acota-MR; Alsolide-MR; Antipen-T; Asflam; Avisera-MR; Bestogesic MR; Brufen-MR; Canmet-MR; Carnil MR; Cipzone-TN; Citanz; Dicloran-MR; Diplonim-MR; Doloflam-MR; Etiza; Gesnim-MR; Gonim; Icobit-MR; Ingesic-MR; Itzgon; Jusgo-MR; Kinectine-MR†; Leofenac-MR; Lumbril-T; Mef-T; Meftal-MR; Minipar-TZ; Mortrin-T; Movon-MR; Nelsid-MR; Neomol-MR; Niciflex-T; Nicip T; Nile-TZ; Nimat-MR; Nimdin; Nimeril-T; Nimetiz; Nimi-LB; Nimitiz; Nimofen-T; Nimotiz MR; Nimpain T; Nimsaid-T; Nimtiz-MR; Nimudin; Nimulid MR; Nimvar-MR; Nimven-T; Nise-MR; Nizapas-MR; Nizi; Nizox-MR; Nobel-MR; Novolid-MR; Onalide-MR; Opel-MR; Orthobid-MR; Orthodex-MR; Zerodol-MR.

Pharmacopoeial Preparations
USP 36: Tizanidine Tablets.

Tolperisone Hydrochloride *(BANM, rINNM)*

AV-650; Hidrocloruro de tolperisona; N-553; Tolperisona, hidrocloruro de; Tolpérisone, Chlorhydrate de; Tolperisoni Hydrochloridum; Тольперизона Гидрохлорид.

2,4′-Dimethyl-3-piperidinopropiophenone hydrochloride.

$C_{16}H_{23}NO,HCl$=281.8

CAS — 728-88-1 (tolperisone); 3644-61-9 (tolperisone hydrochloride).

ATC — M03BX04.

ATC Vet — QM03BX04.

UNII — 8Z075K2TIG.

Pharmacopoeias. In *Jpn*.

Profile

Tolperisone hydrochloride is a centrally acting muscle relaxant that has been used for the symptomatic treatment of spasticity (p. 2014.2) and muscle spasm (p. 2014.1), in usual oral doses of 50 to 150 mg three times daily. It has also been given by injection.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Miodom; ***Austria***: Mydocalm; ***Cz.***: Mydocalm; ***Ger.***: Mydocalm; Viveo†; ***Hong Kong***: Mydocalm; Quali-Docalm; ***Hung.***: Miderizone; Myderison†; Mydeton; ***Jpn***: Muscalm; ***Pol.***: Mydocalm; Tolperis; ***Rus.***: Mydocalm (Мидокалм); ***Switz.***: Mydocalm; Tolflex; ***Thai.***: Biocalm; Musocalm; Mydocalm; Mydonol†; Mydosone; Myoxan; Risocalm; Soneriper; Spamus; Tanderon; Usocalm; ***Ukr.***: Mydocalm (Мидокалм); Tolperil (Толперил).

Multi-ingredient Preparations. ***Mex.***: Mydocalm-A.

Neuromuscular Blockers

Anaesthesia, p. 2028
Intensive care, p. 2028
Tetanus, p. 2029

Neuromuscular blockers (myoneuronal blockers) affect transmission at the neuromuscular junction and are used as adjuncts to general anaesthesia, particularly to enable adequate muscle relaxation to be achieved with light anaesthesia. There are 2 main types of neuromuscular blockers: competitive (non-depolarising neuromuscular blockers) and depolarising neuromuscular blockers (see Table 1, below).

Table 1. Classification of neuromuscular blockers.

Competitive		Depolarising
Aminosteroidal	*Benzylisoquinolinium*	Suxamethonium
Pancuronium	Alcuronium	
Pipecuronium	Atracurium	
Rocuronium	Cisatracurium	
Vecuronium	Gallamine	
	Mivacurium	
	Tubocurarine	

- **Competitive neuromuscular blockers** act by competing with acetylcholine for receptors on the motor end-plate. Their action can be opposed by increasing the local concentration of acetylcholine, for example by giving an anticholinesterase such as neostigmine (p. 687.1). Tubocurarine (p. 2040.1) was formerly the standard reference drug of this type but its use has declined, therefore details of the actions and uses of competitive neuromuscular blockers are discussed under Atracurium, p. 2030.1.
- **Depolarising neuromuscular blockers** act by depolarising the motor end-plate to prevent the normal response to acetylcholine; their action is not reversed by anticholinesterases. Suxamethonium (p. 2037.1) is the standard reference drug of this type.

Other drugs that have muscle relaxant properties and which are used in the management of musculoskeletal and neuromuscular disorders are discussed in the chapter on Muscle Relaxants, p. 2014.1.

General references.

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Anaesthesia

Neuromuscular blockers are used in general anaesthesia for their muscle relaxant effects to facilitate intubation at induction and to provide continued relaxation during maintenance. Their use is determined partly by their onset and duration of action (see Table 2, below), but both onset and duration are dose-dependent and can therefore vary. Generally, *competitive neuromuscular blockers*, due to their slower onset and longer duration of action, are used in major operations, while the *depolarising neuromuscular blockers* (usually suxamethonium), with a much faster onset and shorter duration, are used for minor operations or manipulations and particularly for intubation. After use of suxamethonium to aid intubation, a longer-acting competitive drug may then be given to maintain muscle relaxation throughout the operation. Competitive neuromuscular blockers with a short to intermediate duration of action, such as atracurium and vecuronium, are more widely used than those with a longer duration of action such as pancuronium.

Suxamethonium has been widely used after induction of anaesthesia to aid **intubation**; however, because of the adverse effects such as myalgia associated with suxamethonium (see also below), alternative neuromuscular blockers have been investigated for intubation and some questioned the use of suxamethonium for *elective* procedures,[1] especially in day-case patients.[2] Some competitive blockers such as vecuronium have a relatively rapid onset of action and have been used for intubation during routine, planned surgery. However, they act too slowly to enable rapid intubation in an *emergency*, when suxamethonium remains the drug of choice. Although rocuronium, a competitive blocker, is only slightly slower in onset, and may be suitable in emergencies if suxamethonium is contra-indicated,[3-5] it has a much longer duration of action, and needs to be given with an opioid such as alfentanil,[6] or with propofol,[4] to obtain equivalent intubating conditions.

In attempting to create more favourable conditions for rapid intubation with competitive neuromuscular blockers and thus provide an alternative to suxamethonium, anaesthetists have tried using large doses[3] or combinations[7] of competitive blockers. Other methods tried include giving competitive neuromuscular blockers in divided doses in an attempt to shorten the onset to paralysis.[3,8] This so-called *priming principle* involves giving a small initial dose, termed the priming dose, followed by a large paralysing dose. Priming may be with 2 doses of the same competitive relaxant or a combination of 2 different relaxants which may then show synergism. However, some consider[8] that priming techniques are associated with unacceptable adverse effects such as muscle weakness and aspiration, and that they are not safe, especially in the elderly.[3] In another technique, a single large dose of a neuromuscular blocker is given, followed by the induction anaesthetic as soon as the patient complains of weakness.[3] This is called the *timing principle* and although it has been successfully used with some neuromuscular blockers, problems such as perceived muscle weakness or shortness of breath may occur if the anaesthetic is not injected at the right moment.

The use of anaesthetic regimens that avoid or reduce the need for a neuromuscular blocker during intubation has also been investigated. The anaesthetic propofol with a short-acting opioid such as alfentanil has often been tried. In addition to its use alone, such a regimen has been combined successfully with low doses of suxamethonium[9] or rocuronium,[10] or standard doses of vecuronium,[11] to produce suitable conditions for intubation.

Procedures such as intubation can cause **complications**: an undesirable pressor response may occur, resulting in increased heart rate and arterial blood pressure. There may also be an increase in intracranial pressure and intra-ocular pressure. Furthermore, the use of suxamethonium to aid intubation is itself associated with a transient increase in intra-ocular pressure. Small doses of a competitive neuromuscular blocker have been given before suxamethonium[12] to prevent this rise in intra-ocular pressure, although some consider such a measure ineffective.[13] Opioids such as alfentanil and fentanyl appear to be effective in attenuating both the pressor response[14-16] and the rise in intra-ocular pressure[17,18] associated with intubation, but the use of lidocaine has produced conflicting results.[19-23] Many anaesthetics, with the exception of ketamine, reduce intra-ocular pressure to some extent and giving thiopental beforehand may help to counteract the effect of suxamethonium.[24]

Table 2. Relative speed of onset and duration of action of neuromuscular blockers.

Neuromuscular blocker	Onset*	Duration†
Alcuronium	Intermediate	Intermediate
Atracurium	Intermediate	Short/Intermediate
Cisatracurium	Intermediate	Short/Intermediate
Gallamine	Rapid	Intermediate
Mivacurium	Intermediate	Short
Pancuronium	Rapid	Long
Pipecuronium	Intermediate	Intermediate/Long
Rocuronium	Rapid	Intermediate
Suxamethonium	Ultra-rapid	Ultra-short
Tubocurarine	Intermediate/Slow	Intermediate
Vecuronium	Rapid	Intermediate

*Onset:	†Duration:
Ultra-rapid, less than 1 minute	Ultra-short, less than 8 minutes
Rapid, 1 to 2 minutes	Short, 8 to 20 minutes
Intermediate, 2 to 4 minutes	Intermediate, 20 to 50 minutes
Slow, more than 4 minutes	Long, more than 50 minutes

Onset and duration of action are dose-dependent

Other drugs that have been used or tried in the prevention of the haemodynamic response to intubation include magnesium sulfate[25] and propofol.[26,27]

Competitive neuromuscular blockers are usually used to provide muscle relaxation during **maintenance** anaesthesia. Patients given a neuromuscular blocker generally require less anaesthetic permitting a state of 'lighter anaesthesia' and hence reducing the adverse effects of the anaesthetic. At the end of the procedure any residual block should be reversed, either with an anticholinesterase or the selective relaxant binding agent sugammadex if appropriate, and the patient should be monitored until spontaneous respiration has resumed. For further details see Anaesthesia under Uses of General Anaesthetics, p. 1896.1.

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Intensive care

The use of neuromuscular blockers in patients requiring mechanical ventilation as part of intensive care has been discussed in reviews[1-3] and guidelines.[4] Neuromuscular blockers are used to provide additional relaxation and facilitate ventilatory support in patients who fail to respond to sedation alone. It is important to ensure that such patients are adequately sedated and relatively pain free

before these drugs are used. Patients who are considered most likely to benefit are those with spontaneous respiration that is counterproductive to mechanical ventilation. Patients with little inherent respiratory muscle activity are less likely to obtain an improvement in oxygenation. Neuromuscular blockers may also improve control of intracranial pressure in patients with intracranial hypertension, including prevention of rises in intracranial pressure associated with routine tracheobronchial suction.

Pancuronium has been widely used as a neuromuscular blocker in intensive care because of its tendency to increase arterial pressure and the majority of patients requiring a neuromuscular blocker can be adequately managed with pancuronium; however, its long duration of action may be a problem in some circumstances, and its vagolytic activity can also produce tachycardia. Vecuronium, atracurium, and cisatracurium have relatively few cardiovascular effects, but there has been some concern over the ability of the atracurium metabolite laudanosine to accumulate in the CNS (see Biotransformation, under Pharmacokinetics, p. 2033.3). Atracurium and cisatracurium may also be more suitable in patients with hepatic or renal impairment as their metabolism does not lead to the accumulation of active metabolites. Other neuromuscular blockers that have been used in intensive care include doxacurium, pipecuronium, and rocuronium.

Close monitoring of neuromuscular blockade is recommended since the pharmacodynamics and pharmacokinetics of neuromuscular blockers may be altered in patients in intensive care;[1-4] this should also allow the lowest effective neuromuscular blocking dose to be used, and reduce adverse events. Prolonged neuromuscular blockade has been related to dosage.

Other factors that may potentiate neuromuscular blockade include drug interactions, electrolyte imbalance, hypothermia, or changes in acid–base balance.[1,3] Conversely, dosage requirements may be increased in patients with burns or in those receiving prolonged therapy. Tachyphylaxis has occurred with some neuromuscular blockers, but may resolve on switching to another blocker.

Prolonged neuromuscular blockade has been associated with adverse effects and should be avoided when possible. Recovery after withdrawal of prolonged treatment may be longer than pharmacologically predicted due to the accumulation of active metabolites; this is a particular problem for neuromuscular blockers with a long duration of action and for patients with hepatic or renal impairment. An acute myopathy has also followed prolonged use, most commonly with aminosteroid neuromuscular blockers (see Table 1, p. 2028); there are case reports suggesting that use of corticosteroids might increase the risk.[4,5]

When rapid reversal of paralysis is necessary an anticholinesterase such as neostigmine may be used, but relatively little is known about the efficacy of anticholinesterases in reversing prolonged paralysis.[6]

Neonatal intensive care. Neuromuscular blockers such as pancuronium bromide are used in neonatal intensive care to obtain muscle relaxation during mechanical ventilation in infants with severe pulmonary disease, especially in those whose respiratory efforts are out of phase with the ventilator.[7] They are only used in infants at high risk of complications such as *pneumothorax* or *intraventricular haemorrhage*; their routine use in all ventilated neonates is not recommended.[8]

Abolition of spontaneous respiration during mechanical ventilation has had variable effects on the incidence of *pneumothorax* in infants with respiratory distress syndrome. Although a reduced incidence was found in one study[9] involving infants of less than 33 weeks' gestation, in another study[10] the incidence was reduced only in infants with a gestational age of 27 to 32 weeks; no reduction was obtained in those below 26 weeks' gestation. Paralysis also failed to reduce the incidence of pneumothorax or interstitial emphysema in a study[11] of infants with hyaline membrane disease but did appear to speed recovery of lung function.

The aetiology of *intraventricular haemorrhage* remains obscure but there is a well recognised association with gestational age;[12] less mature neonates are more susceptible and the incidence decreases sharply after 30 weeks' gestation. There appears to be an association between fluctuating cerebral blood-flow velocity in the first day of life and subsequent development of intraventricular haemorrhage.[13] Respiratory paralysis from the first day of life until 72 hours of age has been reported[14] to stabilise both cerebral and arterial blood-flow velocity and to produce a decrease in the incidence and severity of intraventricular haemorrhage in infants with respiratory distress syndrome. However, respiratory paralysis has also been reported to have no effect on the development of intraventricular haemorrhage.[9,10]

The use of neuromuscular blockers in the newborn is not without complications. Multiple joint contractures, possibly potentiated by use of aminoglycosides or phenobarbital, have been reported[15,16] in infants given pancuronium, and regular passive limb movements should be performed during paralysis. Marked oedema, severe disturbances of fluid balance, renal failure and death have been reported in 2 neonates.[17] Hypoxaemia may develop after induction of paralysis unless a significant increase in ventilator support is made;[9,13,18] hypotension may also occur.[19] Drugs such as pancuronium which are metabolised in the liver and excreted in the urine have a prolonged action in premature infants.[7] As with adults (see above), continuous use of neuromuscular blockers in neonates has been associated with prolonged neuromuscular block on withdrawal.[20]

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Tetanus

The clinical manifestations of tetanus after infection with *Clostridium tetani* are caused by the highly potent neurotoxin tetanospasmin produced by its germinating spores.

The muscular symptoms of generalised tetanus include trismus (lockjaw), glottal spasm, generalised muscle spasm, opisthotonus (spasm of the back muscles resulting in backward arching of the body), respiratory spasm, and paralysis. Other complications include electrolyte disturbances and autonomic dysfunction leading to cardiovascular effects such as hypertension, tachycardia, and peripheral vasoconstriction. Patients may have a milder form in which the twitching and muscle spasms are limited to the area near the site of the injury, but such localised tetanus is rare and can progress to the generalised form.

The goal of treatment is to relieve muscle spasm, prevent respiratory and metabolic complications, neutralise unbound or circulating toxin, and eliminate the source of toxin. For the **antibacterial treatment** of tetanus and neutralisation of tetanospasmin, see p. 209.2. The mainstay of treatment for **rigidity and spasms** is sedation with *benzodiazepines* such as diazepam or midazolam; they may also reduce patient anxiety. *Opioid analgesics* can be added to treatment to provide analgesia and additional sedation; in addition, *fentanyl*, *morphine*, and *sufentanil* may control autonomic overactivity. *Antiepileptics*, particularly phenobarbital, may also provide additional sedation. *Chlorpromazine* is sometimes used with benzodiazepines to minimise rigidity and muscle spasms. Sedation with *propofol* may also control spasms and rigidity without the need for an additional relaxant; however, mechanical ventilation is required. Centrally acting muscle relaxants have also been tried to control muscle spasms. *Baclofen* has been given by the intrathecal route, but its therapeutic range in severe tetanus may be very narrow and deep coma and loss of spontaneous respiration has been reported. *Dantrolene* has also been reported to be effective. When muscle spasms are severe or interfere with respiration, *competitive neuromuscular blockers* have been used in addition to benzodiazepine sedation, to control spasms and to induce therapeutic paralysis so mechanical ventilation can be started.

Control of **autonomic overactivity** may be achieved with sedation; benzodiazepines, antiepileptics, and opioid analgesics have all been used (see above). *Beta blockers* such as propranolol have also been used; however, they are no longer recommended because of the potential for severe cardiovascular effects. Labetalol has both alpha- and beta-blocking activity but offers no advantage over propranolol. More recently, *esmolol*, a short-acting beta blocker, has been used. *Magnesium sulfate* has been found to minimise autonomic disturbance in ventilated patients and controls spasms in non-ventilated patients, but there is need for further investigation. **Electrolyte disturbance** is corrected with calcium and magnesium salts.

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Alcuronium Chloride *(BAN, USAN, rINN)*

Alcuronii Chloridum; Alcuronio, cloruro de; Alcuronium, chlorure d'; Alcuroniumchlorid; Alkuronio chloridas; Alkuronium-chlorid; Alkurónium-klorid; Alkuroniumklorid; Alkuroniumkloridi; Allnortoxiferin Chloride; Cloruro de alcuronio; Diallylnortoxiferine Dichloride; Diallyltoxiferine Chloride; Dicloruro de dialilnortoxiferina; Ro-4-3816; Алкуроний Хлорид.

NN'-Diallylbisnortoxiferinium dichloride.

$C_{44}H_{50}Cl_2N_4O_2$=737.8

CAS — 23214-96-2 (alcuronium); 15180-03-7 (alcuronium chloride).

ATC — M03AA01.

ATC Vet — QM03AA01.

UNII — 490DW6501Y.

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

Ph. Eur. 8: (Alcuronium Chloride). A white or slightly greyish-white, crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol; practically insoluble in cyclohexane. Store under nitrogen in an airtight container. Protect from light.

Profile

Alcuronium chloride is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p. 2030.1) that is used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p. 2028.1). It can induce histamine release to some degree. Anaphylactoid reactions have been associated with the use of alcuronium. It has some vagolytic action and may produce tachycardia; hypotension may also occur.

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. An initial dose of 150 to 250 micrograms/kg has been given intravenously. Muscle relaxation occurs after about 2 minutes and the effect lasts for about 20 to 30 minutes. Supplementary doses of 30 micrograms/kg have been given to provide additional periods of muscle relaxation.

Pregnancy. Alcuronium crosses the placenta. No evidence of neuromuscular block was seen in any of the neonates born to 12 women who received alcuronium 15 to 30 mg by intravenous injection, 5 to 10.5 minutes before delivery[1] but caution was advised if alcuronium was given in obstetrics in high doses or for a prolonged period.

1. Ho PC, *et al.* Caesarean section and placental transfer of alcuronium. *Anaesth Intensive Care* 1981; 9: 113–18.

Renal impairment. Alcuronium is excreted mainly by the kidneys and accumulation, with prolonged paralysis, may therefore be expected in patients with renal impairment given large or repeated doses. A prolonged elimination half-life has been reported in anuria.[1] However, doses of 160 micrograms/kg have been used without any problems in patients with chronic renal failure undergoing renal transplantation.[2] The average duration of action of this dose was 37 minutes and any residual neuromuscular blockade at the end of surgery was successfully reversed using atropine and neostigmine.

1. Raaflaub J, Prey P. Zur Pharmakokinetik von Diallyl-nor-toxiferin beim Menschen. *Arzneimittelforschung* 1972; 22: 73–8.
2. Kaushik S, *et al.* Use of alcuronium in patients undergoing renal transplantation. *Br J Anaesth* 1984; 56: 1229–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Alloferin†; *S.Afr.*: Alloferin; *Ukr.*: Alloferin (Аллоферин)†.

Atracurium Besilate *(BAN, rINN)*

33A74; Atracurii Besilas; Atracurio, besilato de; Atracurium, Bésilate d'; Atracurium Besylate (USAN); Atracurium Besylate; Atracuriumbesilat; Atrakurio besilatas; Atrakuriumbesilaatti; Atrakuriumbesilat; Atrakurium-besylát; Atrakuryum Besilat; Besilato de atracúrio; BW-33A; Атракурия Безилат.

2,2'-(3,11-Dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) di(benzenesulphonate).

$C_{53}H_{72}N_2O_{12}.2C_6H_6O_3S$=1243.5

CAS — 64228-81-5.

ATC — M03AC04.

ATC Vet — QM03AC04.

UNII — 40AX66P76P.

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

Ph. Eur. 8: (Atracurium Besilate). A white to yellowish-white, slightly hygroscopic powder. It contains 55.0 to 60.0% of the *cis-cis* isomer, 34.5 to 38.5% of the *cis-trans* isomer, and 5.0 to 6.5% of the *trans-trans* isomer. Soluble in water; very soluble in alcohol, in acetonitrile, and in dichloromethane. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Atracurium Besylate). A white to off-white solid. It contains not less than 5.0% and not more than 6.5% of the *trans-trans* isomer, not less than 34.5% and not more than 38.5% of the *cis-trans* isomer, and not less than 55.0% and not more than 60.0% of the *cis-cis* isomer. It is unstable at room temperature. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Cisatracurium Besilate *(BAN, rINN)*

51W89 (cisatracurium); Bésilate de Cisatracurium; Besilato de cisatracurio; BW-51W (cisatracurium); BW-51W89 (cisatracurium); Cisatracurii Besilas; Cisatracurio, besilato de; Cisatracurium, Bésilate de; Cisatracurium Besylate; Sisatrakuryum Bezilat; Цисатракурия Безилат.

(1*R*,1'*R*,2*R*,2'*R*)-2,2'-(3,11-Dioxo-4,10-dioxatridecamethylene) bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) dibenzenesulfonate.

CAS — 96946-42-8.

ATC — M03AC11.

ATC Vet — QM03AC11.

UNII — 80YS8O1MBS.

Incompatibility. Neuromuscular blockers are generally incompatible with alkaline solutions, for example barbiturates such as thiopental sodium. It is good practice not to give neuromuscular blockers in the same syringe, or simultaneously through the same needle, as other drugs.

Licensed product information states that cisatracurium is incompatible with ketorolac trometamol or propofol emulsion; in addition, lactated Ringer's injection with glucose 5% or lactated Ringer's solution should not be used as a diluent when preparing solutions of cisatracurium for infusion.

Stability. In a stability study,[1] solutions of cisatracurium (as the besilate) in concentrations of 2 or 10 mg/mL were stable for at least 90 days when stored in the original vials at 4 degrees either exposed to or protected from light; similar solutions stored at 23 degrees were stable for at least 45 days. Solutions of 2 mg/mL stored in plastic syringes at 4 degrees or 23 degrees were stable for at least 30 days. Solutions of 0.1, 2, or 5 mg/mL in 5% glucose injection or 0.9% sodium chloride injection in PVC minibags were stable for at least 30 days stored at 4 degrees; the 5 mg/mL solution was also stable for at least 30 days stored at 23 degrees.

1. Xu QA, *et al.* Stability of cisatracurium besylate in vials, syringes, and infusion admixtures. *Am J Health-Syst Pharm* 1998; 55: 1037–41.

Uses and Administration

Competitive neuromuscular blockers act by competing with acetylcholine for receptors on the motor end-plate of the neuromuscular junction to produce blockade. The muscles that produce fine rapid movements such as those of the face are the first to be affected, followed by those of the limbs and torso; the last to be affected are those of the diaphragm. The paralysis is reversible with recovery occurring in reverse order. Restoration of normal neuromuscular function can be hastened by increasing the concentration of acetylcholine at the motor end-plate by giving an anticholinesterase such as neostigmine.

Atracurium and cisatracurium are competitive benzylisoquinolinium neuromuscular blockers. The commercial preparation of atracurium is a mixture of 10 stereoisomers of which cisatracurium constitutes about 15%. Cisatracurium, the *R-cis,1'R-cis*-isomer of atracurium, is about 3 times more potent than the mixture of isomers of atracurium. After an intravenous dose of atracurium, muscle relaxation begins in about 2 minutes and lasts for 15 to 35 minutes; onset may be slightly slower for cisatracurium.

Atracurium besilate and cisatracurium besilate are used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p. 2028.1) and to aid controlled ventilation (see Intensive Care, p. 2028.3).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage.

For **atracurium besilate**, in the UK, the usual initial dose for adults and children over 1 month of age is 300 to 600 micrograms/kg by intravenous injection. Subsequent doses of 100 to 200 micrograms/kg may be given as necessary, typically every 15 to 25 minutes for maintenance in prolonged procedures. It is recommended that in patients with cardiovascular disease the initial dose should be given over a period of 60 seconds.

Atracurium besilate may also be given by continuous intravenous infusion at a rate of 5 to 10 micrograms/kg per minute to maintain neuromuscular block during prolonged procedures. Somewhat higher infusion rates may be used in patients undergoing controlled ventilation in intensive care.

Although unlicensed in the UK, the *BNFC* suggests that neonates may be given atracurium in doses similar to those used in older children (see above).

Cisatracurium is given as the besilate but doses are expressed as the base. Cisatracurium 1 mg is equivalent to about 1.34 mg of cisatracurium besilate. In the UK, the usual initial dose for intubation of adults and children over 1 month of age is 150 micrograms/kg by intravenous injection. In adults, the neuromuscular block may be extended with maintenance doses of 30 micrograms/kg (each dose provides about 20 minutes of additional block). In children aged 2 years and over, the neuromuscular block may be extended with maintenance doses of 20 micrograms/kg (each dose provides about 9 minutes of additional block). The *BNFC* suggests that a maintenance dose of 30 micrograms/kg, repeated about every 20 minutes, may be given to younger children aged 1 month and over; however, such use is unlicensed in the UK.

Cisatracurium besilate may also be given by continuous intravenous infusion to adults and children over 2 years of age at an initial rate equivalent to cisatracurium 3 micrograms/kg per minute followed by a rate of 1 to 2 micrograms/kg per minute after stabilisation.

Similar doses of atracurium and cisatracurium are used in the USA.

Reviews.

1. Bryson HM, Faulds D. Cisatracurium besilate: a review of its pharmacology and clinical potential in anaesthetic practice. *Drugs* 1997; 53: 848–66.

Administration in children. Children generally require larger doses of competitive neuromuscular blockers on a weight basis than adolescents or adults to achieve similar degrees of neuromuscular blockade and may recover more quickly. In contrast, neonates and infants under 1 year of age are more sensitive and usual doses may produce prolonged neuromuscular blockade (see also Uses and Administration, above for some suggested doses).

References.

1. Brandom BW, Fine GF. Neuromuscular blocking drugs in pediatric anesthesia. *Anesthesiol Clin North America* 2002; 20: 45–58.

ECT. Competitive neuromuscular blockers have been used to reduce the intensity of muscle contractions and minimise trauma in patients receiving ECT, but suxamethonium (p. 2037.3) is generally preferred because of its short duration of action.

Intravenous regional anaesthesia. Competitive neuromuscular blockers and/or opioid analgesics have been added to the local anaesthetic used in intravenous regional anaesthesia (p. 1977.2) to improve the quality of anaesthesia. However atracurium (see Tourniquets under Precautions, p. 2031.3) and mivacurium (see Tourniquets, p. 2035.1) might be unsuitable for such use.

Shivering. Various drugs have been tried in the treatment of postoperative shivering (p. 1897.2). There are reports of neuromuscular blockers being used to treat shivering after cardiac surgery in order to reduce cardiovascular stress;[1] one study[2] has suggested that vecuronium might be preferable to pancuronium as it does not increase myocardial work and may be associated with fewer complications.

1. Cruise C, *et al.* Comparison of meperidine and pancuronium for the treatment of shivering after cardiac surgery. *Can J Anaesth* 1992; 39: 56–8.
2. Dupuis J-Y, *et al.* Pancuronium or vecuronium for the treatment of shivering after cardiac surgery. *Anesth Analg* 1994; 79: 472–81.

Tetanus. For mention of the role of competitive neuromuscular blockers in the management of muscle spasms caused by tetanus, see p. 2029.2.

Adverse Effects

The adverse effects of competitive neuromuscular blockers are generally similar although they differ in their propensity to cause histamine release and associated cardiovascular effects. The latter appear to be rare with the aminosteroidal blockers and the benzylisoquinolinium blocker cisatracurium (see below). Competitive neuromuscular blockers with vagolytic activity may produce tachycardia and a rise in blood pressure. The use of blockers that lack an effect on the vagus will not counteract the bradycardia produced during anaesthesia by the other drugs employed or by vagal stimulation. Reduction in blood pressure with compensatory tachycardia may occur with some competitive neuromuscular blockers, in part because of sympathetic ganglion blockade or the release of histamine. Reduction in gastrointestinal motility and tone may occur as a result of ganglionic blockade.

Histamine release may also lead to wheal-and-flare effects at the site of injection, flushing, occasionally bronchospasm, and rarely anaphylactoid reactions.

Malignant hyperthermia has been associated rarely with competitive neuromuscular blockers.

Some competitive neuromuscular blockers such as pancuronium, tubocurarine, and vecuronium can cause a decrease in the partial thromboplastin time and prothrombin time.

In overdosage there is prolonged apnoea due to paralysis of the intercostal muscles and diaphragm, with cardiovascular collapse and the effects of histamine release.

Atracurium and its isomer cisatracurium have no significant vagal or ganglionic blocking activity at recommended doses. Unlike atracurium, cisatracurium does not induce histamine release and is therefore associated with greater cardiovascular stability.

For possible risks from their major metabolite laudanosine, see Biotransformation, under Pharmacokinetics, p. 2033.3.

Effects on body temperature. Competitive neuromuscular blockers are not considered to be a trigger factor for malignant hyperthermia; however, there have been rare case reports of apparent association. Two cases of mild malignant hyperthermia have been reported[1] where tubocurarine was probably the triggering drug. Each episode developed in a member of a family known to be susceptible to malignant hyperthermia, despite preventive measures such as prophylactic cooling, and avoidance of potent inhalation anaesthetics and depolarising neuromuscular blockers. Another case[2] was associated with the use of pancuronium.

1. Britt BA, *et al.* Malignant hyperthermia induced by curare. *Can Anaesth Soc J* 1974; 21: 371–5.
2. Waterman PM, *et al.* Malignant hyperthermia: a case report. *Anesth Analg* 1980; 59: 220–1.

Effects on the muscles. For reference to acute myopathy and prolonged muscle weakness after withdrawal of long-term continuous infusions of competitive neuromuscular blockers, see Intensive Care, p. 2028.3.

Hypersensitivity. There have been reports of severe anaphylactoid reactions after use of atracurium[1,2] or cisatracurium.[3-5] For a discussion of hypersensitivity reactions associated with neuromuscular blockers, see under Suxamethonium Chloride, p. 2038.2.

1. Stirton-Hopkins C. Life-threatening reaction to atracurium. *Br J Anaesth* 1988; 60: 597–8.
2. Oh TE, Horton JM. Adverse reactions to atracurium. *Br J Anaesth* 1989; 62: 467–8.
3. Briassoulis G, *et al.* Persistent anaphylactic reaction after induction with thiopentone and cisatracurium. *Paediatr Anaesth* 2000; 10: 429–34.
4. Legros CB, *et al.* Severe anaphylactic reaction to cisatracurium in a child. *Anesth Analg* 2001; 92: 648–9.
5. Fraser BA, Smart JA. Anaphylaxis to cisatracurium following negative skin testing. *Anaesth Intensive Care* 2005; 33: 816–19.

Treatment of Adverse Effects

It is essential to maintain assisted respiration in patients who have received a competitive neuromuscular blocker until spontaneous breathing is fully restored; in addition a cholinesterase inhibitor such as neostigmine is usually given intravenously, with atropine or glycopyrronium, to hasten reversal of the neuromuscular block. Patients need to be closely monitored after reversal of block to ensure that muscle relaxation does not return.

Severe hypotension may require intravenous fluid replacement and cautious use of a pressor agent; the patient should be positioned to facilitate venous return from the muscles.

Giving an antihistamine before induction of neuromuscular blockade may help to prevent histamine-induced adverse effects in patients with asthma or those susceptible to bronchospasm.

Reversal of neuromuscular blockade. For a discussion of the use of anticholinesterases for reversal of residual neuromuscular block produced by intermediate- or short-acting blockers after surgical or similar procedures, see under Neostigmine, p. 688.1.

Precautions

Patients who have received a neuromuscular blocker should always have their respiration assisted or controlled until the drug has been inactivated or antagonised.

Atracurium and other competitive neuromuscular blockers should be used with great care, if at all, in respiratory insufficiency or pulmonary disease and in the dehydrated or severely ill patient. The response to neuromuscular blockers is often unpredictable in patients with neuromuscular disorders and they should be used with great care in these patients (see below). Caution is also needed in patients with a history of conditions such as asthma where release of histamine would be a hazard. Care is also required in patients with a history of hypersensitivity to any neuromuscular blocker because high rates of cross-sensitivity have been reported. For a discussion of hypersensitivity reactions associated with neuromuscular blockers, see under Adverse Effects of Suxamethonium Chloride, p. 2038.2.

Resistance to the effects of competitive neuromuscular blockers may occur in patients with burns (see below). The effect of competitive neuromuscular blockers may vary in patients with hepatic impairment: resistance appears to occur to some, such as doxacurium, metocurine, pancuronium, and tubocurarine, while dosage of others, including mivacurium and rocuronium, may need to be reduced because of a prolonged action.

Competitive neuromuscular blockers excreted mainly in the urine should be used with caution in renal impairment; a reduction in dosage may be necessary. Doses may need to be reduced in infants and neonates because of increased sensitivity to competitive muscle relaxants. Doses in obese patients should usually be based upon the patient's ideal body-weight rather than actual body-weight.

The effects of competitive neuromuscular blockers are increased by metabolic or respiratory acidosis and hypokalaemia, hypermagnesaemia, hypocalcaemia, and hypophosphataemia and dehydration. Competitive neuromuscular blockade may also be enhanced by raised body temperature and reduced in hypothermia.

In contrast to other competitive neuromuscular blockers, reduction in body temperature may necessitate a dosage reduction for *atracurium and its isomer cisatracurium* since cooling reduces the rate of inactivation of atracurium and cisatracurium, but physiological variations in body temperature and pH will not significantly affect their action.

Burns. The dose requirements of competitive neuromuscular blockers are increased in patients with burns,[1-3] the dose correlating with both the extent of the burn and time after injury. This resistance is usually not seen in patients with less than 10% body-surface burns but if more than 40% of the body-surface is affected the dose of competitive blocker may need to be up to five times higher than in patients without burns. Resistance peaks about 2 weeks after injury, persists for many months in patients with major burns, and decreases gradually with healing of the burn. The mechanism of resistance is multifactorial but may be partly explained by increased protein binding, increased volume of distribution, and increased numbers of acetylcholine receptors at the motor end-plate requiring more muscle relaxant to produce a given effect. Despite the high doses of competitive relaxants that are required, recovery from neuromuscular blockade is not seriously impaired and their effects can be reversed with usual doses of an anticholinesterase.

1. Martyn J, *et al.* Clinical pharmacology of muscle relaxants in patients with burns. *J Clin Pharmacol* 1986; 26: 680–5.
2. Anonymous. Neuromuscular blockers in patients with burns. *Lancet* 1988; ii: 1003–4.
3. Tschida SJ, *et al.* Resistance to nondepolarizing neuromuscular blocking agents. *Pharmacotherapy* 1996; 16: 409–18.

Cardiopulmonary bypass. The effect of cardiopulmonary bypass on the pharmacokinetics and pharmacodynamics of competitive neuromuscular blockers can be complex but generally their dosage may need to be reduced. Although the intensity of neuromuscular blockade of most competitive neuromuscular blockers is reduced by hypothermia[1] used during cardiopulmonary bypass, their use during this procedure is associated with rises in plasma concentrations, reduced clearance, and prolongation of the elimination half-life.[2-6] Various mechanisms, including reduced distribution to highly perfused tissues such as the lungs, have been proposed to explain this effect.[2] For atracurium, it appears that it is a reduction in the temperature-dependent inactivation by Hofmann elimination during hypothermia that enables lower doses to be used.[7]

1. Buzello W, *et al.* Unequal effects of cardiopulmonary bypass-induced hypothermia on neuromuscular blockade from constant infusion of alcuronium, d-tubocurarine, pancuronium, and vecuronium. *Anesthesiology* 1987; 66: 842–6.
2. Walker JS, *et al.* Alcuronium kinetics in patients undergoing cardiopulmonary bypass surgery. *Br J Clin Pharmacol* 1983; 15: 237–44.
3. Walker JS, *et al.* Altered d-tubocurarine disposition during cardiopulmonary bypass surgery. *Clin Pharmacol Ther* 1984; 35: 686–94.
4. Wierda JMKH, Agoston S. Pharmacokinetics of vecuronium during hypothermic bypass. *Br J Anaesth* 1989; 63: 627P–628P.
5. Smeulers NJ, *et al.* Hypothermic cardiopulmonary bypass influences the concentration-response relationship and the biodisposition of rocuronium. *Eur J Anaesthesiol* 1995; 12 (suppl 11): 91–4.
6. Asokumar B, *et al.* Pharmacokinetics of doxacurium during normothermic and hypothermic cardiopulmonary bypass surgery. *Can J Anaesth* 1998; 45: 515–20.
7. Flynn PJ, *et al.* Use of atracurium in cardiac surgery involving cardiopulmonary bypass with induced hypothermia. *Br J Anaesth* 1984; 56: 967–72.

Hepatic impairment. The effect of competitive neuromuscular blockers may vary in patients with hepatic impairment (see Precautions, above) but alterations in the pharmacokinetics of atracurium and cisatracurium in patients with hepatic impairment (see Biotransformation, under Pharmacokinetics, p. 2033.3) do not appear to be clinically significant and a reduction in dosage is not generally recommended.

Neuromuscular disorders. Caution is needed if competitive neuromuscular blockers are given to patients with neuromuscular disease since severe complications have been reported.[1] Increased response may be seen in patients with paraplegia or quadriplegia, but resistance has been reported in patients with hemiplegia. Increased response also may occur in patients with amyotrophic lateral sclerosis, neurofibromatosis, and poliomyelitis; this is of little concern unless the respiratory muscles are involved when prolonged apnoea may occur. Patients with myasthenia gravis usually show increased sensitivity to competitive neuromuscular blockers although small doses have been given without complications. During remission of myasthenia gravis a normal response is usual but since remission is often incomplete, small intermittent doses are advised. A significantly greater exaggeration of response is seen in patients with the myasthenic syndrome. Both normal and increased responses have been reported in patients with myotonias or muscular dystrophies but exquisite sensitivity occurs in patients with ocular muscular dystrophy. A normal response to competitive relaxants may be expected in patients with multiple sclerosis, muscular denervation, Parkinson's disease, and tetanus.

1. Azar I. The response of patients with neuromuscular disorders to muscle relaxants: a review. *Anesthesiology* 1984; 61: 173–87.

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

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pregnancy. A review[1] of the pharmacokinetics of neuromuscular blockers in pregnancy concluded that atracurium and mivacurium are the best choice in pregnancy since their actions are predictable; their duration of action is either unchanged or only slightly prolonged. Atracurium also has a low umbilical to maternal vein concentration (uv/mv) ratio. In general, it is advisable[1] to choose a neuromuscular blocker with a low uv/mv ratio and a short duration of action, and to inject the lowest dose required to produce adequate surgical conditions.

Atracurium 300 micrograms/kg given to 26 women undergoing caesarean section, with subsequent incremental doses of 100 or 200 micrograms/kg if necessary, produced good surgical relaxation in all patients without any complications.[2] Of the 26 neonates delivered, respiration was established within 90 seconds in 21, with an Apgar score of 10 at 5 minutes. The remaining 5 neonates were delivered by caesarean section because of fetal distress and were slower to start breathing.

A study[3] of 22 women in the immediate postpartum period found the onset and duration of cisatracurium to be significantly shorter when compared with nonpregnant patients.

1. Guay J, *et al.* Clinical pharmacokinetics of neuromuscular relaxants in pregnancy. *Clin Pharmacokinet* 1998; 34: 483–96.
2. Frank M, *et al.* Atracurium in obstetric anaesthesia: a preliminary report. *Br J Anaesth* 1983; 55: 113S–114S.
3. Fan PH, Moore C. Comparison of cisatracurium-induced neuromuscular blockade between immediate postpartum and nonpregnant patients. *J Clin Anesth* 2001; 13: 112–17.

Renal impairment. Although some differences in the pharmacokinetics of atracurium and cisatracurium have been reported in patients with renal impairment (see Biotransformation, under Pharmacokinetics, p. 2033.3), duration of their neuromuscular blocking action is not significantly dependent on renal function and usual doses may be given to such patients.[1,2] Atracurium has been given by infusion to patients with end-stage renal failure[3] when the initial dose required for induction of neuromuscular block was 37% higher than that required by patients without renal impairment. The increase could be explained by the larger extracellular fluid volume in patients with chronic renal failure.

Although the pharmacokinetics of atracurium and cisatracurium are not appreciably different in renal impairment, those of their metabolites may be (see Biotransformation, under Pharmacokinetics, p. 2033.3) and therefore it has been suggested that neuromuscular function should be monitored during use of atracurium.[4]

1. Hunter JM, *et al.* Use of the muscle relaxant atracurium in anephric patients: preliminary communication. *J R Soc Med* 1982; 75: 336–340.
2. Boyd AH, *et al.* Pharmacodynamics of the 1*R* cis-1'*R* cis isomer of atracurium (51W89) in health and chronic renal failure. *Br J Anaesth* 1995; 74: 400–404.
3. Gramstad L. Atracurium, vecuronium and pancuronium in end-stage renal failure: dose-response properties and interactions with azathioprine. *Br J Anaesth* 1987; 59: 995–1003.
4. Vandenbrom RHG, *et al.* Pharmacokinetics and neuromuscular blocking effects of atracurium besylate and two of its metabolites in patients with normal and impaired renal function. *Clin Pharmacokinet* 1990; 19: 230–40.

Resistance. The aetiology of resistance to competitive blockers is not clear but might be due to pharmacodynamic or pharmacokinetic alterations associated with disease states such as burn injuries (see above) or hepatic impairment (see above) or therapy with other drugs (see Interactions, below). One review[1] noted that there had been several case reports of resistance to competitive neuromuscular blockers; most had been associated with use of single doses or short-term intermittent therapy, but more recent reports had documented resistance during continuous infusions in 9 patients of whom 7 had received atracurium and 2 rocuronium. Resistance to atracurium had followed 2 different patterns. Patients had required either usual or raised doses for initial control but both groups had subsequently required progressive increases. Most patients with resistance to atracurium were successfully managed by transfer to pancuronium or doxacurium.

1. Tschida SJ, *et al.* Resistance to nondepolarizing neuromuscular blocking agents. *Pharmacotherapy* 1996; 16: 409–18.

Tourniquets. Atracurium might be unsuitable for neuromuscular blockade of a limb that has been isolated with a tourniquet in order to provide a bloodless field for surgery.[1] Atracurium undergoes non-enzymatic degradation in plasma and would therefore continue to degrade locally leading to a loss of blockade in the limb, which could not be corrected by further doses unless the tourniquet was deflated.

1. Shannon PF. Neuromuscular block and tourniquets. *Br J Anaesth* 1994; 73: 726.

Interactions

Some drugs may influence neuromuscular transmission and thus interfere with the action of both competitive and depolarising neuromuscular blockers, resulting in potentiation or antagonism of neuromuscular block. Some interactions may be advantageous, such as the reversal of competitive neuromuscular block by anticholinesterases. In general, adverse interactions are potentially more serious in patients with impaired neuromuscular function (see Neuromuscular Disorders, above, and under Suxamethonium Chloride, p. 2039.1).

Drug interactions affecting neuromuscular blockers of either type (competitive and depolarising) as well as those specific for competitive neuromuscular blockers are discussed below. For drug interactions specific to depolarising neuromuscular blockers see under Interactions of Suxamethonium Chloride, p. 2039.2.

Reviews.

1. Feldman S, Karalliedde L. Drug interactions with neuromuscular blockers. *Drug Safety* 1996; 15: 261–73.
2. Cammu G. Interactions of neuromuscular blocking drugs. *Acta Anaesthesiol Belg* 2001; 52: 357–63.

Antiarrhythmics. *Lidocaine, procainamide, quinidine,* and *verapamil* all have some neuromuscular blocking activity and may enhance the block produced by neuromuscular blockers. Large doses of lidocaine may reduce the release of acetylcholine and act directly on the muscle membrane. Quinidine has a curare-like action at the neuromuscular

junction and depresses the muscle action potential. If given during recovery from neuromuscular block it can result in muscle weakness and apnoea and it should be avoided, if possible, in the immediate postoperative period. For details regarding interactions with calcium-channel blockers, see below.

Antibacterials. Some antibacterials in very high concentration can produce a muscle paralysis that may be additive to or synergistic with that produced by neuromuscular blockers. The neuromuscular block produced by antibacterials may be enhanced in patients with intracellular potassium deficiency, low plasma-calcium concentration, neuromuscular disease, or a tendency to a high plasma-antibacterial concentration, for example after large doses or in renal impairment. The interaction appears to be more important for competitive neuromuscular blockers. The antibacterials most commonly implicated are aminoglycosides, lincosamides, polymyxins, and, more rarely, tetracyclines.

The *aminoglycosides* reduce release of, and sensitivity to, acetylcholine and their effect can be reversed, at least in part, by calcium, fampridine, or an anticholinesterase. The interaction can occur with aminoglycosides given by most routes. There are reports of potentiation of neuromuscular blockade occurring with many different aminoglycoside-neuromuscular blocker combinations[1-6] and all aminoglycosides should be used with extreme caution during surgery and in the postoperative period.

The *lincosamides* (*clindamycin* and *lincomycin*) can prolong the action of muscle relaxants producing a neuromuscular block that may be difficult to reverse with calcium or anticholinesterases.[7-9] Patients should be monitored for prolonged paralysis.

There have been reports of prolonged apnoea[1,4,8] after use of *polymyxins* (*colistin, polymyxin B*) with a neuromuscular blocker. The block is difficult to reverse; calcium may be partially successful, but neostigmine may increase the block.

Tetracyclines have weak neuromuscular blocking properties; potentiation of neuromuscular block has been reported in patients with myasthenia gravis.[1] Reversal of the block may be partly achieved with calcium, but the value of anticholinesterases is questionable.

The *ureidopenicillins* (*azlocillin* and *mezlocillin*), and the closely related *piperacillin*, are reported to prolong the block produced by vecuronium.[10,11]

Vancomycin has been reported to increase neuromuscular blockade by vecuronium.[12] Prolonged paralysis and apnoea has occurred in a patient recovering from suxamethonium-induced blockade after being given vancomycin.[13]

1. Pittinger CB, *et al.* Antibiotic-induced paralysis. *Anesth Analg Curr Res* 1970; 49: 487–501.
2. Hall DR, *et al.* Gentamicin, tubocurarine, lignocaine and neuromuscular blockade. *Br J Anaesth* 1972; 44: 1329–32.
3. Waterman PM, Smith RB. Tobramycin-curare interaction. *Anesth Analg Curr Res* 1977; 56: 587–8.
4. Glaia MM, Paradelis AG. Two cases of prolonged respiratory depression due to interaction of pancuronium with colistin and streptomycin. *J Antimicrob Chemother* 1979; 5: 234–5.
5. Regan AG, Perumbetti PPV. Pancuronium and gentamicin interaction in patients with renal failure. *Anesth Analg* 1980; 59: 393.
6. Jedeikin R, *et al.* Prolongation of neuromuscular blocking effect of vecuronium by antibiotics. *Anaesthesia* 1987; 42: 858–60.
7. Booij LHD, *et al.* Neostigmine and 4-aminopyridine antagonism of lincomycin-pancuronium neuromuscular blockade in man. *Anesth Analg* 1978; 57: 316–21.
8. de Gouw NE, *et al.* Interaction of antibiotics on pipecuronium-induced neuromuscular blockade. *J Clin Anesth* 1993; 5: 212–15.
9. Sloan PA, Rasul M. Prolongation of rapacuronium neuromuscular blockade by clindamycin and magnesium. *Anesth Analg* 2002; 94: 123–4.
10. Tryba M. Wirkungsverstärkung nicht-depolarisierender Muskelrelaxantien durch Acylaminopenicilline: Untersuchungen am Beispiel von Vecuronium. *Anaesthesist* 1985; 34: 651–5.
11. Tryba M, Klemm D. Wechselwirkungen zwischen Acylaminopenicillinen und nicht depolarisierenden Muskelrelaxantien. *Forschr Antimikrob Antineoplast Chemother* 1985; 4–7: 1827–33.
12. Huang KC, *et al.* Vancomycin enhances the neuromuscular blockade of vecuronium. *Anesth Analg* 1990; 70: 194–6.
13. Albrecht RF, Lanier WL. Potentiation of succinylcholine-induced phase II block by vancomycin. *Anesth Analg* 1993; 77: 1300–2.

Anticholinesterases. Anticholinesterases, including *ecothiopate, edrophonium, galantamine, neostigmine, pyridostigmine, rivastigmine,* and possibly *donepezil,* antagonise the effect of competitive neuromuscular blockers. Some anticholinesterases such as neostigmine inhibit both acetylcholinesterase and plasma cholinesterase, and are used clinically to antagonise competitive neuromuscular blockade. Conversely, anticholinesterases enhance the action of depolarising muscle relaxants such as suxamethonium thus prolonging neuromuscular block, although suxamethonium-induced phase II block can be reversed with an anticholinesterase. See also Interactions in Suxamethonium Chloride, p. 2039.3.

Antiepileptics. Resistance to competitive neuromuscular blockers has been reported in patients receiving chronic treatment with *carbamazepine*[1,2] or *phenytoin*[3,4] and rapid recovery from neuromuscular block may occur. In addition, children on chronic antiepileptic drugs (carbamazepine and/or phenytoin) were found to recover quicker from rocuronium-induced paralysis than those not on antiepileptics.[5] In a study[6] with cisatracurium, faster recovery rates were also recorded in patients receiving acute or chronic treatment with unspecified antiepileptics. However, atracurium[1] and mivacurium[7] appear to be unaffected by chronic carbamazepine therapy and the effect of chronic phenytoin treatment on atracurium has usually been minimal.[3] Although one study[8] did report that epileptic patients receiving one or more antiepileptics had significantly shorter times to recovery from atracurium, the authors pointed out that the patient populations were different from those in the previous studies.[1,3]

A report of sensitivity to vecuronium[9] has suggested that acute dosage of phenytoin may increase rather than decrease the effect of competitive neuromuscular blockers.

1. Ebrahim Z, *et al.* Carbamazepine therapy and neuromuscular blockade with atracurium and vecuronium. *Anesth Analg* 1988; 67: 555.
2. Whalley DG, Ebrahim Z. Influence of carbamazepine on the dose-response relationship of vecuronium. *Br J Anaesth* 1994; 72: 125–6.
3. Ornstein E, *et al.* The effect of phenytoin on the magnitude and duration of neuromuscular block following atracurium or vecuronium. *Anesthesiology* 1987; 67: 191–6.
4. Hernández-Palazón J, *et al.* Rocuronium-induced neuromuscular blockade is affected by chronic phenytoin therapy. *J Neurosurg Anesthesiol* 2001; 13: 79–81.
5. Soriano SG, *et al.* Onset and duration of action of rocuronium in children receiving chronic anticonvulsant therapy. *Paediatr Anaesth* 2000; 10: 133–6.
6. Koenig RM, Edwards TL. Cisatracurium-induced neuromuscular blockade in anticonvulsant treated neurosurgical patients. *J Neurosurg Anesthesiol* 2000; 12: 314–18.
7. Spacek A, *et al.* Chronic carbamazepine therapy does not influence mivacurium-induced neuromuscular block. *Br J Anaesth* 1996; 77: 500–502.
8. Tempelhoff R, *et al.* Resistance to atracurium-induced neuromuscular blockade in patients with intractable seizure disorders treated with anticonvulsants. *Anesth Analg* 1990; 71: 665–9.
9. Baumgardner JE, Bagshaw R. Acute versus chronic phenytoin therapy and neuromuscular blockade. *Anaesthesia* 1990; 45: 493–4.

Antineoplastics. It has been recommended that atracurium should be used with care in patients receiving anti-oestrogenic drugs,[1] after a case of prolonged neuromuscular blockade with atracurium in a patient receiving *tamoxifen*. See also under Interactions of Suxamethonium Chloride, p. 2039.3.

1. Naguib M, Gyasi HK. Antiestrogenic drugs and atracurium—a possible interaction? *Can Anaesth Soc J* 1986; 33: 682–3.

Aprotinin. After reports of apnoea, caution has been advised when aprotinin is used with neuromuscular blockers.[1,2]

1. Chasapakis G, Dimas C. Possible interaction between muscle relaxants and the kallikrein-trypsin inactivator "Trasylol". *Br J Anaesth* 1966; 38: 838–9.
2. Marcello B, Forati U. Trasylol e blocco neuromuscolare: nota preventiva. *Minerva Anestesiol* 1967; 33: 814–15.

Benzodiazepines. There are conflicting reports of the effect of *diazepam* on neuromuscular blockers; potentiation,[1,2] or antagonism[1] of neuromuscular block, and a lack of interaction[3-5] have all been reported.

1. Feldman SA, Crawley BE. Interaction of diazepam with the muscle-relaxant drugs. *BMJ* 1970; 2: 336–8.
2. Yuan H-B, *et al.* The interaction of diazepam with vecuronium: a clinical study. *Chin Med J* 1994; 54: 259–64.
3. Bradshaw EG, Maddison S. Effect of diazepam at the neuromuscular junction. *Br J Anaesth* 1979; 51: 955–60.
4. Asbury AJ, *et al.* Effect of diazepam on pancuronium-induced neuromuscular blockade maintained by a feedback system. *Br J Anaesth* 1981; 53: 859–63.
5. Driessen JJ, *et al.* Benzodiazepines and neuromuscular blocking drugs in patients. *Acta Anaesthesiol Scand* 1986; 30: 642–6.

Beta blockers. There is conflicting evidence for the effect of beta blockers on the activity of neuromuscular blockers. Lack of effect on depolarising neuromuscular block[1] and antagonism[2,3] or enhancement[4,5] of both competitive and depolarising block have been reported. The exact mechanism of interaction is not clear. There have also been reports of some neuromuscular blockers such as atracurium[6,7] and alcuronium[8] increasing the hypotension and bradycardia associated with the use of anaesthesia in patients receiving beta blockers; these include reports in patients using beta blockers in eye drops.

1. McCammon RL, *et al.* The effect of esmolol on the onset and duration of succinylcholine-induced neuromuscular blockade. *Anesthesiology* 1985; 63: A317.
2. Varma YS, *et al.* Effect of propranolol hydrochloride on the neuromuscular blocking action of d-tubocurarine and succinylcholine in man. *Indian J Med Res* 1972; 60: 266–72.
3. Varma YS, *et al.* Comparative effect of propranolol, oxprenolol and pindolol on neuromuscular blocking action of d-tubocurarine in man. *Indian J Med Res* 1973; 61: 1382–6.
4. Rozen MS, Whan FM. Prolonged curarization associated with propranolol. *Med J Aust* 1972; 1: 467–8.
5. Murthy VS, *et al.* Cardiovascular and neuromuscular effects of esmolol during induction of anesthesia. *J Clin Pharmacol* 1986; 26: 351–7.
6. Glynne GL. Drug interaction? *Anaesthesia* 1984; 39: 293.
7. Rowlands DE. Drug interaction? *Anaesthesia* 1984; 39: 1252.
8. Yate B, Mostafa SM. Drug interaction? *Anaesthesia* 1984; 39: 728.

Botulinum A toxin. Theoretically, the neuromuscular block induced by botulinum toxins may be enhanced by competitive neuromuscular blockers.

Calcium-channel blockers. Calcium-channel blockers such as diltiazem, nicardipine, nifedipine, and verapamil enhance the effect of competitive neuromuscular blockers.[1-6] *Verapamil* may interfere with the release of acetylcholine and prolonged use may lead to a reduction in intracellular calcium concentration. Potentiation of neuromuscular blockade has been reported[1,2] and the block may be resistant to reversal with neostigmine; edrophonium may be required. The dose requirement for vecuronium was reduced by as much as 50% in surgical patients receiving *diltiazem*.[4,6] A similar effect was seen with *nicardipine*,[5] which reduced the requirement for vecuronium in a dose-dependent fashion. The interaction of vecuronium with diltiazem appeared to be due to a pharmacodynamic mechanism[4] but nicardipine also reduced the plasma clearance of vecuronium, indicating a partial pharmacokinetic mechanism as well.[5] *Nifedipine* also caused an increase in the intensity and duration of action of atracurium and vecuronium when given during anaesthesia.[3]

1. van Poorten JF, *et al.* Verapamil and reversal of vecuronium neuromuscular blockade. *Anesth Analg* 1984; 63: 155–7.
2. Jones RM, *et al.* Verapamil potentiation of neuromuscular blockade: failure of reversal with neostigmine but prompt reversal with edrophonium. *Anesth Analg* 1985; 64: 1021–5.
3. Jelen-Esselborn S, Blobner M. Wirkungsverstärkung von nichtdepolarisierenden Muskelrelaxanzien durch Nifedipin i.v. in Inhalationsanaesthesie. *Anaesthesist* 1990; 39: 173–8.
4. Sumikawa K, *et al.* Reduction in vecuronium infusion dose requirements by diltiazem in humans. *Anesthesiology* 1992; 77: A939.
5. Kawabata K, *et al.* Decrease in vecuronium infusion dose requirements by nicardipine in humans. *Anesth Analg* 1994; 79: 1159–64.
6. Takasaki Y, *et al.* Diltiazem potentiates the neuromuscular blockade by vecuronium in humans. *Jpn J Anesthesiol* 1995; 44: 503–7.

Cardiac inotropes. Pancuronium or suxamethonium may interact with *cardiac glycosides*[1] resulting in an increased incidence of arrhythmias; the interaction is more likely with pancuronium.

1. Bartolone RS, Rao TLK. Dysrhythmias following muscle relaxant administration in patients receiving digitalis. *Anesthesiology* 1983; 58: 567–9.

Corticosteroids. Antagonism of the neuromuscular blocking effects of pancuronium[1] and vecuronium[2] has been reported in patients taking corticosteroids. This interaction may occur only with long-term corticosteroid treatment and may be expected with all competitive neuromuscular blockers.

For reference to a suggestion that use of corticosteroids might increase the risk of acute myopathy associated with prolonged use of neuromuscular blockers, see Intensive Care, p. 2028.3.

1. Azar I, *et al.* Resistance to pancuronium in an asthmatic patient treated with aminophylline and steroids. *Can Anaesth Soc J* 1982; 29: 280–2.
2. Parr SM, *et al.* Betamethasone-induced resistance to vecuronium: a potential problem in neurosurgery? *Anaesth Intensive Care* 1991; 19: 103–5.

Diuretics. *Furosemide,* and possibly *mannitol,* have been reported to enhance tubocurarine neuromuscular block in patients with renal failure,[1] but antagonism of tubocurarine by furosemide has also occurred.[2] Small doses of furosemide (less than 100 micrograms/kg) may inhibit protein kinase, which inhibits muscle contraction and potentiates neuromuscular blockade, whereas high doses inhibit phosphodiesterase, increasing cAMP activity and resulting in antagonism of neuromuscular blockade. The potassium-depleting effect of diuretics may enhance the effect of competitive neuromuscular blockers.

1. Miller RD, *et al.* Enhancement of d-tubocurarine neuromuscular blockade by diuretics in man. *Anesthesiology* 1976; 45: 442–5.
2. Azar I, *et al.* Furosemide facilitates recovery of evoked twitch response after pancuronium. *Anesth Analg* 1980; 59: 55–7.

Ganglion blockers. Prolonged neuromuscular blockade has been reported[1,2] in patients given neuromuscular blockers and *trimetaphan.* Trimetaphan may have direct neuromuscular blocking activity and some activity against plasma cholinesterase.

1. Wilson SL, *et al.* Prolonged neuromuscular blockade associated with trimethaphan: a case report. *Anesth Analg Curr Res* 1976; 55: 353–6.
2. Poulton TH, *et al.* Prolonged apnea following trimethaphan and succinylcholine. *Anesthesiology* 1979; 50: 54–6.

General anaesthetics. Neuromuscular blockers are potentiated in a dose-dependent manner by inhalation anaesthetics.[1-5] The dose of neuromuscular blocker may need to be reduced by up to 70%[1] depending on the anaesthetic used and its concentration, and on the choice of blocker; the interaction is of greater clinical importance with competitive blockers. *Isoflurane, enflurane, desflurane,* and *sevoflurane* produce the greater potentiation, followed by *halothane* and *cyclopropane*. Reversal of competitive block with an anticholinesterase has been reported to be reduced.[6,7] See also under Interactions of Suxamethonium Chloride, p. 2039.3.

Potentiation of the neuromuscular blocking effects of tubocurarine[8] and atracurium[9] has been reported after the intravenous use of *ketamine*. Results from studies *in vitro* suggest that ketamine decreases sensitivity to acetylcholine

and it would therefore be expected to potentiate all neuromuscular blockers, but no interaction was reported for pancuronium.[8] Early data[10] suggesting that ketamine potentiates suxamethonium-induced blockade have not been confirmed by later studies.[8,11]

For incompatibility between neuromuscular blockers and alkaline solutions such as thiopental sodium, see under Incompatibility, p. 2030.1.

1. Cannon JE, *et al.* Continuous infusion of vecuronium: the effect of anesthetic agents. *Anesthesiology* 1987; 67: 503–6.
2. Swen J, *et al.* Interaction between nondepolarizing neuromuscular blocking agents and inhalation anesthetics. *Anesth Analg* 1989; 69: 752–5.
3. Ghourin AP, White PF. Comparative effects of desflurane and isoflurane on vecuronium-induced neuromuscular blockade. *J Clin Anesth* 1992; 4: 34–8.
4. Vanlinthout LEM, *et al.* Effect of isoflurane and sevoflurane on the magnitude and time course of neuromuscular block produced by vecuronium, pancuronium and atracurium. *Br J Anaesth* 1996; 76: 389–95.
5. Wulf H, *et al.* Augmentation of the neuromuscular blocking effects of cisatracurium during desflurane, sevoflurane, isoflurane or total i.v. anaesthesia. *Br J Anaesth* 1998; 80: 308–12.
6. Delisle S, Bevan DR. Impaired neostigmine antagonism of pancuronium during enflurane anaesthesia in man. *Br J Anaesth* 1982; 54: 441–5.
7. Gill SS, *et al.* Edrophonium antagonism of atracurium during enflurane anaesthesia. *Br J Anaesth* 1990; 64: 300–5.
8. Johnston RR, *et al.* The interaction of ketamine with d-tubocurarine, pancuronium, and succinylcholine in man. *Anesth Analg Curr Res* 1974; 53: 496–501.
9. Toft P, Helbo-Hansen S. Interaction of ketamine with atracurium. *Br J Anaesth* 1989; 62: 319–20.
10. Bovill JG, *et al.* Current status of ketamine anaesthesia. *Lancet* 1971; i: 1285–8.
11. Helbo-Hansen HS, *et al.* Ketamine does not affect suxamethonium-induced neuromuscular blockade in man. *Eur J Anaesthesiol* 1989; 6: 419–23.

Histamine H_2-antagonists. There are conflicting reports of the effects of histamine H_2-antagonists on neuromuscular blockade. *Cimetidine* has been variously reported to prolong suxamethonium-induced paralysis[1] or to have no effect.[2] *Famotidine* and *ranitidine* have been reported[2] not to interact with suxamethonium. Cimetidine, but not ranitidine, has been reported[3] to delay recovery from vecuronium-induced neuromuscular block. Neither drug appeared to affect recovery after the use of atracurium.

1. Kambam JR, *et al.* Effect of cimetidine on duration of action of succinylcholine. *Anesth Analg* 1987; 66: 191–2.
2. Turner DR, *et al.* Neuromuscular block by suxamethonium following treatment with histamine type 2 antagonists or metoclopramide. *Br J Anaesth* 1989; 63: 348–50.
3. McCarthy G, *et al.* Effect of H2-receptor antagonist pretreatment on vecuronium- and atracurium-induced neuromuscular blockade. *Br J Anaesth* 1991; 66: 713–15.

Immunosuppressants. Antagonism of the neuromuscular blocking effects of competitive neuromuscular blockers has been reported with *azathioprine*,[1] although the effect may not be clinically important. Azathioprine probably inhibits phosphodiesterase activity at the motor nerve terminal resulting in increased release of acetylcholine. There have been reports of prolonged neuromuscular blockade with atracurium, pancuronium, and vecuronium in some patients receiving *ciclosporin* intravenously.[2,3] This effect has been attributed to an interaction with polyoxyl castor oil used as the solvent for intravenous ciclosporin but a similar reaction has been reported in a patient receiving ciclosporin orally.[4]

1. Gramstad L. Atracurium, vecuronium and pancuronium in end-stage renal failure: dose-response properties and interaction with azathioprine. *Br J Anaesth* 1987; 59: 995–1003.
2. Crosby E, Robblee JA. Cyclosporine-pancuronium interaction in a patient with a renal allograft. *Can J Anaesth* 1988; 35: 300–302.
3. Sidi A, *et al.* Prolonged neuromuscular blockade and ventilatory failure after renal transplantation and cyclosporine. *Can J Anaesth* 1990; 37: 543–8.
4. Ganjoo P, Tewari P. Oral cyclosporine-vecuronium interaction. *Can J Anaesth* 1994; 41: 1017.

Lithium. There have been isolated reports of prolonged neuromuscular blockade after the use of neuromuscular blockers in patients receiving lithium.[1,2]

1. Borden H, *et al.* The use of pancuronium bromide in patients receiving lithium carbonate. *Can Anaesth Soc J* 1974; 21: 79–82.
2. Hill GE, *et al.* Potentiation of succinylcholine neuromuscular blockade by lithium carbonate. *Anesthesiology* 1976; 44: 439–42.

Local anaesthetics. Healthy subjects who had undergone regional anaesthesia of the forearm had symptoms suggestive of local anaesthetic toxicity on deflation of the tourniquet cuff when mivacurium and *prilocaine* had been used together for anaesthesia;[1] giving prilocaine or mivacurium alone did not produce such an effect. The suggestion that mivacurium may alter vascular permeability, allowing a more rapid diffusion of prilocaine back into the blood from the tissues, should be investigated.[2]

The interaction between neuromuscular blockers and *lidocaine* is discussed in Antiarrhythmics p. 2031.3.

1. Torrance JM, *et al.* Low-dose mivacurium supplementation of prilocaine i.v. regional anaesthesia. *Br J Anaesth* 1997; 78: 222–3.
2. Torrance JM, *et al.* Interactions between mivacurium and prilocaine. *Br J Anaesth* 1997; 78: 262.

Magnesium salts. Parenteral magnesium salts may potentiate the effects of competitive and depolarising neuromuscular blockers;[1] the neuromuscular block is deepened and prolonged and a reduction in the dose of the blocker may be needed. Magnesium salts should be used with caution in the postoperative period, as use shortly after recovery from neuromuscular block can lead to recurarisation.[2] Magnesium salts reduce release of and sensitivity to acetylcholine, thus contributing to neuromuscular blockade.

1. Ghoneim MM, Long JP. The interaction between magnesium and other neuromuscular blocking agents. *Anesthesiology* 1970; 32: 23–7.
2. Fuchs-Buder T, Tassonyi E. Magnesium sulphate enhances residual neuromuscular block induced by vecuronium. *Br J Anaesth* 1996; 76: 565–6.

MAOIs. There appears to be a theoretical hazard with pancuronium in patients receiving MAOIs since it releases stored adrenaline;[1] alcuronium, atracurium, or vecuronium would appear to be suitable alternatives.

1. Stack CG, *et al.* Monoamine oxidase inhibitors and anaesthesia: a review. *Br J Anaesth* 1988; 60: 222–7.

Neuromuscular blockers. A competitive neuromuscular blocker given shortly before a depolarising blocker such as suxamethonium antagonises the depolarising neuromuscular block. This interaction has been used clinically to reduce muscle fasciculations caused by suxamethonium (see Effects on the Muscles, p. 2038.1) and tried for other adverse effects associated with suxamethonium (see Effects on Plasma-potassium Concentration, p. 2038.2). To achieve this antagonism a small non-paralysing dose of a competitive blocker is given before suxamethonium. If a paralysing dose of a competitive blocker is followed some time later with a dose of suxamethonium, for example to facilitate abdominal closure, the resulting neuromuscular block is influenced by the competitive blocker used, the depth of residual block, the dose of suxamethonium, and whether an anticholinesterase is given; antagonism, enhancement, and a combination of the two have been seen.[1,2]

A competitive blocker is often given after the short-acting suxamethonium to maintain neuromuscular blockade during long procedures. The action of the competitive blocker has been reported to be considerably potentiated and prolonged in these circumstances,[3,4] and reduction in the dose of the competitive blocker may be appropriate.

Combination of competitive blockers may have additive or synergistic effects and the interaction may differ depending on which blocker is given first. Caution is needed if a small dose of a shorter-acting blocker is given near the end of an operation in which a long-acting blocker has been given previously, since the resulting block may be greater than expected and much longer than desired.[5–8]

1. Scott RPF, Norman J. Effect of suxamethonium given during recovery from atracurium. *Br J Anaesth* 1988; 61: 292–6.
2. Black AMS. Effect of suxamethonium given during recovery from atracurium. *Br J Anaesth* 1989; 62: 348–9.
3. d'Hollander AA, *et al.* Clinical and pharmacological actions of a bolus injection of suxamethonium: two phenomena of distinct duration. *Br J Anaesth* 1983; 55: 131–4.
4. Ono K, *et al.* Influence of suxamethonium on the action of subsequently administered vecuronium or pancuronium. *Br J Anaesth* 1989; 62: 324–6.
5. Rashkovsky OM, *et al.* Interaction between pancuronium bromide and vecuronium bromide. *Br J Anaesth* 1985; 57: 1063–6.
6. Middleton CM, *et al.* Use of atracurium or vecuronium to prolong the action of tubocurarine. *Br J Anaesth* 1989; 62: 659–63.
7. Kim KS, *et al.* Interactions between mivacurium and pancuronium. *Br J Anaesth* 1997; 79: 19–23.
8. Mohamed C, *et al.* Interaction between mivacurium and pancuronium: impact of the order of administration. *Eur J Clin Pharmacol* 2005; 61: 175–7.

Sex hormones. Resistance to the neuromuscular blocking effects of suxamethonium and vecuronium in a patient was attributed to previous long-term therapy with *testosterone*,[1] although the exact mechanism could not be explained. See also under Interactions of Suxamethonium Chloride, p. 2040.1.

1. Reddy P, *et al.* Resistance to muscle relaxants in a patient receiving prolonged testosterone therapy. *Anesthesiology* 1989; 70: 871–3.

Smoking. Smoking may affect the dose requirements for neuromuscular blockers. One study[1] found that smokers needed more vecuronium than non-smokers; it was considered that the effect might be explained at the receptor level, although increased metabolism of vecuronium could not be excluded. In contrast, an earlier study[2] found the amount of atracurium required was reduced in smokers.

1. Teiriä H, *et al.* Effect of smoking on dose requirements for vecuronium. *Br J Anaesth* 1996; 76: 154–5.
2. Kroeker KA, *et al.* Neuromuscular blockade in the setting of chronic nicotine exposure. *Anesthesiology* 1994; 81: A1120.

Sympathomimetics. Intravenous *salbutamol* has been reported to enhance the blockade obtained with pancuronium and vecuronium.[1] See also under Interactions of Suxamethonium Chloride, p. 2040.1.

1. Salib Y, Donati F. Potentiation of pancuronium and vecuronium neuromuscular blockade by intravenous salbutamol. *Can J Anaesth* 1993; 40: 50–3.

Xanthines. Resistance to neuromuscular block with pancuronium, requiring an increase in dosage or transfer to vecuronium, has been reported in patients receiving *aminophylline* with[1] or without[2] corticosteroid therapy. It was suggested that this effect might be due to inhibition of phosphodiesterase by aminophylline resulting in increased release of acetylcholine at the nerve terminal.

1. Azar I, *et al.* Resistance to pancuronium in an asthmatic patient treated with aminophylline and steroids. *Can Anaesth Soc J* 1982; 29: 280–2.
2. Daller JA, *et al.* Aminophylline antagonizes the neuromuscular blockade of pancuronium but not vecuronium. *Crit Care Med* 1991; 19: 983–5.

Pharmacokinetics

On intravenous injection both atracurium besilate and cisatracurium besilate undergo spontaneous degradation via Hofmann elimination (a non-enzymatic breakdown process occurring at physiological pH and temperature) to produce laudanosine and other metabolites. There is also ester hydrolysis by non-specific plasma esterases. The metabolites have no neuromuscular blocking activity.

About 80% of atracurium besilate is bound to plasma proteins. Atracurium besilate and its metabolites cross the placenta in clinically insignificant amounts. Excretion of atracurium and cisatracurium is in urine and bile, mostly as metabolites. The elimination half-life has been reported to be about 20 minutes for atracurium and 22 to 29 minutes for cisatracurium but laudanosine has an elimination half-life of about 3 to 6 hours.

Reviews.

1. Kisor DF, Schmith VD. Clinical pharmacokinetics of cisatracurium besilate. *Clin Pharmacokinet* 1999; 36: 27–40.
2. Atherton DPL, Hunter JM. Clinical pharmacokinetics of the newer neuromuscular blocking drugs. *Clin Pharmacokinet* 1999; 36: 169–89.
3. Booij LHDJ, Vree TB. Skeletal muscle relaxants: pharmacodynamics and pharmacokinetics in different patient groups. *Int J Clin Pract* 2000; 54: 526–34.

Biotransformation. Atracurium and cisatracurium are degraded by Hofmann elimination and metabolised by non-specific plasma esterases. Hofmann elimination is generally believed to be the main route of degradation but *in-vitro work* suggests ester hydrolysis is more important.[1] Both routes are independent of renal and hepatic function and no dosage reduction is recommended for elderly patients or those with impaired renal or hepatic function. However, the elimination half-life of atracurium has been found to be slightly longer in elderly patients[2] and in those with hepatic cirrhosis[3] compared with young and healthy patients, although others[4] have found no change in the pharmacokinetics of atracurium in the elderly. Renal and hepatic involvement in the metabolism of atracurium[2] may help to explain any tendency to reduced elimination but this does not appear to be clinically significant. Although clearance of cisatracurium has been reported to be reduced in patients with renal failure[5] this appears to have little significant effect on its pharmacodynamics.[6] Differences in the pharmacokinetics of cisatracurium in patients with hepatic impairment have been reported to be minor.[7]

The major biotransformation product of atracurium and cisatracurium is *laudanosine*; it has no clinical neuromuscular blocking activity but has been associated with CNS stimulation in *animal* studies. It is more lipid soluble than atracurium and cisatracurium and has a half-life of around 3 hours compared with one of about 20 minutes for atracurium. Higher plasma-laudanosine concentrations have been reported in patients with renal failure[5,8,9] than in patients with normal renal function. The elimination half-life of laudanosine was found to be significantly greater in patients with hepatic cirrhosis[3] and in elderly patients[2] compared with healthy and young patients respectively. High plasma-laudanosine concentrations were also seen in 10 critically ill patients with acute respiratory distress syndrome;[10] no adverse effects were noted.

Laudanosine crosses the blood-brain barrier in man. The concentration of laudanosine in the CSF increases during an infusion of atracurium and the CSF-to-plasma ratio gradually increases. A ratio of 0.14 was found at 125 to 140 minutes[11] during an infusion of atracurium at a mean rate of 510 micrograms/kg per hour. No evidence of CNS stimulation has been reported in man although patients given atracurium[12] had a 20% higher mean arterial-thiopental concentration at awakening compared with patients given vecuronium, suggesting that laudanosine may have had a minor stimulatory effect on the CNS. The blood-brain barrier appears to be effective in preventing a very high concentration of laudanosine from reaching the CNS and it is considered unlikely[13] that concentrations great enough to provoke seizures will be reached. Cisatracurium

may be associated with the production of less laudanosine than atracurium.[14]

1. Stiller RL, *et al.* In vitro degradation of atracurium in human plasma. *Br J Anaesth* 1985; 57: 1085–8.
2. Kent AP, *et al.* Pharmacokinetics of atracurium and laudanosine in the elderly. *Br J Anaesth* 1989; 63: 661–6.
3. Parker CJR, Hunter JM. Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis. *Br J Anaesth* 1989; 62: 177–83.
4. d'Hollander AA, *et al.* Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: lack of age-related effects. *Anesthesiology* 1983; 59: 237–40.
5. Eastwood NB, *et al.* Pharmacokinetics of 1R-cis 1'R-cis atracurium besylate (51W89) and plasma laudanosine concentrations in health and chronic renal failure. *Br J Anaesth* 1995; 75: 431–5.
6. Boyd AR, *et al.* Pharmacodynamics of the 1R cis-1'R cis isomer of atracurium (51W89) in health and chronic renal failure. *Br J Anaesth* 1995; 74: 400–404.
7. De Wolf AM, *et al.* Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation. *Br J Anaesth* 1996; 76: 624–8.
8. Fahey MR, *et al.* Effect of renal failure on laudanosine excretion in man. *Br J Anaesth* 1985; 57: 1049–51.
9. Vandenbrom RHG, *et al.* Pharmacokinetics and neuromuscular blocking effects of atracurium besylate and two of its metabolites in patients with normal and impaired renal function. *Clin Pharmacokinet* 1990; 19: 230–40.
10. Farenc C, *et al.* Pharmacokinetic-pharmacodynamic modeling of atracurium in intensive care patients. *J Clin Pharmacol* 2001; 41: 44–50.
11. Eddleston JM, *et al.* Concentrations of atracurium and laudanosine in cerebrospinal fluid and plasma during intracranial surgery. *Br J Anaesth* 1989; 63: 525–30.
12. Beemer GH, *et al.* Production of laudanosine following infusion of atracurium in man and its effects on awakening. *Br J Anaesth* 1989; 63: 76–80.
13. Yate PM, *et al.* Clinical experience and plasma laudanosine concentrations during the infusion of atracurium in the intensive therapy unit. *Br J Anaesth* 1987; 59: 211–17.
14. Boyd AR, *et al.* Comparison of the pharmacokinetics and pharmacodynamics of an infusion of cis-atracurium (51W89) or atracurium in critically ill patients undergoing mechanical ventilation in an intensive therapy unit. *Br J Anaesth* 1996; 76: 382–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Gelolagar; Nimbium; Tracrium; Tracurix; Tracuron; *Austral.*: Nimbex; Tracrium; *Austria*: Nimbex; Tracrium; *Belg.*: Nimbex; Tracrium; *Braz.*: Abbottracurium; Besitrac; Nimbium; Tracrium; Tracur; *Canad.*: Nimbex; *Chile*: Nimbex; Tracrium; *China*: Nimbex (赛机宁); Tracrium (卡肌宁); *Cz.*: Nimbex; Tracrium; *Denm.*: Nimbex; *Fin.*: Nimbex; *Fr.*: Nimbex; Tracrium; *Ger.*: Nimbex; Tracrium†; *Gr.*: Nimbex; Tracrium; *Hong Kong*: Nimbex; Tracrium; *Hung.*: Nimbex; Tracrium; *India*: Acris; Artacil; Atcurium; Atcuron; Atracade; Atrakt; Atrelax; Tracrium; *Indon.*: Farelax; Notrixum; Tracrium; Tramus; *Irl.*: Nimbex; Tracrium; *Israel*: Mycurium; Tracrium; *Ital.*: Acurmil; Nimbex; Tracrium; *Malaysia*: Atralex; Nimbex†; Tracrium; *Mex.*: Nimbex; Relatrac†; Trablok†; Tracrium; *Neth.*: Nimbex; Tracrium; *Norw.*: Nimbex; *NZ*: Tracrium; *Philipp.*: Atracor; Trac; Tracrium; *Pol.*: Abbocurium†; Nimbex; Tracrium; *Port.*: Faulcurium; Nimbex; Tracrium; *Rus.*: Nimbex (Нимбекс); Tracrium (Тракриум); *S.Afr.*: Nimbex; Tracrium; *Singapore*: Tracrium; *Spain*: Nimbex; Tracrium; *Swed.*: Nimbex†; Tracrium†; *Switz.*: Nimbex; Tracrium; *Thai.*: Atra; Nimbex; Notrixum; Tracrium; *Turk.*: Dematrac; Nimbex; Tracrium; *UK*: Nimbex; Tracrium; *Ukr.*: Intuban (Интубан); Tracrium (Тракриум); *USA*: Nimbex; Tracrium†.

Pharmacopoeial Preparations
USP 36: Atracurium Besylate Injection.

Gallamine Triethiodide *(BANM, rINN)*

Benzcurine Iodide; Galamin Trietiyodür; Galamina, trietioduro de; Galamino trietjodidas; Gallamiinitrietjodid; Gallamine Triéthiodure de; Gallamini triethiodidum; Gallamin-triethiodid; Gallamin-triethojodid; Gallamin-trietjodid; Gallamintrietjodid; Gallamone Triethiodide; Trietioduro de galamina; Галламина Триэтиодид.

2,2',2''-(Benzene-1,2,3-triyltrioxy)tris(tetraethylammonium) tri-iodide.

$C_{30}H_{69}I_3N_3O_3$=891.5

CAS — 153-76-4 (gallamine); 65-29-2 (gallamine triethiodide).
ATC — M03AC02.
ATC Vet — QM03AC02.
UNII — Q3254X40X2.

Pharmacopoeias. In *Int.* and *US.*

USP 36: (Gallamine Triethiodide). A white, hygroscopic, odourless, amorphous powder. Very soluble in water; sparingly soluble in alcohol; very slightly soluble in chloroform. pH of a 2% solution in water is between 5.3 and 7.0. Store in airtight containers. Protect from light.

Profile

Gallamine triethiodide is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p. 2030.1). It has been used to provide muscle relaxation in general anaesthesia for surgical procedures and to aid controlled ventilation. Gallamine has some vagolytic action and may produce tachycardia; blood pressure may also be raised. It has a small effect on histamine release and occasionally anaphylactoid reactions have been reported.

Gallamine triethiodide has also been given intramuscularly, with or without hyaluronidase.

Renal impairment. Significantly prolonged elimination half-life and reduced clearance have been reported[1] in patients with chronic renal failure given gallamine triethiodide in initial doses of 2 mg/kg intravenously.

1. Ramzan MI, *et al.* Gallamine disposition in surgical patients with chronic renal failure. *Br J Clin Pharmacol* 1981; 12: 141–7.

Preparations

Pharmacopoeial Preparations
BP 2014: Gallamine Injection;
USP 36: Gallamine Triethiodide Injection.

Mivacurium Chloride *(BAN, USAN, rINN)*

BW-B1090U; Cloruro de mivacurio; Mivacurii Chloridum; Mivacurio, cloruro de; Mivacurium, Chlorure de; Mivakuriumklorid; Mivakuriumkloridi; Mivakuryum Klorür; Мивакурия Хлорид.

A mixture of the stereoisomers of (*E*)-1,1',2,2',3,3',4,4'-octahydro-6,6',7,7'-tetramethoxy-2,2'-dimethyl-1,1'-bis(3,4,5-trimethoxybenzyl)-2,2'-[oct-4-enedioylbis(oxytrimethylene)]di-isoquinolinium dichloride.

$C_{58}H_{90}Cl_2N_2O_{14}$=1100.2

CAS — 106861-44-3 (mivacurium chloride, total racemate).
ATC — M03AC10.
ATC Vet — QM03AC10.
UNII — 600ZG213C3.

Incompatibility. See under Atracurium, p. 2030.1 for details regarding the incompatibility of neuromuscular blockers.

Uses and Administration

Mivacurium chloride is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p. 2030.1).

On intravenous injection muscle relaxation occurs within 1.5 to 2.5 minutes, depending on the dose with a duration of action of about 10 to 20 minutes. It is used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p. 2028.1) and to aid controlled ventilation (see Intensive Care, p. 2028.3).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. Mivacurium is given as the chloride although doses are expressed in terms of mivacurium base. The initial dose by intravenous injection in adults and children over 12 years of age is 70 to 250 micrograms/kg. Doses up to 150 micrograms/kg may be given over 5 to 15 seconds but higher doses should be given over 30 seconds. In patients with asthma or cardiovascular disease, or those who are sensitive to falls in arterial blood pressure, it should be given over 60 seconds. To give a dose of 250 micrograms/kg for tracheal intubation, an injection of 150 micrograms/kg may be followed 30 seconds later by an injection of 100 micrograms/kg. Maintenance doses of 100 micrograms/kg may be given at intervals of 15 minutes. In children aged 2 to 6 months an initial dose of 150 micrograms/kg has been given; in children aged 7 months to 12 years, an initial dose of 200 micrograms/kg has been given. A maintenance dose of 100 micrograms/kg may be given every 6 to 9 minutes for children aged 2 months to 12 years.

Mivacurium chloride may also be given by continuous intravenous infusion for maintenance of block. For adults and children aged over 12 years the initial rate is 8 to 10 micrograms/kg per minute adjusted every 3 minutes if necessary by increments of 1 microgram/kg per minute to a usual rate of 6 to 7 micrograms/kg per minute; in children aged 2 months to 12 years the usual rate is 11 to 14 micrograms/kg per minute.

Reduced doses may be required in the elderly and in patients with hepatic or renal impairment (see below).

Reviews.

1. Mirakhur RK. Newer neuromuscular blocking drugs: an overview of their clinical pharmacology and therapeutic use. *Drugs* 1992; 44: 182–99.
2. Frampton JE, McTavish D. Mivacurium: a review of its pharmacology and therapeutic potential in general anaesthesia. *Drugs* 1993; 45: 1066–89.
3. Feldman S. Mivacurium. *Br J Hosp Med* 1997; 57: 199–201.

Action. Mivacurium has a shorter duration of action than most other competitive neuromuscular blockers. Studies[1-3] suggest that it is a useful alternative to suxamethonium for the production of neuromuscular block of short duration and has the advantage that its block can be reversed with an anticholinesterase. For a discussion of the choice of anticholinesterase for reversal of neuromuscular block produced by short-acting blockers such as mivacurium, see under Neostigmine, p. 688.1. Although its onset of action may be accelerated by giving a priming dose,[4] mivacurium has a slower onset than suxamethonium and so may not be a suitable alternative[5] when rapid intubation is required. For a general review of neuromuscular blockers, see Anaesthesia, p. 2028.1.

1. Brandom BW, *et al.* Comparison of mivacurium and suxamethonium administered by bolus and infusion. *Br J Anaesth* 1989; 62: 488–93.
2. Caldwell JE, *et al.* Comparison of the neuromuscular block induced by mivacurium, suxamethonium or atracurium during nitrous oxide-fentanyl anaesthesia. *Br J Anaesth* 1989; 63: 393–9.
3. Goldberg ME, *et al.* Comparison of tracheal intubating conditions and neuromuscular blocking profiles after intubating doses of mivacurium chloride or succinylcholine in surgical outpatients. *Anesth Analg* 1989; 69: 93–9.
4. Haxby EJ, *et al.* Mivacurium priming intervals. *Br J Anaesth* 1994; 72: 485P.
5. Anonymous. Mivacurium—a new neuromuscular blocker. *Med Lett Drugs Ther* 1992; 34: 82.

Administration in children. For details of uses and dosage of mivacurium chloride in infants and children, see Uses and Administration, above.

Administration in the elderly. In a study[1] comparing the effects of mivacurium in elderly and young adults, the duration of neuromuscular effects was prolonged in elderly patients by about 30%. The mean infusion requirement in elderly patients was 3.67 micrograms/kg per minute compared with 5.5 micrograms/kg per minute in young adults.

Licensed product information states that elderly patients may require decreased infusion rates or smaller or less frequent maintenance bolus doses.

1. Maddineni VR, *et al.* Neuromuscular and haemodynamic effects of mivacurium in elderly and young adult patients. *Br J Anaesth* 1994; 73: 608–12.

Administration in hepatic or renal impairment. The pharmacokinetics of mivacurium have been studied in patients with renal[1-3] or hepatic impairment.[1,4,5] The duration of relaxation produced by mivacurium was about 1.5 times greater than normal in patients with end-stage renal disease and up to about 3 times greater than normal in patients with end-stage liver disease. Reduced plasma-cholinesterase activity in the patients with hepatic impairment may have played an important part in this effect. Although an anticholinesterase such as neostigmine hastens recovery by only a few minutes in healthy subjects, its use may be indicated in patients in whom recovery is delayed.[2]

Licensed product information recommends that in patients with end-stage renal or liver disease, the dose should be adjusted according to individual clinical response.

1. Cook DR, *et al.* Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure. *Br J Anaesth* 1992; 69: 580–5.
2. Phillips BJ, Hunter JM. Use of mivacurium chloride by constant infusion in the anephric patient. *Br J Anaesth* 1992; 68: 492–8.
3. Head-Rapson AG, *et al.* Pharmacokinetics and pharmacodynamics of the three isomers of mivacurium in health, in end-stage renal failure and in patients with impaired renal function. *Br J Anaesth* 1995; 75: 31–6.
4. Devlin JC, *et al.* Pharmacodynamics of mivacurium chloride in patients with hepatic cirrhosis. *Br J Anaesth* 1993; 71: 227–31.
5. Head-Rapson AG, *et al.* Pharmacokinetics of the three isomers of mivacurium and pharmacodynamics of the chiral mixture in hepatic cirrhosis. *Br J Anaesth* 1994; 73: 613–18.

Adverse Effects, Treatment, and Precautions

As for competitive neuromuscular blockers in general (see Atracurium, p. 2030.3). Mivacurium chloride has no significant vagal or ganglion blocking activity at recommended doses. It may induce histamine release especially when given in large doses rapidly.

Mivacurium should be used with caution, if at all, in patients with plasma cholinesterase deficiency, since its duration of action will be prolonged in such patients.

Burns. In common with other competitive muscle relaxants patients with burns may develop resistance to mivacurium and require increased doses (see under Atracurium, p. 2031.1). However, as these patients may also have reduced plasma cholinesterase activity dosage requirements could also be reduced. Licensed product information recommends that such patients should be given a test dose of 15 to 20 micrograms/kg with subsequent dosage adjustments being guided by monitoring of the block.

Neuromuscular disorders. Neuromuscular blockade was successfully achieved with mivacurium in an obese elderly patient with myasthenia gravis requiring surgery.[1] Only about half the usual dose was required and even then recovery was delayed. See Atracurium, p. 2031.2 for a dis-

cussion of the use of competitive neuromuscular blockers in patients with neuromuscular disorders.

1. Seigne RD, Scott RPF. Mivacurium chloride and myasthenia gravis. *Br J Anaesth* 1994; 72: 468–9.

Plasma cholinesterase deficiency. There have been reports of prolonged neuromuscular block produced by mivacurium in patients with plasma cholinesterase deficiency.[1-4] Time to full recovery varied; one patient required up to 8 hours.

1. Goudsouzian NG, *et al.* Prolonged neuromuscular block from mivacurium in two patients with cholinesterase deficiency. *Anesth Analg* 1993; 77: 183–5.
2. Sockalingam L, Green DW. Mivacurium-induced prolonged neuromuscular block. *Br J Anaesth* 1995; 74: 234–6.
3. Fox MR, Hunt PCW. Prolonged neuromuscular block associated with mivacurium. *Br J Anaesth* 1995; 74: 237–8.
4. Zimmer S. Mivacurium and prolonged neuromuscular block. *Br J Anaesth* 1995; 75: 823.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mivacurium 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)

Tourniquets. Mivacurium might be unsuitable for neuromuscular blockade of a limb which has been isolated with a tourniquet in order to provide a bloodless field for surgery.[1] It is largely inactivated by the enzymatic action of plasma cholinesterase and would therefore continue to degrade locally leading to a loss of blockade in the limb, which could not be corrected by further doses unless the tourniquet was deflated. However, as for other competitive neuromuscular blockers, the use of mivacurium to supplement regional anaesthesia has produced prolonged muscle weakness well beyond cuff deflation.[2] This suggests that mivacurium is not broken down in the ischaemic limb and that recovery is not dependent on plasma concentrations of mivacurium.

See also Local Anaesthetics, under Interactions of Atracurium, p. 2033.1, for a report of symptoms suggestive of local anaesthetic toxicity when prilocaine and mivacurium were used together.

1. Shannon PF. Neuromuscular block and tourniquets. *Br J Anaesth* 1994; 73: 726.
2. Torrance JM, *et al.* Low-dose mivacurium supplementation of prilocaine i.v. regional anaesthesia. *Br J Anaesth* 1997; 78: 222–3.

Interactions

For interactions associated with competitive neuromuscular blockers, see Atracurium, p. 2031.3.

Metoclopramide. Metoclopramide, an inhibitor of plasma cholinesterase, was found to significantly prolong the duration of action of mivacurium in patients undergoing surgery, although in this study only marginal inhibition of plasma cholinesterase by metoclopramide occurred.[1]

1. Skinner HJ, *et al.* Influence of metoclopramide on plasma cholinesterase and duration of action of mivacurium. *Br J Anaesth* 1999; 82: 542–5.

Pharmacokinetics

Mivacurium is a mixture of 3 stereoisomers, 2 of which (*cis-trans* and *trans-trans*) are considered to account for most of the neuromuscular blocking effect. All 3 isomers are inactivated by plasma cholinesterase. Renal and hepatic mechanisms are involved in their elimination with excretion in urine and bile.

Reviews.

1. Atherton DPL, Hunter JM. Clinical pharmacokinetics of the newer neuromuscular blocking drugs. *Clin Pharmacokinet* 1999; 36: 169–89.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Mivacron; *Austral.*: Mivacron; *Austria*: Mivacron; *Belg.*: Mivacron; *Chile*: Mivacron; *China*: Mivacron (美维松); *Cz.*: Mivacron; *Denm.*: Mivacron; *Fin.*: Mivacron; *Fr.*: Mivacron; *Ger.*: Mivacron; *Gr.*: Mivacron; *Hong Kong*: Mivacron; *Hung.*: Mivacron; *Irl.*: Mivacron; *Ital.*: Mivacron; *Malaysia*: Mivacron; *Neth.*: Mivacron; *Norw.*: Mivacron; *NZ*: Mivacron; *Pol.*: Mivacron; *Port.*: Mivacron; *Rus.*: Mivacron (Мивакрон); *S.Afr.*: Mivacron; *Singapore*: Mivacron; *Spain*: Mivacron†; *Swed.*: Mivacron; *Switz.*: Mivacron; *Turk.*: Mivacron; *UK*: Mivacron.

Pancuronium Bromide *(BAN, USAN, rINN)*

Bromuro de pancuronio; NA-97; Org-NA-97; Pancuronii Bromidum; Pancurônio, bromuro de; Pancurónium, Bromure de; Pancuroniumbromid; Pankuronio bromidas; Pankuroniowy bromek; Pankuronium-bromid; Pankuroniumbromid; Pankuroniumbromidi; Pankuronyum Bromür; Панкурония Бромид.

1,1′-(3α,17β-Diacetoxy-5α-androstan-2β,16β-ylene)bis(1-methylpiperidinium) dibromide.

$C_{35}H_{60}Br_2N_2O_4$=732.7

CAS — 15500-66-0.

ATC — M03AC01.

ATC Vet — QM03AC01.

UNII — U9LY9Y75XZ.

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

Ph. Eur. 8: (Pancuronium Bromide). White, yellowish-white, or slightly pink, hygroscopic crystalline powder. Very soluble to freely soluble in water; freely soluble in alcohol; very soluble in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Pancuronium Bromide). A white, yellowish-white, or slightly pink, crystalline hygroscopic powder. Freely soluble in water, in alcohol, and in dichloromethane. Store in airtight containers. Protect from light and moisture.

Uses and Administration

Pancuronium bromide is an aminosteroidal competitive neuromuscular blocker (see Atracurium, p. 2030.1). Muscle relaxation occurs within about 1.5 to 2 minutes of intravenous injection and lasts for about 45 to 60 minutes.

Pancuronium bromide is used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p. 2028.1) and to aid controlled ventilation (see Intensive Care, p. 2028.3).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. The initial dose for intubation is usually 50 to 100 micrograms/kg by intravenous injection, with maintenance doses of 10 to 20 micrograms/kg. Children may be given similar doses. Some manufacturers recommend a reduction in the initial dose to 20 to 60 micrograms/kg when pancuronium is given following suxamethonium. Doses of 30 to 40 micrograms/kg initially have been recommended in neonates, with maintenance doses of 10 to 20 micrograms/kg as necessary. In the UK, the *BNFC* suggests that higher doses may be used in neonates for muscle relaxation in prolonged surgical procedures; an initial dose of 100 micrograms/kg, with maintenance doses of 50 micrograms/kg as necessary, has been suggested. In the USA, dosage based on an initial test dose of 20 micrograms/kg has been advocated for the neonate.

Adult patients under intensive care who require assisted ventilation for conditions such as intractable status asthmaticus or tetanus may be given 60 micrograms/kg intravenously every 1 to 1½ hours or less frequently.

Care should be taken when giving pancuronium to patients with hepatic or renal impairment, see below.

Administration in children. For details of uses and dosage of pancuronium bromide in infants and children, see Uses and Administration, above.

Administration in hepatic impairment. Prolonged neuromuscular blockade may occur in patients with liver disease given pancuronium bromide since increased elimination half-life with increased volume of distribution and reduced clearance has been reported.[1] However, the expanded distribution volume may necessitate an increase in the dose of pancuronium in these patients[1,2] and may be interpreted as resistance to the neuromuscular blocking effects of pancuronium.

1. Duvaldestin P, *et al.* Pancuronium pharmacokinetics in patients with liver cirrhosis. *Br J Anaesth* 1978; 50: 1131–6.
2. Ward ME, *et al.* Alfhesin and pancuronium in chronic liver disease. *Br J Anaesth* 1975; 47: 1199–1204.

Administration in renal impairment. Prolonged neuromuscular blockade may occur when pancuronium is given to patients with severe renal impairment. Pancuronium distributes rapidly into extracellular fluid after intravenous injection and the initial neuromuscular blockade produced will depend upon the peak drug concentration in this fluid. Since extracellular fluid volume is increased in chronic renal failure such patients may require a larger initial dose of pancuronium and a 45% increase in dose requirement has been reported[1] in patients with end-stage renal failure. Renal excretion is the main route of elimination and prolonged elimination half-life with reduced clearance may be expected in renal failure; total dose requirements may be reduced. The main infusion rate of pancuronium to maintain 90% blockade in patients with end-stage renal failure was reported to be 61.5% less than for patients with normal renal function.

1. Gramstad L. Atracurium, vecuronium and pancuronium in end-stage renal failure. *Br J Anaesth* 1987; 59: 995–1003.

Fetal paralysis. Pancuronium bromide 100 micrograms/kg of the estimated fetal-weight, given into the umbilical vein, produced fetal paralysis for about 40 minutes during intravascular exchange transfusion.[1] A dose of 200 to 300 micrograms/kg produced fetal paralysis for about 1 to 8 hours for more complicated transfusion procedures.[2] No adverse effects were reported.

1. Copel JA, *et al.* The use of intravenous pancuronium bromide to produce fetal paralysis during intravascular transfusion. *Am J Obstet Gynecol* 1988; 158: 170–1.
2. Moise KJ, *et al.* Intravenous pancuronium bromide for fetal neuromuscular blockade during intrauterine transfusion for red-cell alloimmunization. *Obstet Gynecol* 1989; 74: 905–8.

Neuroleptic malignant syndrome. Pancuronium is one of several drugs for which there have been isolated reports[1] of success in the management of neuroleptic malignant syndrome (p. 1050.2).

1. Sangal R, Dimitrijevic R. Neuroleptic malignant syndrome: successful treatment with pancuronium. *JAMA* 1985; 254: 2795–6.

Adverse Effects, Treatment, and Precautions

As for competitive neuromuscular blockers in general (see Atracurium, p. 2030.3).

Pancuronium has vagolytic and sympathomimetic action, which may cause tachycardia and hypertension, but does not produce ganglionic blockade. It has little histamine-releasing effect. Hypersensitivity reactions are relatively rare but bradycardia, bronchospasm, hypotension, and cardiovascular collapse have been reported. Pancuronium has been associated with excessive salivation in some patients.

Pancuronium should be used with caution in patients with raised catecholamine concentrations, or in those who are receiving drugs with sympathomimetic effects, as cardiovascular adverse effects are more likely in these patients.

Effects on the ears. A study[1] found that neonates who survived congenital diaphragmatic hernia were more likely to suffer from sensorineural hearing loss after prolonged use of pancuronium bromide during the neonatal period. However, the authors commented that the association is not necessarily causal and that further investigation is required.

1. Cheung P-Y, *et al.* Prolonged use of pancuronium bromide and sensorineural hearing loss in childhood survivors of congenital diaphragmatic hernia. *J Pediatr* 1999; 135: 233–9.

Hypersensitivity. Reports[1-4] of anaphylactoid or anaphylactic reactions associated with pancuronium bromide.

See also under Suxamethonium Chloride, p. 2038.2.

1. Brauer PS, Ananthanarayan CR. Histamine release by pancuronium. *Anesthesiology* 1978; 49: 434–5.
2. Patriarca G, *et al.* Pancuronium allergy: a case report. *Br J Anaesth* 1989; 62: 210–12.
3. Moneret-Vautrin DA, *et al.* Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases. *Br J Anaesth* 1990; 64: 743–5.
4. Sanchez-Guerrero IM, *et al.* Anaphylactoid reaction induced by pancuronium during general anaesthesia. *Eur J Anaesthesiol* 1998; 15: 613–14.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pancuronium 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)

Postoperative complications. Because of its prolonged duration of action, pancuronium may be more likely than other neuromuscular blockers to produce residual neuromuscular block; such residual block is associated with an increased incidence of postoperative respiratory complications.[1,2]

1. Berg H, *et al.* Residual neuromuscular block is a risk factor for postoperative pulmonary complications: a prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. *Acta Anaesthesiol Scand* 1997; 41: 1095–1103.
2. Bissinger U, *et al.* Postoperative residual paralysis and respiratory status: a comparative study of pancuronium and vecuronium. *Physiol Res* 2000; 49: 455–62.

Interactions

For interactions associated with competitive neuromuscular blockers, see Atracurium, p. 2031.3.

Pharmacokinetics

On intravenous injection pancuronium bromide is rapidly distributed into body tissues; about 80% may be bound to plasma proteins. A small proportion is metabolised in the liver to metabolites with weak neuromuscular blocking activity. It is largely excreted in urine as unchanged drug and metabolites; a small amount is excreted in bile. The

plasma elimination half-life is about 2 hours. It crosses the placenta in small amounts.

Pregnancy. In 15 patients undergoing caesarean section[1] given pancuronium bromide 100 micrograms/kg intravenously with other agents, mean maternal arterial and umbilical venous serum concentrations of pancuronium bromide and metabolites were 520 and 120 nanograms/mL, respectively at delivery (mean of 13 minutes after injection), giving a fetal to maternal ratio of 0.23.

1. Wingard LB, *et al.* Modified fluorometric quantitation of pancuronium bromide and metabolites in human maternal and umbilical serums. *J Pharm Sci* 1979; **68**: 914–15.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bemicin; Pancuron; Pavulon; Plumger; *Austral.*: Pavulon†; *Braz.*: Pancuron; Pavulon†; *Chile*: Pavulon; *China*: Pavulon (潘龙); *Cz.*: Pavulon; *Fin.*: Pavulon†; *Fr.*: Pavulon†; *Gr.*: Pavulon; *Hong Kong*: Pavulon; *India*: Neocuron; Panconium; Panuron; *Indon.*: Pavulon; *Israel*: Pavulon; *Ital.*: Pavulon; *Jpn*: Mioblock†; *Malaysia*: Pavulon; *Mex.*: Bromurex†; Panlem†; *Neth.*: Pavulon†; *Philipp.*: Pavulon†; *Port.*: Pancurox; *Rus.*: Pavulon (Павулон); *S.Afr.*: Curon-B†; Pavulon†; *Singapore*: Pavulon†; *Swed.*: Pavulon†; *Switz.*: Pavulon†; *Thai.*: Pavulon†; *Turk.*: Pavulon; *Venez.*: Panuron; Pavulon; Pesium.

Pharmacopoeial Preparations
BP 2014: Pancuronium Injection;
USP 36: Pancuronium Bromide Injection.

Pipecuronium Bromide *(BAN, USAN, rINN)*

Bromuro de pipecurio; Bromuro de pipecuronio; Pipecurium Bromide; Pipecuronii Bromidum; Pipecuronio, bromuro de; Pipécuronium, Bromure de; Pipekuroniumbromid; Pipekuroniumbromidi; RGH-1106; Пипекурония Бромид.

1,1,1′,1′-Tetramethyl-4,4′-(3α,17β-diacetoxy-5α-androstan-2β,16β-diyl)dipiperazinium dibromide.

$C_{35}H_{62}Br_2N_4O_4$=762.7

CAS — 52212-02-9 (anhydrous pipecuronium bromide); 68399-57-5 (pipecuronium bromide dihydrate).

ATC — M03AC06.

ATC Vet — QM03AC06.

UNII — R6ZTY81RE1.

Profile

Pipecuronium bromide is an aminosteroidal competitive neuromuscular blocker (see Atracurium, p. 2030.1). It has been used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures and to aid mechanical ventilation. Pipecuronium is reported to have no significant cardiovascular adverse effects or histamine-related effects.

Reviews and studies.

1. Mirakhur RK. Newer neuromuscular blocking drugs: an overview of their clinical pharmacology and therapeutic use. *Drugs* 1992; **44**: 182–99.
2. Tassonyi E, *et al.* Pharmacokinetics of pipecuronium in infants, children and adults. *Eur J Drug Metab Pharmacokinet* 1995; **20**: 203–8.
3. Melloni C. Farmacologia clinica del pipecuronium: studio comparativo della sua durata clinica in anestesia bilanciata (propofol/fentanyl) vs isoflurano. *Minerva Anestesiol* 1995; **61**: 491–500.
4. Meretoja OA, Brkola O. Pipecuronium revisited: dose-response and maintenance requirement in infants, children, and adults. *J Clin Anesth* 1997; **9**: 125–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Arduan (阿端); *Cz.*: Arduan; *Gr.*: Arduan; *Hung.*: Arduan; *India*: Arduan; *Pol.*: Arduan; *Rus.*: Aperomid (Аперомид); Arduan (Ардуан); *Ukr.*: Arduan (Ардуан).

Rocuronium Bromide *(BAN, USAN, rINN)*

Bromuro de rocuronio; Org-9426; Rocuronii Bromidum; Rocuronio, bromuro de; Rocuronium, Bromure de; Rocuroniumbromid; Rokuroniowy bromek; Rokuroniumbromid; Rokuronium-Bromid; Rokuroniumbromidi; Rokuroniyum Bromür; Рокурония Бромид.

1-Allyl-1-(3α,17β-dihydroxy-2β-morpholino-5α-androstan-16β-yl)pyrrolidinium bromide 17-acetate; 1-(17β-Acetoxy-3α-hydroxy-2β-morpholino-5α-androstan-16β-yl)-1-allylpyrrolidinium bromide.

$C_{34}H_{59}BrN_2O_5$=655.7

CAS — 119302-91-9.

ATC — M03AC09.

ATC Vet — QM03AC09.

UNII — I65MW4OFHZ.

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

Ph. Eur. 8: (Rocuronium Bromide). An almost white or pale yellow, slightly hygroscopic, powder. Freely soluble in water and in dehydrated alcohol; very soluble in dichloromethane. A 1.0% solution in water has a pH of 8.9 to 9.5. Store in airtight containers at a temperature below -15 degrees. Protect from light.

USP 36: (Rocuronium Bromide). An almost white or pale yellow, slightly hygroscopic powder. Freely soluble in water and in dehydrated alcohol. pH of a 1% solution in water is 8.9 to 9.5. Store in airtight containers at a temperature of -25 degrees to -10 degrees. Protect from light and moisture.

Uses and Administration

Rocuronium bromide is an aminosteroidal competitive neuromuscular blocker (see Atracurium, p. 2030.1). After intravenous injection it produces muscle relaxation within 1 to 2 minutes with a duration of about 30 to 50 minutes. Rocuronium bromide is used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p. 2028.1) and to aid controlled ventilation (see Intensive Care, p. 2028.3).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. A usual initial dose in adults is 600 micrograms/kg by intravenous injection; however, higher doses of 1 mg/kg are recommended for intubation during rapid sequence induction of anaesthesia. Usual maintenance doses are 150 micrograms/kg by injection, although these should be reduced to 75 to 100 micrograms/kg if prolonged inhalational anaesthesia is planned. Maintenance may also be by infusion at a rate of 300 to 600 micrograms/kg per hour although higher rates have been suggested in US licensed product information. Similar doses to those used in adults have been used in the UK in children older than one month but maintenance doses may be required more frequently. In the USA, rocuronium is licensed for use in children from birth onwards; again doses are similar to those used in adults.

For obese patients weighing more than 30% over their ideal body-weight UK licensed product information recommends that doses should be calculated according to lean body-mass; in the USA it is recommended that dosage should be based on actual body-weight. UK product information also recommends reduced maintenance doses of 75 to 100 micrograms/kg by injection in the elderly. For doses in hepatic or renal impairment, see below.

Reviews and discussions.

1. Mirakhur RK. Newer neuromuscular blocking drugs: an overview of their clinical pharmacology and therapeutic use. *Drugs* 1992; **44**: 182–9.
2. Hunter JM. Rocuronium: the newest aminosteroid neuromuscular blocking drug. *Br J Anaesth* 1996; **76**: 481–3.

Administration in children. In a study involving 70 children, conditions for intubation were judged to be good to excellent within one minute of intravenous doses of rocuronium 600 or 900 micrograms/kg, with a trend to better conditions with the higher dose[1] (see also Uses and Administration, above for recommended doses).

1. Fuchs-Buder T, Tassonyi E. Intubating conditions and time course of rocuronium-induced neuromuscular block in children. *Br J Anaesth* 1996; **77**: 335–8.

INTRAMUSCULAR ROUTE. Intramuscular injection of rocuronium 1 mg/kg into the deltoid muscle permitted tracheal intubation to be carried out in lightly anaesthetised infants after 2.5 minutes.[1] In children a dose of 1.8 mg/kg enabled tracheal intubation after 3 minutes. However, the mean time to initial recovery after these large doses was 57 minutes in infants and 70 minutes in children. This prolonged duration of action may limit intramuscular use for brief procedures, particularly in children.

1. Reynolds LM, *et al.* Intramuscular rocuronium in infants and children: dose-ranging and tracheal intubating conditions. *Anesthesiology* 1996; **85**: 231–9.

Administration in hepatic or renal impairment. Regardless of the anaesthetic technique used, UK licensed product information recommends an initial dose of rocuronium bromide 600 micrograms/kg by intravenous injection and a reduced maintenance dose of 75 to 100 micrograms/kg by intravenous injection, or 300 to 400 micrograms/kg per hour by continuous infusion, in patients with hepatic or biliary-tract disease, or renal failure.

Adverse Effects, Treatment, and Precautions

As for competitive neuromuscular blockers in general (see Atracurium, p. 2030.3). Rocuronium is reported to have minimal cardiovascular and histamine-releasing effects. High doses (greater than 900 micrograms/kg of rocuronium bromide) have mild vagolytic activity. It should be used with caution in patients with biliary disease or hepatic or renal impairment.

Hepatic impairment. There have been conflicting reports of the pharmacokinetics and pharmacodynamics of rocuronium in patients with hepatic impairment. In contrast to earlier studies[1,2] one group of workers[3] found a significant reduction in the plasma clearance of rocuronium in patients with cirrhosis. The elimination half-life has been variously reported to be unchanged[1] or prolonged[2,3] with delayed recovery.[3] Some studies[2,3] found that the onset of action was not affected while one group of workers reported a delay.

Licensed product information recommends that care should be taken when giving rocuronium to patients with clinically significant hepatic impairment (see also under Uses and Administration, above).

1. Khalil M, *et al.* Pharmacokinetics and pharmacodynamics of rocuronium in patients with cirrhosis. *Anesthesiology* 1994; **80**: 1241–7.
2. Magorian T, *et al.* The pharmacokinetics and neuromuscular effects of rocuronium bromide in patients with liver disease. *Anesth Analg* 1995; **80**: 754–9.
3. van Miert MM, *et al.* The pharmacokinetics and pharmacodynamics of rocuronium in patients with hepatic cirrhosis. *Br J Clin Pharmacol* 1997; **44**: 139–44.

Hypersensitivity. Although rocuronium is considered to have minimal histamine-releasing effects, histaminoid reactions have been reported[1] on induction of anaesthesia in 3 patients who had been given rocuronium. An increased incidence of severe hypersensitivity reactions (particularly anaphylactic shock) has been reported with rocuronium compared with other neuromuscular blockers available in France.[2] Fatalities have occurred.[3]

See also the discussion of the relative risks of hypersensitivity associated with neuromuscular blockers, under Suxamethonium Chloride, p. 2038.2.

1. Neal SM, *et al.* Histaminoid reactions associated with rocuronium. *Br J Anaesth* 2000; **84**: 108–11.
2. Mayer M. Information importante de pharmacovigilance: Esméron et manifestations allergiques. Available at: http://www.afssaps.fr/content/download/12056/143941/version/1/file/letesmer.pdf (accessed 12/02/10)
3. Baillard C, *et al.* Anaphylaxis to rocuronium. *Br J Anaesth* 2002; **88**: 600–602.

Pain on administration. Severe transient burning pain associated with injection of rocuronium was considered[1] to be responsible for the spontaneous movement sometimes seen in the arm or wrist into which rocuronium is given. It is recommended that rocuronium should be given only when a deep stage of unconsciousness has been achieved.

1. Borgeat A, Kwiatkowski D. Spontaneous movements associated with rocuronium: is pain on injection the cause? *Br J Anaesth* 1997; **79**: 382–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rocuronium 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)

Renal impairment. In a study[1] of the pharmacokinetics and neuromuscular effects of rocuronium, the clearance of rocuronium was reduced in patients with renal failure when compared with healthy subjects, but the accompanying increase in duration of clinical relaxation did not reach statistical significance. However, it was recommended that rocuronium should be used with caution in the presence of renal failure as there were large interpatient variations in both clinical response and pharmacokinetic parameters. It has been suggested[2] that chronic renal failure may have played a role in the prolongation of neuromuscular blockade in a 47-year-old woman given rocuronium 1 mg/kg. Although this dose is within the recommended adult dose range, it was criticised[3] as being excessive for a patient with renal impairment.

For recommendation that care should be taken when giving rocuronium to patients with renal failure, see under Uses and Administration, above.

1. Cooper RA, *et al.* Time course of neuromuscular effects and pharmacokinetics of rocuronium bromide (ORG 9426) during isoflurane anaesthesia in patients with and without renal failure. *Br J Anaesth* 1993; **71**: 222–6.
2. Lewis KS, *et al.* Prolonged neuromuscular blockade associated with rocuronium. *Am J Health-Syst Pharm* 1999; **56**: 1114–18.
3. Cozanitis DA, Boolj HD. Muscle relaxants and renal failure. *Am J Health-Syst Pharm* 2000; **57**: 1713–14.

Interactions

For interactions associated with competitive neuromuscular blockers, see Atracurium, p. 2031.3.

Pharmacokinetics

On intravenous use plasma concentrations of rocuronium follow a three-compartment open model. There is an initial

distribution phase with a half-life of 1 to 2 minutes followed by a slower distribution phase with a half-life of 14 to 18 minutes. It is reported to be about 30% bound to plasma proteins. The elimination half-life is about 1.2 to 1.4 hours. Up to 40% of a dose may be excreted in the urine within 24 hours; rocuronium is also excreted in the bile. The main metabolite of rocuronium, 17-desacetylrocuronium, is reported to have a weak neuromuscular blocking effect.

References.
1. Khuenl-Brady KS, Sparr H. Clinical pharmacokinetics of rocuronium bromide. *Clin Pharmacokinet* 1996; 31: 174–83.
2. McCoy EP, *et al.* Pharmacokinetics of rocuronium after bolus and continuous infusion during halothane anaesthesia. *Br J Anaesth* 1996; 76: 29–33.
3. Wierda JMKH, *et al.* Pharmacokinetics and pharmacokinetic-dynamic modelling of rocuronium in infants and children. *Br J Anaesth* 1997; 78: 690–5.
4. Atherton DPL, Hunter JM. Clinical pharmacokinetics of the newer neuromuscular blocking drugs. *Clin Pharmacokinet* 1999; 36: 169–89.
5. Proost JH, *et al.* Urinary, biliary and faecal excretion of rocuronium in humans. *Br J Anaesth* 2000; 85: 717–23.

Intensive care. The pharmacokinetics of rocuronium appear to differ between intensive care patients given prolonged dosage and surgical patients.[1] The volume of distribution at steady state may be increased, the plasma clearance decreased, and the terminal half-life prolonged. Recovery time on stopping may also be longer.

1. Sparr HJ, *et al.* Pharmacodynamics and pharmacokinetics of rocuronium in intensive care patients. *Br J Anaesth* 1997; 78: 267–73.

Pregnancy. The mean concentration of rocuronium in venous plasma of 32 patients given a dose of 600 micrograms/kg before undergoing caesarean section was 2412 nanograms/mL at delivery;[1] the ratio of mean concentrations of rocuronium in umbilical venous plasma to maternal venous plasma at this time was 0.16. In 12 of these patients the mean concentration of rocuronium in umbilical arterial plasma was 271 nanograms/mL giving a ratio of 0.62 for the mean concentration of rocuronium in arterial to venous umbilical plasma. The concentration of 17-desacetylrocuronium in maternal venous plasma was 178 nanograms/mL and was less than 25 nanograms/mL in umbilical plasma.

1. Abouleith R, *et al.* Rocuronium (Org 9426) for Caesarean section. *Br J Anaesth* 1994; 73: 336–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Esmeron; *Austria*: Esmeron; *Belg.*: Esmeron; *Braz.*: Esmeron; Rocuron; Romeran; *Canad.*: Zemuron; *Chile*: Esmeron; *China*: Esmeron (爱可松); *Cz.*: Esmeron; *Denm.*: Esmeron; *Fin.*: Esmeron; *Fr.*: Esmeron; *Ger.*: Esmeron; *Gr.*: Esmeron; *Hong Kong*: Esmeron; *Hung.*: Esmeron; *India*: Esmeron; *Indon.*: Esmeron; Roculax; *Irl.*: Esmeron; *Israel*: Esmeron; *Ital.*: Esmeron; *Jpn*: Eslax; *Malaysia*: Esmeron; *Mex.*: Esmeron; *Neth.*: Esmeron; *Norw.*: Esmeron; *NZ*: Esmeron; *Philipp.*: Esmeron; Rocuron; *Pol.*: Esmeron; Roqurum; *Port.*: Esmeron; *Rus.*: Esmeron (Эсмерон); *S.Afr.*: Esmeron; *Singapore*: Esmeron; *Spain*: Esmeron; *Swed.*: Esmeron; *Switz.*: Esmeron; *Thai.*: Esmeron; *Turk.*: Esmeron; *UK*: Esmeron; *Ukr.*: Esmeron (Эсмерон); *USA*: Zemuron; *Venez.*: Esmeron.

Suxamethonium Chloride *(BAN, pINN)*

Choline Chloride Succinate; Cloruro de succinilcolina; Cloruro de suxametonio; Succicurarium Chloride; Succinylcholine Chloride; Suksametonio chloridas; Suksametoniowy chlorek; Suksametoniumkloridi; Süksinilkolin Klorür; Suxamethonii Chloridum; Suxamethonii Chloridum Dihydricum; Suxamethonium chlorid dihydrát; Suxaméthonium, chlorure de; Suxamethoniumchlorid; Suxametonio, cloruro de; Suxametoniumklorid; Suxametonklorid; Szuxametóniumklorid; Сукцаметония Хлорид.

2,2'-Succinyldioxybis(ethyltrimethylammonium) dichloride dihydrate.

$C_{14}H_{30}Cl_2N_2O_4,2H_2O=397.3$.

CAS — 306-40-1 (suxamethonium); 55-94-7 (suxamethonium bromide); 71-27-2 (anhydrous suxamethonium chloride); 6101-15-1 (suxamethonium chloride dihydrate); 541-19-5 (suxamethonium iodide).

ATC — M03AB01.

ATC Vet — QM03AB01.

UNII — I9L0DDD30I.

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

Ph. Eur. 8: (Suxamethonium Chloride). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; slightly soluble in alcohol. A 0.5% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 36: (Succinylcholine Chloride). A white, odourless, crystalline powder. The anhydrous form is hygroscopic. Soluble 1 in 1 of water and 1 in 350 of alcohol; slightly soluble in chloroform; practically insoluble in ether. Its solutions in water have a pH of about 4. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Incompatibility. Incompatibilities of neuromuscular blockers are discussed under Atracurium, p. 2030.1.

Stability. A study of the loss of potency of suxamethonium chloride 20 mg/mL in water indicated that decomposition occurred at a considerably higher rate at 40 degrees than at 25 degrees and that the pH range of maximum stability was 3.75 to 4.50 for unbuffered solutions.[1] Assuming the usual conditions of manufacturing, transit, and storage the total loss of potency was estimated to be 7% and 9% respectively for injections kept at room temperature for 4 and 6 weeks. If unbuffered, suxamethonium chloride injection complying with USP 36 pH limits (3.0 to 4.5) must be stored at room temperature; it should not be kept for longer than 4 weeks.

1. Boehm JJ, *et al.* Shelf life of unrefrigerated succinylcholine chloride injection. *Am J Hosp Pharm* 1984; 41: 300–2.

Uses and Administration

Suxamethonium is a depolarising neuromuscular blocker used to produce muscle relaxation. It combines with cholinergic receptors of the motor end-plate to produce depolarisation but is resistant to breakdown by acetylcholinesterase. This prevents repolarisation and subsequent depolarisation, and a flaccid muscle paralysis occurs. This initial depolarisation block is commonly known as a **phase I block**. The muscles that produce fine rapid movements such as those of the face are the first to be affected followed by those of the limbs, abdomen, and chest; the diaphragm is affected last. Recovery occurs in reverse order. When excessive amounts of suxamethonium accumulate at the neuromuscular junction, for example after high or prolonged dosage, the nature of the block may change to one with characteristics similar to competitive block. This is commonly termed **phase II block** or **dual block** and may be associated with prolonged neuromuscular blockade and apnoea.

After intravenous injection suxamethonium chloride acts in about 30 to 60 seconds and has a duration of action of about 2 to 6 minutes. After intramuscular injection it acts in 2 to 3 minutes and has a duration of action of about 10 to 30 minutes.

Suxamethonium is used in surgical and other procedures in which a rapid onset and brief duration of muscle relaxation is needed (see Anaesthesia, p. 2028.1), including intubation, endoscopies, and ECT. It is used as suxamethonium chloride, and is normally given by intravenous injection. The content of preparations of suxamethonium chloride may be described in terms of either the dihydrate or the anhydrous form, depending on the country of origin, and this should be borne in mind when evaluating the literature although the differences are small (anhydrous suxamethonium chloride 1 mg is equivalent to about 1.1 mg of the dihydrate).

Suxamethonium should be given after induction of general anaesthesia because paralysis is usually preceded by painful muscle fasciculations. A competitive neuromuscular blocker may sometimes be given before suxamethonium to try to reduce some of the adverse effects on the muscles (see Effects on the Muscles, p. 2038.1). Premedication with an antimuscarinic may be of value in reducing bradycardia and excessive salivation. Assisted ventilation is necessary.

An initial test dose of 100 micrograms/kg, or 5 to 10 mg, of suxamethonium chloride may be given intravenously if increased sensitivity is suspected. Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. The response to suxamethonium varies considerably and the usual single dose of suxamethonium chloride for an adult is 0.3 to 1.1 mg/kg by intravenous injection. Supplementary doses of 50 to 100% of the initial dose may be given at 5 to 10 minute intervals if required but the total dose given by repeated intravenous injection or continuous infusion (see below) should not exceed 500 mg/hour. Infants and children are more resistant to suxamethonium than adults. A recommended intravenous dose for infants under 1 year of age is 2 mg/kg; a dose of 1 mg/kg is recommended for children 1 to 12 years old.

When a suitable vein is inaccessible suxamethonium chloride has been given by intramuscular injection in a dose of 3 to 4 mg/kg to a maximum total dose of 150 mg. The intramuscular dose for children aged under 1 year is up to 5 mg/kg and for older children is up to 4 mg/kg to a maximum total dose of 150 mg.

For prolonged procedures in adults sustained relaxation may be obtained by continuous intravenous infusion of a 0.1 to 0.2% solution. A rate of 2.5 to 4 mg/minute is usually adequate but may be adjusted as necessary. The total dose given by repeated intravenous injection (see above) or continuous infusion should not exceed 500 mg/hour.

Suxamethonium bromide and suxamethonium iodide have also been used.

Administration in children. For details of uses and dosage of suxamethonium chloride in infants and children, see Uses and Administration, above.

ECT. Suxamethonium chloride is used to decrease the muscular contractions associated with electrically induced convulsions. It temporarily paralyses muscles during ECT, preventing violent muscle contractions that can potentially result in broken bones and fractures.

Suxamethonium chloride remains the most commonly used neuromuscular blocker in ECT. However, patients with a history of malignant hyperthermia, neuroleptic malignant syndrome, catatonic schizophrenia, and organophosphate poisoning are more susceptible to adverse effects.[1] Mivacurium has been used, with satisfactory results, in at-risk-patients, although histamine release and hypotension may be a problem. Other competitive neuromuscular blockers tried include atracurium and vecuronium.

1. Ding Z, White PF. Anesthesia for electroconvulsive therapy. *Anesth Analg* 2002; 94: 1351–64.

Adverse Effects

The neuromuscular blocking action of suxamethonium chloride is terminated by the enzyme plasma cholinesterase and prolonged apnoea may occur in patients with an atypical enzyme or with low enzyme activity. Apnoea may also occur following development of phase II block (see Uses and Administration, above) after high or repeated doses of suxamethonium chloride, although tachyphylaxis may also occur with repeated doses.

Transient fasciculations occur during the onset of depolarising block. Rhabdomyolysis, myoglobinaemia, and myoglobinuria have been reported and may be associated with muscle damage after fasciculations. Postoperative muscle pain occurs in some patients but is not directly related to the degree of fasciculation. A transient rise in intra-gastric pressure may occur secondary to fasciculation of abdominal muscles. A transient increase in intra-ocular pressure often occurs. Depolarisation of skeletal muscle produces an immediate increase in plasma-potassium concentration and this can have serious consequences in some patients (see p. 2038.2).

Stimulation of the vagus nerve and parasympathetic ganglia by suxamethonium chloride may be followed by bradycardia, other arrhythmias, and hypotension, and may be exacerbated by the raised plasma-potassium concentration; cardiac arrest has been reported. Tachycardia and an increase in blood pressure due to stimulation of sympathetic ganglia have also been reported.

Suxamethonium chloride may cause an increase in salivary, bronchial, and gastric secretion and other muscarinic effects. Salivary gland enlargement has occurred.

Direct release of histamine from mast cells occurs but this is not the main mechanism of hypersensitivity reactions (see Hypersensitivity, p. 2038.2). Flushing, rashes, bronchospasm, and shock have been reported.

Other reported effects include prolonged respiratory depression and apnoea.

Suxamethonium chloride is implicated in the development of malignant hyperthermia (p. 2024.1) in those patients with a genetic predisposition to the syndrome.

Reviews.
1. Book WJ, *et al.* Adverse effects of depolarising neuromuscular blocking agents: incidence, prevention and management. *Drug Safety* 1994; 10: 331–49.
2. Orebaugh SL. Succinylcholine: adverse effects and alternatives in emergency medicine. *Am J Emerg Med* 1999; 17: 715–21.

Effects on intra-ocular pressure. Doses of suxamethonium are often followed 20 to 30 seconds later by a transient increase in intra-ocular pressure, which may be due in part to contracture of extra-ocular muscles. If suxamethonium is used during eye surgery after incision of the eyeball or in patients with a penetrating eye injury, there is a theoretical risk that any increase in intra-ocular pressure may result in extrusion of ocular contents and loss of sight. However, there appear to be few reports of vitreous extrusion associated with suxamethonium,[1] and a large retrospective study[2] has failed to find any evidence that suxamethonium caused additional eye damage in patients with penetrating eye injuries. Furthermore, the procedure of intubation itself is associated with a greater increase in intra-ocular pressure than that seen with suxamethonium. Nonetheless, some suggest that a rapid competitive neuromuscular blocker would be preferable to aid intubation in patients with penetrating eye injuries, after incision of the eyeball, and in glaucoma, although others consider that

the risk of a transient rise of intra-ocular pressure in these situations should be weighed against the need for rapid intubation.[1,3] For a discussion on the use of various drugs to counteract the rise in intra-ocular pressure associated with suxamethonium and intubation in general, see under Anaesthesia, p. 2028.1.

1. Book WJ, *et al.* Adverse effects of depolarising neuromuscular blocking agents: incidence, prevention and management. *Drug Safety* 1994; 5: 331–49.
2. Libonati MM, *et al.* The use of succinylcholine in open eye surgery. *Anesthesiology* 1985; 62: 637–40.
3. Edmondson L. Intraocular pressure and suxamethonium. *Br J Anaesth* 1997; 79: 146.

Effects on the muscles. Muscle fasciculations and postoperative muscle pain commonly follow use of suxamethonium. **Fasciculations** (generalised and desynchronised contractions of skeletal muscle fibres) occur during the onset of depolarising block in almost all patients given suxamethonium and may cause muscle damage. They are seen especially in the 'fine' muscles of the hands and face, and can be useful as an indication that suxamethonium is working. Attempts have been made to prevent their development with the aim of reducing postoperative muscle pain. However, there appears to be no direct correlation between the extent of visible fasciculations and muscle pain.[1,2] Slow infusion of suxamethonium[3] or giving divided doses[4] reduces fasciculations but not muscle pain.

Postoperative **muscle pain** is one of the most common adverse effects of suxamethonium and has been noted in about 50% of patients, although the reported incidence varies widely from around 1.5 to about 90%.[2] It usually occurs on the first postoperative day and lasts for 2 or 3 days, and most often affects muscles of the neck, shoulders, and upper abdomen.[2] The incidence and severity of muscle pain is increased in patients who are mobile soon after surgery and in females, but it occurs less often in children, pregnant women, and the elderly.[2]

The mechanism of suxamethonium-induced muscle pain is not fully understood; there have been many attempts to prevent it. Pretreatment with a small dose of a competitive neuromuscular blocker reduces both visible fasciculations and the incidence and severity of muscle pain,[1,2,5-8] but may delay the onset and alter the intensity of subsequent suxamethonium block[9] and impair conditions for intubation[1,9] (see Neuromuscular Blockers, under Interactions in Atracurium, p. 2033.2). In addition, larger doses of suxamethonium are required;[10] consequently the practice is considered controversial by some.[10,11] Pretreatment with a small dose (10 mg) of suxamethonium in a 'self-taming' technique appears to offer no protection against muscle pain.[1,2] The choice of anaesthetic induction agent has been suggested to be significant, as has the timing of doses, but despite claims for benefit with, for example, propofol, this remains questionable.[2] Pretreatment with benzodiazepines or NSAIDs has produced conflicting results.[2] Other drugs that have been tried include lidocaine, calcium gluconate, and vitamin C; there is some evidence that lidocaine may be the most effective pretreatment.[2] Not all methods have concentrated on drug treatment. A simple regimen of stretching exercises before premedication has reduced the incidence of both fasciculations and postoperative muscle pain.[12]

Suxamethonium may also produce an increase in **jaw tension** (masseter spasm or trismus)[13] in both adults[14] and children[15,16] during the onset of neuromuscular blockade. Tracheal intubation is greatly hindered in affected patients. It is not possible to predict which patients will show this response and the mechanism is unknown, although in about 50% of patients it may indicate the onset of malignant hyperthermia. Pretreatment with a paralysing dose of a competitive neuromuscular blocker prevents the response[16] but it is unknown whether this is clinically useful.

1. O'Sullivan EP, *et al.* Differential effects of neuromuscular blocking agents on suxamethonium-induced fasciculations and myalgia. *Br J Anaesth* 1988; 60: 367–71.
2. Wong SP, Chung F. Succinylcholine-associated postoperative myalgia. *Anaesthesia* 2000; 55: 144–52.
3. Feingold A, Velazquez JL. Suxamethonium infusion rate and observed fasciculations: a dose-response study. *Br J Anaesth* 1979; 51: 241–5.
4. Wilson DB, Dundee JW. Failure of divided doses of succinylcholine to reduce the incidence of muscle pains. *Anesthesiology* 1980; 52: 273–5.
5. Bennetts FE, Khalil KI. Reduction of post-suxamethonium pains by pretreatment with four non-depolarising agents. *Br J Anaesth* 1981; 53: 531–6.
6. Erkola O, *et al.* Five non-depolarizing muscle relaxants in precurarization. *Acta Anaesthesiol Scand* 1983; 27: 427–32.
7. Sosis M, *et al.* Comparison of atracurium and d-tubocurarine for prevention of succinylcholine myalgia. *Anesth Analg* 1987; 66: 657–9.
8. Findlay GP, Spittal MJ. Rocuronium pretreatment reduces suxamethonium-induced myalgia: comparison with vecuronium. *Br J Anaesth* 1996; 76: 526–9.
9. Pauca AL, *et al.* Inhibition of suxamethonium relaxation by tubocurarine and gallamine pretreatment during induction of anaesthesia in man. *Br J Anaesth* 1975; 47: 1067–73.
10. McManus CM. Neuromuscular blockers in surgery and intensive care, part 2. *Am J Health-Syst Pharm* 2001; 58: 2381–99.
11. Mencke T, *et al.* Pretreatment before succinylcholine for outpatient anesthesia? *Anesth Analg* 2002; 94: 573–6.
12. Magee DA, Robinson RJS. Effect of stretch exercises on suxamethonium induced fasciculations and myalgia. *Br J Anaesth* 1987; 59: 596–601.
13. Saddler JM. Jaw stiffness—an ill understood condition. *Br J Anaesth* 1991; 67: 515–16.
14. Leary NP, Ellis FR. Masseteric muscle spasm as a normal response to suxamethonium. *Br J Anaesth* 1990; 64: 488–92.
15. Van Der Spek AFL, *et al.* Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular relaxants. *Br J Anaesth* 1990; 64: 21–7.
16. Smith CE, *et al.* Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children. *Br J Anaesth* 1990; 64: 577–81.

Effects on plasma-potassium concentration. Suxamethonium causes depolarisation of motor end-plates in skeletal muscle, resulting in an immediate increase in plasma-potassium concentration. The rise is usually small, being about 0.5 mmol or less per litre, but suxamethonium is best avoided in patients whose plasma-potassium concentration is already high, such as those with renal impairment. An exaggerated response, with severe hyperkalaemia resulting in ventricular fibrillation and cardiac arrest, has been reported in patients with burns,[1,2] massive trauma, closed head injury, neuromuscular disease (see Neuromuscular Disorders, under Precautions, p. 2039.1), and severe long-lasting sepsis.[3] See also Children, under Precautions, p. 2039.1 for reference to fatal cardiac arrest associated with hyperkalaemia in children. With burns or trauma the period of greatest risk is from about 10 to 90 days after the injury, but may be further prolonged if there is delayed healing or persistent infection. These patients may still react abnormally to suxamethonium 2 years after the injury. In neuromuscular disease the greatest risk period is usually from 3 weeks to 6 months after onset, but severe hyperkalaemia may occur after 24 to 48 hours or later than 6 months. Patients with severe sepsis for more than a week should be considered at risk of hyperkalaemia and suxamethonium should not be given until the infection has cleared. The mechanism of this hyperkalaemic response appears to be a supersensitivity of acetylcholine receptors in which the entire muscle fibre membrane, rather than discrete motor end-plate sites, becomes directly excitable by depolarising drugs. Depolarisation by suxamethonium thus results in release of potassium over the entire muscle fibre membrane and hyperkalaemia results.

Various methods have been tried to attenuate the hyperkalaemia, including pretreatment with a small dose of a competitive neuromuscular blocker[3,4] or with suxamethonium itself.[5,6] No method is reliable enough to be used clinically.

Anaesthetics such as thiopental and halothane can increase the hyperkalaemic response.[4]

1. Martyn J, *et al.* Clinical pharmacology of muscle relaxants in patients with burns. *J Clin Pharmacol* 1986; 26: 680–5.
2. Anonymous. Neuromuscular blockers in patients with burns. *Lancet* 1988; II: 1003–4.
3. Kohlschütter B, *et al.* Suxamethonium-induced hyperkalaemia in patients with severe intra-abdominal infections. *Br J Anaesth* 1976; 48: 557–62.
4. Dhanaraj VJ, *et al.* A study of the changes in serum potassium concentration with suxamethonium using different anaesthetic agents. *Br J Anaesth* 1975; 47: 516–19.
5. Magee DA, Gallagher EG. "Self-taming" of suxamethonium and serum potassium concentration. *Br J Anaesth* 1984; 56: 977–9.
6. Plötz J, Schreiber W. Side effects induced by suxamethonium on the skeletal muscle and their prevention. *Br J Anaesth* 1985; 57: 1044–5.

Hypersensitivity. Hypersensitivity reactions to neuromuscular blockers are more common in women than in men,[1,2] in atopic patients and those who have a history of asthma or allergy,[2] and in patients who have had a previous reaction to anaesthetic drugs.[2] Circulatory collapse, flushing, rash, urticaria, and bronchospasm have occurred in hypersensitivity reactions associated with suxamethonium;[1,3,4] deaths have been reported.[3,5]

Data from intradermal testing have been used to qualify the risk of allergic reactions associated with the neuromuscular blockers:[6]

- benzylisoquinolinium blockers *alcuronium* and *tubocurarine* and the depolarising blocker *suxamethonium* were considered to be associated with the highest risk
- benzylisoquinolinium blockers *atracurium, cisatracurium, gallamine,* and *mivacurium* and the aminosteroid *rocuronium* presented an intermediate risk
- the aminosteroids *pancuronium* and *vecuronium* were considered to have the lowest risk

A type I immediate hypersensitivity reaction involving IgE antibodies is considered to be the **mechanism** of most hypersensitivity reactions associated with neuromuscular blockers.[2,5,7,8] Antibodies reacting with neuromuscular blockers, including suxamethonium, have been noted.[5,8] The antibodies appear to be directed against quaternary or tertiary ammonium-ion groups which are present in neuromuscular blockers; such groups are also found in other drugs, cosmetics, disinfectants, and foods. Some have suggested that pholcodine consumption may cause sensitisation to neuromuscular blockers.[9] Such phenomena may help explain the cross-reactivity reported between different neuromuscular blockers[1,2,5,8,10] and how sensitisation occurs without prior exposure to any neuromuscular blocker.[2,5] At least 50% of patients sensitive to one neuromuscular blocker will react to one or more others[11] with some patients sensitive to most.[1] Intradermal skin tests are used to investigate and predict sensitivity to neuromuscular blockers, but their interpretation is controversial and it cannot be concluded that all patients with positive skin tests will have clinical sensitivity.[1,11] Although radioallergosorbent tests can detect antibodies to suxamethonium, alcuronium, and thiopental[3,12] some consider that their routine use is not justified as reactions could be avoided by taking an adequate patient history.[13]

However, neuromuscular blockers also have a direct effect on mast cells, releasing histamine without immunological involvement, and could cause anaphylactoid reactions. Histamine release associated with use of aminosteroidal blockers is rare compared with the benzylisoquinolinium blockers.[14] Tubocurarine is considered to be the most potent releaser of histamine, with pancuronium and vecuronium having only very weak activity. Suxamethonium is considered to have only 1% of the histamine-releasing activity of tubocurarine but is more likely to produce serious hypersensitivity reactions.

1. Youngmen PR, *et al.* Anaphylactoid reactions to neuromuscular blocking agents: a commonly undiagnosed condition? *Lancet* 1983; II: 597–9.
2. Fisher MM, Munro I. Life-threatening anaphylactoid reactions to muscle relaxants. *Anesth Analg* 1983; 62: 559–64.
3. Brahams D. Fatal reaction to suxamethonium: case for screening by radioallergosorbent test? *Lancet* 1989; I: 1400–1.
4. Moneret-Vautrin DA, *et al.* Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases. *Br J Anaesth* 1990; 64: 743–5.
5. Fisher M, Baldo B. Adverse reactions to alcuronium: an Australian disease? *Med J Aust* 1983; 1: 630–2.
6. Rose M, Fisher M. Rocuronium: high risk for anaphylaxis? *Br J Anaesth* 2001; 86: 678–82.
7. Vervloet D. Anaphylactoid reactions to suxamethonium. *Lancet* 1983; I: 1197.
8. Harle DG, *et al.* Detection of IgE antibodies to suxamethonium after anaphylactoid reactions during anaesthesia. *Lancet* 1984; I: 930–2.
9. Florvaag E, Johansson SGO. The pholcodine story. *Immunol Allergy Clin North Am* 2009; 29: 419–27.
10. Harle DG, *et al.* Cross-reactivity of metocurine, atracurium, vecuronium and fazadinium with IgE antibodies from patients unexposed to these drugs but allergic to other myoneural blocking drugs. *Br J Anaesth* 1985; 57: 1073–6.
11. Withington DE. Relevance of histamine to the anaesthetist. *Br J Hosp Med* 1988; 40: 264–70.
12. Assem ESK. Anaphylactic anaesthetic reactions: the value of paper radioallergosorbent tests for IgE antibodies to muscle relaxants and thiopentone. *Anaesthesia* 1990; 45: 1032–8.
13. Noble DW, Yap PL. Screening for antibodies to anaesthetics. *BMJ* 1989; 299: 2.
14. Naguib M, *et al.* Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine. *Br J Anaesth* 1995; 75: 588–92.

Treatment of Adverse Effects

Once suxamethonium chloride has been given assisted respiration should be maintained until spontaneous respiration has been fully restored. Transfusion of fresh frozen plasma or other source of plasma cholinesterase will help the destruction of the suxamethonium when prolonged paralysis is a result of atypical or low serum concentrations of plasma cholinesterase. Anticholinesterases should not normally be used since they potentiate the usual phase I block (see Uses and Administration, p. 2037.2). If the neuromuscular block ceases to be depolarising in type and acquires some features of a competitive block (phase II block) the cautious use of an anticholinesterase may be considered. A short-acting anticholinesterase such as edrophonium may be given intravenously and if an obvious improvement is maintained for several minutes, neostigmine may be given with atropine.

Severe hypersensitivity reactions should be treated promptly with supportive and symptomatic measures.

If malignant hyperthermia develops, it may be treated as described on p. 2024.1.

The muscarinic effects of suxamethonium chloride, such as bradycardia and excessive salivary secretion, may be reduced by giving an antimuscarinic such as atropine before suxamethonium. A small dose of a competitive neuromuscular blocker given before suxamethonium has been used to reduce some of the adverse effects of suxamethonium on the muscles (see Effects on the Muscles, above).

Precautions

Patients given a neuromuscular blocker should always have their respiration assisted or controlled until the drug has been inactivated or antagonised.

Suxamethonium chloride is contra-indicated in patients with atypical plasma cholinesterase and should be used with caution in patients with reduced plasma cholinesterase activity (see p. 2039.1), which may occur in certain disease states and following exposure to certain drugs. Plasma cholinesterase concentrations fall during pregnancy and the puerperium and therefore maternal paralysis may be mildly prolonged. Suxamethonium is contra-indicated in patients with burns, massive trauma, renal impairment with a raised plasma-potassium concentration, severe long-lasting sepsis,

and severe hyperkalaemia, since suxamethonium-induced rises in plasma-potassium concentration can have serious consequences in such patients; patients who have been immobilised for prolonged periods may be at similar risk. It is contra-indicated in patients with a history of hypersensitivity to the drug and, because high rates of cross-sensitivity have been reported (see p. 2038.2), should be used with caution when hypersensitivity to any neuromuscular blocker has previously occurred. Suxamethonium should be avoided in patients with a penetrating eye injury, raised intra-ocular pressure or glaucoma, or those about to undergo incision of the eyeball in eye surgery, because of the risks from increased intra-ocular pressure (although see under Adverse Effects, p. 2037.3). Suxamethonium chloride produces muscle contractions before relaxation and should therefore be used with caution in patients with bone fractures. It is contra-indicated in patients with a personal or family history of malignant hyperthermia.

The response to suxamethonium chloride is often unpredictable in patients with neuromuscular disorders and it should be used with great caution in these patients (see below). Caution is also needed if it is given to a patient with cardiac or respiratory disease. Children may be at special risk from cardiac arrest associated with hyperkalaemia (see below).

Hypothermia may enhance the neuromuscular blocking effects of suxamethonium chloride and an increase in body temperature may reduce them.

Children. Reports of fatal cardiac arrests[1,2] in apparently healthy children and adolescents, who were subsequently found to have had undiagnosed myopathies, led to restrictions in the USA on the use of suxamethonium in this age group. Suxamethonium was contra-indicated except for emergency tracheal intubation or where an immediate securing of an airway was essential. Many anaesthetists disagreed[2] with this contra-indication and an FDA Committee advised[3] that it should be replaced by a warning about the possibility of cardiac arrest associated with hyperkalaemia with special attention being paid to male children who are considered to be at the highest risk. One British anaesthetist who questioned the rationale behind restricting the elective use of suxamethonium pointed out that alternatives to suxamethonium had not been shown to be as safe or effective for airway management.[4] The rare occurrence of cardiac arrest in children might be further reduced by taking a careful family history to exclude undiagnosed myopathies and by using an intravenous as opposed to inhalation induction when suxamethonium is to be used.[4] A survey had found that most cases of cardiac arrest in children in the UK associated with the use of suxamethonium had been caused by vagal overactivity in non-atropinised patients.

1. Rosenberg H, Gronert GA. Intractable cardiac arrest in children given succinylcholine. *Anesthesiology* 1992; 77: 1054.
2. Book WJ, *et al.* Adverse effects of depolarising neuromuscular blocking agents: incidence, prevention and management. *Drug Safety* 1994; 10: 331–49.
3. FDA. *FDC Reports Pink Sheet* 1994; June 13: 16.
4. Hopkins PM. Use of suxamethonium in children. *Br J Anaesth* 1995; 75: 675–7.

Neuromuscular disorders. Caution is needed if suxamethonium is to be given to patients with neuromuscular disease, since severe complications have been reported.[1] Hyperkalaemia and cardiac arrhythmias or cardiac arrest have been reported after use of suxamethonium in patients with hemiplegia, diffuse intracranial lesions (head injury, encephalitis, ruptured cerebral aneurysm), tetanus, paraplegia, acute anterior horn cell disease, and muscular dystrophies. An exaggerated response to suxamethonium has been reported in the myasthenic syndrome but resistance may occur in patients with neurofibromatosis. Resistance may also occur in patients with myasthenia gravis, but uneventful use has also been reported, although early onset of phase II block is possible in these patients. Muscle contractures and hyperkalaemia may be expected in amyotrophic lateral sclerosis and muscular denervation. Suxamethonium should be avoided in patients with myotonias, as response is unpredictable. It is recommended that suxamethonium is also avoided in hemiplegia, paraplegia, muscular denervation, and muscular dystrophies.

1. Azar I. The response of patients with neuromuscular disorders to muscle relaxants: a review. *Anesthesiology* 1984; 61: 173–87.

Plasma cholinesterase deficiency. Suxamethonium is normally rapidly hydrolysed by plasma cholinesterase and the clinical effects usually last for only several minutes. Activity of the enzyme varies between individuals and prolonged paralysis following suxamethonium is commonly due to a hereditary or acquired reduction in plasma cholinesterase activity. The genes involved in the control of plasma cholinesterase production are termed usual, atypical (dibucaine-resistant), fluoride-resistant, and silent. About 96% of the population are homozygous for the usual gene. The commonest variant in western populations is the atypical form with about 3 to 4% of the population being heterozygous for this variant. They have a slightly prolonged response to suxamethonium. Homozygotes for the atypical variant have a frequency of about 0.04%. They exhibit markedly prolonged apnoea after a standard dose of suxamethonium but can be readily identified by biochemical tests. The fluoride-resistant and silent variants occur very rarely. A measure of plasma cholinesterase activity can be obtained from the percentage inhibition of the enzyme by the local anaesthetic cinchocaine (commonly known in this context by its American name, dibucaine) to give the **dibucaine number**. Most normal people have a dibucaine number of about 80.

Acquired plasma cholinesterase deficiency is clinically less important than genetically determined deficiency. The enzyme is synthesised in the liver and **severe liver impairment** or malnutrition may cause abnormally low enzyme levels with some prolongation of suxamethonium activity. Reduced enzyme activity may also be found in severe anaemia, burns, cancer, collagen diseases, severe dehydration, severe infections, malnutrition, myocardial infarction, myxoedema, and renal impairment; plasmapheresis or plasma exchange removes significant amounts of plasma cholinesterase.

During **pregnancy** there is a rapid fall in plasma cholinesterase concentration that persists throughout pregnancy and for up to several weeks into the puerperium. The concentration of atypical plasma cholinesterase is also reduced in pregnancy and the puerperium. Some **drugs** reduce plasma cholinesterase synthesis or activity and may prolong suxamethonium paralysis as discussed under Interactions, below.

References.

1. Wood GJ, Hall GM. Plasmapheresis and plasma cholinesterase. *Br J Anaesth* 1978; 50: 945–9.
2. Evans RT, Wroe JM. Plasma cholinesterase changes during pregnancy: their interpretation as a cause of suxamethonium-induced apnoea. *Anaesthesia* 1980; 35: 651–4.
3. Lumley J. Prolongation of suxamethonium following plasma exchange. *Br J Anaesth* 1980; 52: 1149–50.
4. Williams PM. Clinical significance of esterases in man. *Clin Pharmacokinet* 1985; 10: 392–403.
5. Robson N, *et al.* Plasma cholinesterase changes during the puerperium. *Anaesthesia* 1986; 41: 243–9.
6. Cherala SR, *et al.* Placental transfer of succinylcholine causing transient respiratory depression in the newborn. *Anaesth Intensive Care* 1989; 17: 202–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies suxamethonium 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)

Renal impairment. Suxamethonium chloride may be given in usual doses to patients with renal failure[1,2] although it is usually recommended that it should be avoided if hyperkalaemia is also present (see Effects on Plasma-potassium Concentration p. 2038.2). However, in a retrospective review[3] of 38 patients with serum potassium levels greater than 5.5 mmol/litre given a standard intubation dose of suxamethonium, there were no reports of dysrhythmias or unexpected admissions to the intensive care unit.

Patients with renal failure given repeated doses of suxamethonium did not show an excessive increase in serum potassium; however sinus bradycardia commonly occurred and it was recommended that repeated injections should be avoided in such patients.[2] If necessary, pretreatment with glycopyrrolate or atropine to protect against bradycardia should be considered.

1. Ryan DW. Preoperative serum cholinesterase concentration in chronic renal failure. *Br J Anaesth* 1977; 49: 945–9.
2. Thapa S, Brull SJ. Succinylcholine-induced hyperkalemia in patients with renal failure: an old question revisited. *Anesth Analg* 2000; 91: 237–41.
3. Schow AJ, *et al.* Can succinylcholine be used safely in hyperkalemic patients? *Anesth Analg* 2002; 95: 119–22.

Interactions

Some drugs may interact with depolarising neuromuscular blockers such as suxamethonium. The mechanisms of interaction can include a direct effect on neuromuscular transmission or an alteration of enzyme activity and may result in potentiation or antagonism of neuromuscular block. In general, such interactions are potentially more serious in patients with impaired neuromuscular function or reduced activity of plasma cholinesterase, who are more sensitive to suxamethonium's effects.

Interactions common to competitive and depolarising neuromuscular blockers are covered under Atracurium, p. 2031.3 whereas those specific for depolarising blockers are discussed below.

Antiarrhythmics. See under Atracurium, p. 2031.3.

Antibacterials. See under Atracurium, p. 2032.1.

Anticholinesterases. The action of suxamethonium may be markedly prolonged in patients using eye drops containing *ecothiopate*, a long-acting anticholinesterase that inhibits both acetylcholinesterase and plasma cholinesterase. After systemic absorption of ecothiopate, plasma cholinesterase activity may rapidly be reduced to 5% or less of normal and prolonged apnoea after use of suxamethonium has occurred. On stopping ecothiopate, enzyme activity remains depressed for 1 to 2 months. If a patient has used ecothiopate eye drops in the previous 2 months, suxamethonium should not be given unless normal plasma cholinesterase activity can be shown; a competitive neuromuscular blocker is preferable. Exposure to *organophosphorus insecticides* may also reduce plasma cholinesterase activity resulting in prolonged paralysis after use of suxamethonium; enzyme activity may be totally abolished. Anticholinesterases including *edrophonium, neostigmine, pyridostigmine, rivastigmine,* and possibly *donepezil* enhance the action of suxamethonium, although suxamethonium-induced phase II block can be reversed with an anticholinesterase. Care should be taken if there is a need to use suxamethonium for urgent short procedures after a competitive-neuromuscular-induced block has been antagonised with an anticholinesterase, as the resulting block may be greatly prolonged.[1]

1. Fleming NW, *et al.* Neuromuscular blocking action of suxamethonium after antagonism of vecuronium by edrophonium, pyridostigmine or neostigmine. *Br J Anaesth* 1996; 77: 492–5.

Antiepileptics. The mean time to recovery from suxamethonium-induced neuromuscular block was 14.3 minutes in 9 patients receiving chronic treatment with *phenytoin* and/or *carbamazepine* compared with 10.0 minutes in 9 patients not receiving antiepileptics.[1]

1. Melton AT, *et al.* Prolonged duration of succinylcholine in patients receiving anticonvulsants: evidence for mild upregulation of acetylcholine receptors? *Can J Anaesth* 1993; 40: 939–42.

Antineoplastics. *Cyclophosphamide* has been reported to prolong the neuromuscular block produced by suxamethonium through reduction of plasma cholinesterase activity, possibly by alkylation of the enzyme.[1] Since enzyme activity may be reduced by up to 70% for several days to several weeks, it was suggested[2] that suxamethonium should be avoided if possible in patients receiving cyclophosphamide. A more recent case report[3] would also support this suggestion. Other alkylating agents also reported to reduce plasma cholinesterase activity include *chlormethine, thiotepa,* and *tretamine*.[2]

1. Walker IR, *et al.* Cyclophosphamide, cholinesterase and anaesthesia. *Aust N Z J Med* 1972; 3: 247–51.
2. Zsigmond EK, Robins G. The effect of a series of anti-cancer drugs on plasma cholinesterase activity. *Can Anaesth Soc J* 1972; 19: 75–82.
3. Koseoglu V, *et al.* Acquired pseudocholinesterase deficiency after high-dose cyclophosphamide. *Bone Marrow Transplant* 1999; 24: 1367–8.

Aprotinin. See under Atracurium, p. 2032.2.

Benzodiazepines. See under Atracurium, p. 2032.2.

Beta blockers. See under Atracurium, p. 2032.2.

Cardiac inotropes. See under Atracurium, p. 2032.3.

Ganglion blockers. See under Atracurium, p. 2032.3.

General anaesthetics. Tachyphylaxis and phase II block (see Uses and Administration, p. 2037.2) develop earlier, and after smaller total doses of suxamethonium, when inhalation anaesthetics are used. *Halothane* may increase the incidence of arrhythmias associated with suxamethonium and can potentiate suxamethonium-induced muscle damage.[1] Suxamethonium should be used with caution with other drugs that might produce additive cardiovascular effects. Severe bradycardia and asystole have occurred when used in anaesthetic regimens with *propofol* and opioids such as *fentanyl*.

See also under Interactions of Atracurium, p. 2032.3.

1. Laurence AS, Henderson P. Serum myoglobin after suxamethonium administration to children: effect of pretreatment before iv and inhalation induction. *Br J Anaesth* 1986; 58: 126P.

Histamine H_2 antagonists. See under Atracurium, p. 2033.1.

Lithium. See under Atracurium, p. 2033.1.

Local anaesthetics. *Procaine, cocaine,* and *chloroprocaine* are ester-type local anaesthetics which are hydrolysed by plasma cholinesterase and may competitively enhance the neuromuscular blocking activity of suxamethonium. See also Antiarrhythmics under Atracurium, p. 2031.3.

Magnesium salts. See under Atracurium, p. 2033.2.

MAOIs. Reduction of plasma cholinesterase activity by *phenelzine* has been reported[1] to cause significant prolongation of suxamethonium paralysis. Enzyme activity may be reduced to 10% of normal and recovery can take up to a month. The dosage of suxamethonium may need to be substantially reduced or a competitive neuromuscular blocker used.

1. Bodley PO, *et al.* Low serum pseudocholinesterase levels complicating treatment with phenelzine. *BMJ* 1969; 3: 510–12.

Metoclopramide. Dose-dependent prolongation of suxamethonium-induced neuromuscular blockade has been reported in patients given metoclopramide.[1,2] The potent inhibitory effect of metoclopramide on plasma cholinesterase may account for this interaction.

1. Turner DR, *et al.* Neuromuscular block by suxamethonium following treatment with histamine type 2 antagonists or metoclopramide. *Br J Anaesth* 1989; 63: 348–50.
2. Kao YJ, *et al.* Dose-dependent effect of metoclopramide on cholinesterases and suxamethonium metabolism. *Br J Anaesth* 1990; 65: 220–4.

Neuromuscular blockers. See under Atracurium, p. 2033.2.

Sex hormones. *Oestrogens* and oestrogen-containing *oral contraceptives* reduce plasma cholinesterase activity[1] possibly due to suppression of hepatic synthesis of the enzyme, but little prolongation of suxamethonium paralysis may be expected since activity is reduced by only about 20%. See also under Atracurium, p. 2033.2.

1. Robertson GS, Aberd MB. Serum protein and cholinesterase changes in association with contraceptive pills. *Lancet* 1967; i: 232–5.

Sympathomimetics. *Bambuterol* can inhibit plasma cholinesterase activity and so prolong the activity of suxamethonium.[1] Phase II block has been reported in some patients with abnormal plasma cholinesterase.[2]

1. Staun P, *et al.* The influence of 10 mg and 20 mg bambuterol on the duration of succinylcholine-induced neuromuscular blockade. *Acta Anaesthesiol Scand* 1990; 34: 498–500.
2. Bang U, *et al.* The effect of bambuterol on plasma cholinesterase activity and suxamethonium-induced neuromuscular blockade in subjects heterozygous for abnormal plasma cholinesterase. *Acta Anaesthesiol Scand* 1990; 34: 600–604.

Pharmacokinetics

After injection, suxamethonium is rapidly hydrolysed by plasma cholinesterase. One molecule of choline is split off rapidly to form succinylmonocholine which is then slowly hydrolysed to succinic acid and choline. About 10% of suxamethonium is excreted unchanged in the urine. Succinylmonocholine has weak muscle-relaxant properties mainly of a competitive nature.

The gene responsible for the expression of plasma cholinesterase exhibits polymorphism and enzyme activity varies between individuals (see Plasma Cholinesterase Deficiency, under Precautions, p. 2039.1).

Small amounts of suxamethonium cross the placenta.

Reviews.

1. Booij LHDJ, Vree TB. Skeletal muscle relaxants: pharmacodynamics and pharmacokinetics in different patient groups. *Int J Clin Pract* 2000; 54: 526–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Actirelax; Fosfitone; Succi: ***Austral.***: Scoline†; ***Austria***: Lysthenon; ***Braz.***: Quelicin; Succitrat; Succnil Colin; ***Canad.***: Quelicin; ***Denm.***: Suxameton; ***Fin.***: Sukolin; ***Fr.***: Celocurine; ***Ger.***: Lysthenon; Pantolax; ***Gr.***: Lyctrope; Mioflex; ***India***: Entubate; Midarine; Myorelex; ***Indon.***: Quelicin; ***Irl.***: Anectine; ***Israel***: Succinyl; ***Ital.***: Midarine; ***Jpn***: Relaxin; ***Malaysia***: Ethicoline; ***Mex.***: Anectine†; Uxicolin†; ***Neth.***: Curalest; ***Norw.***: Curacit; ***Philipp.***: Anekcin; Anektil; Quelicin; ***Pol.***: Chlorsuccillin; ***Port.***: Mioflex; ***Rus.***: Dithylin (Дитилин); Lysthenon (Листенон); ***S.Afr.***: Scoline†; ***Singapore***: Ethicholine; ***Spain***: Anectine; Mioflex; ***Swed.***: Celocurin; ***Switz.***: Lysthenon; Midarine; Succinolin; ***Thai.***: Succinyl; ***Turk.***: Lysthenon; ***UK***: Anectine; ***USA***: Anectine; Quelicin.

Pharmacopoeial Preparations
BP 2014: Suxamethonium Chloride Injection;
USP 36: Succinylcholine Chloride for Injection; Succinylcholine Chloride Injection.

Tubocurarine Chloride *(BAN, rINN)*

Cloruro de tubocurarina; Tubocurarina, cloruro de; Tubocurarinchlorid; *d*-Tubocurarine Chloride; (+)-Tubocurarine Chloride Hydrochloride Pentahydrate; Tubocurarine Chlorure de; Tubocurarini chloridum; Tubocurarinii Chloridum Pentahydricum; Tubokurariinikloridi; Tubokurarinium-chlorid pentahydrát; Tubokurarin-klorid; Tubokurarinklorid; Tubokurarino chloridas; Тубокурарина Хлорид.

(+)-7′,12′-Dihydroxy-6,6′-dimethoxy-2,2′,2′-trimethyltubocuraranium dichloride pentahydrate.

$C_{37}H_{42}Cl_2N_2O_6.5H_2O$=771.7.

CAS — 57-95-4 (tubocurarine); 57-94-3 (anhydrous tubocurarine chloride); 6989-98-6 (tubocurarine chloride, pentahydrate).

ATC — M03AA02.

ATC Vet — QM03AA02.

UNII — 900961Z8VR.

Pharmacopoeias. In *Chin.*, *Int.*, *Jpn*, and *US*.

USP 36: (Tubocurarine Chloride). A white or yellowish-white to greyish-white, crystalline powder. Soluble 1 in 20 of water and 1 in 45 of alcohol. Store in airtight containers.

Profile

Tubocurarine is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p. 2030.1). It may be obtained from extracts of the stems of *Chondodendron tomentosum* (Menispermaceae) and is one of the active principles of curare, by which name it is sometimes referred to in anaesthetic literature. A transient fall in blood pressure commonly occurs after its use, due in part to ganglionic blockade and the release of histamine; there may also be an increase in heart rate. Tubocurarine chloride is the chloride of (+)-tubocurarine and has been used similarly to other competitive neuromuscular blockers to produce muscle relaxation in various procedures but has largely been replaced by other drugs with fewer cardiovascular effects and a lower potential for histamine release. Tubocurarine chloride has also been used to control the muscle spasms of tetanus (p. 2029.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Decurin†.

Pharmacopoeial Preparations
USP 36: Tubocurarine Chloride Injection.

Vecuronium Bromide *(BAN, USAN, rINN)*

Bromuro de vecuronio; Org-NC-45; Vecuronii Bromidum; Vecuronio, bromuro de; Vécuronium, bromure de; Vecuroniumbromid; Vekuroniumbromid; Vekuronium-bromid; Vekuroniumbromidi; Vekuronyum Bromür; Wekuroniowy bromek; Векурония бромид.

1-(3α,17β-Diacetoxy-2β-piperidino-5α-androstan-16β-yl)-1-methylpiperidinium bromide.

$C_{34}H_{57}BrN_2O_4$=637.7.

CAS — 50700-72-6.

ATC — M03AC03.

ATC Vet — QM03AC03.

UNII — 7E4PHP5N1D.

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

Ph. Eur. 8: (Vecuronium Bromide). White or almost white crystals or crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol and in acetonitrile; freely soluble in dichloromethane. Store in airtight containers. Protect from light and moisture.

USP 36: (Vecuronium Bromide). White or creamy white crystals, or a crystalline powder. Slightly soluble in water and in acetone; sparingly soluble in alcohol. Store in airtight containers.

Incompatibility. A solution containing vecuronium bromide 1 mg/mL was found to be visually incompatible with furosemide.[1] For incompatibilities of competitive neuromuscular blockers in general, see under Atracurium on p. 2030.1.

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.

Stability. In a stability study,[1] solutions of vecuronium bromide 1 mg/mL in preservative-free sterile water for injection were stable for at least 21 days when stored in polypropylene syringes at 23 to 25 degrees or at 3 to 5 degrees.

1. Johnson CE, Cober MP. Stability of vecuronium in sterile water for injection stored in polypropylene syringes for 21 days. *Am J Health-Syst Pharm* 2007; 64: 2356–8.

Uses and Administration

Vecuronium bromide is an aminosteroidal competitive neuromuscular blocker (see Atracurium, p. 2030.1).

After intravenous injection muscle relaxation occurs within about 1.5 to 2 minutes and lasts for about 20 to 30 minutes.

Vecuronium bromide is used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p. 2028.1) and to aid controlled ventilation (see Intensive Care, p. 2028.3).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. The usual initial dose for intubation in adults is 80 to 100 micrograms/kg by intravenous injection, although reduced initial doses of 30 to 50 micrograms/kg are suggested after the use of suxamethonium. Higher initial doses ranging from 150 to 300 micrograms/kg have sometimes been used for other procedures. However, it is recommended that the dose should not exceed 100 micrograms/kg in caesarean section or neonatal surgery. Maintenance doses of 20 to 30 micrograms/kg may be given as required during prolonged procedures; in the USA a lower maintenance dose of 10 to 15 micrograms/kg is recommended. Neuromuscular blockade may also be maintained with an intravenous infusion given at a rate of 0.8 to 1.4 micrograms/kg per minute but should be preceded by an initial bolus injection of 80 to 100 micrograms/kg. UK licensed product information recommends that in obese patients the dosage of vecuronium should be reduced taking into account ideal body-weight.

Licensed product information recommends that, in general, children can be given adult doses:

- children up to 1 year may have a more rapid response and the high initial dose for intubation may not be necessary
- neonates and infants below 5 months of age may be more sensitive to vecuronium and it is recommended that they should be given an initial test dose of 10 to 20 micrograms/kg, followed by increments according to response
- the duration of action and recovery is longer in neonates and infants than in children and adults and they may require smaller maintenance doses given less frequently
- dose requirements in children aged 2 to 10 years are higher than for adults and neonates but usually within the ranges given above; the duration of action is also shorter in children and more frequent maintenance doses may be required

Administration in children. For details of uses and dosage of vecuronium bromide in infants and children, see Uses and Administration, above.

Administration in hepatic impairment. Although the manufacturers make no specific recommendations for dosage reduction in hepatic impairment, the duration of action of vecuronium was reported to be significantly prolonged in patients with cholestasis[1] or cirrhosis with oesophageal varices[2] given a dose of 200 micrograms/kg intravenously. Plasma clearance was significantly reduced and the elimination half-life significantly increased from a mean of 58 to 98 minutes.[1] A dose of 150 micrograms/kg was found to have a similar onset and duration of action in patients with hepatic impairment and healthy controls,[2] but a dose of 100 micrograms/kg had a slower onset and slightly shorter duration of action in those with liver disturbance.[3] After a dose of vecuronium, rapid and extensive hepatic uptake occurs, which largely determines its short duration of action. However, as the dose increases this mechanism becomes saturated, and hepatic elimination becomes more important in terminating activity. This would help to explain the variation in results seen with the different doses. Caution is needed if large single doses or repeated doses are given to patients with hepatic impairment.

1. Lebrault C, *et al.* Pharmacokinetics and pharmacodynamics of vecuronium in patients with cholestasis. *Br J Anaesth* 1986; 58: 983–7.
2. Hunter JM, *et al.* The use of different doses of vecuronium in patients with liver dysfunction. *Br J Anaesth* 1985; 57: 758–64.
3. Bell CF, *et al.* Use of atracurium and vecuronium in patients with oesophageal varices. *Br J Anaesth* 1985; 57: 160–8.

Administration in renal impairment. As vecuronium bromide is excreted in urine only in small amounts, it may be given in usual doses to patients with renal failure.[1,2] No clinically significant difference in elimination half-life, clearance, or duration of action were reported[1] between patients with renal failure and those with normal renal function. The onset of neuromuscular block may be slightly slower in renal failure[2] and these patients may require an increase of around 20% in the initial dose of vecuronium.[3] However, the dosage requirement for maintenance of neuromuscular block may be reduced by about 20%[3] and slight prolongation of block may occur if dosage is not adjusted, but reversal of residual block with neostigmine is prompt and effective.[2]

Resistance to vecuronium has been reported[2] in 2 anephric patients. Total doses of 620 and 660 micrograms/kg produced maximum neuromuscular block of 77% and 36%, respectively but, despite the high doses used, there were no adverse effects or residual curarisation.

1. Fahey MR, *et al.* Pharmacokinetics of Org NC 45 (Norcuron) in patients with and without renal failure. *Br J Anaesth* 1981; 53: 1049–53.

2. Hunter JM, *et al.* Comparison of vecuronium, atracurium and tubocurarine in normal patients and in patients with no renal function. *Br J Anaesth* 1984; 56: 941–51.
3. Gramstad L. Atracurium, vecuronium and pancuronium in end-stage renal failure: dose-response properties and interactions with azathioprine. *Br J Anaesth* 1987; 59: 995–1003.

Adverse Effects, Treatment, and Precautions

As for competitive neuromuscular blockers in general (see Atracurium, p. 2030.3).

Vecuronium bromide has little histamine-releasing activity although a local reaction at the site of injection has been reported; bronchospasm and anaphylactoid reactions have been rarely reported. It also has little vagolytic or ganglion-blocking activity and produces no significant adverse cardiovascular effects at usual doses.

Caution may be needed in patients with hepatic or renal impairment (see under Uses and Administration, p. 2040.3); dosage adjustments may be required in renal failure.

The elderly. It has been recommended that neuromuscular function should be monitored in elderly patients receiving vecuronium since there may be a risk of prolonged block.[1]

1. Slavov V, *et al.* Comparison of duration of neuromuscular blocking effect of atracurium and vecuronium in young and elderly patients. *Br J Anaesth* 1995; 74: 709–11.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies vecuronium 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)

Pregnancy. The proportion of vecuronium crossing the placenta after doses of 60 to 80 micrograms/kg was considered clinically insignificant and its use during obstetric anaesthesia was considered safe for the newborn.[1]

1. Demetriou M, *et al.* Placental transfer of Org NC 45 in women undergoing caesarean section. *Br J Anaesth* 1982; 54: 643–5.

Interactions

For interactions associated with competitive neuromuscular blockers, see Atracurium, p. 2031.3.

Pharmacokinetics

On intravenous injection vecuronium is rapidly distributed. It is taken up by the liver and partly metabolised; the metabolites have some neuromuscular blocking activity. It is excreted mainly in bile as unchanged drug and metabolites; some is also excreted in urine. The plasma elimination half-life is reported to range from about 30 to 80 minutes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Galaren; Gobbicuronio; Rivecrum; Vecural; Vecuron; *Austral.*: Norcuron; Vecure; *Austria*: Norcuron; *Belg.*: Norcuron; *Braz.*: Norcuron†; Vecuron; *Canad.*: Norcuron†; *Chile*: Norcuron; *China*: Norcuron (万可松); Xian Lin (仙林); *Cz.*: Norcuron; *Fin.*: Norcuron; *Fr.*: Norcuron; *Ger.*: Norcuron; *Gr.*: Alnorcon; Norcuron; Vecurol; *Hong Kong*: Norcuron; *Hung.*: Norcuron; *India*: Neovec; Norcuron; *Indon.*: Ecron; Norcuron; *Irl.*: Norcuron; *Israel*: Norcuron; *Ital.*: Norcuron; *Jpn*: Musculax; *Malaysia*: Norcuron; *Mex.*: Bromivec; Curlem†; Nodescron; Norcuron; *Neth.*: Norcuron; *Norw.*: Norcuron; *NZ*: Norcuron; *Philipp.*: Norcuron; Noruvec; Vecuron; *Pol.*: Norcuron; *Port.*: Norcuron; *Rus.*: Norcuron (Норкурон); *S.Afr.*: Muscuron; Norcuron; *Singapore*: Norcuron†; *Spain*: Norcuron; *Swed.*: Norcuron†; *Switz.*: Norcuron; *Thai.*: Norcuron; *Turk.*: Blok-L; Norcuron; *UK*: Norcuron; *Ukr.*: Norcuron (Норкурон)†; *USA*: Norcuron†; *Venez.*: Prorelax; Vecuron.

Nutritional Agents and Vitamins

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The principal constituents of food are carbohydrates, fats, minerals, proteins, vitamins, indigestible fibre, and water. Energy is provided by the metabolism of carbohydrates, fats, surplus protein, and alcohol.

Carbohydrates found in foods may be classified according to their degree of polymerisation into three main groups, namely sugars, oligosaccharides, and polysaccharides; all of these are made up only of carbon, hydrogen, and oxygen. Sugars can be further subdivided into *monosaccharides* (single-molecule sugars), such as fructose and glucose, *disaccharides* (whose molecules consist of two monosaccharides joined together), such as lactose and sucrose, and *sugar alcohols* (polyols) such as sorbitol and mannitol. *Oligosaccharides* typically consist of 3 to 9 monosaccharides joined together, and include maltooligosaccharides such as maltodextrins. *Polysaccharides* consist of many monosaccharides joined together and include starches and non-starch polysaccharides such as cellulose. Non-starch polysaccharides are the major fraction of dietary fibre, and many authorities now consider this term to be preferable to dietary fibre.

Fats have the same elemental composition as carbohydrates, but with a lower proportion of oxygen. Dietary fat is usually in the form of triglycerides, esters of glycerol with three fatty acid molecules. Essential fatty acids are ones that cannot be made in the body and which must be supplied by the food.

Proteins are made up of carbon, hydrogen, oxygen, and nitrogen; most proteins also contain sulfur and some contain phosphorus. They are required for the regulation of body processes such as growth and tissue maintenance. Excess protein can be converted into carbohydrate and used to provide energy.

Proteins consist of chains of **amino acids** of which there are *essential* and *non-essential* types. Essential amino acids (indispensable amino acids) cannot be synthesised in sufficient amounts in the body and must therefore be present in food; non-essential amino acids can be synthesised in the body. There are eight essential amino acids: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. Arginine and histidine are also essential for infant growth while synthesis of cysteine, taurine, and tyrosine may be inadequate in premature infants.

Several inorganic elements, or minerals, are essential dietary constituents; those which are required in relatively small amounts are known as **trace elements** (see p. 2045.3). Their main function is to act as essential cofactors in various enzyme systems.

Vitamins and their general role in health are described p. 2045.3.

Dietary Modification

Infants, children, elderly people, and pregnant or lactating women have particular nutritional requirements, but in most cases, provided that they are in good general health, adjustment to intake is all that is required rather than extensive modification or supplementation.

Dietary modification is important in the management of some disorders. Calorie restriction is fundamental to the management of obesity, although it may be difficult to motivate patients to accept long-term changes to their eating habits, and some fashionable diets are at best of little value.

The role of diet in the aetiology of cardiovascular disorders (such as salt intake in hypertension and fat intake in ischaemic heart disease) is recognised to be of importance and has lead to public health campaigns for healthier eating patterns.

Dietary modification is also an accepted part of the management of diabetes mellitus, while protein restriction is important in the management of uraemia or hepatic encephalopathy.

There are also metabolic disorders such as phenylketonuria, or forms of intolerance to dietary components, such as coeliac disease, in which the diet must be modified to exclude or drastically reduce certain food components.

Amino acid metabolic disorders. Various inborn errors of amino-acid metabolism are known. They are not common but their consequences are often serious or fatal. Although in some cases there is no effective treatment, early diagnosis is important as some conditions can be managed by dietary modification and/or the use of vitamins. Two of the better known syndromes, homocystinuria and phenylketonuria, are discussed briefly below. Cystinosis, another disorder of amino acid metabolism, is discussed on p. 2555.1. Urea cycle disorders are discussed under Hyperammonaemia on p. 2049.3.

Homocystinuria. Homocystinuria in its classical form is an autosomal recessive disorder in which a genetic deficiency of the enzyme cystathionine synthetase (cystathionine β-synthase), results in accumulation of homocysteine (oxidised extracellularly to homocystine).[1,2] Manifestations may include mental retardation, atherosclerosis, thromboembolism, osteoporosis, and ocular symptoms including lens dislocation, glaucoma, cataract, and retinal detachment.[2] Dietary restriction of methionine with cystine supplementation has been used for treatment; some patients may respond to treatment with B vitamins (pyridoxine, cobalamins, and folic acid),[1-3] or to betaine.[2-4] Compliance with betaine is often poor, however; choline, which is converted to betaine by the liver, has also been given, although experience with its use is limited.[3]

Phenylketonuria. Phenylketonuria is an autosomal recessive disorder that is usually due to a defect in the enzyme phenylalanine hydroxylase. This results in raised blood concentrations of phenylalanine in the neonate, and if untreated produces a syndrome of skin rash, depigmentation, hypertonia, seizures, and severe mental retardation.[5,6] Variants of phenylalanine hydroxylase deficiency include atypical or mild phenylketonuria and hyperphenylalaninaemia; some patients have an inherited defect in the metabolism of tetrahydrobiopterin causing a 'malignant phenylketonuria'.[7]

The disease is controlled by use of a diet very low in phenylalanine,[5,8,9] which if started early can permit relatively normal intellectual development. Protein substitutes are recommended, but the optimal dose remains to be determined; there is some evidence that phenylalanine tolerance increases, and blood phenylalanine levels decrease, when total protein intake from the protein substitute is increased.[10] Controversy exists as to whether dietary restrictions may eventually be relaxed,[7,9] and most consider lifelong metabolic control necessary.[5,11] Metabolic control is important in pregnant women as the consequences of fetal exposure to high phenylalanine concentrations include microcephaly, mental deficiency, and congenital heart disease.[5,12-14]

No consensus exists as to optimal blood concentrations of phenylalanine, although frequent monitoring is necessary. In the UK and USA, values between 2 and 6 mg per 100 mL are usually recommended for neonates, children up to age 12, and pregnant women; for patients over 12 years, concentrations between 2 and 10 mg per 100 mL have been advocated.[5]

High-dose tyrosine does not appear to be an effective alternative to a diet low in phenylalanine.[15-19] Sapropterin (p. 2610.2) is a synthetic form of tetrahydrobiopterin that has been used, with dietary phenylalanine restriction, neurotransmitter replacement, and folinic acid, to treat malignant phenylketonuria;[7,20] it has also shown some promise for the treatment of maternal phenylketonuria.[21,22] Some have suggested sapropterin may even replace a low-phenylalanine diet in certain patients.[23] Enzyme replacement or substitution are under investigation.[6,7,14,24]

1. Isherwood DM. Homocystinuria. *BMJ* 1996; 313: 1025–6.
2. Yap S. Classical homocystinuria: vascular risk and its prevention. *J Inherit Metab Dis* 2003; 26: 259–65.
3. Walter JH, *et al.* Strategies for the treatment of cystathionine β-synthase deficiency: the experience of the Willink Biochemical Genetics Unit over the past 30 years. *Eur J Pediatr* 1998; 157 (suppl): S71–S76.
4. Lawson-Yuen A, Levy HL. The use of betaine in the treatment of elevated homocysteine. *Mol Genet Metab* 2006; 88: 201–7.
5. National Institutes of Health Consensus Development Panel. National Institutes of Health Consensus Development Conference Statement: Phenylketonuria: screening and management. October 16-18, 2000. *Pediatrics* 2001; 108: 972–82. Also available at: http://pediatrics.aappublications.org/cgi/reprint/108/4/972.pdf (accessed 13/01/06)
6. Klim W, *et al.* Trends in enzyme therapy for phenylketonuria. *Mol Ther* 2004; 10: 220–4.
7. Hanley WB. Adult phenylketonuria. *Am J Med* 2004; 117: 590–5.
8. Medical Research Council. Report of the Medical Research Council Working Party on Phenylketonuria. Recommendations on the dietary management of phenylketonuria. *Arch Dis Child* 1993; 68: 426–7.
9. Poustie VJ, Wildgoose J. Dietary interventions for phenylketonuria. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley: 2010 (accessed 24/05/10).
10. MacDonald A, *et al.* Protein substitutes for PKU: what's new? *J Inherit Metab Dis* 2004; 27: 363–71.
11. Cederbaum S. Phenylketonuria: an update. *Curr Opin Pediatr* 2002; 14: 702–6.
12. Rouse B, *et al.* Maternal phenylketonuria syndrome: congenital heart defects, microcephaly, and developmental outcomes. *J Pediatr* 2000; 136: 57–61.
13. Rouse B, Azen C. Effect of high maternal blood phenylalanine on offspring congenital anomalies and developmental outcome at age 4 and 6 years: the importance of strict dietary control preconception and throughout pregnancy. *J Pediatr* 2004; 144: 235–9.
14. American Academy of Pediatrics, Committee on Genetics. Policy statement: maternal phenylketonuria. *Pediatrics* 2008; 122: 445–9. Also available at: http://aappolicy.aappublications.org/cgi/reprint/pediatrics;122/2/445.pdf (accessed 20/04/09)
15. Pietz J, *et al.* Effect of high-dose tyrosine supplementation on brain function in adults with phenylketonuria. *J Pediatr* 1995; 127: 936–40.
16. Smith ML, *et al.* Randomised controlled trial of tyrosine supplementation on neuropsychological performance in phenylketonuria. *Arch Dis Child* 1998; 78: 116–21.
17. Poustie VJ, Rutherford P. Tyrosine supplementation for phenylketonuria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley: 1999 (accessed 13/01/06).
18. van Spronsen FJ, *et al.* Phenylketonuria: tyrosine supplementation in phenylalanine-restricted diets. *Am J Clin Nutr* 2001; 73: 153–7.
19. van Spronsen FJ, *et al.* Phenylketonuria: tyrosine beyond the phenylalanine-restricted diet. *J Inherit Metab Dis* 2001; 24: 1–4.
20. Michals-Matalon K. Sapropterin dihydrochloride, 6-R-L-erythro-5,6,7,8-tetrahydrobiopterin, in the treatment of phenylketonuria. *Expert Opin Invest Drugs* 2008; 17: 245–51.
21. Trefz FK, Blau N. Potential role of tetrahydrobiopterin in the treatment of maternal phenylketonuria. *Pediatrics* 2003; 112: 1566–9.
22. Koch R. Maternal phenylketonuria and tetrahydrobiopterin. *Pediatrics* 2008; 122: 1367–8.
23. Levy HL, *et al.* Sapropterin Research Group. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study. *Lancet* 2007; 370: 504–10.
24. Sarkissian CN, Gámez A. Phenylalanine ammonia lyase, enzyme substitution therapy for phenylketonuria, where are we now? *Mol Genet Metab* 2005; 86 (suppl 1): S22–S26.

Cardiovascular disease. Modification of the diet may be helpful in patients with, or at risk of, cardiovascular disease. In patients with hypertension (p. 1251.1), reduction in salt intake may be tried before starting drug therapy or used as an adjunct to such therapy. Reduction in the total intake of dietary fat, and in particular of saturated fatty acids, is considered important for both the general population and those considered at high risk of ischaemic heart disease (see Cardiovascular Risk Reduction, p. 1246.1). An increased intake of long chain n-3 polyunsaturated fatty acids has been recommended and also a restriction on *trans* fatty acids. Dietary cholesterol should be restricted although it may make less of a contribution to plasma cholesterol levels than dietary saturates.[1-3]

For discussion of the possibility that antoxidant vitamins may reduce the risk of ischaemic heart disease see under Vitamins, p. 2047.1. The link between folic acid

homocysteine, and ischaemic heart disease is discussed on p. 2063.3.

1. DoH. Nutritional aspects of cardiovascular disease. *Report on health and social subjects* 46. London: HMSO, 1994. [COMA report.]
2. Gidding SS, *et al.* Dietary recommendations for children and adolescents: a guide for practitioners. Consensus statement from the American Heart Association. *Circulation* 2005; 112: 2061–75. Also available at: http://circ.ahajournals.org/cgi/reprint/112/13/2061 (accessed 13/01/09) Correction. *ibid.*; 2375. Correction. *ibid.* 2006; 113: e857.
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Coeliac disease. Coeliac disease (gluten-sensitive enteropathy; coeliac sprue) is an inflammatory disorder of the small intestine that results from an immunological reaction to the protein fraction of gluten (p. 2517.2). The inflammation leads to mucosal atrophy with subsequent malabsorption, although the extent and severity of mucosal inflammation varies widely, and some patients are asymptomatic. In adults, anaemia and mild gastrointestinal symptoms that may be confused with irritable bowel syndrome are the usual symptoms. In infants and children there may be growth retardation or failure to thrive, and gastrointestinal symptoms may be more marked. Other nutritional deficiencies, including calcium malabsorption leading to osteopenia, may also occur, and mouth ulcers are also common. Provisional diagnosis usually involves serological tests for IgA anti-transglutaminase 2 or antiendomysial antibodies, and multiple intestinal biopsies.

Treatment of coeliac disease involves a strict, life-long, gluten-free diet. Nutritional supplements may be necessary at the start of treatment but can usually be stopped once mucosal recovery has occurred. Diagnosis is confirmed by clinical improvement or normalisation of the mucosa on repeat biopsy after 3 to 4 months. Dermatitis herpetiformis (p. 1683.2) is a non-gastrointestinal manifestation of coeliac disease. Patients may have no gastrointestinal symptoms, although mucosal abnormalities are generally apparent on biopsy. These patients also respond to a gluten-free diet.

Coeliac disease is associated with other auto-immune diseases, including type 1 diabetes, thyroid disease, and IgA deficiency. Patients with coeliac disease have an increased incidence of small-bowel lymphoma and a slight increase in the incidence of some other gastrointestinal cancers. There is some evidence that this incidence is reduced in patients maintaining a strict diet.

Patients who do not respond to or relapse while on a strict gluten-free diet are considered to have refractory coeliac disease, which can be classified as type 1 or 2. Type 1 is responsive to corticosteroids and other immunosuppressants and only rarely evolves into enteropathy-associated T-cell lymphoma, whereas type 2 is considered a premalignant condition with about half of patients developing T-cell lymphoma within 5 years of diagnosis. Refractory type 2 coeliac disease and T-cell lymphoma is treated with cytotoxic chemotherapy (see Lymphomas, p. 695.3), although results have been disappointing; autologous haematopoietic bone marrow transplantation has induced remissions in some patients, although relapses have occurred.

Alternative or adjunctive treatments to a gluten-free diet are being investigated. Therapies with an intraluminal action aim to reduce gluten immunogenicity by modifying wheat strains or pretreating flour, or preventing the uptake of gluten by the intestinal epithelium. Another approach is to modify the immune response; in refractory disease or enteropathy-associated T-cell lymphoma, systemic T-cell or cytokine antagonists such as the CCR9 chemokine receptor inhibitor CCX-282 have been tried. Desensitisation or attempted restoration of tolerance to gluten is also being studied.

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Diabetes mellitus. Dietary control is important in both type 1 and type 2 diabetes mellitus (p. 459.1). The goals of dietary modification are to maintain glucose concentrations in the normal range or as close to normal as possible, and a lipid and lipoprotein profile and blood pressure that reduce the risk of macrovascular disease.

Fish odour syndrome. Fish odour syndrome (trimethylaminuria) is an inherited metabolic disorder in which there is impaired hepatic *N*-oxidation of trimethylamine. Trimethylamine is formed in the intestine by bacterial degradation of foods rich in choline and carnitine, and is readily absorbed from the gut. If not oxidised in the liver, it is excreted in the breath, urine, sweat, and vaginal secretions. It smells of rotting fish, and has a high olfactory potency. Treatment involves dietary modification to avoid choline-rich foods such as eggs, liver, peas, soya beans, and sea fish. Short-term treatments to reduce the intestinal flora, and thereby decrease the production of trimethylamine, are occasionally used; examples include metronidazole, neomycin, and lactulose.

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Hepatic encephalopathy. Restriction of dietary protein intake is a mainstay of the treatment of hepatic encephalopathy, but care is required to avoid malnutrition (see p. 1808.2).

Inflammatory bowel disease. In inflammatory bowel diseases (p. 1808.3) dietary modification or supplementation may often be necessary to maintain the nutritional status of the patient. Specific nutritional problems include protein deficiency, fluid and electrolyte depletion, iron deficiency, and deficiencies of certain minerals, vitamins and trace elements, such as magnesium, calcium and vitamin D, vitamin K, and folic acid.[1,2] Supplementation may be oral, nasogastric, or parenteral. In general, although they are considered to have equal efficacy,[3] enteral feeding is preferred to parenteral nutrition. The latter is generally reserved for those who cannot tolerate the enteral route, for perioperative use, or for specific clinical circumstances such as bowel obstruction or perforation.[4,5]

Improvement in nutritional status, elimination of dietary antigens, down-regulation of inflammatory cytokines or up-regulation of anti-inflammatory cytokines, or alteration in bacterial flora are also possible mechanisms whereby nutritional therapy may exert a **therapeutic** effect in inflammatory bowel disease.[5-7] Although controversial as primary therapy, enteral feeding, particularly with elemental diets, has been shown to be effective in the treatment of active *Crohn's disease*,[8] but probably less effective than corticosteroids.[9-11] It may also have some benefit in maintaining remission.[12] There are beneficial effects in children with growth failure, which is exacerbated by corticosteroids,[13,14] and some consider enteral nutrition the first choice of management in paediatric patients with Crohn's disease.[3] Combining an elemental diet with low-dose corticosteroids has also been suggested as a therapeutic approach in children, although it is as yet untested.[14] Adult patients with Crohn's disease who are considered candidates for enteral nutrition include those on potentially high cumulative corticosteroid doses, or who are corticosteroid-refractory or corticosteroid-intolerant, or those at high risk for osteoporosis.[5]

Data are considered insufficient to assess the efficacy of enteral nutrition in *ulcerative colitis*.[5,7]

The term **elemental diet** was originally coined to describe diets containing free amino acids and glucose and was often prefixed by the phrase 'chemically defined'. However, it came to embrace diets whose nitrogen sources included peptides and were often also called predigested diets. It was suggested[15] that the term elemental diet could be used for either type but that for those with an amino acid nitrogen source the term chemically defined elemental diet should be used whereas for those with a peptide nitrogen source predigested elemental diet was suitable. The term polymeric diet should be used for those diets with a whole protein nitrogen source (such as milk or soya).

There appears to be little difference between formulas in terms of therapeutic response, although compliance may be better with polymeric feeds due to the unpalatability of elemental diets.[3,5,13] Several different elemental diets are available; some contain long-chain triglycerides as the fat source, but for patients with impaired fat digestion, medium-chain triglycerides are considered preferable.[1] There is some suggestion that the effectiveness of enteral diets in treating active Crohn's disease might relate to the fat rather than nitrogen composition,[1,3,7] with less inflammation occurring with those containing the fewest long-chain triglycerides.[1]

Other potentially beneficial components of diets for Crohn's disease include omega-3 triglycerides, which may have beneficial effects on inflammatory processes, and in achieving remission;[4,14,16] no clinical benefit has been seen with fatty acid or dietary fish oil supplementation in active ulcerative colitis.[17] Short-chain fatty acids have been proposed as a means of increasing butyrate levels, which may have a direct anti-inflammatory effect on the colon; butyrate enemas have shown benefit in ulcerative colitis.[5,13,17] The use of a substrate ('pre-biotic') to deliver short-chain fatty acids, or directly delivering probiotics to the intestine, have also been proposed.[5,17] Glutamine has been suggested as being beneficial for epithelial integrity of the small intestine,[1,16] although useful data are lacking.[1,4,5]

Much interest also surrounds the use of **growth factors** in enteral formulas, such as epidermal growth factor or transforming growth factor-β, which may have anti-inflammatory actions on the gut mucosa.[7]

Elimination diets, whereby foods are slowly reintroduced once remission has been achieved, aim to reduce relapse rates in Crohn's disease, but the process is prolonged and complicated.[1,3] In a study of patients with ulcerative colitis in remission, consumption of red and processed meat, protein, or alcohol increased the likelihood of relapse;[18] these foods are rich sources of sulfur or sulfate, and sulfide toxicity may be important in the pathogenesis of ulcerative colitis.[17] There is also some suggestion that titanium may be harmful in Crohn's disease, and diets low in titanium have been advocated, with preliminary data suggesting a benefit.[3]

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Malignant neoplasms. For a discussion of the possible link between an increased intake of antoxidant vitamins and a reduced risk of developing malignancies, see under Vitamins, p. 2047.3.

Obesity. Obesity is relatively common in the developed world, and is accompanied by an increased risk of cardiovascular disease, diabetes, and other disorders. Methods such as dietary modification, behaviour therapy, and exercise with adjunctive drug therapy, where indicated (see p. 2315.1) can produce weight loss, but the essence of treatment is a reduction in calorific intake, usually by about 300 to 500 kcal daily in patients with a body-mass index (BMI) of 27 to 35, and 500 to 1000 kcal in those with a BMI greater than 35. This would be expected to produce a weight loss of about 0.25 to 1 kg weekly. Very low calorie diets (less than 600 to 800 kcal daily) should only be considered after the failure of determined attempts to lose weight by conventional calorie restriction. For weight loss to be achieved and sustained, eating behaviour must be permanently modified, which may pose difficulties. The proportion of calories from fat in particular, and also alcohol and sugars should be reduced and those from high carbohydrate foods increased. It is obviously important to maintain an adequate intake of essential nutrients.

Artificial sweeteners or other non-sucrose sweeteners are often used as part of weight-reducing diets.

Renal failure. Low-protein diets may be of value in preventing or slowing the progression of chronic renal failure (p. 1779.1). Patients with renal failure who adopt a protein-restricted diet have fewer symptoms of uraemia than those on a normal diet. Some results have also suggested that protein restriction can slow the progression of renal failure, but the value of low-protein diets in delaying the onset of end-stage renal disease has been the subject of much controversy.[1] Two large multicentre studies provided little evidence of a substantial benefit,[2,3] but a systematic review[4] provided support for dietary protein restriction in adults, although another such review[5] could not find evidence of benefit in children. *Animal* studies

suggest that modification of the protein source from animal to soya protein might slow renal disease progression, especially at high intakes.[6]

Generally, low-protein diets providing between 600 to 800 mg/kg daily have been recommended,[1,7-9] although a very low-protein diet providing 300 mg of vegetable origin protein, supplemented with a mixture of essential amino acids, has been recommended for highly motivated patients with advanced renal failure.[1]

Once the patient starts dialysis, however, protein losses through the dialysis membrane or peritoneum may require an increase of protein intake to between 1.2 and 1.3 g/kg daily.[7,9] Because energy intake needs to remain constant, food selection has to change qualitatively.[7] Sodium, potassium and phosphate intake also need to be controlled.[7,9] During dialysis, restricting dietary phosphate while maintaining sufficient protein intake may be difficult, and modification of the protein source may be necessary.[10]

After kidney transplantation, if renal function stabilises, protein restriction is again advisable;[7] between 1.3 and 1.5 g/kg daily is recommended initially, then 1 g/kg daily for maintenance.[9] However, adverse effects of immunosuppressant drugs may complicate the dietary targets, with the patient at risk of diabetes, dyslipidaemia, and possible hypertension.[7] The importance of salt restriction and reduction of the sodium dialysate content in controlling hypertension in renal patients has been emphasised.[11]

It has been suggested that the benefit of other interventions such as the use of ACE inhibitors,[12] as well as the difficulties in obtaining patient compliance with such a restrictive diet,[13] may have limited the benefits to be obtained from protein restriction, but there is also evidence that response and outcome vary depending on the cause of renal failure.[3,14]

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Enteral and Parenteral Nutrition

Malnutrition of varying degrees is not uncommon in hospitalised patients, and some form of nutritional support is important in patients who cannot eat an adequate normal diet. Such support should provide for the patient's requirements for energy, in the form of carbohydrate and fat, nitrogen as amino acids or protein, water and electrolytes; where appropriate, vitamins and trace elements should also be supplied. Indications for nutritional support may include unconsciousness, obstruction or inability to swallow, inflammatory bowel disease, fistula, short bowel syndrome, and weakness and malnutrition associated with trauma, surgery, or malignant disease. If possible, nutritional support should be by the enteral route; it is easier, more physiological, and less prone to complications than the parenteral route.

Enteral nutrition includes feeding by mouth, by nasogastric or nasoenteric tube, or directly into a gastrostomy or other enterostomy. It may be supplemental, if normal food intake is possible but inadequate, or total. Individual patients vary in their requirements according to age, size, and metabolic state, but a diet supplying 2000 to 3000 kcal of energy and 10 to 15 g of nitrogen (as 60 to 90 g of protein) in 2 to 3 litres of fluid is fairly typical; because absorption from the gastrointestinal tract is incomplete requirements are higher than by the parenteral route. Preparations containing whole protein (often derived from milk or soya) are generally preferred; elemental diets, in which nitrogen is supplied as amino acids or oligopeptides, are less well tolerated and less palatable, although they may have a role in impaired digestion or when a zero-residue diet is desired.

Although preferred to parenteral nutrition, enteral feeding is not without complications. Patients may be at risk of oesophagitis, aspiration, and regurgitation as a result of the tube insertion; other potential problems include diarrhoea, nausea and vomiting, gastric retention, hyperglycaemia, fluid and electrolyte disturbances, and microbial contamination of the feed regimen.

Parenteral nutrition is reserved for situations in which it is impossible to meet nutritional requirements by the enteral route. Like enteral nutrition it may be given supplementally or as the sole source of body requirements (total parenteral nutrition or TPN). It is normally given via a dedicated central venous catheter. However, peripheral veins are increasingly used for short-term feeding. This reduces some complications and insertion is less complex, but because of the risk of thrombophlebitis the feeds used should have low osmolality and neutral pH. Other measures to delay the development of peripheral thrombophlebitis are mentioned under Adverse Effects and Precautions, p. 2045.1.

The formulation of the nutritional solution must be adjusted according to the patient's requirements. The solution should supply sufficient energy to allow for the resting energy expenditure (around 25 kcal/kg in the average adult) but must also take into account any increased energy expenditure of illness. Conversely, starvation can reduce resting metabolism and energy requirements. Various formulae exist for the calculation of energy expenditure in patients. Energy is best supplied in the form of carbohydrate (at least 30%, and preferably 60% of energy requirements should be in this form) and fat. Glucose is the optimal carbohydrate energy source, while fat is supplied as a lipid emulsion, often of soya oil. Nitrogen is supplied as amino acids, but to ensure that these are used for protein synthesis rather than as sources of energy it is important to control the ratio of non-protein energy to nitrogen in the solution. A ratio of 150 to 200 kcal per g of nitrogen is usually considered optimal but in hypercatabolic patients (e.g. in sepsis) lower ratios of 120 kcal per g or less may be appropriate. All essential amino acids are supplied although there is some variation between solutions as to which non-essential amino acids are present.

Parenteral nutrition must also supply the patient's requirements for fluid, essential electrolytes such as sodium, potassium, magnesium, bicarbonate, and calcium (as well as phosphate, since glucose infusion may provoke hypophosphataemia), and, particularly if treatment is prolonged, vitamins and trace elements. If glucose loading produces signs of hyperglycaemia insulin may be added to correct it.

The major complication of parenteral nutrition is bacterial colonisation of the catheter, which can lead to septicaemia. Other problems may include venous thrombosis or air embolism, extravasation due to misplacement of the catheter tip, and metabolic disturbances. Adverse effects of overfeeding include respiratory and hepatic dysfunction. Complications of long-term total parenteral nutrition include gallbladder sludging, gallstones, cholestasis, and abnormal liver function tests.

Stability and compatibility. The complex nature of solutions for parenteral nutrition renders them susceptible to compatibility problems.[1-18] Stability is dependent upon several factors including pH and relative concentrations of the components. Amino acids exert a buffering effect on the overall pH of mixed solutions containing amino acids, glucose, and fat emulsions but amino acids with glucose undergo the Maillard reaction (browning) and the life of combined solutions is therefore limited. Solutions containing electrolytes, particularly divalent cations, are not stable, and aggregation will eventually occur. Additives should be added only if there is known compatibility, and any additions performed aseptically before the start of the infusion.

The most significant cause of precipitation is higher concentrations of calcium and phosphate,[13,18] and the most important factor governing calcium phosphate precipitation is the final pH of the mixture. The pH is itself determined by several factors, including the commercial source of the amino acid infusion, and the final amino acid and glucose concentrations. The use of organic phosphate compounds may reduce the likelihood of precipitation. Trace element precipitation may also occur and amino acid infusions can contain detectable quantities of trace elements as contaminants. The most significant cause of chemical instability is the degradation of specific vitamins, through exposure to light or binding with the plastic of the bag or giving sets. Two particular reactions, the oxidation of ascorbic acid, and the reduction of thiamine, are of concern.

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Uses. Parenteral and enteral nutrition now have an established place either for supplemental use or for providing total nutritional requirements in many conditions. General reviews as well as those pertaining to special groups of patients or disorders have been published.[1-26]

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Adverse effects and precautions. *ENTERAL NUTRITION.* Complications of enteral feeding can arise from mechanical, gastrointestinal, metabolic or other causes, such as infection or aspiration.[1] The most common nutritional complication of enteral feeding is failure to meet nutritional requirements, and overzealous feeding may lead to the 'refeeding syndrome' manifested by glucose intolerance, fluid retention, and electrolyte imbalances.[2-5] High-protein formulas with low water intake may also cause this syndrome.[1] These rapid *metabolic* and electrolyte changes can lead to severe or even fatal cardiopulmonary and neurological problems.[6] To avoid these problems, low levels of feeding for the first few days have been recommended; about 20 kcal/kg daily has been suggested but even this may be too high, especially in patients with existing

electrolyte abnormalities, and about 10 kcal/kg daily may be more suitable for high-risk patients;[3,7] *UK guidelines*[3] suggest that a maximum of 5 kcal/kg daily may be considered in extreme cases (e.g. patients with a BMI less than 14 kg/m^2 or negligible intake for more than 15 days). Mechanical or *physical complications* include displacement or clogging of the tube, or patient discomfort.[1,2,6-8] Many of the problems encountered can be avoided by using a fine bore tube, giving the feed by continuous infusion, and by careful monitoring of the patient for metabolic abnormalities.[9] However, tubes become clogged more often if the calibre of the tube is small, the tube is long, placed in the stomach, the feeding continuous, or if medication is given through the tube.[2,8] Inadequate flushing and protein precipitation may also occur.[6]

Positioning the tube in the small bowel rather than the stomach has been suggested to reduce the incidence of *aspiration*,[2,8,10] although few studies have been done comparing intraduodenal and intragastric feeding in terms of clinical outcomes, and there are concerns about appropriate placement, infection, and reflux.[11] A meta-analysis[12] failed to find any clinical benefit of post-pyloric feeding over gastric feeding in terms of the incidence of pneumonia, length of stay, and mortality; the study was limited by a relatively small number of patients, and did not include patients considered at high risk of aspiration. Prokinetic drugs such as metoclopramide, or erythromycin, have been used to promote gastric emptying and reduce residual gastric volumes.[10-12]

Complexation of the nutrients with aluminium-containing antacids, also given via the tube, may occur and this *deposition* of solid masses may cause oesophageal obstruction.[13]

Diarrhoea in patients receiving enteral nutrition may not necessarily be caused by the tube feeding itself;[14,15] malabsorption, infections and microbial contamination, underlying disease, and concomitant drug therapy can be possible contributors.[1,2,7,16,17] However, enteral feeding has been shown to be associated with increased colonic secretion, which can be reversed by infusion of short-chain fatty acids.[18] Because colonic microflora may play a role in the pathogenesis of diarrhoea associated with enteral feeds, manipulation of the microflora using pre- or probiotics has been suggested as a means of reducing the incidence, duration or severity thereof, and some enteral feeding formulas contain prebiotics. However, few studies have investigated the effect on diarrhoea, and further research is warranted.[17]

While enteral tube feeding and the presence of a nasogastric tube are risk factors for *infection*, optimal nourishment through enteral feeding in high-risk patients unable to tolerate oral nutrition may also improve their immune status.[19]

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PARENTERAL NUTRITION. A common complication of parenteral nutrition is *infection* of the intravenous feeding catheter site,[1-3] which can lead to septicaemia. Infection and colonisation of central venous catheters may be reduced if the catheter is tunnelled through subcutaneous tissue before emerging through the skin.[4] Strict aseptic techniques should be used[1] for changing the dressing or bags containing the nutrient fluids. Misplacement of the catheter has been reported.[3,5] Precipitation of minerals, lipids, and medications can cause line occlusion.[3]

Thrombophlebitis can occur after the use of either peripheral or central veins. Although it has been suggested that infusion of hyperosmolar solutions via a central line is less likely to produce thrombophlebitis, because the feed is immediately diluted by a large volume of blood, major thrombotic complications such as pulmonary embolism and right atrial thrombosis could be more common than hitherto recognised in children and adolescents receiving long term parenteral nutrition via central catheters.[6,7] The use of a fine-bore silicone catheter peripherally may avoid the need for central vein cannulation[8] and there is a lower incidence of thrombophlebitis when fine-bore silicone catheters rather than teflon ones are used for peripheral parenteral nutrition.[9] The use of giving sets with filters may decrease thrombophlebitis during peripheral infusion.[10,11] The addition of heparin or buffer solutions to the feed, and the use of local hydrocortisone and glyceryl trinitrate, have also been reported to prolong the survival of peripheral infusion sites.[11,12] Extravasation may also be a problem, particularly with hyperosmolar solutions, and has led to severe tissue damage; hyaluronidase or thiomucase may be used in the treatment of such extravasation.[13]

Parenteral nutrition may be associated with *atrophic changes* in the mucosal structure and enzymic activity of the intestine, leading to increased permeability with a possible increased risk of bacteraemia and endotoxaemia. These changes, which have been attributed to lack of glutamine (which is unstable in solution), can reportedly be prevented by addition of glutamine-releasing dipeptides to solutions for total parenteral nutrition—see p. 2070.3. Some have questioned the extent of this mucosal atrophy or bacterial translocation associated with parenteral feeding.[14,15]

Prolonged parenteral nutrition has been associated with *hepatobiliary complications*, especially in children;[16,17] cholelithiasis and cholestasis have been reported, with the latter sometimes progressing to liver failure.[16] Although the aetiology is considered multifactorial,[18] contamination of the solution with manganese (see Accumulation under Adverse Effects of Manganese, p. 2081.3) or aluminium[19] has been suggested as one possible cause of the cholestasis.

Aluminium toxicity has also been implicated in the *bone changes*, manifesting as osteomalacia, seen in patients on long-term parenteral nutrition.[3,17] Osteopenia and osteoporosis have also been reported;[17] possible mechanisms include calcium, phosphate, or magnesium deficiencies, vitamin D deficiency or toxicity, vitamin K deficiency, or excessive protein.[3] A review, however, considered the risk to be minimal, with little deleterious effect on cortical bone and an improvement on trabecular bone.[5] Other factors implicated in possible metabolic bone disease include calcium deficiency and vitamin D toxicity.[17]

Other metabolic complications associated with parenteral nutrition include hyperglycaemia, hypoglycaemia, hyperlipidaemia, hypercapnia, acid–base disturbances, and 'refeeding syndrome'.[20] Hyperglycaemia may be due to excessive glucose infusion, and can lead to immunodepression and an increased risk of infection; insulin therapy is indicated if it persists. Hypoglycaemia, although less common, may occur if parenteral nutrition is interrupted or as a result of an insulin overdose. Hyperlipidaemia is caused by excessive fatty acid synthesis from glucose, or impaired lipid clearance. The use of a mixture of medium-chain and long-chain triglycerides (rather than long-chain triglyceride emulsions alone) may result in fewer serum lipid abnormalities since medium-chain triglycerides are oxidised faster than long-chain triglycerides. Overfeeding of total calories and glucose can lead to hypercapnia which can cause acute respiratory acidosis.[20] While most acid–base disturbances are related to the underlying condition, excess chloride or acetate in the parenteral nutrition solution may cause metabolic acidosis or alkalosis, respectively.[17] The 'refeeding syndrome' can occur when severely malnourished patients are given rapid nutritional repletion, leading to fluid and electrolyte imbalances, glucose intolerance, and vitamin deficiencies. These may result in significant or even fatal cardiac, pulmonary, renal, gastrointestinal, and neuromuscular complications. Electrolyte disturbances include sodium retention, hypophosphataemia, hypokalaemia, and hypomagnesaemia; thiamine deficiency may lead to Wernicke's encephalopathy in malnourished patients or in thiamine-deficient patients given high carbohydrate loads.[20]

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Trace Elements

Trace elements are inorganic substances found in small amounts in the tissues and required for various metabolic processes; together with the vitamins (see below) they are sometimes referred to as micronutrients. The elements considered essential are chromium, copper, fluorine, iodine, iron, manganese, molybdenum, selenium, and zinc. Iron, in the form of haem, plays an essential role in oxygen transport while iodine is required by the thyroid for the formation of thyroid hormones; most of the other essential trace elements are cofactors for various enzymes. Boron, nickel, silicon, and vanadium may also be essential, and it has been suggested on the basis of *animal* studies that there might be a requirement for tin.

Well-defined deficiency syndromes exist for copper, iodine, iron, selenium, and zinc; although deficiency of other trace elements is possible, their deficiency syndromes are not well defined because of their ubiquity in the diet. Guidance concerning the intake of various trace elements has been published—see also Human Requirements under Vitamins, p. 2046.1.

References.

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Vitamins

Vitamins are organic substances required by the body in small amounts for various metabolic processes. Most are not synthesised in the body, or are synthesised in small or insufficient quantities. Vitamins are sometimes classified as fat soluble or water soluble. Substances in the vitamin A, D, E, and K groups are generally fat soluble, and biotin, folic acid, niacin, pantothenic acid, vitamins B_1, B_2, B_6, and B_{12}, and vitamin C substances are generally water soluble.

Vitamin deficiency may result from an inadequate diet, perhaps due to increased requirements such as during pregnancy, or may be induced by disease or drugs. Vitamins may be used clinically for the prevention and treatment of specific vitamin deficiency states and details of these uses are provided under the individual drug monographs.

Large doses of vitamins (megavitamin therapy) have been proposed for a variety of disorders, but adequate evidence of their value is lacking. Excessive intakes of most water-soluble vitamins have little effect due to their rapid excretion in urine, but excessive intakes of fat-soluble vitamins accumulate in the body and are potentially dangerous.

Stability. Water-soluble vitamins are liable to degrade in solution especially if exposed to light. Addition of vitamin mixtures to infusion solutions for parenteral nutrition should therefore be carried out as soon as possible before infusion. Solutions should be used within 24 hours of preparation and be protected from light.

Carcinogenicity. For mention of an increased risk of lung cancer in patients receiving betacarotene and vitamin A, and an increased incidence of second primary cancers in patients given vitamin E (and betacarotene initially), see Prophylaxis of Malignant Neoplasms, p. 2047.3. For a dis-

cussion of possible carcinogenic effects in children given vitamin K intramuscularly, see Carcinogenicity, p. 2124.2.

Effects on mortality. Although vitamin supplements have been widely taken in the hope of improving mortality from various diseases, a large systematic review[1] concluded that there was no evidence that antoxidant vitamin supplements improved mortality, and some, such as vitamin A, betacarotene, and vitamin E, might increase it.

For mention of possible adverse effects on mortality with betacarotene supplementation, see Effects on Mortality, p. 2051.3.

For discussion on the effects on mortality with Vitamin A, see p. 2102.1.

For mention of possible beneficial effects of high serum ascorbic acid levels on all-cause mortality, see under Vitamin C, p. 2111.3.

For mention of beneficial effects on mortality with vitamin D supplementation in a mainly elderly population, see UK and US Recommended Dietary Intake, p. 2118.1.

For mention of possible dose-dependent adverse effects on mortality with use of vitamin E, see Effects on Mortality, p. 2121.2.

For discussion of the effects of various antoxidant vitamins on cardiovascular disease and cancer, see Prophylaxis of Ischaemic Heart Disease, p. 2047.1, and Prophylaxis of Malignant Neoplasms, p. 2047.3.

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Human requirements. Vitamins and trace elements are essential nutrients and in many countries guidance has been published concerning their intake.

In the UK various terms are used to define intake:[1]

- estimated average requirement (**EAR**) is used for the requirements of energy, proteins, vitamins, or minerals of a group of people and usually about half will need more and half less than the specified figure
- lower reference nutrient intake (**LRNI**) is applied to proteins, vitamins, or minerals and is that amount that is enough for only a few people who have low needs
- reference nutrient intake (**RNI**) is also applied to proteins, vitamins, or minerals and is an amount that is enough, or more than enough, for about 97% of people in a group
- a safe intake is used to indicate an intake or range of intakes where there is not enough information to estimate EAR, LRNI, or RNI, but rather it is an amount enough for almost everyone but is not so large as to cause undesirable effects
- dietary reference value (**DRV**) is used to cover EAR, LRNI, RNI, and safe intake.

It is emphasised in a 1991 report[1] that these intakes are not meant to be recommendations for any individual or group; they do not reflect either a recommendation that such an amount should be taken daily in the diet or as a supplement. They are intended rather as yardsticks for the assessment of dietary surveys and food supply statistics; to provide guidance on appropriate dietary composition and meal provision; or for food labelling purposes in which case it is envisaged that an EAR will be used.

An Expert Group on Vitamins and Minerals, established in the UK to review data on the safe intake of vitamins and minerals from food and food supplements, recommended the use of safe upper levels (**SULs**). These were the doses of vitamins and minerals that individuals could take daily on a lifelong basis without significant risk to health on the basis of available evidence.[2]

In the USA the National Academy of Sciences has traditionally set recommended dietary allowances (**RDAs**),[3] defined as the levels of intake of essential nutrients that, on the basis of scientific knowledge, are judged to be adequate to meet the known nutrient needs of practically all healthy persons. The allowances are amounts that are intended to be consumed as part of a normal diet. However, new dietary reference intakes (**DRIs**) have been developed,[4] which include 3 reference values in addition to the traditional RDA as follows:

- the EAR is the intake that meets the needs of half the individuals in a group
- the adequate intake is the mean intake level that appears to sustain a desired marker of health, and will be set when there is insufficient evidence to establish an RDA
- the tolerable upper intake level is the maximum intake that is not likely to adversely affect health.

WHO[5] has similar definitions for the EAR and the tolerable upper intake level, but uses the term recommended nutrient intake (**RNI**) for the daily intake which meets the nutrient requirements of almost all healthy individuals in an age- and sex-specific group (set at the EAR plus 2 standard deviations).

Information pertaining to the requirements of specific vitamins and minerals is provided under the individual monographs.

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4. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes: applications in dietary assessment*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309071836 (accessed 21/07/08)
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Supplementation. An adequate dietary intake of vitamins is necessary for good health but whether vitamin supplementation in the absence of any demonstrable deficiency is beneficial or even worthwhile remains debatable.

It is generally considered that healthy persons eating a normal balanced diet should have no need for vitamin supplementation.[1,2] A review of the topic[1] pointed out that the vitamins that people chose for self medication are often not the ones that are actually present in inadequate amounts in their diets and that the commercial preparations available often do not make it clear whether the amounts they contain are near the physiological requirements or many times greater. Supplementation should concentrate on groups of people at risk of deficiency such as neonates, who need vitamin K; pregnant and lactating women, who need calcium, folic acid, and iron; and certain groups who need vitamin D; vegans and their infants may require vitamin B_{12} supplements. A multivitamin supplement might be considered for some groups such as the elderly and those with reduced calorie intake.[1,3] However, it might be difficult to find a good multivitamin preparation containing all 13 vitamins but no non-vitamins. Also with many of the multivitamin preparations the doses and ratios varied inexplicably.[1]

A review[4] of supplementation specifically in children concluded that, provided schoolchildren and adolescents eat a wide variety of foods, there was no need for vitamin supplementation. However, it was recommended that supplementation with vitamins A, C, and D should be given to those between the ages of 6 months and 2 years and preferably up to the age of 5 years. Several authorities in different countries have set upper safety limits for vitamins; these vary considerably.[5]

Vitamin and mineral supplementation has been investigated in various disorders (see below). However, a systematic review for the National Institutes of Health in the USA led to the consensus that evidence was insufficient to recommend either for or against the use of multivitamin and mineral supplements to prevent cancer and chronic disease.[6,7] (For a systematic review that concluded against use of antoxidant supplements see Effects on Mortality, above.)

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2. Waine C. Vitamin and mineral supplements. *Pharm J* 2001; 267: 352–4.
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7. NIH State-of-the-Science Panel. National Institutes of Health State-of-the-science conference statement: multivitamin/mineral supplements and chronic disease prevention. *Ann Intern Med* 2006; 145: 364–71.

EYE DISORDERS. Vitamin therapy has been investigated for the prophylaxis or treatment of various eye disorders. **Vitamin A** is used in the management of xerophthalmia, see p. 2101.1. There is some suggestion of benefit with vitamin A for retinitis pigmentosa, p. 2101.1; results with **vitamin E** are conflicting. Vitamin E has been used for the treatment of retinopathy of prematurity, p. 2120.3. For discussion of the effect of **vitamins C, E, betacarotene**, and **zinc** on age-related macular degeneration, see under Betacarotene, p. 2051.2.

HIV INFECTION AND AIDS. Low serum micronutrient concentrations are common in HIV-positive individuals, especially in the developing world; malabsorption, anorexia, diarrhoea, and increased energy demands contribute to malnutrition,[1,2] which in turn contributes to immune impairment and increased mortality. It is generally agreed that in the setting of poverty and lack of adequate nutrition, provision of food programs and/or some form of supplementation is vital,[3] as an adjunct to antiretroviral therapy,[1,2,4] but the specific benefits of vitamin supplementation are extremely unclear, and recommendations have therefore varied.[1,2,4,5]

Conflicting results have been seen in studies of **vitamin A** supplementation (see p. 2100.2). Other studies have suggested that **multivitamin** supplementation, with or without other micronutrients such as selenium and zinc might have some benefits,[4] including increases in CD4+ and CD8+ cell counts,[6-8] in some cases with the suggestion that this delayed disease progression[8] or decreased adverse pregnancy outcomes.[7] However, an unexpected increase in genital shedding of HIV-1 has also been reported,[6] and a meta-analysis failed to show that multivitamin supplementation during pregnancy prevented vertical transmission or premature delivery, or improved childhood mortality at 1 year.[5] In contrast, a later systematic review[4] considered that the evidence did suggest some benefits to both pregnant and lactating women and their offspring from maternal multivitamin supplementation, and multivitamins might also be of benefit in patients co-infected with HIV and tuberculosis. However, antiretroviral therapy remained the one intervention that had consistently been shown to reduce morbidity and mortality and improve nutritional status in HIV-infected patients.

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8. Fawzi WW, *et al.* A randomized trial of multivitamin supplements and HIV disease progression and mortality. *N Engl J Med* 2004; 351: 23–32.

INFECTION. **Vitamin A** has an important role in the prevention of complications from measles (see p. 2100.3), but evidence for benefit in respiratory-tract infections is less compelling (see p. 2100.3). Some studies show evidence of benefit for **vitamin C** in treating the common cold (p. 951.1), but routine high-dose prophylaxis is not considered justified. **Vitamin E** has shown conflicting results in respiratory-tract infections, see p. 2120.3.

For a discussion of the role of vitamins in HIV infection and AIDS see above.

MENTAL FUNCTION. Giving vitamin and mineral supplements to children was reported in 1988 to increase non-verbal *intelligence*[1] and the topic has since remained highly controversial. In the next 2 years more studies were published but these failed to substantiate the earlier possible effect and concluded that vitamin supplementation did not improve mental functioning or reasoning in children.[2,3] Suggestions were made shortly after these publications that there might be a subset of children with poor nutritional status who would receive some benefit[4] but this again was disputed.[5]

In 1991 another study was published,[6] this time coinciding with the launch of the proprietary product used in the study, with the publication of a book on the subject, and with the showing on British television of a documentary concerning the study. This study purported to show that supplementation with exactly the recommended dietary allowances of vitamins improved the IQ of children, a finding that was said not to occur significantly with other quantities of vitamin supplementation. This view attracted extremely harsh criticism[7-9] from physicians, nutritionists, psychologists, and epidemiologists.

Despite conflicting data on the effect of **vitamin E** intake on cognitive decline, US guidelines have suggested that vitamin E be considered in patients with *Alzheimer's disease* in an attempt to slow progression of the disease. A subsequent meta-analysis found no evidence of efficacy of vitamin E in cognitive impairment (see Dementia, p. 2120.2). A cohort study found low **folate** concentrations to be the predominant risk factor for cognitive decline in elderly people.[10] Raised homocysteine concentrations have also been found in patients with cognitive decline and dementia.[11] While a 2-year controlled study in elderly patients without cognitive impairment found that daily homocysteine-lowering treatment with folate, **vitamin B_6**, and **vitamin B_{12}** did not improve cognitive performance,[12] another found that daily folic acid supplementation for 3 years significantly improved measures of cognitive function.[13] A meta-analysis,[14] which included the latter study, came to the conclusion that the few studies carried out provided no consistent evidence either way that folic acid, with or without vitamin B_{12}, had a beneficial effect on

the cognitive function of elderly people with or without dementia. A subsequent placebo-controlled study[15] in patients with mild to moderate Alzheimer's disease given folic acid, vitamin B_6, and vitamin B_{12} supplements to lower homocysteine concentrations did not show any slowing of cognitive decline. Depression was also reported more often in supplemented patients, a surprising result given the reported association between raised homocysteine levels and depression (see below). Routine supplementation was therefore not recommended for these patients in the absence of vitamin B deficiency.

Similarly, low folate concentrations and increased homocysteine concentrations have been implicated in *depression*, and supplementation has been proposed,[11] both as monotherapy, or as a means of augmenting antidepressant efficacy.[16] Although supplementation with folic acid, vitamin B_6, and vitamin B_{12} failed to show any benefit over placebo on the incidence or severity of depression in 299 elderly men, the study was underpowered and did not take into account use of antidepressants.[17]

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PREGNANCY. **Folic acid** protects against the development of neural tube defects (p. 2064.3) and supplementation during pregnancy is advised; **vitamin B_{12}** supplementation may also be warranted. Antenatal supplementation with **iron** plus folic acid or micronutrients may have further benefits for the child, see Iron-deficiency Anaemia, p. 2073.2. **Vitamin A**, however, may be teratogenic and maximum intakes in pregnancy have been recommended, see p. 2102.1. The risks to the fetus of untreated maternal hypoparathyroidism are considered greater than the risks of hypercalcaemia due to **vitamin D** therapy (see p. 2117.3). Systematic reviews[1,2] of supplementation in pregnancy lacked enough data to indicate whether **vitamin C** or **E**, alone or with other supplements, were of benefit. There was some suggestion of decreased risk of developing pre-eclampsia with either vitamin C or E; however, preterm births may have increased with vitamin C supplementation.

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PROPHYLAXIS OF ISCHAEMIC HEART DISEASE. Hypercholesterolaemia is a major risk factor for the development of atherosclerosis and consequently ischaemic heart disease. Since oxidation of lipids, particularly low-density-lipoprotein (LDL) cholesterol,[1] has been proposed as a factor in atherogenesis, the possibility of preventing atherosclerosis by the use of dietary antoxidants such as **vitamins E** and **C** and **betacarotene** has been investigated. A six-year study of supplementation with vitamins C and E in hypercholesterolaemic patients showed a slowing of atherosclerotic progression, especially in men.[2] Prospective epidemiological studies have revealed a reduced risk of ischaemic heart disease in individuals taking vitamin E supplements,[3,4] and those with a high carotene intake (particularly smokers).[3] In a further prospective cohort study,[5] dietary vitamin E consumption, but not vitamin E supplementation, was associated with decreased risk of death from ischaemic heart disease. Intake of vitamin C, however, did not appear to be associated with a decreased risk of ischaemic heart disease in these studies,[3-5] although another study[6] found a significantly lower risk in those taking vitamin C supplements. Data from some studies assessing serum or fat concentrations also provide evidence that high betacarotene concentrations are associated with decreased cardiovascular disease.[7-9]

However, despite these promising results, randomised placebo-controlled studies have failed to find any benefit for betacarotene supplements in the primary or secondary prevention of ischaemic heart disease, and those for vitamin E supplements are inconclusive. In the Alpha Tocopherol, Beta Carotene Cancer Prevention (ATBC) study, which monitored cardiovascular disease as a secondary end-point, vitamin E was not associated with a decreased incidence of ischaemic heart disease, and betacarotene was associated with a small increased risk.[10] In further analyses, neither supplement appreciably altered the incidence of angina pectoris,[11] nor showed any beneficial effect on cardiovascular deaths in the subset of men with previous myocardial infarction.[12] It has been suggested that the lack of effect of vitamin E in this study may be due to an insufficiently high dose of tocopherol. Similarly, neither the Betacarotene and Retinol Efficacy Trial (CARET)[13] nor the Skin Cancer Prevention Study[9] found an effect for betacarotene supplementation on the risk of death from cardiovascular disease.

In studies specifically on cardiovascular end-points, no benefit from betacarotene supplements was seen in a large, randomised, placebo-controlled study[14] in healthy men. Studies of supplementation with high-dose vitamin E in patients with evidence of ischaemic heart disease,[15] or after *myocardial infarction*,[16] failed to show any beneficial effect on cardiovascular deaths, although in one study[15] there was a reduction in non-fatal myocardial infarction and major cardiovascular events. The Heart Outcomes Prevention Evaluation (HOPE) study also showed that vitamin E treatment for 4 to 6 years had no effect on cardiovascular events in high-risk patients;[17] further follow-up[18] raised the possibility of an increased risk of heart failure with vitamin E. Long-term (7 to 10 years) vitamin E or vitamin C supplementation failed to reduce the incidence of cardiovascular events in low-risk patients in the Physicians' Health Study II;[19] although there was no difference in the rate of heart failure with either vitamin, an increase in haemorrhagic stroke was noted with vitamin E use. Another large-scale study, the Heart Protection Study, assessed the effect of a 'cocktail' of vitamin E, vitamin C, and betacarotene on the development of ischaemic heart disease in high-risk subjects, and again found no evidence of benefit.[20] Another study[21] using a similar cocktail in patients with established heart disease found no effect on clinical outcome. In view of the lack of evidence of benefit with vitamin supplements, it has been recommended that the emphasis should instead be on consuming a balanced diet including antoxidant-rich fruits, vegetables, and whole grains rather than vitamin supplements;[22,23] authors of a meta-analysis[24] of studies of antoxidant vitamins for the prevention of cardiovascular disease concluded that, in view of a possibly harmful effect of betacarotene and inefficacy of vitamin E, the use of these supplements be discouraged. It has been pointed out[25] that differences between the observational and clinical studies may be due to intrinsic differences between individuals who choose to take supplements and the high-risk populations studied in randomised studies, who may be less amenable to cardiovascular risk reduction with antoxidant supplementation. It has also been suggested[26] that high-dose antoxidants may only benefit patients who suffer from particularly high levels of oxidative stress. After 18 months of vitamin E supplementation, high-risk patients with diabetes mellitus and the haptoglobin 2-2 genotype (associated with reduced antoxidant protection) had a reduced incidence of cardiovascular events, particularly non-fatal myocardial infarction. A pharmacogenomic approach has been proposed to identify those who might benefit from treatment.

For a discussion of the possibility that **folic acid** and **vitamin B** may reduce ischaemic heart disease through a homocysteine-lowering effect, see p. 2063.3. For uncertainty about the value of **vitamin D** supplementation in preventing cardiovascular disease see p. 2115.1.

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PROPHYLAXIS OF MALIGNANT NEOPLASMS. There is evidence that a diet rich in fruit and vegetables is associated with a lower incidence of malignant disease, particularly of the respiratory and digestive tracts.[1] It has been hypothesised that some of the benefits of such a diet derive from the role of antoxidant vitamins such as the carotenoids and vitamins C and E in scavenging free radicals.[2,3] However, it is by no means certain that these are the only, or necessarily the most important, dietary components responsible for benefit, since components such as dietary fibre may also play a role. In addition, different antoxidants may vary in their properties and efficacy,[3,4] and the appropriate dosage remains largely conjectural, and perhaps as a result the evidence of benefit is often conflicting.

Several clinical studies of the use of **vitamin A** or **betacarotene** in the secondary or primary prevention of malignancy have been reported. Prolongation of disease-free interval in patients with various malignant neoplasms was reported in 1 study of betacarotene,[5] and others reported remission of oral leucoplakia (p. 750.3) in patients treated with betacarotene and vitamin A,[6,7] or betacarotene alone.[8] Vitamin A alone was reported to reduce the incidence of primary tobacco-related neoplasms in a study of patients treated surgically for lung cancer.[9] In a prospective, cohort study,[10] vitamin A intake, including preformed vitamin A and carotenoids, was associated with a reduced risk of breast cancer among smokers. However, other results have largely failed to substantiate any benefit for secondary prevention. No reduction in the incidence of new skin cancers,[11-13] or in malignant transformation of cervical dysplasia,[14] or in new colorectal adenomas[15] was reported in other studies. In a primary prevention study, a combination of betacarotene, vitamin E, and selenium was associated with a reduction in stomach and oesophageal cancers in a population at high risk of these cancers and with a diet low in micronutrients in China.[16] In contrast, other primary prevention studies have failed to show any benefit, and possibly some harm, from betacarotene supplements in well-nourished populations. A study in smokers[17-19] showed an increase in lung cancer and associated mortality in those receiving betacarotene, but not those receiving vitamin E. Similarly, an increased risk of

lung cancer was noted in recipients of betacarotene with vitamin A in another study in individuals at high risk of lung cancer, and this study was stopped early as a result.[20,21] In a 6-year follow-up,[22] this risk was found to persist, albeit at lower and not statistically significant levels. A third study in healthy men found no benefit or harm for betacarotene supplements in terms of incidence of malignant neoplasms, including those of the lung;[23] a subgroup analysis of this study suggested that supplementation may reduce the risk of prostate cancer in those men with low baseline betacarotene levels.[24] Among subjects with colorectal adenoma,[25] who neither smoked nor drank alcohol, betacarotene supplementation was associated with a decrease in the risk of recurrent adenoma, but risk was increased in those who smoked or drank alcohol. A meta-analysis[26] of studies of antoxidant supplementation found that betacarotene had no anticarcinogenic effects on gastrointestinal cancer, and that given alone, it increased mortality. When given with vitamin A and E, mortality increased further. A further systematic review and meta-analysis[27] found that betacarotene supplementation was associated with an increased incidence of cancer among smokers, but not among non-smokers. There was also a trend towards increased cancer mortality with betacarotene supplementation. A 24% increase in the risk of lung cancer was reported in current smokers taking betacarotene supplements in a meta-analysis of 4 studies in high-risk patients.[28]

Vitamin C has also been proposed for prevention of malignancy but there is no real evidence to justify it. It certainly appears to be ineffective as adjuvant therapy in the treatment of advanced malignancy,[29] and the incidence of prostate or total cancer was not reduced by vitamin C supplementation in a large, placebo-controlled study.[30] Combination with betacarotene and vitamin E also failed to show any effect in preventing colorectal adenoma.[15] At physiological concentrations vitamin C is an important antoxidant,[3] but while low serum ascorbic acid concentrations have been inversely related to cancer mortality,[31,32] supplementation is unlikely to be justified in anyone eating a balanced diet.[1]

There is epidemiological evidence that **vitamin D** has protective effects against the development of malignant neoplasms,[33] but it is still unclear whether supplementation, and if so to what degree, would be appropriate—see also p. 2116.1.

Vitamin E substances are also known to play an important antoxidant role in the body. *Animal* studies have suggested that they should inhibit tumour production, and the Chinese study mentioned above found combined antoxidant therapy including vitamin E to be of benefit in the primary prevention of stomach and oesophageal cancers.[16] Other studies in western populations have generally been disappointing; vitamin E had no effect on lung cancer incidence in those at risk,[17,18] and did not prevent the development of new colorectal adenomas.[15] In a study of patients with head and neck cancer, supplementation with vitamin E led to a higher incidence of second primary cancers and reduced cancer-free survival; patients on supplements had initially also been given betacarotene. While noting the fact that the study population were at high-risk for second primary cancers, the authors cautioned against the use of high-dose vitamin E supplements for cancer prevention.[34] There is also suggestion of increased all-cause mortality with high-dose vitamin E (see p. 2121.2). However, further analysis of the lung-cancer study[35] suggested that vitamin E may have protected against prostate cancer. Despite preliminary evidence that selenium (see p. 2087.2) or vitamin E supplementation may reduce the risk of prostate cancer, a large, randomised, controlled study[36] found no evidence of benefit with either selenium or vitamin E supplementation alone or vitamin E plus selenium. Similarly, vitamin E supplementation did not reduce the risk of prostate or total cancer in another large, placebo-controlled study.[30]

Results from the Nurses' Health Study have indicated that prolonged use of multivitamins was associated with reduced risk of developing cancer of the colon.[37] This effect was thought to be due to the **folate** component and could be demonstrated after 15 years of use, but not after shorter-term ingestion. Dietary folate was also associated with a modest reduction in risk for colon cancer, and folic acid intake might reduce the risk of breast cancer, especially in those regularly consuming alcohol.[38,39] Combined treatment with folic acid, vitamin B_6 and vitamin B_{12} had no effect on the overall risk of invasive cancer or breast cancer among women at high risk of cardiovascular disease.[40] For the suggestion that folic acid may have dual modulatory effects on carcinogenesis, see Carcinogenicity, under Folic Acid, p. 2065.3.

Concerns have been raised about the potential for antoxidants to protect tumour cells as well as healthy cells from oxidative damage generated by radiation therapy and some chemotherapy. Although data are limited and sometimes conflicting, some have suggested that the use of antoxidant supplements should be discouraged during radiotherapy or chemotherapy.[41]

While a diet involving frequent consumption of fruits and vegetables is likely to be beneficial,[1,42] others have also suggested that these associations may have been overstated, and that weight control and regular exercise should be prioritised.[38]

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Alanine *(BAN, USAN, rINN)*

A; Ala; Alaniini; Alanin; Alanina; L-Alanina; Alaninas; L-Alanine; Alaninum; NSC-206315; Аланин.

L-2-Aminopropionic acid.

$C_3H_7NO_2$=89.09

CAS — 56-41-7.

UNII — OF5P57N2ZX (L-alanine); 1FU7983T0U (DL-alanine).

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

Ph. Eur. 8: (Alanine). A white or almost white crystalline powder or colourless crystals. Freely soluble in water; very slightly soluble in alcohol. Protect from light.

USP 36: (Alanine). White, odourless, crystals or crystalline powder. Freely soluble in water; slightly soluble in 80% alcohol; insoluble in ether. pH of a 5% solution in water is between 5.5 and 7.0. Store in airtight containers.

Profile

Alanine is an aliphatic non-essential amino acid. It is used as a dietary supplement. The dipeptide *N* (2)-L-alanyl-L-glutamine is used similarly.

The isomeric compound β-alanine (3-aminopropionic acid), which does not have a chiral centre, is a precursor of the muscle peptide carnosine, and has been promoted for its possible benefits in decreasing fatigue and increasing exercise performance in athletes.

Hypoglycaemia. References to the investigational use of alanine in the management of insulin-induced hypoglycaemia.[1-5]

1. Wiethop BV, Cryer PE. Glycemic actions of alanine and terbutaline in IDDM. *Diabetes Care* 1993; 16: 1124–30.
2. Wiethop BV, Cryer PE. Alanine and terbutaline in treatment of hypoglycemia in IDDM. *Diabetes Care* 1993; 16: 1131–6.
3. Saleh TY, Cryer PE. Alanine and terbutaline in the prevention of nocturnal hypoglycemia in IDDM. *Diabetes Care* 1997; 20: 1231–6.
4. Evans ML, *et al.* Alanine infusion during hypoglycaemia partly supports cognitive performance in healthy human subjects. *Diabet Med* 2004; 21: 440–6.
5. Porcellati F, *et al.* Effect of the amino acid alanine on glucagon secretion in non-diabetic and type 1 diabetic subjects during hyperinsulinaemic euglycaemia, hypoglycaemia and post-hypoglycaemic hyperglycaemia. *Diabetologia* 2007; 50: 422–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Abufene; Betalane; *Rus.*: Klimalanin (Клималанин); *Singapore*: Abufene; *Ukr.*: Abufene (Абьюфен).

Multi-ingredient Preparations. *Arg.*: Normoprost Compuesto; *China*: Pu Luo Si Tai (普罗司泰); *Fr.*: ProstaSecurA; *India*: Nerfit; *Ital.*: Chetonex; *Pol.*: Naturapia Prostata†; *Spain*: Tebetane Compuesto.

Amino Acid Chelates

Amino Acid Complexes; Hydrolysed Protein Chelates; Proteinates; Vegetable Protein Complexes.

Profile

Chelation of minerals with amino acids is thought to improve their intestinal absorption and preparations containing minerals with either specific amino acids or hydrolysed proteins have been used as dietary supplements. Minerals and trace elements that have been given in this form include boron (p. 2052.3), calcium (p. 1783.1), chromium (p. 2055.3), iron (p. 2073.1), magnesium (p. 1786.3), manganese (p. 2081.2), molybdenum (p. 2082.3), nickel, potassium (p. 1793.1), and zinc (p. 2126.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Bioglan Zinc Chelate†; *Braz.*: Calato; Calcichell; Ferrini; Mag-Tab; Repocal; *Ger.*: Zinkamin; *Israel*: Light Iron; *Ital.*: Tecnofer.

Multi-ingredient Preparations. *Austral.*: AB Extra Bone-Care +; AB Oriostin; Antioxidant Forte Tablets†; Antioxidant Tablets†; Beta A-C; Beta A-C; Bio ACE Excell; Bio ACE; Bio Magnesium; Bio Zinc; Chelated Cal-Mag with Vitamin D; Citri Slim+Trim†; Echinacea 4000†; Echinacea ACE + Zinc; Echinacea Complex†; Enhance for Men; FAB; Fe-Max; Femme-F; Gluco Support; Homme-P; Iron Max; Joint Mobility†; Lyp-Sine; Machlor; Mag-

Oro; PM IQShield; PM Kids Intelligent; Prostate Care; Radiance; Skin Support; The Blue One†; Zinc Plus; Zinc Zenith; Zn-A-C†; *Braz.*: Ceglen Zinco; Ferrini Folico; Follifer; *Canad.*: Osteo-Guard†; Osteo-Life†; Phytopro†; *Hung.*: Salus Herz-Schutz; *India*: Enerjex; Probofex Caps; *Indon.*: Carni Plus; *Mex.*: Ferricol; Ferrivax F; Intrafer F-800; Intrafer TF; Intrafer; *Singapore*: Arthro-Flex; Ruflex; *USA*: CalMag Plus; Posteum; Poly-Vi-Flor with Iron; REQ49+.

Arginine *(rINN)*

Arg; Arginiini; Arginin; Arginina; Argininas; L-Arginine; Argininum; R; Аргинин.

L-2-Amino-5-guanidinovaleric acid.

$C_6H_{14}N_4O_2$=174.2

CAS — 74-79-3.

UNII — 94ZLA3W45F.

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

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

USP 36: (Arginine). White, practically odourless crystals. Freely soluble in water; sparingly soluble in alcohol; insoluble in ether.

Arginine Aspartate

Arginiiniaspartaatti; Arginina, aspartato de; Argininaspartat; Arginin-aspartát; Arginine, aspartate d'; Arginini aspartas; Arginino aspartatas; Asparginīnum; Аргинина Аспартат.

(2*S*)-2-Amino-5-guanidinopentanoic acid (2*S*)-2-aminobutanedioate.

$C_{10}H_{21}N_5O_6$=307.3

CAS — 7675-83-4.

UNII — LZBJG2I725.

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

Ph. Eur. 8: (Arginine Aspartate). White or almost white granules or powder. Very soluble in water, practically insoluble in alcohol and in dichloromethane.

Arginine Glutamate *(BAN, USAN, rINNM)*

Arginina, glutamato de; Arginine, Glutamate d'; Arginini Glutamas; Glutamato de arginina; Аргинина Глутамат.

L-Arginine L-glutamate.

$C_6H_{14}N_4O_2C_5H_9NO_4$=321.3

CAS — 4320-30-3.

ATC — A05BA01.

ATC Vet — QA05BA01.

UNII — TU1X77K34Q.

Arginine Hydrochloride *(USAN, rINNM)*

Arginiinihydrokloridi; Arginina, hidrocloruro de; Arginine, chlorhydrate d'; L-Arginine Monohydrochloride; Argininhidroklorid; Argininhydrochlorid; Arginin-hydrochlorid; Argininhydroklorid; Arginini Hydrochloridum; Arginino hidrochloridas; Hidrocloruro de arginina; Аргинина Гидрохлорид.

$C_6H_{14}N_4O_2$.HCl=210.7

CAS — 1119-34-2.

ATC — B05XB01.

ATC Vet — QB05XB01.

UNII — F7LTH1E20Y.

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

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

USP 36: (Arginine Hydrochloride). White, practically odourless, crystals or crystalline powder. Freely soluble in water.

Uses and Administration

Arginine is a basic amino acid that is essential for growth. It is used as a **dietary supplement**, to treat or prevent deficiency, or to aid recovery during convalescence. It is given orally as the aspartate, glutamate, or hydrochloride; 1 g of arginine is equivalent to about 1.76 g of arginine aspartate, or 1.84 g of arginine glutamate, or 1.21 g arginine hydrochloride. A usual oral dose, expressed as arginine aspartate, is 2 to 5 g daily, given with or after food.

Arginine stimulates the release of growth hormone by the pituitary gland and may be used instead of, or in addition to, other tests such as insulin-induced hypoglycaemia, for the **evaluation of growth disorders**; false-positive and false-negative results are relatively common and evaluation therefore should not be made on the basis of a single arginine test. It is used as a 10% solution of the hydrochloride in usual doses of 30 g by intravenous infusion given over 30 minutes. A further test may be given after 24 hours.

For doses in children, see below.

Arginine is used in certain conditions accompanied by **hyperammonaemia**; for further details see below.

Arginine hydrochloride has also been used as an **acidifying agent**. In severe metabolic alkalosis intravenous doses have been calculated by the formula:

$$\text{intravenous dose (in grams)} = \text{desired decrease in plasma-bicarbonate concentration (mEq or mmol/litre)} \times [\text{patient's body-weight (in kg)}/9.6]$$

In forced acid diuresis to hasten drug elimination after overdose a suggested dose has been 10 g intravenously over 30 minutes. However, this has the potential to cause myoglobinuria with acute renal failure, and is rarely used.

Arginine may also be used in the form of the acetylaspartate, citrate, malate, oxoglurate, tidiacicate (thiazolidine-2,4-dicarboxylate), and timonacicate (thiazolidine-4-carboxylate). Formulation as an arginine salt is used to improve the solubility of several drugs, notably analgesics and antibacterials.

References.

1. Tapiero H, *et al.* Arginine. *Biomed Pharmacother* 2002; 56: 439–45.
2. Tong BC, Barbul A. Cellular and physiological effects of arginine. *Mini Rev Med Chem* 2004; 4: 823–32.
3. Zhou M, Martindale RG. Arginine in the critical care setting. *J Nutr* 2007; 137 (suppl 2): 1687S–1692S.
4. Barbul A, Ulbyargoli A. Use of exogenous arginine in multiple organ dysfunction syndrome and sepsis. *Crit Care Med* 2007; 35 (suppl): S564–S567.
5. Coman D, *et al.* New indications and controversies in arginine therapy. *Clin Nutr* 2008; 27: 489–96.
6. Wu G, *et al.* Arginine metabolism and nutrition in growth, health and disease. *Amino Acids* 2009; 37: 153–68.

Administration in children. Arginine is used in children as a **dietary supplement**, to treat or prevent deficiency, or to aid recovery during convalescence. Children from 6 years of age have been given an oral dose of arginine aspartate 1 g once or twice daily.

Arginine is also given intravenously for the **evaluation of growth disorders** in children. A usual dose of arginine hydrochloride 500 mg/kg is given as a 10% solution infused over 30 minutes in children weighing less than 60 kg; children weighing 60 kg or more may be given the adult dose (see above). A further test may be given after 24 hours.

For doses of arginine used in children with **hyperammonaemia**, see below.

Cardiovascular use. Arginine is the physiological precursor of nitric oxide and this has been suggested as an explanation for the **hypotensive effect** that has been reported in healthy subjects[1-3] and hypertensive patients[1,4] given infusions of arginine, although effects unrelated to nitric oxide generation cannot be excluded.[4]

Oral arginine has also been reported to significantly decrease mean systolic blood pressure in hypertensive patients,[5] in patients on haemodialysis, and in renal transplant recipients.[6] In patients with essential *hypertension*, a single oral dose of arginine had no effect on blood pressure, although it did improve endothelium-dependent flow-mediated dilatation of the brachial artery compared with placebo.[7] In patients with pulmonary hypertension, short-term use of arginine has reduced pulmonary arterial pressure.[8-10]

In pregnant women with *pre-eclampsia* (see Hypertension, p. 1251.1), plasma-arginine concentrations were found to be markedly reduced compared with control subjects.[11] Arginine infusions of 20 g, given to women with mild to moderate gestational hypertension,[12] and 30 g given to pre-eclamptic women,[13] significantly reduced systolic and diastolic blood pressure, with no adverse effect on fetal heart rate in the one study.[12] In a study of pre-eclamptic women given oral arginine 12 g daily for 2 days, no significant differences in diastolic blood pressure were seen compared with those receiving placebo.[14] However, in another study of pre-eclamptic women given oral arginine 3 g daily for 3 weeks, systolic, diastolic and mean arterial pressure were significantly reduced compared with those taking placebo.[15]

Because of apparent **improvement in endothelial function** with arginine,[16] some interest has surrounded its potential role in other cardiovascular diseases, such as *coronary artery disease* and *heart failure*.[17] Decrease in plasma-cholesterol concentrations has also been reported in 2 hypercholesterolaemic patients given arginine infusions.[18] However, long-term supplementation was found not to be helpful (and possibly harmful) in patients with *peripheral arterial disease*,[19] and arginine therapy has been implicated in increased mortality when given to patients after *myocardial infarction* (see under Adverse Effects and Precautions, p. 2050.2). Nonetheless, some interest in its possibilities continues.[16]

There are case reports[20] of successful use of arginine in the management of the multisystem syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (*MELAS*), with a reduction in the frequency of major stroke-like attacks. A small study[21] in 24 patients with MELAS found that their plasma-arginine concentrations (during both the acute and interictal phases) were lower than those of controls. Arginine given intravenously in the acute phase of stroke-like attacks resulted in an improvement of symptoms within 24 hours in nearly all patients. Treatment with oral arginine was continued for 18 months in 6 patients, with a reduction in the frequency and severity of attacks.

1. Nakaki T, *et al.* L-arginine-induced hypotension. *Lancet* 1990; 336: 696.
2. Hishikawa K, *et al.* L-arginine-induced hypotension. *Lancet* 1991; 337: 683–4.
3. Petros AJ, *et al.* L-arginine-induced hypotension. *Lancet* 1991; 337: 1044–5.
4. Pedrinelli R, *et al.* Pressor, renal and endocrine effects of L-arginine in essential hypertensives. *Eur J Clin Pharmacol* 1995; 48: 195–201.
5. Palloshi A, *et al.* Effect of oral L-arginine on blood pressure and symptoms and endothelial function in patients with systemic hypertension, positive exercise tests, and normal coronary arteries. *Am J Cardiol* 2004; 93: 933–5.
6. Kelly BS, *et al.* Oral arginine improves blood pressure in renal transplant and hemodialysis patients. *J Parenter Enteral Nutr* 2001; 25: 194–202.
7. Lekakis JP, *et al.* Oral L-arginine improves endothelial dysfunction in patients with essential hypertension. *Int J Cardiol* 2002; 86: 317–23.
8. Mehta S, *et al.* Short-term pulmonary vasodilation with L-arginine in pulmonary hypertension. *Circulation* 1995; 92: 1539–45.
9. Nagaya N, *et al.* Short-term oral administration of L-arginine improves hemodynamics and exercise capacity in patients with precapillary pulmonary hypertension. *Am J Respir Crit Care Med* 2001; 163: 887–91.
10. Morris CR, *et al.* Arginine therapy: a new treatment for pulmonary hypertension in sickle cell disease? *Am J Respir Crit Care Med* 2003; 168: 63–9.
11. D'Aniello G, *et al.* Plasma L-arginine is markedly reduced in pregnant women affected by preeclampsia. *J Chromatogr B Biomed Sci Appl* 2001; 753: 427–31.
12. Neri I, *et al.* Effects of acute L-arginine infusion on non-stress test in hypertensive pregnant women. *J Matern Fetal Neonatal Med* 2004; 16: 23–6.
13. Facchinetti F, *et al.* L-Arginine infusion reduces blood pressure in preeclamptic women through nitric oxide release. *J Soc Gynecol Investig* 1999; 6: 202–7.
14. Staff AC, *et al.* Dietary supplementation with L-arginine or placebo in women with pre-eclampsia. *Acta Obstet Gynecol Scand* 2004; 83: 105–7.
15. Rytlewski K, *et al.* Effects of prolonged oral supplementation with L-arginine on blood pressure and nitric oxide synthesis in preeclampsia. *Eur J Clin Invest* 2005; 35: 32–7.
16. Hefferman KS, *et al.* L-arginine as a nutritional prophylaxis against vascular endothelial dysfunction with aging. *J Cardiovasc Pharmacol Ther* 2010; 15: 17–23.
17. Cheng JWM, Balwin SN. L-arginine in the management of cardiovascular diseases. *Ann Pharmacother* 2001; 35: 755–64.
18. Korbut R, *et al.* Effect of L-arginine on plasminogen-activator inhibitor in hypertensive patients with hypercholesterolemia. *N Engl J Med* 1993; 328: 287–8.
19. Wilson AM, *et al.* L-arginine supplementation in peripheral arterial disease: no benefit and possible harm. *Circulation* 2007; 116: 188–95.
20. Geberhiwot T, *et al.* Case 36-2005: a woman with seizure, disturbed gait, and altered mental status. *N Engl J Med* 2006; 354: 1096–7.
21. Koga Y, *et al.* L-arginine improves the symptoms of strokelike episodes in MELAS. *Neurology* 2005; 64: 710–12.

Hyperammonaemia. Hyperammonaemia is a characteristic feature of inborn errors of the urea cycle, caused by defects in the enzymes carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase (causing hyperargininaemia), or *N*-acetylglutamate synthase (NAGS).[1,2] During the urea cycle, waste ammonia, in the form of the ammonium ion, is normally condensed with bicarbonate and ATP to form carbamoyl phosphate which undergoes several more reactions, including one leading to the synthesis of arginine, and ultimate transformation to urea for excretion. Thus, in defects of this cycle ammonia accumulates and arginine synthesis is deficient.[3] Hyperammonaemia is most severe when the enzyme defect occurs in the early steps of the urea cycle, such as in CPS or OTC deficiency, and is less severe at later stages, as in ASL or arginase deficiency.[2] Hyperammonaemia is often associated with respiratory alkalosis in patients with urea cycle disorders.[3]

The basis of **treatment** is dietary protein restriction, to decrease the requirement for waste nitrogen synthesis,[4] and the use of drugs to stimulate alternative pathways of waste nitrogen excretion.[5,6] Such drugs include arginine, citrulline, sodium benzoate, sodium phenylacetate, and sodium phenylbutyrate. In the initial management of severe hyperammonaemia, haemodialysis is preferred over peritoneal dialysis because it is more effective.[3,7]

Arginine supplements are given except in hyperargininaemia.[5,7] *Citrulline* may be used in some cases instead;[8] it may be useful for CPS and OTC deficiency (in doses of about 170 mg/kg daily or 3.8 g/m^2 daily),[5,6,9] but it is not recommended for patients with ASS or ASL deficiency, as levels of citrulline are already elevated.[5,10] Some recommend citrulline with arginine in acute hyperammonaemia to aid additional removal of nitrogen.[9] For the treatment of acute hyperammonaemia, some recommend a loading dose of arginine 600 mg/kg over 90 minutes pending definitive diagnosis.[5,10] Alternatively, a loading dose of 200 mg/kg or 4 g/m^2 has been advocated for CPS or OTC deficiency,[6,9,10] and 600 mg/kg or 12 g/m^2 for ASS or

ASL deficiency.[6,9,10] The same dose as the loading dose is then given over 24 hours, as a constant maintenance infusion,[6,9,10] until conversion to oral medication is made.[10] For long-term management of ASS or ASL deficiency, doses of arginine ranging from 400 to 700 mg/kg daily have been recommended.[5,6,9,10] The *BNFC* suggests arginine doses for neonates and children up to 18 years of age, to be given under specialist supervision:

- For acute hyperammonaemia in CPS or OTC deficiency, an initial intravenous infusion of 200 mg/kg over 90 minutes, is followed by a continuous infusion of 8 mg/kg per hour; for maintenance, an oral dose of 100 mg/kg is given daily in 3 or 4 divided doses.
- For acute hyperammonaemia in citrullinaemia or arginosuccinic aciduria, an initial intravenous infusion of 600 mg/kg over 90 minutes, is followed by a continuous infusion of 25 mg/kg per hour; for maintenance, an oral dose of 100 to 175 mg/kg is given three or four times daily with food, and adjusted according to response.

Patients also receive treatment with *sodium benzoate* and *sodium phenylacetate*[6,10] or *sodium phenylbutyrate*.[5,6] ASL deficiency can be managed with protein restriction and arginine alone,[6,11] although some still advocate the use of sodium phenylbutyrate.[5,8] When sodium benzoate is conjugated with glycine and excreted as hippuric acid it provides an alternative pathway of nitrogen excretion, while sodium phenylacetate and sodium phenylbutyrate provide a second and even more effective pathway by conjugation with glutamine.[6,7,10] Some consider intravenous sodium benzoate and sodium phenylacetate the treatment of choice in acute hyperammonaemia; sodium phenylbutyrate is recommended for chronic management.[9] In a 25-year, open-label, uncontrolled study, intravenous therapy with sodium phenylacetate and sodium benzoate clearly improved survival in patients with acute hyperammonaemia, with an overall survival rate of 84%; survival was also related to peak plasma ammonium concentration and age. Haemodialysis was also used to control hyperammonaemia, especially in neonates and older patients who were less responsive to intravenous therapy.[12]

It has been suggested that *carnitine* supplementation (at 100 mg/kg daily[9] either orally or intravenously) should be added to minimise neurological symptoms and toxicity, but its value is uncertain.[4,13] Low carnitine levels are reportedly rare in patients with urea cycle disorders, and in patients treated with sodium benzoate benzoyl carnitine may form, negating any potential benefit from carnitine supplementation.[8]

Liver transplantation (p. 1936.3) may achieve long-term correction of urea cycle disorders, even in the very young patient, and *gene replacement* therapy is under investigation.[14]

Hyperammonaemia and hepatic encephalopathy (p. 1808.2) can also arise from other causes[7,13] for which arginine may not be advocated. *Carglumic acid* (p. 2471.1) is the treatment of choice for patients with hyperammonaemia arising from NAGS deficiency.

1. Summar M, Tuchman M. Proceedings of a consensus conference for the management of patients with urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S6–S10.
2. Shih VE. Alternative-pathway therapy for hyperammonemia. *N Engl J Med* 2007; **356**: 2321–2.
3. The Urea Cycle Disorders Conference Group. Consensus statement from a conference for the management of patients with urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S1–S5.
4. Leonard JV. The nutritional management of urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S40–S45.
5. Berry GT, Steiner RD. Long-term management of patients with urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S56–S61.
6. Batshaw ML, *et al.* Alternative pathway therapy for urea cycle disorders: twenty years later. *J Pediatr* 2001; **138** (suppl): S46–S55.
7. Leonard JV, Morris AAM. Urea cycle disorders. *Semin Neonatol* 2002; **7**: 27–35.
8. Wilcken B. Problems in the management of urea cycle disorders. *Mol Genet Metab* 2004; **81** (suppl): S86–S91.
9. Kleppe S, *et al.* Urea cycle disorders. *Curr Treat Options Neurol* 2003; **5**: 309–19.
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11. Brusilow SW, *et al.* Treatment of episodic hyperammonemia in children with inborn errors of urea synthesis. *N Engl J Med* 1984; **310**: 1630–4.
12. Enns GM, *et al.* Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. *N Engl J Med* 2007; **356**: 2282–92.
13. Leonard JV, Morris AAM. Inborn errors of metabolism around time of birth. *Lancet* 2000; **356**: 583–7.
14. Lee B, Goss J. Long-term correction of urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S62–S71.

Necrotising enterocolitis. A systematic review[1] considered that although there was evidence suggesting that supplementation of the feed of premature neonates with arginine could prevent the development of necrotising enterocolitis (p. 185.1), it was insufficient to recommend the practice without further study.

1. Shah P, Shah V. Arginine supplementation for prevention of necrotising enterocolitis in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 24/06/08).

Adverse Effects and Precautions

Nausea, vomiting, flushing, headache, numbness, and local venous irritation may occur if arginine solutions are infused too rapidly; extravasation leading to a burn-like reaction and/or skin necrosis has been reported. Hypersensitivity reactions including rash and anaphylaxis have occurred, and treatment should be stopped if these are serious. Arginine therapy has been associated with haematuria that sometimes occurred 1 or 2 days after dosing. There have also been isolated reports of a decrease in platelet count. Elevated plasma-potassium concentrations have been reported in uraemic patients and arginine should therefore be used with caution in patients with renal disease or anuria. Arginine hydrochloride should be given cautiously to patients with electrolyte disturbances as its high chloride content could lead to the development of hyperchloraemic acidosis.

Extravasation. Full-thickness skin necrosis has been reported[1,2] after extravasation of a 10% solution of arginine hydrochloride. Both osmotic and local hyperkalaemic effects have been proposed as a mechanism for the injury.[1]

1. Bowiby HA, Elanjian SI. Necrosis caused by extravasation of arginine hydrochloride. *Ann Pharmacother* 1992; **26**: 263–4.
2. Salameh Y, Shoufani A. Full-thickness skin necrosis after arginine extravasation—a case report and review of literature. *J Pediatr Surg* 2004; **39**: E9–E11.

Hyperkalaemia. Two alcoholic patients with severe liver disease and moderate renal insufficiency developed severe hyperkalaemia when given arginine hydrochloride and one died.[1] Both patients had received a total of 300 mg of spironolactone some time before arginine hydrochloride, but the contribution of spironolactone to the hyperkalaemia was not known. In a study to investigate the mechanism of metabolic changes due to arginine, plasma-potassium concentrations were found to be significantly higher in diabetic subjects than those for normal subjects, leading the authors to suppose that while arginine-induced hyperkalaemia may be promoted by low insulin blood levels, it could not be attributed to glucagon, pH changes, or aldosterone inhibition.[2]

In another fatal case due to an overdose of arginine,[3] a 21-month-old girl developed an acute metabolic acidosis with transient but severe hyponatraemia, and irreversible brain death; no hyperkalaemia was seen. Unlike the previously reported case, the patient had normal renal function, and the authors supposed the absence of hyperkalaemia to be due to a rapid increase in renal potassium excretion.

1. Bushinsky DA, Gennari FJ. Life-threatening hyperkalemia induced by arginine. *Ann Intern Med* 1978; **89**: 632–4.
2. Massara F, *et al.* The risk of pronounced hyperkalaemia after arginine infusion in the diabetic subject. *Diabete Metab* 1981; **7**: 149–53.
3. Gerard JM, Lutsiri A. A fatal overdose of arginine hydrochloride. *J Toxicol Clin Toxicol* 1997; **35**: 621–5.

Hypersensitivity. Two reports of anaphylactic reactions that occurred shortly after the start of infusions of arginine 5 or 10% given to test growth-hormone output.[1,2]

1. Tiwary CM, *et al.* Anaphylactic reaction to arginine infusion. *N Engl J Med* 1973; **288**: 218.
2. Resnick DJ, *et al.* Case report of an anaphylactoid reaction to arginine. *Ann Allergy Asthma Immunol* 2002; **88**: 67–8.

Myocardial infarction. A placebo-controlled study investigated whether the addition of arginine to standard therapy after myocardial infarction would decrease vascular stiffness and improve left ventricular function. The study was stopped early due to an increased number of deaths in the arginine group. The authors commented that, while the results could be due to chance, nevertheless arginine should not be given to patients after a myocardial infarction.[1] This prompted Canadian health authorities (Health Canada) to issue similar advice and stipulate that all arginine products must carry a warning label to this effect.[2]

1. Schulman SP, *et al.* L-Arginine therapy in acute myocardial infarction: the Vascular Interaction with Age in Myocardial Infarction (VINTAGE MI) randomized clinical trial. *JAMA* 2006; **295**: 58–64.
2. Health Canada. Advisory: Health Canada advises heart patients not to use products containing L-arginine (issued 16th May 2006). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2006/2006_30-eng.php (accessed 05/02/09)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lacorene; Multio; *Austria*: Sangenor; *Braz.*: Reforgan; Targifor; *China*: Hua Shi Ai Er (华士艾尔); Jing Ning (净宁); Kang Si Ke Wei (康司科韦); Pu Luo Chuan (普洛川); Xian Ding (先丁); Xian Jing (先京); Xin Qi Bang (欣其邦); YiXin (逸欣); *Fr.*: Dynamisan; Energitum†; Eucol†; Pargine; Sargenor; Tiadilon; *Gr.*: Amargine; *India*: Arginitric; Nitriga; *Ital.*: Bioarginina; Dynamisan; Sargenor; *Malaysia*: Arginitric; *Port.*: Asparten; Bio-Energol Plus; Bioenergex; Pan-Astenico R; Sargenor; Sulfile†; *Rus.*: Glutargin (Глутаргин); *Spain*: Potenciator; Sargisthene; Sorbenor; *Switz.*: Dynamisan; *Ukr.*: Glutargin (Глутаргин); Tivortin (Тивортин); *USA*: R-Gene.

Multi-ingredient Preparations. *Arg.*: Acrea; ADX; Energizant; Vital con ginseng; Energizante; Holomagnesio Vital; Potenci; Synapsys; Total Magnesiano Sport; Triconal; VNS 45; *Austria*: Leberinfusion; *Braz.*: Dinavital C; Energoplex; Estafan; Ornitagin; Targifor C; Taurargin; Viatop AM; *Chile*: Dynamisan; Kenium Anticaspa -Caspa Seca; Ureadin 30; Ureadin Rx DB; Ureadin Rx RD; *Fr.*: Arginotri-B; Citrarginine†; D-Stress; Fasteny; Hepagrume; Hepargitol; Sargenor a la Vitamine C; *Gr.*: Tonotil-N; *Hong Kong*: Profile B Plus Fat Burner†; *Hung.*: Glutarsin E; *India*: Aminocal 500; Arg-9; Bio-10; Cavenor; Elnutra; Endurantz; Enlarge; Purtipil-L; Hi-Q; Hi-Q; Hyrase; Jivak; Lutamin; Lutivit; Lycobal Forte; Lytox; N-Care Forte; *Indon.*: Asten; Aviter; Maxirex; Menolla†; Neo Hormoviton Greng; Neo Hormoviton; Reximax; Sirec; Viusid; *Ital.*: Anasten Plus; Argidam; Edodes; Ipoazotal Complex; Isoram; Linfoflu; Linfoiodine†; Salovit; Sargenor Plus; Sargenor Sport†; Somatron; Vitalmix Fos; *Jpn*: Q & P Gold; *Mex.*: Zumba; *Spain*: Dynamogen; Tomevit†; *Switz.*: Vitasprint Complex†; *UK*: Neurozan; *Ukr.*: Citrarginin (Цитраргинин); Corargin (Кораргин); Energin (Энергин); Vitrum Beauty Elite (Витрум Бьюти Элит); *USA*: Cardiotek Rx; *Venez.* Brugesic Plus; Ocoxin; Viusid.

Pharmacopoeial Preparations

BP 2014: Arginine Hydrochloride Infusion; Arginine Hydrochloride Oral Solution;

USP 36: Arginine Capsules; Arginine Hydrochloride Injection Arginine Tablets; Aztreonam for Injection; Aztreonam Injection Cefepime for Injection.

Asparagine Monohydrate

L-α-Aminosuccinamic Acid Monohydrate; Asparagiinimonohydraatti; Asparagin monohydrát; Asparagin-Monohydrat; Asparagina, monohidrato de; Asparaginas monohidratas; L-Asparagine Monohydrate; Asparagine monohydratée; Asparaginmonohydrat; Asparaginum monohydricum; Asparamide; Aspartamic acid; Aspartic acid beta-amide; N (asparagine); NSC-82391; Аспарагин Моногидрат.

(2*S*)-2,4-Diamino-4-oxobutanoic acid monohydrate.

$C_4H_8N_2O_3,H_2O$=150.1

CAS — 70-47-3 (anhydrous asparagine); 5794-13-8 (asparagine monohydrate).

UNII — 2PD79VF521 (asparagine monohydrate); 5Z33R5TKO7 (l-asparagine); 7NG0A2TUHQ (anhydrous l-asparagine).

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii). Also in *USNF*, which specifies the anhydrous form or the monohydrate.

Ph. Eur. 8: (Asparagine Monohydrate). A white or almost white, crystalline powder or colourless crystals. Slightly soluble in water; practically insoluble in alcohol and in dichloromethane. A 2% solution in water has a pH of 4.0 to 6.0.

USNF 31: (Asparagine). It is anhydrous or contains one molecule of water of hydration. A white, crystalline powder or white crystals. Soluble in water; practically insoluble in alcohol and in ether. Its solutions are acid to litmus. Protect from light.

Profile

Asparagine is a non-essential amino acid.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Acutil Fosforo; Neuralfa; Tiofort; *Spain*: Agudil†.

Aspartic Acid *(USAN, rINN)*

Acide aspartique; Ácido aspártico; Acidum Asparticum; Asp; Asparagiinihappo; Asparaginic Acid; Asparaginsyra; L-Aspartic Acid; Aspártico, ácido; Aspartinsäure; Asparto rūgštis; Aszparaginsav; D; Kwas asparaginowy; Kyselina asparagová; Аспарагиновая Кислота.

L-Aminosuccinic acid.

$C_4H_7NO_4$=133.1

CAS — 56-84-8.

UNII — 30KYC7MIAI.

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

Ph. Eur. 8: (Aspartic Acid). A white or almost white crystalline powder, or colourless crystals. Slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 36: (Aspartic Acid). A white or almost white crystalline powder, or colourless crystals. Slightly soluble in water; practically insoluble in alcohol and in ether; soluble in dilute solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

Profile

Aspartic acid is a non-essential amino acid. It is used as a dietary supplement.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Ubiten; *China*: Ge Mei Nai Xin (格美乃欣); Hu Tian Bao (护天保); Jia He Mei (佳合美); Pai Ke Xin (课可欣); Piaojiamei (朴佳美); Qiang Pu Jin (强普金); Sheng Yi Ge (圣益格); Tian Jia Mei (天甲美); Tuo Qi (妥奇); Wan Pu Ding (万普定); Wei Fu De (维复德); Wei Le Nuo (威乐诺); Wei Ou Lu (维欧路); Wei Shuang (唯双); Xin Mei Jia (欣美佳); Yu Di Ning (玉迪宁); *Hung.*: Reergin.

Betacarotene *(BAN, rINN)*

all-*trans*-β-Carotene; Beetakaroteeni; Beta Carotene (USAN); Bétacarotène; Betacaroteno; Betacarotenum; Betacarotin; Betakaroten; Betakarotenas; Bétakarotin; E160(a); Provitamin A; Provitamina A; Βετακαροτεη.

β,β-Carotene; (*all-E*)-1,1'-(3,7,12,16-Tetramethyl-1,3,5,7,9,11,13,15,17-octadecanonaene-1,18-diyl)bis[2,6,6-trimethylcyclohexene].

$C_{40}H_{56}$=536.9.

CAS — 7235-40-7.

ATC — *A11CA02; D02BB01.*

ATC Vet — *QA11CA02; QA11HA90; QD02BB01.*

UNII — *01YAE03M7J.*

Description. Carotene exists in 3 isomeric forms, all of which are converted to some extent into vitamin A in the livers of man and *animals*. Of the 3 isomers of carotene, the *beta* compound is more active than the *alpha-* or *gamma-*isomers. The vitamin A activity of plants is due to the presence of *alpha-*, *beta-*, and *gamma-*carotenes and to kryptoxanthine; that of *animal* tissues is due to both vitamin A and carotene, while fish-liver oils contain vitamin A but no carotene.

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

Ph. Eur. 8: (Betacarotene). A brown-red or brownish-red crystalline powder. Practically insoluble in water and in dehydrated alcohol; slightly soluble in cyclohexane. It is sensitive to air, heat and light, especially in solution. Store in airtight containers at a temperature not exceeding 25 degrees. Protect from light.

USP 36: (Beta Carotene). Red or reddish-brown to violet-brown crystals or crystalline powder. Insoluble in water, in acids, and in alkalis; practically insoluble in alcohol and in methyl alcohol; soluble in carbon disulfide, in chloroform, and in benzene; sparingly soluble in ether, in petroleum spirit, and in vegetable oils. Store in airtight containers. Protect from light.

Units

Vitamin A activity in foods is expressed in terms of retinol equivalents: 6 micrograms of betacarotene represents 1 retinol equivalent (or 10 of the former International units for provitamin A—see p. 2099.2).

Uses and Administration

Betacarotene is a carotenoid precursor of vitamin A (p. 2098.3). In the *treatment* of **vitamin A deficiency**, vitamin A is preferred to betacarotene. However, betacarotene has been used for the *prevention* of vitamin A deficiency at a dose of 6 to 15 mg daily.

Betacarotene may be given orally to reduce the severity of photosensitivity reactions in patients with **erythropoietic protoporphyria** (see also Porphyria, below). Doses are in the range of 30 to 300 mg daily, depending upon severity; they may be taken as either single daily doses or divided doses but should preferably be taken with meals. The protection offered by betacarotene is not total and generally 2 to 6 weeks of treatment resulting in a yellow coloration of palms and soles is necessary before patients should attempt to increase their exposure to sunlight.

For doses in children, see below.

Betacarotene and other carotenoids (alphacarotene and gammacarotene) are used as **colouring agents** for foods and medicinal products.

Betacarotene has **antoxidant** activity and has been studied for its possible protective benefit in a number of disorders (but see Effects on Mortality, below).

Administration in children. Betacarotene may be used in children for the management of photosensitivity reactions in erythropoietic protoporphyria (see also Porphyria, below). Although not licensed in the UK, the *BNFC* suggests oral doses for specialist use:

- 1 to 5 years: 60 to 90 mg daily
- 5 to 9 years: 90 to 120 mg daily
- 9 to 12 years: 120 to 150 mg daily
- 12 to 16 years: 150 to 180 mg daily
- 16 to 18 years: 180 to 300 mg daily

The daily dose may be given in single or divided doses. The protection offered by betacarotene is not total and generally 2 to 6 weeks of treatment is necessary before increasing exposure to sunlight. Doses should be adjusted according to levels of exposure.

For discussion of deficiency states in children, see below.

Age-related macular degeneration. A study in patients with age-related macular degeneration (p. 880.2) indicated that the risk of developing this disorder (a leading cause of irreversible blindness among elderly persons) was markedly decreased amongst those with the highest dietary carotenoid intake;[1] in particular, lutein and zeaxanthin, or green leafy vegetables (which contain high concentrations of these carotenoids) were associated with a lower risk. Increasing the dietary intake of these carotenoids may be of benefit in reducing the development of this disorder. Despite this, systematic reviews found no evidence that antoxidant vitamin and mineral supplementation would either prevent[2,3] or delay the onset of macular degeneration. However, one study[4] has shown modest benefit from vitamin C, vitamin E, betacarotene, and zinc supplementation in those with moderate to severe signs of the disease. A systematic review to assess the effects of antoxidant vitamin or mineral supplementation on the progression of age-related macular degeneration included this study, and noted that the generalisability of these findings to other populations (with differing nutritional status) was unknown. Long-term harm from supplementation could not be ruled out.[5]

1. Seddon JM, *et al.* Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. *JAMA* 1994; 272: 1413–20.
2. Evans JR, Henshaw K. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2008 (accessed 11/03/08).
3. Chong EW-T, *et al.* Dietary antioxidants and primary prevention of age related macular degeneration: systematic review and meta-analysis. *BMJ* 2007; 335: 755–9.
4. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no.8. *Arch Ophthalmol* 2001; 119: 1417–36.
5. Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2006 (accessed 11/03/08).

Deficiency states. A study in Senegalese children with vitamin A deficiency found that supplementation with betacarotene (in a single dose equivalent to 200 000 units of vitamin A) was as effective as a single 200 000 unit dose of vitamin A palmitate in reversing ocular changes.[1] Since betacarotene is less toxic than vitamin A itself it would have some advantages for supplementation, either as an oral supplement or by encouraging the consumption of carotenoid-rich fruit and vegetables. A study in anaemic Indonesian women found that a supplement containing betacarotene with iron, vitamin C, and folate improved vitamin A status, whereas an additional daily portion of dark-green leafy vegetables containing a similar amount of betacarotene did not.[2] However, others contended that consumption of food sources of carotenoids were effective in improving vitamin A status in deficiency states,[3,4] and that it might not be appropriate to extrapolate these findings in adults (not necessarily deficient in vitamin A) to vitamin A deficient children.[3,5] WHO policy was to promote dietary adjustment wherever vitamin A deficiency was endemic.[5] Despite further studies confirming improved vitamin A status among those given foods high in betacarotene,[6,7] (supplying around 6 mg of betacarotene daily in adults[6] or 3.5 mg daily in children[7]) a review[8] considered the bioavailability of betacarotene from plant foods to be low, and questioned the retinol equivalency determined by WHO (see Units, above). Another study[9] found that increasing dietary fat consumption and eliminating helminthic infection further increased serum retinol concentrations in children given food high in betacarotene.

For a study reporting improved vitamin A status with betacarotene plus zinc compared with betacarotene or zinc alone, and the suggestion that zinc may have a role in the conversion of betacarotene to retinol, see Vitamin A Deficiency, under Zinc, p. 2127.3.

For further discussion of vitamin A deficiency and the value of supplementation in various disease states, see under Vitamin A Substances, p. 2099.2.

1. Carlier C, *et al.* A randomised controlled trial to test equivalence between retinyl palmitate and β carotene for vitamin A deficiency. *BMJ* 1993; 307: 1106–10.
2. de Pee S, *et al.* Lack of improvement in vitamin A status with increased consumption of dark-green leafy vegetables. *Lancet* 1995; 346: 75–81.
3. Reddy V. Vitamin A status and dark green leafy vegetables. *Lancet* 1995; 346: 1634–5.
4. Underwood BA. Vitamin A status and dark green leafy vegetables. *Lancet* 1995; 346: 1635.
5. WHO. Vitamin A status: is dietary replacement practicable. *WHO Drug Inf* 1995; 9: 141.
6. Ncube TN, *et al.* Supplementing lactating women with puréed papaya and grated carrots improved vitamin A status in a placebo-controlled trial. *J Nutr* 2001; 131: 1497–1502.
7. Vuong LT, *et al.* Plasma β-carotene and retinol concentrations of children increase after a 30-d supplementation with the fruit Momordica cochinchinensis (gac). *Am J Clin Nutr* 2002; 75: 872–9.
8. West CE, *et al.* Consequences of revised estimates of carotenoid bioefficacy for dietary control of vitamin A deficiency in developing countries. *J Nutr* 2002; 132 (suppl): 2920S–2926S.
9. Jalal F, *et al.* Serum retinol concentrations in children are affected by food sources of β-carotene, fat intake, and anthelmintic drug treatment. *Am J Clin Nutr* 1998; 68: 623–9.

Ischaemic heart disease. There are results from epidemiological studies suggesting the potential benefits of dietary betacarotene in preventing ischaemic heart disease, particularly in smokers; however, randomised placebo-controlled studies of betacarotene supplements have failed to find any benefit, as discussed on p. 2047.1.

Malignant neoplasms. Some evidence from epidemiological studies suggested that higher dietary intakes of carotenoids and especially betacarotene had a protective effect against cancer. Consequently several randomised placebo-controlled studies examining the use of betacarotene supplements in the primary or secondary prevention of malignancy were instigated. However, the results of studies so far published have generally been disappointing. Moreover, some results suggest that supplementation with betacarotene may lack benefit or may actually be harmful (see Prophylaxis of Malignant Neoplasms, p. 2047.3 and Effects on Mortality, below).

Porphyria. Despite a lack of robust evidence,[1] betacarotene is the most widely used systemic drug for the management of erythropoietic protoporphyria,[2,3] a non-acute porphyria characterised by cutaneous photosensitivity (p. 1556.1). It has been given with canthaxanthin to reduce the skin discoloration caused by betacarotene alone.

1. Minder EI, *et al.* A systematic review of treatment options for dermal photosensitivity in erythropoietic protoporphyria. *Cell Mol Biol (Noisy-le-grand)* 2009; 55: 84–97.
2. Todd DJ. Erythropoietic protoporphyria. *Br J Dermatol* 1994; 131: 751–66.
3. Todd DJ. Therapeutic options for erythropoietic protoporphyria. *Br J Dermatol* 2000; 142: 826.

Adverse Effects and Precautions

Loose stools may occasionally occur during treatment with betacarotene and the skin may assume a slightly yellow discoloration. Bruising, dizziness, and arthralgia have been reported rarely.

Excessive intake of betacarotene does not result in hypervitaminosis A (see Pharmacokinetics, p. 2052.1).

Carcinogenicity. For reference to studies finding an increased incidence of lung cancers in individuals given betacarotene supplements to protect against malignancy, see under Prophylaxis of Malignant Neoplasms, p. 2047.3.

Effects on mortality. A systematic review of the effect of antoxidant supplements on mortality in randomised primary and secondary prevention studies found that betacarotene, used either singly or with other antoxidants, significantly increased all-cause mortality.[1] In another review and meta-analysis, betacarotene supplementation showed a trend towards increased cancer mortality.[2]

1. Bjelakovic G, *et al.* Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).
2. Bardia A, *et al.* Efficacy of antioxidant supplementation in reducing primary cancer incidence and mortality: systematic review and meta-analysis. *Mayo Clin Proc* 2008; 83: 23–34.

Effects on the skin. Yellow pigmentation of the skin may result from an unusually high consumption of carrots or other source of carotene,[1] or from a defect in the enzyme that normally metabolises betacarotene to vitamin A.[2] Hypercarotenaemia can be distinguished from jaundice by the fact that the sclerae retain their normal white colour. Pigmentation occurs first on the palms and soles and may extend to the nasolabial folds. Although it has been stated that the condition is harmless,[1,3] as the body converts carotene to retinol only as required,[1] others consider that long-standing hypercarotenaemia can have clinical sequelae:[2] neutropenia[4] and amenorrhoea[5] have been reported to be associated with the condition.

1. Sharman IM. Hypercarotenaemia. *BMJ* 1985; 290: 95.
2. Vaughan Jones SA, Black MM. Metabolic carotenaemia. *Br J Dermatol* 1994; 131: 145.
3. McGowan R, *et al.* Carotenaemia in children is common and benign: most can stay at home. *Scott Med J* 2004; 49: 82–4.
4. Shoenfeld Y, *et al.* Neutropenia induced by hypercarotenaemia. *Lancet* 1982; i: 1245.
5. Kemmann E, *et al.* Amenorrhoea associated with carotenemia. *JAMA* 1983; 249: 926–9.

Pharmacokinetics

Gastrointestinal absorption of betacarotene depends on the presence of bile and is increased by dietary fat. About 20 to 60% of betacarotene is metabolised to retinol in the intestinal wall, and a small amount is converted to vitamin A in the liver. The proportion of betacarotene converted to vitamin A decreases as the intake of betacarotene increases, and high doses of betacarotene do not lead to abnormally high serum concentrations of vitamin A. Unchanged betacarotene is distributed to various tissues including fat, the adrenal glands, and ovaries.

References.
1. Wang X-D. Review: absorption and metabolism of β -carotene. *J Am Coll Nutr* 1994; 13: 314–25.

Human Requirements

Carotenes, of which betacarotene has the highest activity, are major dietary sources of vitamin A—see p. 2102.2.

UK and US recommended dietary intake. There is currently no UK dietary reference value (see p. 2046.1) for betacarotene, and in the USA recommended dietary allowances or dietary reference intakes (see p. 2046.1) have not been set. However, the Expert Group on Vitamins and Minerals[1] has established a safe upper level (SUL) for betacarotene of 7 mg daily, or about 110 micrograms/kg daily for a 60-kg adult.

1. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 06/01/06)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: B-Caroteno; Bronce Sol; *Austria*: Carotaben; *Braz.*: Vitizin Beta; Zirvit Beta; *China*: Bei Xi Di (贝西迪); Kaluo (卡洛); *Cz.*: Carotaben; *Ger.*: Carotaben; Carotinora; *India*: Oxyma; *Ital.*: Keratoplastica; Tannisol; *Switz.*: Carotaben; *Thai.*: Betacar; *Turk.*: Acecap; Carovit; *UK*: Biocarotine; *USA*: Lumitene.

Multi-ingredient Preparations. *Arg.*: Betabronze; Carotenos; Herbaccion Antioxidante; Hipersel; Indian Health - Urucum; Ipri V Plus; Ipri V Total; Ipri V; Krebs Plus; Krebs; Larotabe; Marathon Antioxidante; Natubrown; Para Sol SD; Perfect Sun; Piel Vital; Rominafort; Senexon Plus; Sigmasol; Sol Bronce Vital; Super Antioxidante; SX-22; Tonovital Antioxidante; Tonovital Plus Antioxidante; Vitamina C Plus; Zinc Antioxidante + Guarana; *Austral.*: Antioxidant Forte Tablets†; Antioxidant Tablets†; Beta A-C; Beta A-C; Bilberry Plus Eye Health†; Bio ACE Excell; Bio ACE; Cholesterol Health; Eye Health Herbal Plus Formula 4†; Ocuvite PreserVision†; Radiance; Skin Support; Supercarotene C&E†; *Austria*: Linola-Fett†; *Braz.*: Licopene†; Livten Vit; Ocuvite PreserVision; *Canad.*: Beta-C†; Ester Aces; Geri-Plus†; Liv-Gd; Liv-Gd; Phytopro†; Protect†; Super AO Factors; Super AO Formula†; Watkins Harvest†; *Chile*: Balans†; Biodif†; Biofax†; Biotonus; Larotabe; Seresis; Unitone; Vitagenol; Vitotal†; *China*: Bei Xi Yi (贝西伊); Difrarel (通法明); *Fr.*: Anti-oxydant 200; Cledist; Difrarel; Imedeen Tan Optimizer†; Oxelio Topique; Oxelio; Photoderm; Superoxylase; *Hong Kong*: Antioxidant Vita Tech†; Sanjukei Panax Ginseng; *Hung.*: Cellactive; Memolife; *India*: Actima; Ala-Plus; Alfaflavon; Alfatoz; Alfex-BT; Alpha B-Cal; Antoxid; Beta-Sclerobion; Bm-Vita; Carofit; Co-Q-Dent; Derantox; Dianuron; Ecome-LY; Elnutra-M; Elrox-AO; Exerge-HC; Fabulae; Flintoff; Preecad; Ginkoriv Plus; Glace; Horac; L-Bex; L-Vit-Z; Leclub; Lutamin; Lutivit; Luvion; Lycogreen; Lycominvit; Lyconerve; Lycosta; Lycozin; Lytox; Macugold; Natoz; NBOxid; Ocugold; Oiz; Orymax; Oxipre; Oxyban; Oxydex; Oxyeye; Oxytret; Oxyvit; *Indon.*: Amaropo Plus; Antion; Antox; Artovit; Asten; Azvit; Bececar; Berry Vision; Beta-CE; Betafort; Bevita; Bevizil; Bioretin†; Brainvit; Colaskin; Curcuma Plus; Danzet; Entrap; Eyebright; Eyevit; Hemaviton Skin Nutrient; Kuminta; Lanavision Plus; Lanavision; Lesifit; Letropar; Lubire; Lutevit; Lycoten; Lycoxy; Matase; Matovit; Maxivit; My Caps; Nicaro; Nu-Derm Sunblock†; nutrivision; Nuvision; Ocu-V; Oculex; Oculex; Opibright; Optha-LL; Optimax Plus; Optimax; Oxcal; Oxypen; Oxyvit; Progence; Qutan-10; Radivit; Reticopen; Retivit Plus; Retivit; Retop; Scaven; Seleca; Selefit Plus; Seloxy AA; Seloxy; Univoxy; Vantiz; Viceten-Z; Vicetent; Vioxy-fm; Vioxy; Vitacore; Vitacur; Vitalene; Vitanox; Vitop; *Irl.*: Seven Seas Active Sport†; *Israel*: Opti-Safe Areds; Opti-Safe†; *Ital.*: AMD; Anaribes Plus; Angstrom Viso; Angstrom Viso; Betaeffe Plus; Caresel; Carovit Forte; Carovit Repair; Carovit; Ecamannan; Eccarvit Plus; Keratolip; Konorderm; Mirtilene; Mirtivit; Riduton Ergo; Seleniun-ACE†; Solecin†; Tannidin Plus; Tanwards Combi; Vitalux; Vitreolux; *Malaysia*: Eurobio Bio-Vizmax; Seresis; *Mex.*: Seresis; Unitone; *Philipp.*: Carofit; Cristane; iiCare; Nutri-Aid; Polynerv-E with lecithin; Pynocare 40 Actisome; Zimuvite; *Pol.*: Biovision; *Port.*: Fortal Vision; Rilastil Anti-Oxidante; Rilastil Dermo Solar; *Rus.*: Antioxycaps (Антиоксикапс); Antioxycaps with Iodine (Антиоксикапс с Йодом); Antioxycaps with Selenium (Антиоксикапс С Селеном); Antioxycaps with Zincum (Антиоксикапс с Цинком); Hematogen C Vita (Гематоген С Вита); Strix (Стрикс); Tri-V Plus (Три-Ви Плюс)†; Triovit (Трювит); *Singapore*: Androlistica; Glutamine Plus; Scar Esthetique; Seresis†; *Spain*: Aceite Acalorico; Mirtilus†; *Switz.*: Visaline†; *Ukr.*: Gold Ray (Голд Рей); Optix (Оптикс); Optix Forte (Оптикс Форте); OxyLic (ОксиЛик); Triovit (Трювит); Vimifor Multivitamin with Beta-Carotene (Вимифор Мультивитамин 3 Бета-каротином)†; Vitrum Foreyes (Витрум Форайз); Vitrum Foreyes Forte (Витрум Форайз Форте); *USA*: Aces; *Venez.*: Biocaps; Opubiol.

Pharmacopoeial Preparations

USP 36: Beta Carotene Capsules; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-soluble Vitamins Capsules; Oil-Soluble Vitamins Oral Solution; Oil-soluble Vitamins Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets.

Biotin *(rINN)*

Biotini; Biotina; Biotinas; Biotine; Biotinum; Coenzyme R; Vitamin H; Биотин.

cis-5-(Hexahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazol-4-yl)valeric acid.

$C_{10}H_{16}N_2O_3S$=244.3

CAS — 58-85-5.

ATC — A11HA05.

ATC Vet — QA11HA05.

UNII — 6SO6U10H04.

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

Ph. Eur. 8: (Biotin). A white or almost white, crystalline powder or colourless crystals. Very slightly soluble in water and in alcohol; practically insoluble in acetone. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Biotin). A practically white crystalline powder. Very slightly soluble in water and in alcohol; insoluble in other common organic solvents. Store in airtight containers.

Profile

Biotin is traditionally considered to be a vitamin B substance. It is an essential coenzyme in fat metabolism and in other carboxylation reactions. Biotin deficiency may result in the urinary excretion of organic acids and changes in skin and hair. Deficiency of biotin is very unlikely in man because of its widespread distribution in food. Egg-yolk and offal are especially good sources. Biotin deficiency has been reported however during long-term parenteral nutrition and in patients with biotinidase deficiency, an inherited metabolic disorder. For dosage in biotinidase or isolated carboxylase deficiency see below. A combination of biotin and chromium tripicolinate (p. 2056.1) has been promoted as an adjunct for the management of diabetes mellitus.

Biotin combines with avidin, a glycoprotein present in raw egg-white, to form an inactive compound.

Adverse effects. For reference to life-threatening eosinophilic pleuropericarditis in a patient receiving biotin and pantothenic acid see p. 2085.3.

Deficiency states. Biotin has been used to treat deficiency of biotinidase or holocarboxylase synthetase, enzymes responsible for the recycling and incorporation of biotin. In the UK, the *BNFC* suggests the following doses:

- for isolated carboxylase defects, biotin may be given to neonates in a dose of 5 mg once daily by mouth or slow intravenous injection, adjusted according to response; older patients may be given 10 mg daily. The usual maintenance dose ranges from 10 to 50 mg daily, though up to 100 mg daily may be needed
- for defects of biotin metabolism, 10 mg once daily may be given by mouth or slow intravenous injection, adjusted according to response. Usual maintenance doses are 5 to 20 mg daily but higher doses may be needed

References.
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Human requirements. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR—see p. 2046.1) has been set for biotin although it was considered that an intake of between 10 and 200 micrograms daily was both safe and adequate.[1] Similarly in the USA an adequate intake of 30 micrograms daily has been set for adults.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065 2 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aminosam; Panabiotil; *Austria*: Bio-H-Tin; Curatin; Medobiotin; Merzbiotin†; *Chile*: Hvit; *Cz.*: Deacura; *Fin.*: Biotisan; *Ger.*: Bio-H-Tin; Deacura; Gabunat; Natubiotin; *Hung.*: Bio-H-Tin†; *India*: Biosure; Biotin; Cosmetin; H-Vit; *Ital.*: Biodermatin; Diathynil; Nebiotin; *Pol.*: Biotebal; *Spain*: Medebiotin; *Switz.*: Bio-H-Tin; Rombellin; *Ukr.*: Medobiotin (Медобиотин); *USA*: Appearex; Hard Nails.

Multi-ingredient Preparations. *Arg.*: Cistidac Cistimax Unguea; Folimax B; HSN; Megaplus; Rain-LY; Valcatil Max; Valcatil Plus; *Austral.*: Gluco Support; *Braz.*: Eximia Fortalize; *Canad.*: Glucoplex; *Chile*: Anastim; Brolin; Vantux Plus; *Fr.*: Forcapil; Zeniac LP; Zeniac; *Hung.*: Forcapil; *India*: Acmic-Alpha; Amec Plus; B-9 Tetra; B7 Plus; Biofair; Derantox; E-Cod Plus; Mex-vit; Pabatab-BZ; *Indon.*: Aldovas; Alicron; Cerebrofort Gol; Neofer; Tiola; Vionin; *Ital.*: Bioesse Plus; Biomineral 5-Alfa Shampoo; Biomineral 5-Alfa; *Malaysia*: Evelle; *Philipp.*: Diachrotin; Optigrow; *Singapore*: Evelle; *Spain*: Doctodermil; Lacerdermol†; *UK*: Pilfood; *Ukr.*: Fitoval Capsules (Фитовал капсулы); Vimifor Multivitamin with Beta-Carotene (Вимифор Мультивитамин 3 Бета-каротином)†; *USA*: Blood Sugar Balance; PNV-Iron†; REQ49+; *Venez.*: Anastim.

Pharmacopoeial Preparations

USP 36: Biotin Capsules; Biotin Tablets; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Boron

Bor; Bore; Borium; Boro; Бор.

B=10.81

CAS — 7440-42-8.

UNII — N9E3X5056Q.

Profile

Boron is a trace element that is widely distributed in nature, mainly in the form of borates. It appears to be essential for plant and animal health. Boron compounds such as borax and boric acid have been used as disinfectants although less toxic preparations are usually preferred. Boron has also been used in nutritional supplements for bone health.

Boron, in the form of injections of boron-10 containing compounds such as sodium borocaptate or boronophenylalanine, is being investigated in boron neutron capture therapy. Boron-10, a stable isotope, when irradiated with low-energy thermal neutrons undergoes nuclear capture and fissure reactions so that the high energy radiation released locally can be used to treat malignant neoplasms including high-grade gliomas, melanomas, and cerebral metastases.

References.
1. Newnham RE. Essentiality of boron for healthy bones and joints. *Environ Health Perspect* 1994; 102 (suppl 7): 83–5.
2. WHO. Boron. *Environmental Health Criteria 204*. Geneva: WHO, 1998. Available at: http://www.inchem.org/documents/ehc/ehc/ehc204.htm (accessed 12/10/10)
3. Barth RF, *et al.* Boron neutron capture therapy of cancer: current status and future prospects. *Clin Cancer Res* 2005; 11: 3987–4002.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Accelerex; Bone Builder; *Chile*: Caprimida D Balance; *India*: Bonjo Aid; Kelcer; Kibocal-M; Orbone Forte; Orbone; Osteo-G; Ospical-M; Osteo-G; *Indon.*: Biocal-95; Cal-95; Calplex; Caltron; Jointace; OA Plus; *Ital.*: Osteo Complex; *Malaysia*: Bio-Cal; *Pol.*: Caltrate Plus; *Singapore*: Shine Bio-Cal; *Thai.*: Calvin Plus; *UK*: Caltrate Plus; Estroven; Ostron; *Ukr.*: Calcemin (Кальцемин); Calcemin Silver (Кальцемин Сильвер); *USA*: Caltrate Plus; Prenate Chewable with Quatrefolic; TheraCal D.

Pharmacopoeial Preparations
USP 36: Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Tablets.

Calcium Ferrous Citrate

Ferrous Calcium Citrate.
Dicalcium iron(2+) bis(2-hydroxypropane-1,2,3-tricarboxylate).
$C_{12}H_{10}Ca_2FeO_{14}$=514.2
CAS — 53684-61-0.
UNII — 4P1IZU59M5.

Profile

Calcium ferrous citrate is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Singapore*: Raricap Combi; Raricap.

Calcium Fluoride

Fluoruro cálcico; Фторид Кальция.
CaF_2=78.07
CAS — 7789-75-5.
UNII — O3B55K4YKI.

Pharmacopoeias. In *Ger.*

Profile

Calcium fluoride is used as a fluoride supplement (see Sodium Fluoride, p. 2089.2) for the prevention of dental caries. Calcium fluoride is also used as a source of calcium.

Homoeopathy
Calcium fluoride has been used in homoeopathic medicines under the following names: Calcarea Fluorica; Calc. Fluor; Calcium Fluoratum; Cal. fl.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Calcifluor†.

Multi-ingredient Preparations. *Austral.*: Duo Celloids SCF†; Duo Celloids SPCF†; *Denm.*: Bifluorid; *Fr.*: Bifluorid; *India*: Calcinol; *Pol.*: Bifluorid; *Swed.*: Bifluorid; *Thai.*: Calcinol-RB.

Homoeopathic Preparations. *Austral.*: Celloids CF 43†; *Austria*: Nebenhohlen-Tropfen Nr 26†; Zahnkugelchen; *Canad.*: Combinaison†; Cutisitum†; Diamite; Formula CI 207†; Formula DE 226†; Formula PC 223†; Hylands Bioplasma; Hylands Hemorrhoids; Melange†; Nuage Bioplasma†; Optalia†; Phyto-Cal; Sinus Ease; Sinuspax†; Sorinoheel; Tyglan†; *Chile*: Calcarea fluor Compuesta; Ikoplex No 10; Ikoplex No 15; Ikoplex No 1; Ikoplex No 24; Ikoplex No 4; Ikoplex No 6; *Cz.*: Galium; *Fr.*: Calcarea Compose; Homeodose 20†; Jenoverine†; Osteocynesine; Silicea Complexe No 11; Sinuspax; *Ger.*: Cefalymphat†; Disco-cyl Ho-Len-Complex; Drufusan N†; Drufusan; Inflossan; Ranocalcin HM; Reproven N; Varicylum N; Venen-Komplex Ho-Pu-Complex; Veno-Injektopas; *Neth.*: Jenoverine†; Kind 0-6 Caltrivat; Lymfelite; Myamolite; Osteocynesine†; Toxex; *Port.*: Osteocynesine; *Rus.*: Mastopol (Мастопол); Rhus-Plus (Рус-Плюс); *Switz.*: Regenaplex Nr. 21c; Regenaplex Nr. 51c; Sinuspax†; *UK*: Medicinal Gargle; New Era Elasto; *Ukr.*: Immunokind (Имунокинд).

Calcium Levomefolate

Calcium L-Methylfolate; Calcium (6S)-5-Methyltetrahydrofolate; Calcium L-5-Methyltetrahydrofolate; Levomefolate Calcium (USAN); Levomefolinate Calcium; LMCA; Кальция L-Метилфолат.
Calcium *N*-[4-({[(6*S*)-2-amino-5-methyl-4-oxo-1,4,5,6,7,8-hexahydropteridin-6-yl]methyl}amino)benzoyl]-L-glutamate.
$C_{20}H_{23}CaN_7O_6$=497.5
CAS — 151533-22-1 (calcium levomefolate); 26560-38-3 (calcium methylfolate).
UNII — A9R10K3F2F.

NOTE. The names calcium levomefolinate and calcium mefolinate have been used for calcium levomefolate and calcium methylfolate respectively. Metafolin is a trade mark that has been used for calcium levomefolate.

Pharmacopoeias. In *US.*

USP 36: (Calcium L-5-methyltetrahydrofolate). It contains not more than 1.0% of calcium D-5-methyltetrahydrofolate calculated on the anhydrous and solvent-free basis. Store in airtight containers at a temperature between 8 degrees and 15 degrees in a dry place.

Profile

Calcium levomefolate is the calcium salt of the (*S*)-isomer of 5-methyltetrahydrofolate, the biologically active metabolite of folic acid (p. 2063.1). It is used as a food supplement and also has similar uses to folic acid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Prefolic; *USA*: Deplin.

Multi-ingredient Preparations. *USA*: ALZ-NAC; Beyaz; Cerefolin NAC; LMTHF/Pyridoxine HCl/Cyanocobalamin; Metanx; PNV-Iron†; Safyral; VitaCirc-B.

Carnitine Derivatives

Производные Карнитина.

Acetylcarnitine Hydrochloride

Acetilcarnitina, hidrocloruro de; Acetyl-L-carnitine Chloride; Levacecarnine Hydrochloride; Levocarnitinum acetilum hydrochloricum; ST-200; Ацетилкарнитина Гидрохлорид.
(3-Carboxy-2-hydroxypropyl)trimethylammonium acetate (ester) chloride.
$C_9H_{17}NO_4HCl$=239.7
CAS — 5080-50-2.
ATC — N06BX12.
ATC Vet — QN06BX12.
UNII — NDW10MX58T.

Carnitine *(rINN)*

Carnitina; Carnitinum; Karnitin; ST-198; Vitamin B_T; Vitamina B_T; Карнитин.
(3-Carboxy-2-hydroxypropyl)trimethylammonium hydroxide, inner salt; 3-Hydroxy-4-trimethylammoniobutyrate.
$C_7H_{15}NO_3$=161.2
CAS — 461-06-3.
UNII — S7UI8SM58A.

Levocarnitine *(BAN, USAN, rINN)*

L-Carnitina; L-Carnitine; L-Karnitin; Levocarnitin; Levocarnitina; Lévocarnitine; Levocarnitinum; Levokarnitiini; Levokarnitin; Levokarnitinas; Левокарнитин.
(*R*)-(3-Carboxy-2-hydroxypropyl)trimethylammonium hydroxide, inner salt; (*R*)-3-Hydroxy-4-trimethylammoniobutyrate.
$C_7H_{15}NO_3$=161.2
CAS — 541-15-1.
ATC — A16AA01.
ATC Vet — QA16AA01.
UNII — 0G389FZZ9M.

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

Ph. Eur. 8: (Levocarnitine). A white or almost white, hygroscopic, crystalline powder or colourless crystals. Freely soluble in water; soluble in warm alcohol; practically insoluble in acetone. A 5% solution in water has a pH of 6.5 to 8.5. Store in airtight containers.

USP 36: (Levocarnitine). White, hygroscopic, crystals or crystalline powder. Freely soluble in water and in hot alcohol; practically insoluble in acetone, in ether, and in benzene. pH of a 5% solution in water is between 5.5 and 9.5. Store in airtight containers.

Levocarnitine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de levocarnitina; Lévocarnitine, Chlorhydrate de; Levocarnitini Hydrochloridum; Левокарнитина Гидрохлорид.
(*R*)-3-Hydroxy-4-trimethylammoniobutyrate hydrochloride.
$C_7H_{15}NO_3HCl$=197.7
CAS — 6645-46-1.
UNII — J3Y5E6IKS3.

Levocarnitine Propionate

L-Carnitine propionate; Lévocarnitine, Propionate de; Levocarnitini Propionas; Propionato de levocarnitina; L-Propionylcarnitine; Propionylcarnitine; Propionyl-L-carnitine; ST-261; Левокарнитина Пропионат.
$C_{10}H_{19}NO_4$=217.3
CAS — 20064-19-7.
UNII — 0HU2UI27HF.

Levocarnitine Propionate Hydrochloride *(USAN)*

Propionyl-L-carnitine Hydrochloride; STI-261.
(2*R*)-3-Carboxy-*N,N,N*-trimethyl-2-(propanoyloxy)propan-1-aminium chloride.
$C_{10}H_{20}ClNO_4$=253.7
CAS — 119793-66-7.
UNII — 12FW2YBF04.

Uses and Administration

Carnitine is an amino acid derivative that is an essential cofactor of fatty acid metabolism.

Carnitine is used in the treatment of primary carnitine deficiency and in carnitine deficiency secondary to a variety of defects of intermediary metabolism or other conditions such as haemodialysis. Both the L- and the DL-isomers have been used, but it is believed that only levocarnitine is effective and in addition, that DL-carnitine supplementation can lead to carnitine deficiency.

In the UK, depending on the condition, up to 200 mg/kg daily of levocarnitine is given orally, in 2 to 4 divided doses. Rarely, higher doses of up to 400 mg/kg daily may be needed. In the USA, lower doses up to about 3 g daily are recommended.

When given intravenously, up to 100 mg/kg daily is given in 3 to 4 divided doses by slow intravenous injection over 2 to 3 minutes. Higher intravenous doses have been given, but are associated with an increased incidence of adverse effects.

Similar doses are used in children, although initial dose recommendations may vary in different countries, see Administration in Children, below.

In patients with carnitine deficiency secondary to haemodialysis, the recommended dose of levocarnitine is 10 to 20 mg/kg intravenously after each dialysis session, adjusted according to plasma-carnitine concentrations. An oral maintenance dose of 1 g daily may be considered (but see Adverse Effects and Precautions, p. 2054.3).

Levocarnitine is under investigation for the treatment of zidovudine-induced mitochondrial myopathy. Carnitine derivatives have been used to treat conditions including cardiovascular disease, peripheral arterial disease, cerebrovascular insufficiency, peripheral neuropathies, and neurological disorders, see below.

Carnitine chloride, carnitine hydrochloride, carnitine orotate, carnitine tartrate, levocarnitine fumarate, levocarnitine tartrate, acetylcarnitine or its hydrochloride, and bicarnitine chloride have also been used.

Administration in children. In the treatment of primary and secondary carnitine deficiency and organic acidaemias in children, levocarnitine is given in doses similar to those used in adults, see Uses and Administration, above. In the USA, an initial oral dose of 50 mg/kg daily is suggested for infants and children, increased gradually if necessary to a maximum of 3 g daily. The *BNFC* suggests that carnitine may also be given to neonates and children up to 18 years of age by intravenous infusion for primary deficiency and organic acidaemias, diluted in sodium chloride 0.9%, or glucose 5 or 10%; an initial dose of 100 mg/kg over 30 minutes is followed by a continuous infusion of 4 mg/kg per hour.

Carnitine supplementation. Carnitine occurs as distinct L- and D-isomers although naturally-occurring carnitine is almost exclusively the L-isomer.[1] Carnitine is an essential co-factor of fatty acid metabolism in the heart, liver, and skeletal muscle.[1,2] It is normally synthesised in the liver, brain, and kidneys in sufficient quantities to meet human requirements but dietary sources such as meat and dairy products also provide carnitine.[1-4] In plasma and tissues carnitine is present in the free form and as acylated esters of which acetylcarnitine is the most abundant.

Although DL-carnitine is the form often present in over-the-counter preparations and dietary supplements, levocarnitine should be preferred, as the two isomers differ in their actions. Levocarnitine acts as a substrate for carnitine acetyltransferase while D-carnitine acts as a competitive inhibitor; also, levocarnitine-induced stimulation of palmitate oxidation is competitively inhibited by D-palmitoylcarnitine. Such differences are believed to account for findings of benefit only with the L-isomer, or unwanted effects when D-carnitine or DL-carnitine was used.[1,5]

Primary carnitine deficiency is a disorder of the membrane transport of carnitine and patients have presented with hypoglycaemia and encephalopathy, skeletal myopathy, and cardiomyopathy. Therapy with carnitine in these primary deficiency states is considered to have a rational basis.[2,4-6] Secondary carnitine deficiency occurs in many inherited metabolic disorders, especially in the organic acidurias and disorders of beta-oxidation. The value of carnitine for these conditions is controversial.[2,4,6-8]

Carnitine deficiency may also arise during the long-term use of drugs such as valproic acid,[5,9-11] pivampicillin,[12,13] or pivmecillinam,[12] which are conjugated with carnitine. Whether carnitine supplementation can prevent or reverse this type of deficiency is unclear: although treatment with carnitine raised plasma-carnitine concentrations, it had no more effect than placebo on the well-being of children receiving valproic acid therapy in one study,[14] but others have found levocarnitine supplementation of value in attenuating valproate-induced hyperammonaemia after a protein-rich meal,[15] and some paediatric neurologists consider supplementation justified in selected children with epilepsy,[16,17] including those with, or at risk of, valproate-induced hepatotoxicity and hyperammonaemic encephalopathy. There is some suggestion that carbamazepine and phenobarbital can also decrease carnitine concentrations.[10,11] Therapy with cisplatin[18] or ifosfamide[19] has been reported to cause increased urinary excretion of carnitine.

There is also some evidence[5,20] that carnitine supplements may be of benefit to low birth-weight preterm infants, but a double-blind study[21] failed to confirm this effect. A systematic review concluded that there are insufficient data to support the use of carnitine supplementation for the treatment of apnoea of prematurity, despite a plausible rationale for such treatment.[22] While some evidence of benefit exists for carnitine supplementation of neonates receiving parenteral nutrition,[5] a systematic review found no evidence of effect on weight gain, fat utilisation, or ketogenesis.[23]

Low concentrations of carnitine have also been reported to occur in a variety of other conditions (see below).

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CARDIOVASCULAR DISEASE. There is some evidence that carnitine supplementation may exert a cardioprotective role. Benefit in patients with *cardiomyopathies*,[1-3] reduction of infarct size in patients with *myocardial infarction*,[4] and increased exercise performance in patients with *angina*[5] or *intermittent claudication*,[6-9] have all been described in patients given carnitine. While variable effects on cholesterol and triglyceride plasma concentrations have been described,[5] studies in diabetic[10] and hyperlipoproteinaemic[11] patients have reported reductions in plasma lipoprotein(a) concentrations. However, carnitine supplementation in patients with chronic *heart failure* failed to increase exercise capacity,[12] and its value outside of actual deficiency is still considered uncertain.[5]

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9. Andreozzi GM. Propionyl L-carnitine: intermittent claudication and peripheral arterial disease. *Expert Opin Pharmacother* 2009; 10: 2697–2707.
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11. Sirtori CR, *et al.* L-carnitine reduces plasma lipoprotein(a) levels in patients with hyper Lp(a). *Nutr Metab Cardiovasc Dis* 2000; 10: 247–51.
12. The Investigators of the Study on Propionyl-L-Carnitine in Chronic Heart Failure. Study on propionyl-L-carnitine in chronic heart failure. *Eur Heart J* 1999; 20: 70–6.

EXERCISE PERFORMANCE. Improved exercise performance in patients with angina or peripheral vascular disease has been described in patients given carnitine supplementation (see Cardiovascular Disease, above). However, evidence of benefit from the use of carnitine in healthy subjects in an attempt to improve athletic performance is lacking.[1,2] Nonetheless, interest in, and research into, the possible effects in healthy subjects and their mechanisms has continued.[3-6]

1. Tonda ME, Hart LL. N,N dimethylglycine and L-carnitine as performance enhancers in athletes. *Ann Pharmacother* 1992; 26: 935–7.
2. Brass EP. Supplemental carnitine and exercise. *Am J Clin Nutr* 2000; 72 (suppl): 618S–623S.
3. Karlic H, Lohninger A. Supplementation of L-carnitine in athletes: does it make sense? *Nutrition* 2004; 20: 709–15.
4. Brass EP. Carnitine and sports medicine: use or abuse? *Ann N Y Acad Sci* 2004; 1033: 67–78.
5. Kraemer WJ, *et al.* L-carnitine supplementation: influence upon physiological function. *Curr Sports Med Rep* 2008; 7: 218–23.
6. Broad EM, *et al.* Carbohydrate, protein, and fat metabolism during exercise after oral carnitine supplementation in humans. *Int J Sport Nutr Exerc Metab* 2008; 18: 567–84.

FATIGUE. Placebo-controlled studies in elderly subjects found that levocarnitine supplementation significantly reduced physical and mental fatigue,[1,2] while an open study in patients with chronic fatigue syndrome reported improvement in mental fatigue with acetylcarnitine, and general fatigue improvement with propionylcarnitine.[3] In a crossover study with amantadine, patients with chronic fatigue syndrome given levocarnitine for 8 weeks showed improvement in 12 out of 18 parameters measuring fatigue; patients who were most ill at the start of the study improved the most.[4] There is also some suggestion that levocarnitine supplementation may be of benefit in alleviating fatigue induced by antineoplastic chemotherapy,[5] or interferon.[6] For reports of carnitine use for fatigue in multiple sclerosis patients, see Neurological Disorders, below.

1. Pistone G, *et al.* Levocarnitine administration in elderly subjects with rapid muscle fatigue: effect on body composition, lipid profile and fatigue. *Drugs Aging* 2003; 20: 761–7.
2. Malaguarnera M, *et al.* L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial. *Am J Clin Nutr* 2007; 86: 1738–44.
3. Vermeulen RCW, Scholte HR. Exploratory open label, randomized study of acetyl- and propionylcarnitine in chronic fatigue syndrome. *Psychosom Med* 2004; 66: 276–82.
4. Plioplys AV, Plioplys S. Amantadine and L-carnitine treatment of chronic fatigue syndrome. *Neuropsychobiology* 1997; 35: 16–23.
5. Graziano F, *et al.* Potential role of levocarnitine supplementation for the treatment of chemotherapy-induced fatigue in non-anaemic cancer patients. *Br J Cancer* 2002; 86: 1854–7.
6. Neri S, *et al.* L-carnitine decreases severity and type of fatigue induced by interferon-α in the treatment of patients with hepatitis C. *Neuropsychobiology* 2003; 47: 94–7.

HAEMODIALYSIS. Carnitine homoeostasis is altered in renal failure[1] and a functional deficiency may develop in patients on dialysis.[2] This dialysis-related carnitine disorder manifests notably as anaemia, intradialytic hypotension, cardiomyopathy, and muscle weakness and fatigability. Treatment with intravenous levocarnitine 20 mg/kg after each dialysis session has been recommended. Clinical response should be evaluated at 3-monthly intervals, and treatment stopped if no improvement is seen within 9 to 12 months.[2] A systematic review suggested a beneficial effect of levocarnitine for the management of anaemia in haemodialysis patients.[3] Since carnitine supplementation has been associated with a reduction[4,5] in the incidence of haemodialysis-induced cramps (p. 1779.3) it has been suggested that these cramps might be due in part to carnitine deficiency. A meta-analysis[6] considered the evidence for benefit in cramp and hypotension to be suggestive, but not conclusive.

1. Matera M, *et al.* History of L-carnitine: implications for renal disease. *J Ren Nutr* 2003; 13: 2–14.
2. Eknoyan G, *et al.* Practice recommendations for the use of L-carnitine in dialysis-related carnitine disorder: National Kidney Foundation Carnitine Consensus Conference. *Am J Kidney Dis* 2003; 41: 868–76.
3. Hurot J-M, *et al.* Effects of L-carnitine supplementation in maintenance hemodialysis patients: a systematic review. *J Am Soc Nephrol* 2002; 13: 708–14.
4. Ahmad S, *et al.* Multicenter trial of L-carnitine in maintenance hemodialysis patients II: clinical and biochemical effects. *Kidney Int* 1990; 38: 912–18.
5. Sakurauchi Y, *et al.* Effects of L-carnitine supplementation on muscular symptoms in hemodialyzed patients. *Am J Kidney Dis* 1998; 32: 258–64.
6. Lynch KE, *et al.* Effects of L-carnitine on dialysis-related hypotension and muscle cramps: a meta-analysis. *Am J Kidney Dis* 2008; 52: 962–71.

HIV INFECTION. Carnitine deficiency has been reported in HIV-infected patients. Causes may include malabsorption or increased excretion due to a wasting syndrome commonly found in these patients, or toxicity from antiretroviral drugs causing metabolic changes or altered lipid metabolism in the patient.[1] Small, mostly uncontrolled studies have suggested benefit from supplementation with levocarnitine or acetylcarnitine in relieving complications of HIV infection and adverse effects of antiretroviral drugs,[2] notably toxic neuropathy.[3,4]

1. Vilaseca MA, *et al.* Low serum carnitine in HIV-infected children on antiretroviral treatment. *Eur J Clin Nutr* 2003; 57: 1317–22.
2. Ilias I, *et al.* L-Carnitine and acetyl-L-carnitine in the treatment of complications associated with HIV infection and antiretroviral therapy. *Mitochondrion* 2004; 4: 163–8.
3. Hertzman C, *et al.* Long-term effect of acetyl-L-carnitine for antiretroviral toxic neuropathy. *HIV Clin Trials* 2005; 6: 344–50.
4. Osio M, *et al.* Acetyl-l-carnitine in the treatment of painful antiretroviral toxic neuropathy in human immunodeficiency virus patients: an open label study. *J Peripher Nerv Syst* 2006; 11: 72–6.

MALE INFERTILITY. Increases in sperm motility have been reported in some infertile men treated with carnitine,[1-3] and some studies have reported improvements in pregnancy rates,[4] although clinical benefit needs to be further evaluated.[4,5]

1. Lenzi A, *et al.* Use of carnitine therapy in selected cases of male factor infertility: a double-blind crossover trial. *Fertil Steril* 2003; 79: 292–300.
2. Lenzi A, *et al.* A placebo-controlled double-blind randomized trial of the use of combined L-carnitine and L-acetyl-carnitine treatment in men with asthenozoospermia. *Fertil Steril* 2004; 81: 1578–84.
3. Vicari E, Calogero AE. Effects of treatment with carnitines in infertile patients with prostato-vesiculo-epididymitis. *Hum Reprod* 2001; 16: 2338–42.
4. Zhou X, *et al.* Effect of L-carnitine and/or L-acetyl-carnitine in nutrition treatment for male infertility: a systematic review. *Asia Pac J Clin Nutr* 2007; 16 (suppl 1): 383–90.
5. Agarwal A. Carnitines and male infertility. *Reprod Biomed Online* 2004; 8: 376–84.

NEUROLOGICAL DISORDERS. A meta-analysis of 21 studies concluded that acetylcarnitine improved mild cognitive impairment and prevented deterioration in patients with mild *Alzheimer's disease*.[1] However, a systematic review of 11 of these trials concluded that, although some evidence of benefit on clinical global impression exists, use of acetylcarnitine could not be routinely recommended in the treatment of Alzheimer's disease.[2]

Although no differences were found in serum carnitine concentrations in *multiple sclerosis* patients with or without disabling fatigue,[3] there is some suggestion of benefit with acetylcarnitine treatment for those patients with fatigue,[4] although a systematic review[5] considered the evidence of benefit insufficient. Carnitine has been reported to be of benefit in other cases of fatigue (see above).

In *Rett syndrome*, a severe neurodevelopmental disorder, supplementation with levocarnitine led to improvements in sleep efficiency, energy levels, and communication skills.[6] Parental and medical assessment of patient well-being improved in another study;[7] girls with classical Rett syndrome also improved in motor behaviour as assessed medically.

1. Montgomery SA, *et al.* Meta-analysis of double-blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. *Int Clin Psychopharmacol* 2003; 18: 61–71.
2. Hudson S, Tabet N. Acetyl-l-carnitine for dementia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 08/11/05).
3. Fukazawa T, *et al.* Serum carnitine and disabling fatigue in multiple sclerosis. *Psychiatry Clin Neurosci* 1996; 50: 323–5.
4. Tomassini V, *et al.* Comparison of the effects of acetyl L-carnitine and amantadine for the treatment of fatigue in multiple sclerosis: results of a pilot, randomised, double-blind, crossover trial. *J Neurol Sci* 2004; 218: 103–8.
5. Tejani AM, *et al.* Carnitine for fatigue in multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2010 (accessed 10/06/10).
6. Ellaway CJ, *et al.* Medium-term open label trial of L-carnitine in Rett syndrome. *Brain Dev* 2001; 23 (suppl): S85–S89.
7. Ellaway C, *et al.* Rett syndrome: randomized controlled trial of L-carnitine. *J Child Neurol* 1999; 14: 162–7.

Adverse Effects and Precautions

Gastrointestinal disturbances such as nausea, vomiting, diarrhoea, and abdominal cramps have been reported after the use of levocarnitine. Body odour has also been noticed in some patients, possibly due to the formation of the metabolite trimethylamine (see Fish Odour Syndrome, p. 2043.2). Decreasing the dosage may reduce or eliminate these effects; oral levocarnitine should be consumed slowly to decrease gastrointestinal disturbances. Seizures have been reported.

Patients with severe renal impairment should not be given high oral doses of levocarnitine for long periods,

because of the accumulation of the metabolites trimethylamine and trimethylamine-*N*-oxide. This is said not to occur to the same extent after intravenous dosage. Diabetic patients given carnitine while receiving insulin or hypoglycaemic drugs should be monitored for hypoglycaemia.

Renal impairment. Of 30 patients given DL-carnitine intravenously after dialysis sessions 3 developed myasthenia-like symptoms but when these 3 were given only levocarnitine the symptoms did not occur.[1] It was considered that in anuric uraemic patients the D-isomer was not excreted adequately and that accumulation had blocked neuromuscular transmission. It was therefore suggested that levocarnitine, rather than the DL-form, should be used. (High and prolonged oral doses of levocarnitine should, however, be avoided—see p. 2054.3.)

1. Bazzato G, *et al.* Myasthenia-like syndrome after DL but not L-carnitine. *Lancet* 1981; i: 1209.

Pharmacokinetics

Oral doses of levocarnitine are absorbed slowly and incompletely from the small intestine. Bioavailability has been reported to be only about 10 to 15%, with peak plasma concentrations occurring about 3 to 4 hours after an oral dose. Plasma concentrations after oral doses represent the sum of endogenous and exogenous material. Levocarnitine does not appear to bind to plasma proteins. It is mainly eliminated by the kidneys, undergoing extensive tubular reabsorption. After intravenous doses, levocarnitine appears to undergo minimal metabolism. Levocarnitine given orally may undergo degradation in the gastrointestinal tract, leading to the formation of metabolites such as trimethylamine-*N*-oxide and γ-butyrobetaine, recovered in the urine and faeces, respectively.

References.
1. Evans AM, Fornasini G. Pharmacokinetics of L-carnitine. *Clin Pharmacokinet* 2003; 42: 941–67.
2. Bain MA, *et al.* Disposition and metabolite kinetics of oral L-carnitine in humans. *J Clin Pharmacol* 2006; 46: 1163–70.
3. Fornasini G, *et al.* A pharmacokinetic model for L-carnitine in patients receiving haemodialysis. *Br J Clin Pharmacol* 2007; 64: 335–45.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Albicar; Fertilix; Laremide; Neurex; Neuroactil; ***Austria***: Nefrocarnit; ***Canad.***: Carnitor; ***Chile***: Actigeron; Carnicor†; ***China***: Ao Bei Li (奥贝利); Ao Shu Jie (澳枢洁); BoWei (博维); Carnitene (可益能); Cartan (卡尔特); Dongweili (东维力); Gai Lei (盖雷); Ke Fei (克非); Ke Ni You (可尼尤); Ke Pu Tuo (可谱妥); Lei ka (雷卡); Lv Ding Fang (律定方); Ni Di Duo (尼迪多); Ni Er (尼尔); Wei Le Rui (威乐瑞); Xin Neng (芯能); Yu Li (誉利); Zhuo Ka (卓卡); ***Fr.***: Levocarnil; ***Ger.***: Biocarn; L-Carn; Nefrocarnit; ***Gr.***: Aminocer; Aveptol; Bicarnesine; Bitobionil; Carniben; Catnidose; Carnil; Carniprol; Carnisac; Carnitop; Carnivit; Corubin; Duocarnic; Energocarnil; Ensial; Ergogen; Frutenor; Growart; Inestom; Intelecta; Koptilan; Lecarna; Levalastine; Levamin; Levars; Levicin; Levocarnil; Levocuor; Levosan; Lisefor; Listover; Locar; Lofostin; Lyzip; Maledrol; Medicardin; Merlit; Mevamyst; Minartine; Minoa; Oskana; Phacovit; Revotonine; Ridovet; Soludamin; Superamin; Tonovit; Trian; Trinalin; Vigorup; Xaritic; ***Hong Kong***: Carnitene; Carnitor; ***India***: Carnicle; Carnitor; L-Tine; Lencar; Nucarnit; ***Ital.***: Bio-Vis; Branigen; Branitil†; Carnitene; Carnovis; Dromos; Elleci; Eucar†; Eucarnil; Eufertil; Farnitin; Lefcar; Levocarvit; Medocarnitin; Megavis†; Miocardin; Miocor; Miotonal; Neo Cardiol†; Nicetile; Normobren; Zibren; ***Jpn***: L-Cartin FF; ***Mex.***: Cardispan; Lipovitasi D; Provicar; ***Neth.***: Nefrocarnit; ***Philipp.***: Cardimax; Carnicor; Cartine; Levocetile; ***Pol.***: Carnivit†; ***Port.***: Cartine†; Disocor; Lacetilina†; ***Rus.***: Carniten (Карнитен); Elcar (Элькар); ***Spain***: Carnicor; Secabiol; ***Turk.***: Carnitene; Nefro-Carnitin; ***UK***: Carnitor; ***USA***: Carnitor; VitaCarn; ***Venez.***: Carnisin; Kativil; Lixi; Provicar.

Multi-ingredient Preparations. *Arg.*: Azodac; Biocell; Biomag Vital; Cistidac; Dermasolutions†; Desgras Burner Fat; Durgel; Garcinol Max; Herbaccion Diet; Metabolic Natural Diet; Reductase; Redumax; Ripped Max; Silueta Plus†; ***Austral.***: Homme-F; Magnesium Powder; PM Kids Intelligent; ***Braz.***: Carnabol; Ferrotrat B12 Plus; Nutrimaiz SM; Trimetabol†; ***Chile***: Cellenergy; Peracon; Ubiten; ***Hung.***: Metabol; ***India***: Cardi-NRG; Cardistim; Carnit; Evion-LC; Exart; Hi-Q Plus; Hi-Q Plus; Hosit-L; Immunace; L-Nit; Lenova-MP; Levo-P; Levo-Forte; Maxoza; NE; Nu-Look; ***Indon.***: Betaslim; Bexicom Fit; Bioquinone; Canergy†; Car-Q; Carni Plus; Carnon; Co-vitala; Combest†; Corsel; DFM; Enercore; Galten; Immunace; Metsel; nu Qten Com; Procardio†; Vitaslim; ***Ital.***: Anasten Plus; Atlantis; Binfolipase; Briovitase Sostegno; Carfosid; Co-Carnetina B12; Creavit; Enercomplex; Linfolipase; Lipoenergy; Memovigor; Phototrop; Riduton Ergo; Salovit; Tripondil; ***Malaysia***: Hovid Q-10 SupraBio + L-Carnitine; Olivenol livin' Vigor†; ***Mex.***: Redumed; Slim-D†; ***Philipp.***: Fit-N-Trim; Fitrum; Godex†; Memorx IQ Plus; Mitodex; Nutrafit; Optigrow; Zeman; ***Pol.***: Kofevit†; ***Singapore***: Cardio-Essentials; Olivenol Livin' Vigor; ***Spain***: Hepadif; Malandil; Pranzo; ***Ukr.***: Cardonat (Кардонат); Hepadif (Гепадиф); Stifimol (Стифимол); Trimetabol (Триметабол); ***USA***: Cardio Tone.

Pharmacopoeial Preparations
USP 36: Levocarnitine Injection; Levocarnitine Oral Solution; Levocarnitine Tablets.

Casein

Kazeina.
CAS — 9000-71-9.
UNII — 48268V50D5.

Profile

Casein is a protein found in milk and has been used as a source of protein in preparations for enteral and parenteral nutrition; it may be used in the production of protein hydrolysate injection. Calcium caseinate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Proteina 100; Proteinex Victus; Secalbum; Sumaprot 90; ***Israel***: Casec†; ***Mex.***: Calsein†; K-Sein; ***USA***: Casec†.

Multi-ingredient Preparations. ***India***: Bioferum Forte; Protone; Protone; ***Mex.***: Calciyodina; ***Switz.***: Cicafissan; Vitafissan N.

Choline Bitartrate

Bitartarato de Colina; Choline Acid Tartrate; Choline Hydrogen Tartrate; Cholinii Tartras; Colina, bitartrato de; Холина Битартрат.
2-Hydroxyethyltrimethylammonium hydrogen tartrate.
$C_9H_{19}NO_7$=253.3
CAS — 87-67-2.
UNII — 6K2W7T9V6Y.

Pharmacopoeias. In *US*.

USP 36: (Choline Bitartrate). A white, hygroscopic, crystalline powder; odourless or with a faint trimethylamine odour. Clear and colourless in solution. Freely soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 10% solution in water is between 3.0 and 4.0.

Choline Chloride *(rINN)*

Choline, Chlorure de; Cholini Chloridum; Cholinii Chloridum; Choliny chlorek; Cloruro de colina; Colina, cloruro de; Koliinikloridi; Kolinklorid; Холина Хлорид.
2-Hydroxyethyltrimethylammonium chloride.
$C_5H_{14}ClNO$=139.6
CAS — 62-49-7 (choline); 67-48-1 (choline chloride).
UNII — 45114D8027.

Pharmacopoeias. In *Fr.* and *US*.

USP 36: (Choline Chloride). Hygroscopic, colourless or white crystals or crystalline powder, usually having a slight odour of trimethylamine. Clear and colourless in solution. Soluble in water and in alcohol. pH of a 10% solution in water is between 4.0 and 7.0.

Profile

Choline is an acetylcholine precursor. It is involved in lipid metabolism and acts as a methyl donor in various other metabolic processes. Choline has traditionally been considered to be a vitamin B substance although its functions do not justify its classification as a vitamin. Choline can be synthesised in the body. However, its absence in total parenteral nutrition causes hepatic steatosis, and it is also thought to be a requirement in the diet of neonates. Sources of choline, which occurs mostly as lecithin, include egg-yolk and vegetable and animal fat.

Choline is used as a dietary supplement and has been used to treat liver disorders such as fatty liver and cirrhosis. It has been tried in the management of Alzheimer's disease (see Dementia, p. 388.1) but without success. Choline is used as the dihydrogen citrate, and orotate salts as well as the bitartrate and the chloride.

Human requirements. In the USA, an adequate intake (see p. 2046.1) of 550 mg daily in men and 425 mg daily in women has been determined for choline.[1] The tolerable upper intake level for adults is 3.5 g daily.[1] There is evidence that dietary requirements may vary between individuals as a result of several genetic polymorphisms in metabolism;[2] premenopausal women also appear to have an increased capacity for choline synthesis, compared with postmenopausal women or with men.

1. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline.* Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)
2. Zeisel SH. Choline: critical role during fetal development and dietary requirements in adults. *Annu Rev Nutr* 2006; 26: 229–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Bitoline; Cidalin; Hepastar; Livat-DS; Livodex.

Multi-ingredient Preparations. *Arg.*: Energizante Vital con ginseng; Energizante; GB 100; Ripped Max; Skin Hair & Nails; ***Austral.***: For Women Multi Plus EPO†; KickStart Detox; Metabolift Fat Burner; PM Syrin; ***Austria***: Vita-Gerin; ***Braz.***: Abcler; Anekron; B-Vesil†; Biohepax†; Chofrafig; Enterofigon; Epativan; Epocler; Extrato Hepatico Composto; Hepalin; Hepatox; Lisotox; Metiocolin B12; Metiocolin Composto; Necro B6; Panvitrop; Xantinon B12; Xantinon Complex; ***Canad.***: Emulsi Factors; Formula 17605 Diaplex; Formula AO†; Hepaticol; Lipofactors & Niacin†; Liv-Gd; Liv-Gd; Live-Rite; Phyto-Marinex; T-BMP; ***Chile***: Hepabil; ***Fr.***: Citrocholine†; Cysticholf†; Desintex-Choline†; Hepagrume; Memoptic; ***Ger.***: Vita-Gerin N; ***Hong Kong***: Anti-Stress Hi B Plus C†; B Complex 50; Executive Stress†; Mega-Antioxidant†; Super Vita Vim; Vita Stress†; Vitabex A†; Vitacymin†; ***India***: Al-Live; Anorexin Plus; Apel-G; Apirich; Apitus-TC; App-Up; Appe-Care; Appet; Appetidin; Asi-Liv; Atric Plus; Auz; Bio Cyp; C-Lysin; Cherrytone; Chocy; Cipliv; Clydin; Cyaptin; Cyp-L; Cypine-TS; Cypolin; Cypon DPS; Cypon-I; Cyprea-T; Cypro-L; Cypro; Cyprobit; Cyproz; Decyp-P; Delphicol†; Devlup; Forliv; Fortil; Gardian; Genoplex Forte; Growise; Hapeast; Hepa; Hepachol; Hepawin Plus; Hepoline; Hepsandinn; Homocyst; Hypetin; In-OZ; Karnatakaiv; Lecyp; Lederplex; Liveril; Livobion; Livobion; Livocip; Livpron; LSky; Lycostar-CM; Lycyp; M-Cyp; Maltviron; Mecolin; Morvit; Multivite Gold; Multivite Woman; NBTone; O-AP; Optifit; Oraxin; Orliv; Orovit; Sorbiline; Sorliv; ***Indon.***: Bio-Curliv; Carni Plus; Curliv Plus; Curliv; DFM; Growee; Hepabion†; Hepatin; Lipagent; Methicol; Methioson; Miniceronal†; Proliver; Vidaylin L; Vionin; Zamel; ***Irl.***: Ketovite; ***Ital.***: Lipoenergy; Nervocel†; Rischiaril; ***Malaysia***: Pharmaton†; Revital; Vi-Daylin; ***Philipp.***: Arcostrong†; BioSil†; Completia†; Energel; Enerzip; K-A Plus; Leginsol-E; Pharmaton; Rejuvenex; ***Pol.***: Methiovit†; ***Rus.***: Doppelherz Energotonik (Доппельгерц Энготоник); Prohepar (Прогепар); ***S.Afr.***: Clusivol; Hepavite†; Neurotone; Prohep†; ***Singapore***: Essentials†; Growee†; ***Switz.***: Vita-Gerin; Vitiron; ***Thai.***: Liporon; Vita Multicap; Vitop; ***UK***: Lipotropic Factors; Skin Care Nutrients; ***Ukr.***: Hepahealth (Гепахелс); PM Sirin (ПМ Сирин); Vitiron (Витирон); Vitrum Beauty (Витрум Бьюти); Vitrum Beauty Elite (Витрум Бьюти Элит); ***USA***: Advanced Ear Health Formula; Alive Once Daily Womens 50+ Ultra Potency; Cholinoid†; Clinical Nutrients 50-Plus Men; Megavite Fruits & Veggies; One A Day Vitacraves; Solo; Tyler Prenatal; ***Venez.***: Hepasil.

Chondroitin Sulfate–Iron Complex

Chondroitin Sulphate–Iron Complex; Ferropolichondrum; Hierro y sulfato de condroitina, complejo de; Железа Сульфат-Хондроитина Комплекс.
CAS — 54391-57-0.
ATC — B03AB07.
ATC Vet — QB03AB07.

Profile

Chondroitin sulfate-iron complex is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in doses of up to 900 mg daily, equivalent to up to 90 mg of iron daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Isairon.

Chromium

Chrom; Chrome; Cromo; Хром.
Cr=51.9961
UNII — X1N4508KF1 (chromium ion); 0R0008Q3JB (chromium).

Chromium Trichloride

Chromic Chloride; Cromo, tricloruro de; Трёххлористый Хром; Хлористый Хром.
$CrCl_3.6H_2O$=266.4
CAS — 10025-73-7 (anhydrous chromium trichloride); 10060-12-5 (chromium trichloride hexahydrate).
UNII — KB1PCR9DMW (chromium trichloride); Z310X5O5RP (anhydrous chromium trichloride).

Pharmacopoeias. In *US*.

USP 36: (Chromic Chloride). Dark green, odourless, slightly deliquescent crystals. Soluble in water and in alcohol; slightly soluble in acetone; practically insoluble in ether. Store in airtight containers.

The symbol † denotes a preparation no longer actively marketed

Chromium Tripicolinate

Chromium Picolinate; Cromo, tripicolinato de; Пиколинат Хрома.
$C_{18}H_{12}N_3O_6Cr$=418.3
CAS — 14639-25-9.
UNII — 5717888Z6P.

Pharmacopoeias. In *US.*

USP 36: (Chromium Picolinate). Store in airtight containers.

Uses and Administration

Chromium is an essential trace element that potentiates insulin action and thus influences carbohydrate, lipid, and protein metabolism. It exists in several oxidation states, of which the trivalent (3+) and hexavalent (6+) are the most important. Trivalent chromium compounds are nutritionally active and are discussed further below; hexavalent compounds have industrial uses and are generally more toxic (see Chromium Trioxide, p. 2476.2). Dietary sources rich in chromium include brewers' yeast, meat, whole grains, and nuts, and usually contain the trivalent form. Chromium trichloride has been given as a chromium supplement in total parenteral nutrition. Chromium tripicolinate is used as a chromium supplement, and is being investigated for improving glycaemic control in patients with diabetes mellitus. Chelates of chromium and nicotinic acid (chromium nicotinate; chromium polynicotinate; niacin-bound chromium) have also been used. One such product has been widely promoted under the name *ChromeMate* (*InterHealth Nutraceuticals, USA*).

Diabetes mellitus. A review[1] of trivalent chromium in the management of diabetes mellitus (p. 459.1) concluded that it may have an adjunctive role. A meta-analysis[2] found no effect of chromium on glucose or insulin concentrations in non-diabetic subjects; data for diabetic patients were inconclusive. A systematic review[3] found no significant effect with chromium supplementation on lipid or glucose metabolism in non-diabetic subjects, but that it might have a modest beneficial effect on glycaemia and dyslipidaemia in those patients with diabetes. Meta-analysis was hampered by the overall poor quality and heterogeneity of available studies,[3] and further research was considered necessary.[1-3]

1. Ryan GJ, *et al.* Chromium as adjunctive treatment for type 2 diabetes. *Ann Pharmacother* 2003; 37: 876–85.
2. Althuis MD, *et al.* Glucose and insulin responses to dietary chromium supplements: a meta-analysis. *Am J Clin Nutr* 2002; 76: 148–55.
3. Balk EM, *et al.* Effect of chromium supplementation on glucose metabolism and lipids: a systematic review of randomized controlled trials. *Diabetes Care* 2007; 30: 2154–63.

Human requirements. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR—see p. 2046.1) has been set for chromium although a safe and adequate intake was believed to be above 25 micrograms daily for adults.[1] Similarly, in the USA a recommended dietary allowance has not been published but the adequate intake was estimated to be 35 micrograms daily for young men and 25 micrograms daily for young women.[2] WHO considers that the minimum population mean intake likely to meet normal needs for chromium might be about 33 micrograms daily, and that supplementation of this element should not exceed 250 micrograms daily until more is known.[3]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.* Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. WHO. Chromium. In: *Trace elements in human nutrition and health.* Geneva: WHO, 1996: 155–60.

Obesity. Chromium picolinate has been promoted as a dietary supplement to assist in weight loss. However, a randomised placebo-controlled study involving 80 obese adults found that supplementation with oral chromium picolinate 1 mg daily for 24 weeks did not affect weight loss in this group.[1]

1. Yazaki Y, *et al.* A pilot study of chromium picolinate for weight loss. *J Altern Complement Med* 2010; 16: 291–9.

Supplementation. Although a daily chromium intake of 200 nanograms/kg has been suggested in children given total parenteral nutrition (TPN), a study in 15 children[1] given long-term parenteral nutrition found that supplementation at about this level was associated with serum-chromium concentrations 4 to 42 times higher than the mean value in 15 children not receiving TPN. Raised serum-chromium concentrations were associated with a decrease in glomerular filtration rate; one year after stopping chromium supplementation, which reduced intake to 50 nanograms/kg daily (as contaminants of water and TPN solutions), chromium concentrations, although lower, were still higher than controls and renal function had not altered. The authors subsequently ceased chromium supplementation in both children and adults, since chromium contamination of TPN solutions appeared adequate to prevent deficiency, although it was acknowledged that signs of chromium deficiency might take some years to appear. The recommendations for chromium supplementation in parenteral nutrition have therefore been queried.[2] Chromium contamination in various preparations used in paediatric parenteral nutrition has been studied.[3]

1. Moukarzel AA, *et al.* Excessive chromium intake in children receiving total parenteral nutrition. *Lancet* 1992; 339: 385–8.
2. Moukarzel A. Chromium in parenteral nutrition: too little or too much? *Gastroenterology* 2009; 137 (suppl): S18–S28.
3. Hak EB, *et al.* Chromium and zinc contamination of parenteral nutrient solution components commonly used in infants and children. *Am J Health-Syst Pharm* 1998; 55: 150–4.

Adverse Effects

Trivalent salts of chromium, such as chromium trichloride, are generally considered to produce few adverse effects. However, hexavalent forms of chromium are notably toxic (see under Chromium Trioxide, p. 2476.2).

Effects on the kidneys. Two cases of renal failure were attributed to ingestion of excessive doses of chromium tripicolinate in women with no history of renal dysfunction.[1,2] Acute renal failure with features of acute tubular necrosis, and requiring haemodialysis, has been reported after ingestion of a chromium picolinate-containing supplement. The amount of chromium in the supplement could not be determined.[3] For mention of decreases in glomerular filtration rate in children receiving chromium-supplemented total parenteral nutrition, see Supplementation, above.

1. Wasser WG, *et al.* Chronic renal failure after ingestion of over-the-counter chromium picolinate. *Ann Intern Med* 1997; 126: 410.
2. Cerulli J, *et al.* Chromium picolinate toxicity. *Ann Pharmacother* 1998; 32: 428–31.
3. Wani S, *et al.* Acute tubular necrosis associated with chromium picolinate-containing dietary supplement. *Ann Pharmacother* 2006; 40: 563–6.

Effects on the skin. There have been rare reports[1,2] of cutaneous reactions to oral chromium tripicolinate, including one of acute generalised exanthematous pustulosis.

1. Young PC, *et al.* Acute generalized exanthematous pustulosis induced by chromium picolinate. *J Am Acad Dermatol* 1999; 41: 820–3.
2. Fowler JF. Systemic contact dermatitis caused by oral chromium picolinate. *Cutis* 2000; 65: 116.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: NH4 Silhouette; Ripped Max; Sigmar Lipo; Tonekin; *Austral.*: Chrome; *Canad.*: Micro Cr; *Chile*: Edul K-200; *India*: CP; *Israel*: Micro Cr; *Ital.*: Croben; *Mex.*: Cromotex; *USA*: Chroma-Pak†.

Multi-ingredient Preparations. *Arg.*: Centellacrom; Garcinia Cambogia Compuesta; Herbaccion Diet; IP6; Metabolic Ripped Max; *Austral.*: 3B Beer Belly Buster†; Citri Slim+Trim†; Digestaid; Gluco Support; Metabolift Fat Burner; *Braz.*: Olig-Trat; *Canad.*: Formula 7441†; Formula 7442†; Glucoplex; *Fr.*: Expuryl; Gynalpha Plus†; Hydrastart; Optibiol; *Hung.*: Dietet-In; Klimin; *India*: Alcrin-M; Alcrin; Alphamix-BT; Alphamix; Beta-Sclerobion; Betonin-CZ; Carofit-D; Chromet; Cobadex-CZS; Cobalvit Plus; Cobanerve Plus; Cromoplex; D-Gard; Dianuron; Ecobal-Plus; Ecobal; Eldervit-ZC; Elmecob Plus; Exerge; Felicita-OD; Glim-C; Glycor-C; Horac; Kefive Plus; Me Plus; Me-Plus; Mecobion-OD; Mecoday Plus; Mindde Plus; Nacrolip; Nervijen-D; Nervz-B; Neuractin Forte; Neuromin-EA; Neurotrat; Nocad; Nuroclad-Plus; Nurokind-More; Nutricobal Plus; Obedeuce; Optisulin; Optivision; Ostebon-M; Oxitra; Oxyglobin; Winofit; *Indon.*: Aldovas; Alicron; Betaslim; Biocholes†; Combes†; F-Slim†; Fres Diab; Kitoles†; Lanavision Plus; nutrivision; Osfit; Tiola; Univoxy; Vitala; Vitaslim; *Ital.*: Eccarvit Plus; *Mex.*: Slim-D†; *Mon.*: Evestrel Physio Profil†; Romarinex Chrome; *Philipp.*: Diachrotin; Diamaxin; Glucontrol; Liposorb; Mordica; Nutrafit; *Singapore*: Apple Cider Vinegar Diet; Chitosano; Multitrace-5; Nutrivision†; Optibiol; *Thal.*: Biotrat; Diavit; *Turk.*: Keten; *UK*: Selenium Bonus; *Ukr.*: Lipomin (Липомин); Stifimol (Стифимол); Vimifor Multivitamin with Beta-Carotene (Вимифор Мультивитамин 3 Бета-каротином)†; *USA*: Blood Sugar Balance; Cro-Man-Zin; Dexatrim Max Daytime Appetite Control.

Pharmacopoeial Preparations

USP 36: Chromic Chloride Injection; Chromium Picolinate Tablets; Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Trace Elements Injection; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Citrulline

Citrulina; L-Citrulline; NSC-27425; N^5-(Aminocarbonyl)-L-ornithine; N^5-Carbamylornithine; Цитруллин.
α-Amino-δ-ureidovaleric acid.
$C_6H_{13}N_3O_3$=175.2
CAS — 372-75-8.
UNII — 29VT07BGDA.

Profile

Citrulline is a non-essential amino acid that is involved in the urea cycle. Citrulline and citrulline malate are used as dietary supplements.

Hyperammonaemia. Citrulline has been given as an alternative to arginine in the management of hyperammonaemia (p. 2049.3) due to **urea cycle disorders.**

Lysinuric protein intolerance is another condition associated with hyperammonaemia and similar neurological sequelae. In this condition there is no deficiency of urea-cycle enzymes but a deficiency of urea-cycle substrate, such as ornithine, which results in reduced synthesis of citrulline. Patients are treated with dietary protein restriction and citrulline supplementation, which improves protein tolerance and nutrition but only slightly ameliorates growth retardation. Osteoporosis may be severe in children with this disorder.[1] A child presenting with osteopenia and diagnosed with lysinuric protein intolerance was given large oral doses of citrulline (up to 5.7 g daily). Aside from a substantial increase in protein tolerance, a striking acceleration in linear growth and bone mass was reported.[2] Lysine deficiency may be implicated in growth retardation,[1] but lysine supplementation may precipitate diarrhoea and malabsorption.[2] Six patients with lysinuric protein intolerance and receiving oral citrulline were supplemented with oral lysine. Larger lysine doses of 0.55 mmol/kg and 1.1 mmol/kg given consecutively, caused profuse diarrhoea, but smaller doses of 0.05 mmol/kg, given three times daily (up to a maximum dose of 2.5 mmol) were well tolerated. Plasma lysine concentrations were normalised with no adverse effects on the urea cycle.[1]

1. Lukkarinen M, *et al.* Oral supplementation corrects plasma lysine concentrations in lysinuric protein intolerance. *Metabolism* 2003; 52: 935–8.
2. Carpenter TO, *et al.* Lysinuric protein intolerance presenting as childhood osteoporosis: clinical and skeletal response to citrulline therapy. *N Engl J Med* 1985; 312: 290–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: MyoCIT; Stimol; *Indon.*: Stimol†; *Port.*: Dynergum; *Rus.*: Stimol (Стимол); *Spain*: Stimol; *Switz.*: Biostimol; *Ukr.*: Stimol (Стимол).

Multi-ingredient Preparations. *Arg.*: Total Magnesiano Sport; *Braz.*: Ornitargin; *Ital.*: Ipoazotal Complex; Promofort.

Cod-liver Oil *(BAN)*

Aceite de Higado de Bacalao; Balık yağı; Cod Liver Oil; Csukamájolaj; Foie de morue, huile de; Huile de Foie de Morue; Iecoris aselli oleum; Kalanmaksaõljy; Lebertran; Menkių kepenų taukai; Ol. Morrh.; Óleo de Bacalhau; Oleum Jecoris Aselli; Oleum Morrhuae; Olio di Fegato di Merluzzo; Rybí olej; Torskleverolja; Тресковый Печёночный Жир.
CAS — 8001-69-2.
UNII — 88L281NWFG.

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

Eur. also includes farmed cod-liver oil.

Ph. Eur. 8: (Cod-liver Oil (Type A) and Cod-liver Oil (Type B)). Purified fatty oils obtained from the fresh livers of wild cod, *Gadus morhua* and other species of Gadidae, solid substances being removed by cooling and filtering. The oils contain 600 units (180 micrograms) to 2500 units (750 micrograms) of vitamin A per g and 60 units (1.5 micrograms) to 250 units (6.25 micrograms) of vitamin D_3(colecalciferol) per g. Antoxidants may be added.

Clear, yellowish liquids. Practically insoluble in water; slightly soluble in alcohol; miscible with petroleum spirit. Store in well-filled airtight containers. Store under an inert gas if no antoxidant is added. Protect from light.

Ph. Eur. 8: (Cod-liver Oil, Farmed). Purified fatty oil obtained from the fresh livers of farmed cod, *Gadus morhua*, solid substances being removed by cooling and filtering. It contains 50 units (15 micrograms) to 500 units (150 micrograms) of vitamin A per gram and a maximum of 50 units (1.3 micrograms) of vitamin D_3 per gram. 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 clear, pale yellowish liquid. Practically insoluble in water; slightly soluble in alcohol; miscible with petroleum spirit. Store in well-filled airtight containers. Store under an inert gas if no antoxidant is added. Protect from light.

USP 36: (Cod Liver Oil). The partially destearinated fixed oil obtained from the fresh livers of *Gadus morrhua* and other species of Gadidae. It contains not less than 600 units (180 micrograms) and not more than 2500 units (750 micrograms) of vitamin A per g and not less than 60 units (1.5 micrograms) and not more than 250 units (6.25 micrograms) of vitamin D per g. It may be flavoured by the addition of not more than 1% of a suitable flavour or a mixture of flavours. A suitable antoxidant may be added.

A thin, oily liquid, having a characteristic, slightly fishy but not rancid odour. Slightly soluble in alcohol; freely soluble in carbon disulfide, in chloroform, in ether, and in ethyl acetate. Store in airtight containers. It may be bottled or packaged in containers from which air has been expelled by the production of a vacuum or by an inert gas.

Profile

Cod-liver oil is a rich source of vitamin D (p. 2112.3) and a good source of vitamin A (p. 2098.3). It also contains several essential fatty acids.

Cod-liver oil dressings or ointment have been advocated to accelerate healing in burns, ulcers, pressure sores, and superficial wounds, but controlled observations have failed to substantiate claims of their value.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Adecaps†; *Fr.*: Lactomorrhuol; *Ger.*: Gelovital; Unguentolan; *Gr.*: Seven Seas; *Hong Kong*: Scott's Emulsion; *India*: Eleven Seas; Elnocod; Seaking; *Ital.*: Dermovitamina; *Mex.*: Bacnutri; *Pol.*: Letin-Tran†; Masc Tranowa; Naturkaps Tran; Tran; *Spain*: Aceite Geve Concentrado; *Switz.*: Morrhulan†; *Turk.*: Seven Seas Pulse; *Venez.*: Scott Tradicional; Supercod.

Multi-ingredient Preparations. *Arg.*: Abanta; Atomoderma A-D; Atomoderma Plus; Cicatrex Baby; Clinal; Eryteal; Hipoglos con Hidrocortisona; Klorane Bebe Eryteal; *Austral.*: Arthro-Eze; Covitol; Desitin Nappy Rash Ointment; Hypol Cherry; Hypol; *Austria*: Dermilon; Dermowund†; Desitin; Leukichtan; Mirfulan; Nuri-Kapseln†; Pudan-Lebertran-Zinksalbe; Vulpuran; *Belg.*: Mitosyl; Polyseptol; *Braz.*: Emulsao Scott; Hiposan; Oxizinco†; Topiglos†; *Canad.*: Desitin; *Chile*: Cikavit; Deltisan; Desitin; Neneglos†; Pediaderm; Vatanal; *Fr.*: Fletagex; Magalite; *Ger.*: Lebertran plus; Mirfulan Spray N; Mirfulan; Mitosyl N; Zinksalbe; *Gr.*: Fissan-Pate; Fissan; *Hong Kong*: Desitin†; Scott's Emulsion Orange†; Scott's Emulsion Original†; *Hung.*: Klimin; *India*: Codesoft; Codvit-E; E-Cod Omega; E-Cod Plus; Ecod; Ecoliv; Evitop-C; Seaking Plus; *Indon.*: Biostrum; Caloma Plus; Calostrum; Co-Q-10; Curvit CL; Scott's Emulsion Vita; Scott's Emulsion; Seltifort Gold; Vidoran Emulsion Rasa; *Irl.*: Caldease; Morhulin; *Israel*: Desitin; Rekasitin†; Zincod; *Ital.*: Fosfarsile Junior; Neo-Ustiol; Steril Zeta; Trofo 5; *Mex.*: Capent; Desitin; Emulsion de Scott; Glossderm; *Pol.*: Rectosec; Tranvit†; *Port.*: Mitosyl; *S.Afr.*: Achromide; Daromide†; SB Universal Ointment†; Ung Vernleigh; *Singapore*: Robovites Multivitamins; Seven Seas JointCare High Strength; Seven Seas JointCare Max; *Spain*: Avril; Carena; *Switz.*: Unguentolan; Vita-Hexin; *Turk.*: Derivit; *UK*: Arheumacare; Clogar; Jointace; JointCare Max; M & M; Morhulin; *Ukr.*: Vitrum Cardio (Вітрум Кардіо); *USA*: A+D Zinc Oxide Cream; Caldesene; Clocream; Desitin; Diaper Rash; Dyprotex.

Homoeopathic Preparations. *Fr.*: Jenoverine†.

Pharmacopoeial Preparations
USP 36: Cod Liver Oil Capsules.

Copper

Cobre; Cuivre; Cuprum; Koppar; Kupari; Kupfer; Miedź; Медь.
Cu=63.546
CAS — 7440-50-8.
UNII — 789U1901CS.

Pharmacopoeias. *Eur.* (see p. vii) includes Copper for Homoeopathic Preparations.

Ph. Eur. 8: (Copper for Homoeopathic Preparations; Cuprum ad Praeparationes Homoeopathicae). A reddish-brown powder. Practically insoluble in water and in alcohol; soluble in hydrochloric acid and in nitric acid.

Calcium Copperedetate

Cuproedetato cálcico.
Calcium [ethylenediaminetetra-acetato(4–)-*N,N',O,O'*]copper (II) dihydrate.
$C_{10}H_{12}CaCuN_2O_8.2H_2O$=427.9
CAS — 66317-91-7 (anhydrous calcium copperedetate).

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Calcium Copperedetate). A blue crystalline powder. It contains 9.1 to 9.7% of Ca and 14.4 to 15.3% of Cu. Freely soluble in water, the solution gradually precipitating the tetrahydrate; practically insoluble in alcohol.

Copper Chloride

Cobre, cloruro de; Cupric Chloride; Miedzi chlorek; Хлористая Медь.
$CuCl_2.2H_2O$=170.5
CAS — 7447-39-4 (anhydrous copper chloride); 10125-13-0 (copper chloride dihydrate).
UNII — 52OG8415GO (cupric chloride dihydrate); P484053J2Y (anhydrous cupric chloride).

Pharmacopoeias. In *US*.

USP 36: (Cupric Chloride). Bluish-green, deliquescent crystals. Freely soluble in water; soluble in alcohol; slightly soluble in ether. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Copper Gluconate

Cobre, gluconato de; D-gluconato de cobre (1:2); Глюконат Меди.
Copper D-gluconate (1:2); Bis(D-gluconato-O^1,O^2) copper.
$C_{12}H_{22}CuO_{14}$=453.8
CAS — 527-09-3.
UNII — RV823G6G67.

Pharmacopoeias. In *US*.

Copper Sulfate

Cobre, sulfato de; Copper Sulph; Copper Sulphate; Cuivre (Sulfate de); Cuivre, sulfate de; Cupri sulfas; Cupri Sulphas; Cupric Sulfate; Kopparsulfat; Kuparisulfaatti; Kupfersulfat; Miedzi(II) siarczan; Réz(II)-szulfát; Síran měďnatý; Sulfato de Cobre; Vario sulfatas; Медный Купорос; Сульфат Меди; Халькантит.
Copper (II) sulphate pentahydrate.
$CuSO_4.5H_2O$=249.7
CAS — 7758-98-7 (anhydrous copper sulfate); 7758-99-8 (copper sulfate pentahydrate).
ATC — V03AB20.
ATC Vet — QV03AB20.
UNII — KUW2Q3U1VV (anhydrous cupric sulfate); LRX7AJ16DT (cupric sulfate pentahydrate).

NOTE. Crude copper sulfate is sometimes known as 'blue copperas', 'blue stone', and 'blue vitriol'.

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

Eur. and *Viet.* also include anhydrous copper sulfate.

Ph. Eur. 8: (Copper Sulfate Pentahydrate). A blue crystalline powder or transparent blue crystals. Freely soluble in water; practically insoluble in alcohol; soluble in methyl alcohol.

Ph. Eur. 8: (Copper Sulfate, Anhydrous). A greenish-grey, very hygroscopic, powder. Freely soluble in water; practically insoluble in alcohol; slightly soluble in methyl alcohol. Store in airtight containers.

USP 36: (Cupric Sulfate). Deep blue, triclinic crystals, or blue, crystalline granules or powder. It effloresces slowly in dry air. Soluble 1 in 3 of water, 1 in 0.5 of boiling water, 1 in 500 of alcohol, and 1 in 3 of glycerol. Its solutions are acid to litmus. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Copper is an essential trace element although severe copper deficiency, which is associated with anaemia, neutropenia, and bone demineralisation, is rare in humans. A copper salt such as the sulfate or chloride can be added to parenteral feeds as a source of copper in the prophylaxis and treatment of deficiency states. Doses that have been used for prophylaxis range from 0.5 to 1.5 mg (7.9 to 23.6 micromoles) of copper daily; up to 3 mg daily has been suggested in established deficiency. The dose should be governed by the serum-copper concentration, which in healthy adults ranges between 0.7 and 1.6 micrograms/mL (0.01 to 0.025 micromol/mL).

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

Copper sulfate and other soluble salts of copper have an astringent action on mucous surfaces and in strong solutions they are corrosive. Copper nitrate has been used in preparations for the removal of warts. The uses of copper acetate are discussed on p. 2486.3.

Copper has a contraceptive effect when present in the uterus, and is added to some intra-uterine contraceptive devices (see Contraception, p. 2232.3); such devices are considered to be effective and safe for several years after insertion, and may be the most effective method for emergency contraception (p. 2233.2). Copper is also reported to have an antimicrobial action.

Copper sulfate has been used to prevent the growth of algae in reservoirs, ponds, and swimming pools and as a molluscicide in the control of fresh-water snails that act as intermediate hosts in the life-cycle of the parasites causing schistosomiasis.

Reagents containing copper sulfate are used in tests for reducing sugars.

In veterinary medicine calcium copperedetate, copper methionate, copper oxide, and cuproxoline are used for the prevention and treatment of copper deficiency.

Copper bracelets are worn as a folk remedy for rheumatic disorders: there is no good evidence to justify such a practice.

Homoeopathy

Copper has been used in homoeopathic medicines under the following names: Cuprum metallicum; Cuprum; Cuprum met.; Cup. met.

Copper chloride has been used in homoeopathic medicines under the following names: Cuprum muriaticum; Cuprum mur.

Copper sulfate has been used in homoeopathic medicines under the following names: Cuprum sulfuricum; Cuprum sulphuricum; Cup. s.; Cuprum sulph.

Copper tetraammine sulfate (tetraminecopper sulfate) has been used in homoeopathic medicines under the following names: Cuprum ammonio-sulphuricum; Cuprum am sulph.

General references.
1. Wang T, Guo Z. Copper in medicine: homeostasis, chelation therapy and antitumor drug design. *Curr Med Chem* 2006; 13: 525–37.

Administration in children. A copper salt such as the chloride or sulfate may be added to parenteral feeds as a source of copper in the prophylaxis and treatment of deficiency states in children. A daily dose of 20 micrograms/kg (0.3 micromoles/kg) of copper has been suggested. In the USA, licensed product information recommends this dose for all children, whereas UK licensed product information suggests a maximum of 300 micrograms of copper daily for children weighing 40 kg or less, and adult doses in children over 40 kg (see above). Infants weighing less than 1.5 kg may have increased requirements due to their low body reserves and increased requirements for growth.

Deficiency states. Acquired copper deficiency is very rare and the small number of cases have usually involved patients on total parenteral nutrition or long-term enteral nutrition.[1] Copper deficiency may also be due to malnutrition,[2] malabsorption, or secondary to excessive zinc consumption.[3,4] Clinical manifestations of deficiency include hypocupraemia, hypoceruloplasminaemia, neutropenia, anaemia, osteoporosis, and fracture of the long bones.[2] However, cases may present with neurological signs resembling the subacute combined degeneration normally associated with vitamin B_{12} deficiency.[3,4] Effects on blood may be absent, and zinc concentrations normal;[3] however, hyperzincaemia may be seen even in the absence of exogenous zinc consumption.[4]

Menkes' disease is an X-linked genetic disorder associated with a defect in copper transport, which almost invariably results in death due to progressive cerebral degeneration by the age of 3 years.[5,6] Clinical features include skeletal abnormalities, severe mental retardation, thrombosis, hypothermia, arterial abnormalities, and characteristic facial features.[7] Early parenteral treatment with copper-histidine complex may be of benefit in such children.[5-8] Optimal response to copper therapy appears to occur only in patients who are identified in the newborn period and who have some residual copper-transport activity. More than 3 years of copper replacement therapy may not be necessary or desirable.[6]

1. Masugi J, *et al.* Copper deficiency anemia and prolonged enteral feeding. *Ann Intern Med* 1994; 121: 386.
2. Cordano A. Clinical manifestations of nutritional copper deficiency in infants and children. *Am J Clin Nutr* 1998; 67 (suppl): 1012S–1016S.
3. Kumar N, *et al.* Copper deficiency myelopathy produces a picture like subacute combined degeneration. *Neurology* 2004; 63: 33–9.
4. Kumar N. Copper deficiency myelopathy (human swayback). *Mayo Clin Proc* 2006; 81: 1371–84.
5. Sarkar B, *et al.* Copper-histidine therapy for Menkes' disease. *J Pediatr* 1993; 123: 828–30.
6. Kaler SG, *et al.* Neonatal diagnosis and treatment of Menkes disease. *N Engl J Med* 2008; 358: 605–14.
7. Kirodian BG, *et al.* Treatment of Menkes disease with parenteral copper histidine. *Indian Pediatr* 2002; 39: 183–5.
8. Cox DW. Disorders of copper transport. *Br Med Bull* 1999; 55: 544–55.

Human requirements. In the UK dietary reference values (see p. 2046.1) have been published for copper.[1] Although

an estimated average requirement (EAR) could not be derived a reference nutrient intake (RNI) of 1.2 mg (19 micromoles) daily was set for adults; RNIs of lower values were also specified for infants and children.[1] The Expert Group on Vitamins and Minerals[2] have established a safe upper level (SUL) for copper of 160 micrograms/kg daily.

In the USA the recommended dietary allowance (RDA) for copper is 900 micrograms daily in adults, and the tolerable upper intake level is 10 mg daily.[3]

WHO has estimated a minimum population mean intake of 1.2 mg daily for women and 1.3 mg daily for men, and safe upper limits of population mean intakes of 10 mg daily for women and 12 mg daily for men;[4] values are also estimated for infants and children.

The difficulties of establishing guidelines for copper requirements have been reviewed.[5]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 10/11/05)
3. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
4. WHO. Copper. In: *Trace elements in human nutrition and health*. Geneva: WHO, 1996: 123–43.
5. Stern BR. Essentiality and toxicity in copper health risk assessment: overview, update and regulatory considerations. *J Toxicol Environ Health A* 2010; 73: 114–27.

Schistosomiasis. Although most control programmes for schistosomiasis (p. 148.1) use niclosamide as a molluscicide, and copper salts have largely been abandoned for snail control, WHO noted in 1993 that copper sulfate was still used for this purpose in Egypt.[1]

1. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993. Available at: http://libdoc.who.int/trs/WHO_TRS_830.pdf (accessed 21/07/08)

Adverse Effects and Treatment

Adverse effects from copper have tended to arise after absorption of the metal from cooking utensils and during dialysis. Ingestion of copper from cooking utensils is associated mainly with hepatotoxicity. Dialysis procedures may supply copper through the water supply or from parts of the equipment and when this happens patients may suffer haemolysis and other haematological reactions, kidney involvement, and hepatotoxicity; the toxicity is generally a result of poor equipment maintenance.

Adverse effects attributed to copper have been reported in women with copper-containing intra-uterine devices. There have been isolated case reports of various effects such as allergy and endometrial changes. However, it is difficult to separate adverse effects due solely to the copper from those due to the device.

The symptoms of Wilson's disease (hepatolenticular degeneration) (see p. 1567.3) are due to an accumulation of copper in various parts of the body.

Copper salts if ingested can produce severe gastrointestinal effects and there may be systemic absorption of copper leading to the effects discussed above. The use of sprays of copper salts in agriculture has been associated with lung changes. Treatment of copper poisoning is symptomatic and may involve the use of a chelating agent to remove any absorbed metal. Dialysis has been tried.

Effects on the liver. Cirrhosis and acute liver failure have been attributed to chronic excessive copper supplement ingestion.[1] Supplementation with 10 mg daily of copper (around the safe upper limit) for 2 months has been reported to be associated with transient mild increases in serum aminotransferase values.[2]

1. O'Donohue J, *et al.* Micronodular cirrhosis and acute liver failure due to chronic copper self-intoxication. *Eur J Gastroenterol Hepatol* 1993; 5: 561–2.
2. Araya M, *et al.* Supplementing copper at the upper level of the adult dietary recommended intake induces detectable but transient changes in healthy adults. *J Nutr* 2005; 135: 2367–71.

Effects on the nervous system. It has been proposed[1-3] that both excess and deficiency of copper ions in the CNS may play a role in the development of Alzheimer's disease and dementia (p. 388.1).

1. Brewer GJ. The risks of copper toxicity contributing to cognitive decline in the aging population and to Alzheimer's disease. *J Am Coll Nutr* 2009; 28: 238–42.
2. Quinn JF, *et al.* Copper in Alzheimer's disease: too much or too little? *Expert Rev Neurother* 2009; 9: 631–7.
3. Hung YH, *et al.* Copper in the brain and Alzheimer's disease. *J Biol Inorg Chem* 2010; 15: 61–76.

Interactions

Large doses of zinc supplements may inhibit the gastrointestinal absorption of copper.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Multiload†; ***Braz.***: Multiload; ***Canad.***: Micro Cu; ***Chile***: Diu-Safe Cu/375; Diuprotect†; Multiload; Safety T; ***China***: Multiload (莫迪司); ***Fr.***: Gynelle 375; Metacuprol†; Multiload; TT 380; UT 380; ***Ger.***: femena†; GyneFlx; Multiload†; ***Hong Kong***: Flexi-T; Multiload; ***Hung.***: Feroglobin-B12; ***India***: Multiload; ***Indon.***: Copper-T; ***Israel***: Micro Cu; Mona-Lisa; ***Ital.***: Gravigard; Gynefix; Multiload; No-Gravid; UT 380; ***Malaysia***: Multiload; ***Mon.***: Algicuivre; ***NZ***: Multiload; ***S.Afr.***: Cuprocept CCL; Dalcept; Tricept; ***Singapore***: Multiload; ***Switz.***: Multiload; ***Thai.***: Multiload; ***Turk.***: Multiload†; ***UK***: Flexi-T; Gynefix; Multiload; ***USA***: Paragard T380A; ***Venez.***: Cicalfate; Multiload.

Multi-ingredient Preparations. ***Arg.***: Agua D'Alibour; Cicalfate; Dermalibour; Gingeron; Glucobefol†; Ipri V Total; Krebs Plus; Nova-T; Senexon Plus; Stress with Zinc; Tonovital Plus Antioxidante; Tricomax; Valeriana Compuesta; ***Austral.***: Ascoxal†; Bone Builder; Caltrate Plus; Haemo-Red; Macu-Vision; Ocuvite PreserVision†; ***Braz.***: Belagin†; Ferrotrat B12 Plus; Ocuvite PreserVision; Olig-Trat; Rubrargil; Stresstabs; Sulfato Ferroso Composto; Zincovit; ***Canad.***: Caltrate Plus; Nova-T; TLI; ***Chile***: Agua Sulfatada Picrica†; Biogenol; Caprimida D Balance; Cellvital†; Cicalfate; Cicaplast; Dermalibour; Larotabe; Sebium H2O†; ***China***: Nova T (新体); Solcoderm (思可得); ***Cz.***: Caltrate Plus; Feroglobin B_{12}; ***Fr.***: Actyferil; Alpharegul Femme; Atoderm moussant; Cicalfate; Cicaplast; Creme de Dalibour; Cu-Zn; Cuivramine; Decramp; Dermalibour; Dermalibour; Dermo-Sulfuryl; Dermocuivre; Dolores; Dynabiane; Eryase†; Naturophta Macula; Oligobiane Fe-Cu; Oligocure; Oligoderm†; Oligorhine; Photoderm; Ramet Dalibour; Ruboderm; Stimunal; Stimuplexe†; Synaptiv; Tot'Hema; Vitacuivre; ***Ger.***: Goldlily; Nova-T; Solco-Derman; ***Hong Kong***: Caltrate Plus; Nova-T†; Solcoderm†; ***Hung.***: Ferrocomp; Humet-R; Multicomp; ***India***: Advit-A; Alcalci-D; Ampucare; Anofer; Antoxid; Avitaz Plus; Aviton; Avpro; Beta-Sclerobion; Calmix; Carbosyl; Deferon; Deoxidant; Derantox; Eldervit-ZC; Elferri Plus; Elnutra; Elrox-AO; Exerge; Fabulae; Facicap; Fejet-OD; Fejet; Ferrimin; Fersolate-CM; Flintoff; Freecad; FRS; Geocal; Haem Up; Haem-Up Gems; Haem-Up; HB-Orange; Hemocare; Hemocare; Hepatoglobine†; I-Lute; Iron-Gold; Ironate; Kibocal-M; Kudamin; Logical-M; Lytox; Macuchek; Maxiferon; Maxo-FE; Menosoft; Mexivit; Moxafav; NBOxid; Nofro; Orbone Forte; Orbone; Ospical-M; Ostebon-M; Osteo-G; Oxi-Red; Oxidon; Oxipre; Oxy-V; Oxyban; Oxydex; Oxyeye; Oxytret; Siderfol; Softeron-Z; ***Indon.***: Adfer; Biosanbe; Caltron; Diabion; Emibion; Embneton; Feritrin; Feroglobin; Feroglobin; Ferokid; Habebion†; Hemafort; ***Inbion***; Jointace; My Caps; Neogobion; Nichobion; Nonemi; Nova-T; Opibion; Osfit; Ossovit Plus; Pronita; Retivit Plus; Retivit; Sangobion; Sangofer; Sangovitin†; Solvitron; Steopor; Suprabion; Tropifer; Vantiz; Viliron; Vloxy-fm; Vioxy; Vitabion; Vitachol; Vitanox; Vitonal; Zevit Grow; Zinc Pharmacore; Zivon; ***Irl.***: Caltrate Plus†; ***Israel***: Nova-T; Stresstabs with Zinc†; ***Ital.***: Artrodue; Artrosulfur; Astar; Chiton; Cuprosodio Plus; Cuprosodio; ***Emmenoiasi***; Flogovis; ***Inflamase***; Linfonorm; Neosulfur†; Nevrtil; Nova-T; Osteo Complex; Rinogutt Atlantic; Sterimar Cu; Zincoral; ***Malaysia***: Caltrate Plus; Eurobio Bio-Vizmax; Nova-T; Opibion; ***Mex.***: Ascoxal†; Dalidome; Daribur; Drusen; Nova-T; ***Mon.***: Algicuivre; ***NZ***: Caltrate Plus; Nova-T†; ***Philipp.***: Caltrate Plus; Macrobee with Iron; Sangobion; ***Pol.***: Caltrate Plus; ***Port.***: Biodin Sebo Care; Tot'Hema; ***Rus.***: Calcemin (Кальцемин); Calcemin Advance (Кальцемин Адванс); Complivit Oftalmo (Компливит Офтальмо); Ferrohematogen (Феррогематоген); Solcoderm (Солкодерм); Tot'Hema (Тотема); Tri-V Plus (Три-Ви Плюс)†; ***S.Afr.***: Dr Williams Pink Pills†; Ferrous Sulphate Compound†; Lotio Pruni Comp cum Cupro†; Muscle Rub†; Nova-T; ***Singapore***: Caltrate Plus; Floron; Hemacaps†; Hemoplex; Multitrace-5; Neogobion; Nova-T; Ocuvite Adult 50+; Opibion; Sangobion; ***Switz.***: Nova-T; Solcoderm; Venadoron; ***Thai.***: Caltrate Plus; Calvin Plus; Diavit; Glufer-C†; Mac-Q-Vis; Temaron; ***Turk.***: Eser Metaller; Nova-T†; ***UK***: Caltrate Plus; Feroglobin; Foresight Iron Formula; Nova-T; Ostron; Vitalux Plus; ***Ukr.***: Calcemin (Кальцемин); Calcemin Advance (Кальцемин Адванс); Calcemin Silver (Кальцемин Сильвер); Fitoval Capsules (Фитовал капсулы); Optix (Оптикс); Quadevit (Квадевит); Revalid (Ревалид); Solcoderm (Солкодерм); Tot'Hema (Тотема); Vimifor Multivitamin with Beta-Carotene (Вимифор Мультивитамин З Бета-каротином)†; Vitrum Foreyes (Витрум Форайз); Vitrum Osteomag (Витрум Остеомаг); ***USA***: Antioxidant Formula; Caltrate Plus; Feocyte; I-Vite Protect; Macular Vitamin Benefit; MacuTrition; NicAzel Forte; Nicomide†; ORA5; PNV-Iron†; Prenatal Plus; Preservision Eye Vitamin; REQ49+; Tri-zel; VP-Zel; ***Venez.***: Cianofer; Cobalfer; Ferroliver; Ferronorm; Folifer B-12; Hepafol con B-12; Nova-T.

Homoeopathic Preparations. ***Canad.***: Allergies; Brocosin; Cocyntal; Col 138†; Drosera Complex; Drosera Plex†; Formula FA 224†; Formula PC 223†; Hay Fever; Homeo-Form AL†; Kids Allergies; Snore No More; Spascupreel; ***Cz.***: Dolicoccil†; Drosetux; Spascupreel S†; ***Fr.***: Abbe Chaupitre no 19†; Abbe Chaupitre no 43†; Cina Compose; Drosera Compose; Drosetux; Homeofortil†; L 25; ***Ger.***: Allergie-Injektopas; Broncho-Injektopas; Drufusan N†; Infi-China; Inffer N; Monapax; Pectapas CPL; Phonix Silybum spag; Phonix Solidago spag; Phonix Thuja-Lachesis spag; Phonix Urtica-Arsenicum spag; Pulmo Bronchialcomplex; Pulmo-cyl Ho-Len-Complex; Rufebran broncho†; Spascupreel; Zahnungstropfen Escatitona; ***Hung.***: Dolicoccil; Drosetux; Spascupreel; ***Neth.***: Emvita 11; Geovita; Homeocare Digesto; Phonix Hydrargyrum; Phonix Solidago comp; Spascupreel H; ***Switz.***: Drosetux; Regenaplex Nr. 12; Regenaplex Nr. 31a; ***Ukr.***: Kindinorm (Киндинорм).

Pharmacopoeial Preparations

USP 36: Calcium and Vitamin D with Minerals Tablets; Cupric Chloride Injection; Cupric Sulfate Injection; Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Cysteine *(rINN)*

C; Cisteína; Cys; Cystéine; L-Cysteine; Cysteinum; E920; L-Cysteina; Цистеин.

L-2-Amino-3-mercaptopropionic acid.

$C_3H_7NO_2S$=121.2

CAS — 52-90-4.

UNII — KB48JZ4886.

Pharmacopoeias. In *Ger.* and *Jpn.*

Cysteine Hydrochloride *(rINNM)*

Cisteína, hidrocloruro de; Cisteino hidrochloridas monohidratas; Cisztein-hidroklorid-monohidrát; Cys Hydrochloride; Cystéine, Chlorhydrate de; Cystéine (chlorhydrate de) monohydraté; L-Cysteine Hydrochloride Monohydrate; Cystein-hydrochlorid monohydrát; Cysteinhydrokloridmonohydrat; Cysteini Hydrochloridum; Cysteini Hydrochloridum Monohydricum; Hidrocloruro de cisteína; Kysteiinihydrokloridimonohydraatti; L-Cysteiny chlorowodorek; Цистеина Гидрохлорид.

L-2-Amino-3-mercaptopropionic acid hydrochloride monohydrate.

$C_3H_7NO_2S,HCl,H_2O$=175.6

CAS — 52-89-1 (anhydrous L-cysteine hydrochloride); 7048-04-6 (L-cysteine hydrochloride monohydrate).

UNII — A9U1687S1S (anhydrous cysteine hydrochloride); ZT934N0X4W (cysteine hydrochloride monohydrate).

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

Ph. Eur. 8: (Cysteine Hydrochloride Monohydrate; Cysteine Hydrochloride BP 2014). A white or almost white crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. Protect from light.

USP 36: (Cysteine Hydrochloride). White crystals or crystalline powder. Soluble in water, in alcohol, and in acetone.

Profile

Cysteine is a non-essential amino acid. Cysteine and cysteine hydrochloride are used as dietary supplements.

Cysteine and cysteine hydrochloride are included in preparations used in ophthalmology; eye drops have been used to prevent corneal ulceration after chemical burns.

References.

1. Soghier LM, Brion LP. Cysteine, cystine or N-acetylcysteine supplementation in parenterally fed neonates. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 24/06/08).
2. Riedijk MA, *et al.* Cysteine: a conditionally essential amino acid in low-birth-weight preterm infants? *Am J Clin Nutr* 2007; 86: 1120–5.
3. Meduri A, *et al.* Role of cysteine in corneal wound healing after photorefractive keratectomy. *Ophthalmic Res* 2009; 41: 76–82.

Precautions. Cysteine, like other sulfhydryl-containing drugs, could produce a false-positive result in the nitroprusside test for ketone bodies used in diabetes and suspected hepatocellular injury.[1]

1. Csako G, Elin RJ. Unrecognized false-positive ketones from drugs containing free-sulfhydryl group(s). *JAMA* 1993; 269: 1634.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Fixcanat†.

Multi-ingredient Preparations. ***Arg.***: Cicatrex Biotic; Dial-ND; Homocisteon Compuesto; Icaps Plus; ***Austral.***: Cicatrin†; Natal Plus; ***Braz.***: Cicatrene; ***Chile***: Brolin Forte; Brolin; ***China***: BiPu (比孚); Bo Luo Ni (博罗尼); Gan Mu Shu (甘木舒); Gan Wei Xin (甘维欣); Gan You Lin (感佑林); Jun Qiang (君强); Kang Er Ning (康尔宁); LiWeiEr (里威尔); Neo-Minophagen C (美能); NuoHao (诺豪); Ruo Jing (若菁); Shu Kang Lin (抒康林); Tuo Di (妥迪); Wei Suan Su (卫算苏); Wei Yi Xing (卫伊兴); Xin-Kang (昕康); Ye Xin (业欣); Yi Nuo Wei (依诺维); Yi Xin (易新); YouNiDi (尤尼迪); Yu Li Sen (宇立森); ***Fr.***: Lobamine-Cysteine; Notrinol†; Phakan†; ***Hong Kong***: Hepatofalk†; ***Hung.***: Antismoke; ***Indon.***: Lanavision Plus; Miniceronal†; ***Irl.***: Cicatrin†; ***Ital.***: Biophase Complex†; Cicatrene; Endoepatox; Lipoacid Combi; ***Port.***: Cicatrin; Lipoacid Combi; ***Rus.***: Prohepar

(Прогепар); *S.Afr.*: Cicatrin†; Prohep†; *Singapore*: Hepasil DTX†; Vitaton Gold; Vitaton; *Switz.*: Cicatrex; *UK*: Skin Care Nutrients; *Ukr.*: Fakovit (Факовит)†; Oko-Health (Око-хелс); Vitrum Beauty (Витрум Бьюти); Vitrum Beauty Elite (Витрум Бьюти Элит); *Venez.*: Ocoxin.

Pharmacopoeial Preparations
USP 36: Cysteine Hydrochloride Injection.

Cystine *(USAN, rINN)*

Cistina; Cistinas; Cisztin; Cystin; L-Cystine; Cystinum; Di(α-aminopropionic)-β-disulphide; Kystiini; L-Cystyna; Цистин; β,β′-Dithiodialanine.
L-3,3′-Dithiobis(2-aminopropionic acid).
$C_6H_{12}N_2O_4S_2$=240.3
CAS — 56-89-3.
UNII — 48TCX9A1VT.

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

Ph. Eur. 8: (Cystine). A white or almost white crystalline powder. Practically insoluble in water and in alcohol. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Cystine). Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Profile

Cystine is a non-essential amino acid. It is used as a dietary supplement.

Low-methionine diets with cystine supplementation have been used in the treatment of congenital homocystinuria (see Amino Acid Metabolic Disorders, p. 2042.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Gelucystine; *Ital.*: Cistidil; Mavigen Sebo; *Spain*: Crecil.

Multi-ingredient Preparations. *Arg.*: Aminoterapia Capilar; Aminoterapia; Cistidac Cistimax; Dial-ND; Formuly Piel; HSN; LOHP; Megacistin; Megaplus; Tricomax; Valcatil Max; Valcatil Plus; Valcatil; *Austria*: Pantogar; Priorin; *Braz.*: Pantogar; *Chile*: Vantux Plus; Vantux; *Cz.*: Merz Speział†; *Fr.*: Anacaps tri-Activ; Anacaps†; Cystichol†; Cystine B$_6$; Forcapil; Phaneres; Solacy; *Ger.*: Pantovigar; *Hong Kong*: Merz Speział†; Pantogar; Perfectil; Pilfood; *Hung.*: Forcapil; Merz Speział; Revalid; *Indon.*: Pantogar; *Ital.*: Biomineral One; Biomineral Plus; Biomineral; Konorderm; *Mex.*: Pantogar; *Pol.*: Merz Speział; Revalid; *Port.*: Neo-Cystine; Onglinex; *Rus.*: Eltacin (Элтацин); Merz Speział Dragees (Специальное Драже Мерц); Pantovigar (Пантовигар); Perfectil (Перфектил); *Singapore*: Pantogar; *Switz.*: Pantogar; Priorin N; *Thai.*: Genquin; *Turk.*: Pantogar; Priorin; *UK*: Pilfood; *Ukr.*: Fitoval Capsules (Фитовал капсулы); Pantogar (Пантогар); Perfectil (Перфектил); Perfectil Plus (Перфектил Плюс); Revalid (Ревалид); *USA*: Amino-Cerv.

Dectaflur *(USAN, rINN)*

Dectafluro; Dectaflurum; SKF-38094; Дектафлур.
9-Octadecenylamine hydrofluoride.
$C_{18}H_{38}NF$=287.5
CAS — 36505-83-6 (nonstereospecific); 1838-19-3 (9-octadecenylamine).
UNII — Q381Y93C1S.

Profile

Dectaflur is used as a source of fluoride (see Sodium Fluoride, p. 2089.2) in the prevention of dental caries. For a report of stomatitis considered to be due to dectaflur, see Hypersensitivity, under Sodium Fluoride, p. 2091.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Port.*: Elmex; Elmex.

Multi-ingredient Preparations. *Austria*: Elmex; Elmex; *Belg.*: Elmex; *Cz.*: Elmex; Elmex; *Fin.*: Elmex; Elmex; *Ger.*: Elmex; Elmex; Ledermix Fluorid; Multifluorid†; *Hung.*: Elmex; Elmex; *Israel*: Elmex; *Ital.*: Elmex; *Neth.*: Elmex; Elmex; *Switz.*: Elmex; Elmex; Paro aux fluorures d'amines Gelee.

Dextrin *(BAN)*

British Gum; Dekstrini; Dekstrinas; Dextrina; Dextrine; Dextrinum; Dextrinum Album; Starch Gum; Декстрин.
$[C_6H_{10}O_5]_n xH_2O$
CAS — 9004-53-9.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Dextrin). Maize, potato, or cassava starch partially hydrolysed and modified by heating with or without the presence of acids, alkalis, or pH control agents. A white or almost white, free-flowing powder. Very soluble in boiling water forming a mucilaginous solution; slowly soluble in cold water; practically insoluble in alcohol. A 5% dispersion in water has a pH of 2.0 to 8.0.

USNF 31: (Dextrin). It is starch, or partially hydrolysed starch, modified by heating in a dry state, with or without acids, alkalis, or pH control agents. A white, yellow, or brown free-flowing powder. Its solubility in water varies; it is usually very soluble, but often contains an insoluble portion.

Icodextrin *(BAN, USAN, rINN)*

Icodextrina; Icodextrine; Icodextrinum; Ikodekstriini; Ikodekstrin; Икодекстрин.
$[C_6H_{10}O_5]_n$
CAS — 337376-15-5.
UNII — 2NX48Z0A9G.

Profile

Dextrin, a glucose polymer, is (1→4)-α-D-glucan derived from the hydrolysis of starch. Icodextrin is dextrin with more than 85% of its molecules with molecular weights between 1640 and 45 000, and a weight-average molecular weight of about 20 000. Dextrin is a source of carbohydrate sometimes used in oral dietary supplements and tube feeding. Glucose is rapidly released in the gastrointestinal tract but because of the high average molecular weight of dextrin, solutions have a lower osmolarity than isocaloric solutions of glucose. Additionally, preparations based on dextrin (such as maltodextrin p. 2080.3), and intended for dietary supplementation, usually have a low electrolyte content and are free of lactose and sucrose. Such preparations may be particularly useful in certain gastrointestinal disorders where malabsorption is a problem, in disaccharide intolerance (without isomaltose intolerance), and in acute and chronic hepatic and renal diseases where protein, mineral, and fluid restriction are often necessary.

Dextrin is used as a tablet and capsule diluent, and as a binding, suspending, and viscosity-increasing agent. It has also been used as an adhesive and stiffening agent for surgical dressings.

Dextrin sulfate intravaginal gel has been investigated in the prophylaxis of HIV infection and AIDS.

Icodextrin is used in dialysis fluids as an alternative to glucose-based solutions (see also below). Icodextrin-based fluids are instilled intraperitoneally to reduce adhesions after gynaecological and other abdominal surgery. They have also been used as vehicles for drugs given via the peritoneal cavity.

Dialysis. Glucose-based solutions are commonly used in dialysis solutions for continuous ambulatory peritoneal dialysis (CAPD). However, there is rapid absorption of glucose across the peritoneal membrane, reducing the duration of ultrafiltration and leading to long-term metabolic complications such as hyperglycaemia, hyperinsulinaemia, hyperlipidaemia and obesity. Other osmotic agents have been investigated. One study reported results in 11 patients[1] receiving CAPD who had suffered repeated fluid overload from glucose-based dialysis solutions, and suggested that replacement of glucose with dextrin as the osmotic agent could reverse fluid overload and possibly reduce the frequency of exchange. However, others[2] considered that the proposed frequency of exchange would not provide adequate removal of urea, and that in addition to underdialysis there would be an accumulation of poorly-metabolisable glucose polymers in the blood.

Icodextrin is another alternative.[3-5] It is a glucose polymer, given in iso-osmolar solution. Studies supported by the manufacturers have found that it can be used in ultrafiltration for up to 12 hours, with lower transperitoneal absorption and potential calorie load than glucose solutions.[6,7] It can also be metabolised by amylases in the blood, so is less likely to accumulate than other glucose polymers if absorbed,[7] although the resultant concentrations of maltose (the primary metabolite) have resulted in falsely elevated blood-glucose measurements with some test methods,[8-11] leading to inappropriate insulin dosing and potentially life-threatening adverse effects. Licensed product information states that glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase based methods should not be used for this reason. In a study in CAPD patients, icodextrin was well-tolerated and produced at least equivalent ultrafiltration to glucose solutions.[6] Another study found that peritoneal dialysis patients on icodextrin lost weight and had improved fluid status compared with patients on glucose.[12] In a small study of peritoneal dialysis patients with fluid overload and due to be transferred to haemodialysis, substitution of icodextrin for one long-dwell exchange daily significantly increased ultrafiltration and extended technique survival-time.[13]

A combination of icodextrin and glucose has also been investigated as a means to reduce glucose exposure while increasing ultrafiltration.[14,15]

1. Stein A, *et al.* Glucose polymer for ultrafiltration failure in CAPD. *Lancet* 1993; **341:** 1159.
2. Martis L, *et al.* CAPD with dialysis solution containing glucose polymer. *Lancet* 1993; **342:** 176–7.
3. Frampton JE, Plosker GL. Icodextrin: a review of its use in peritoneal dialysis. *Drugs* 2003; **63:** 2079–2105.
4. Hamburger RJ, Kraus MA. Icodextrin fulfills unmet clinical need of PD patients: improved ultrafiltration. *Dialysis Transplant* 2003; **32:** 675–80.
5. Chhabra D, Nash K. Icodextrin: an alternative peritoneal dialysis fluid. *Expert Opin Drug Metab Toxicol* 2008; **4:** 1455–64.
6. Mistry CD, *et al.* A randomized multicenter clinical trial comparing isosmolar icodextrin with hyperosmolar glucose solutions in CAPD. *Kidney Int* 1994; **46:** 496–503.
7. Peers E, Gokal R. Icodextrin provides long dwell peritoneal dialysis and maintenance of intraperitoneal volume. *Artif Organs* 1998; **22:** 8–12.
8. Riley SG, *et al.* Spurious hyperglycaemia and icodextrin in peritoneal dialysis fluid. *BMJ* 2003; **327:** 608–9.
9. MHRA. Medical device alert: ref MDA/2007/058 issued 19 July 2007. Available at: http://www.mhra.gov.uk/PrintPreview/PublicationSP/CON2031807 (accessed 21/07/08)
10. Disse E, Thivolet C. Hypoglycemic coma in a diabetic patient on peritoneal dialysis due to interference of icodextrin metabolites with capillary blood glucose measurements. *Diabetes Care* 2004; **27:** 2279.
11. FDA. Icodextrin (marketed as Extraneal) and point-of-care glucose monitoring: a dangerous drug-device interaction. *FDA Drug Safety Newsletter* 2008; **1:** 49. Also available at: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/ucm109178 (accessed 22/07/10)
12. Davies SJ, *et al.* Icodextrin improves the fluid status of peritoneal dialysis patients: results of a double-blind randomized controlled trial. *J Am Soc Nephrol* 2003; **14:** 2338–44.
13. Johnson DW, *et al.* Icodextrin as salvage therapy in peritoneal dialysis patients with refractory fluid overload. *BMC Nephrol* 2001; **2:** 2.
14. Jenkins SB, Wilkie ME. An exploratory study of a novel peritoneal combination dialysate (1.36% glucose/7.5% icodextrin), demonstrating improved ultrafiltration compared to either component studied alone. *Perit Dial Int* 2003; **23:** 475–80.
15. Dallas P, *et al.* Enhanced ultrafiltration using 7.5% icodextrin/1.36% glucose combination dialysate: a pilot study. *Perit Dial Int* 2004; **24:** 542–6.

Hypersensitivity. Skin reactions, sometimes severe and generalised, have occurred in patients given icodextrin.[1-5] Reactions have sometimes been delayed up to about 2 weeks after use.[3]

For the suggestion that recurrent sterile peritonitis in patients receiving icodextrin might be due to a hypersensitivity reaction, see below.

1. Fletcher S, *et al.* Icodextrin allergy in a peritoneal dialysis patient. *Nephrol Dial Transplant* 1998; **13:** 2656–8.
2. Goldsmith D, *et al.* Allergic reactions to the polymeric glucose-based peritoneal dialysis fluid icodextrin in patients with renal failure. *Lancet* 2000; **355:** 897.
3. Queffeulou G, *et al.* Allergy to icodextrin. *Lancet* 2000; **356:** 75.
4. Al-Hoqail IA, Crawford RI. Acute generalized exanthematous pustulosis induced by icodextrin. *Br J Dermatol* 2001; **145:** 1026–7.
5. Valance A, *et al.* Icodextrin cutaneous hypersensitivity: report of 3 psoriasiform cases. *Arch Dermatol* 2001; **137:** 309–10.

Peritonitis. Sterile peritonitis attributed to icodextrin has been reported.[1,2] Subsequently, several batches were withdrawn by the manufacturer in May 2002 because of bacterial contamination with high levels of peptidoglycan.[2,3] However, further incidents of peritonitis have been reported with icodextrin in patients previously exposed to the withdrawn batches,[4-6] prompting theories of sensitisation to icodextrin or peptidoglycans. Concerns were expressed regarding possible cross-sensitisation to dextran polymers in these patients,[6] as well as the possibility that even low levels of peptidoglycans might trigger peritonitis.[7] Histological changes similar to bacterial peritonitis have been found in patients with icodextrin-associated sterile peritonitis.[8] It was suggested that if cloudy dialysate reappeared upon rechallenge, icodextrin should be withdrawn.[8]

In an effort to determine the cause of the aseptic peritonitis, a manufacturer-sponsored analysis determined that recalled batches of dialysis solution were within product and pharmacopoeial specifications for content, safety, and sterility. However, both dialysate solution and icodextrin raw material caused increases in interleukin-6 response *in vitro*, suggesting a non-endotoxin contaminant as the cause of the aseptic peritonitis. Further analysis found peptidoglycan contamination of the raw icodextrin by *Alicyclobacillus acidocaldarius* to be the cause.[3]

A subsequent 2-year prospective multicentre cohort study involving 722 patients undergoing peritoneal dialysis found no evidence that use of icodextrin-based solutions altered rates of peritonitis.[9]

1. Tintillier M, *et al.* Transient sterile chemical peritonitis with icodextrin: clinical presentation, prevalence, and literature review. *Perit Dial Int* 2002; **22:** 534–7.
2. MacGinley R, *et al.* Relapsing culture-negative peritonitis in peritoneal dialysis patients exposed to icodextrin solution. *Am J Kidney Dis* 2002; **40:** 1030–5.
3. Martis L, *et al.* Aseptic peritonitis due to peptidoglycan contamination of pharmacopoeia standard dialysis solution. *Lancet* 2005; **365:** 588–94.
4. Basile C, *et al.* The impact of relapsing sterile icodextrin-associated peritonitis on peritoneal dialysis outcome. *J Nephrol* 2003; **16:** 384–6.

5. Povlsen JV, *et al.* Exposure to the peptidoglycan contaminant in icodextrin may cause sensitization of the patient maintained on peritoneal dialysis. *Perit Dial Int* 2003; 23: 509–10.
6. Enia G, *et al.* Sterile icodextrin-associated peritonitis may induce hypersensitivity and recurrent peritonitis on re-challenge. *Nephrol Dial Transplant* 2003; 18: 626.
7. Seow Y-YT, *et al.* Icodextrin-associated peritonitis among CAPD patients. *Nephrol Dial Transplant* 2003; 18: 1951–2.
8. Goffin E, *et al.* Icodextrin-associated peritonitis: what conclusions thus far? *Nephrol Dial Transplant* 2003; 18: 2482–5.
9. Vychytil A, *et al.* Extraneal Peritonitis Study Group. Icodextrin does not impact infectious and culture-negative peritonitis rates in peritoneal dialysis patients: a 2-year multicentre, comparative, prospective cohort study. *Nephrol Dial Transplant* 2008; 23: 3711–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Adept; ***Austral.***: Poly-Joule; ***Fr.***: Caloreen; ***Gr.***: Caloreen†; ***India***: Benefiber; ***Port.***: Extraneal; ***UK***: Adept; Caloreen; ***USA***: Benefiber.

Multi-ingredient Preparations. ***Arg.***: Extraneal; ***Austral.***: Extraneal; ***Belg.***: Extraneal; ***Canad.***: Extraneal; Polycose; ***Cz.***: Extraneal; ***Denm.***: Extraneal; ***Fin.***: Extraneal; ***Fr.***: Extraneal; ***Hong Kong***: Extraneal; ***Hung.***: Extraneal; ***Irl.***: Extraneal; ***Israel***: Extraneal; ***Ital.***: Extraneal; ***Neth.***: Extraneal; ***Norw.***: Extraneal; ***NZ***: Extraneal; ***Philipp.***: Extraneal; ***Rus.***: Extraneal (Экстранил); ***S.Afr.***: Extraneal†; ***Singapore***: Extraneal; ***Spain***: Extraneal; ***Swed.***: Extraneal; ***Switz.***: Extraneal; ***Thai.***: Extraneal; ***Turk.***: Extraneal; ***USA***: Extraneal.

Pharmacopoeial Preparations
USNF 31: Liquid Glucose.

Ferric Ammonium Citrate

381; Ammonium Ferric Citrate; Citrato amoniacal de hierro; Citrato amónico férrico; Citrato de hierro y amonio; Demir III Amonyum sitrat; Ferricum Citricum Ammoniatum; Iron and Ammonium Citrate; Аммония-Железа (III) Цитрат.
CAS — 1185-57-5.
ATC — V08CA07.
ATC Vet — QV08CA07.
UNII — UVP74NG1C5.

Pharmacopoeias. In *US.*

USP 36: (Ferric Ammonium Citrate). It contains between 16.5% and 18.5% of iron. Store in airtight containers at a temperature of 8 degrees to 15 degrees. Protect from light.

Profile

Ferric ammonium citrate is given orally as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is also used as a food additive, as an acidity regulator, anticaking agent, or source of iron. It has been used as a colouring agent.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Fu Rui Ming (复锐明); ***Gr.***: Ferriseltz; ***India***: Rubraplex; ***Turk.***: Ferro; Nuklofer; Samson; Tonoferrin.

Multi-ingredient Preparations. ***Arg.***: ITE-B12 Forte; ***Braz.***: Ferrotrat B12 Plus; Hematiase B12; Rubrargil; ***Canad.***: Maltlevol; ***Gr.***: Hemovital†; ***Hong Kong***: Nutroplex†; ***Hung.***: China; ***India***: Acufer; Adfe; Adifer-Z; Atovit; Biosyn; Calphos; Calron; Cario; Chemofer-12; Cherifer; Cinred; Dexorange; Dexorange; Disiorange; Emorange; Exifol; Extrafer; Familykair; Feday; Fefo; Fekair; Femina; Fenna; Fephar; Ferglobin; Feric Grow; Feripro; Ferradol†; Ferricos; Ferril; Ferrimin; Ferrisun; Ferritop Iron Tonic; Ferritop Iron; Ferritop Paed; Ferrochelate; Ferrofit; Ferrolac; Fezza; Fruitovit; FV-Tone; Genfol; Glentona Plus; Globac-Z; Globac; Globifex; Globiron-Z; Haem Up; Haem-Up Gems; Haem-Up; Haematinga; Haemo-Z; Haemocare; HB-Act; HB-Norm; HB-Nova; HB-Orange; HB-Orange; Hb-Rich; HB-Up; HB-Up; Hembran-Fe; Hemex; Hemfer; Hemo-G; Hemsi; Hepatoglobine†; Hepatoglobine; Hepp Forte; Hevit; Ifycarb; Ind-Orange; Inpro; Iron-Gold; Irorange; Isofer; Liton; Lohtone; Maxo-FE; Minadex; Minigadine; Neurophosphates-Iron; Nodyfer; Oxi-Red; Sharkoferrol; Vitamon; ***Ital.***: Emopon; ***S.Afr.***: SB Blood Purifying Mixture†; ***UK***: Ironorm; ***Ukr.***: Haemoferon (Гемоферон); Ranferon-12 (Ранферон-12)†; ***USA***: Geritol; Geritonic; ***Venez.***: Beferron; Cianofer; Hepafol.

Pharmacopoeial Preparations
USP 36: Ferric Ammonium Citrate for Oral Solution.

Ferric Carboxymaltose *(BAN, USAN, rINN)*

Carboxidmaltosa férrica; Carboxymaltose Ferrique; Ferricum Carboxymaltosum; Iron Dextri-maltose; VIT-45; Железа Карбоксимальтоза.
Poly(D-glucopyranosyl(1→4))-D-gluconic acid complex of hydrated iron (III) oxide.
CAS — 9007-72-1.
UNII — 6897GXD6OE.

Profile

Ferric carboxymaltose is used as a source of parenteral iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2) when oral iron therapy is ineffective or impractical. The total cumulative dose is calculated according to body-weight and iron deficit. In the UK, the maximum single dose is 1 g of iron and no more than 1 g of iron should be given each week. Ferric carboxymaltose may be given undiluted by intravenous injection; doses between 200 and 500 mg of iron should be injected at a rate of 100 mg/min while those above 500 mg should be given over 15 minutes. Alternatively, it can be diluted with sodium chloride 0.9% and given by intravenous infusion. It should not be given by intramuscular or subcutaneous injection. In patients on haemodialysis, a single maximum daily injection supplying 200 mg of iron may be given undiluted directly into the venous limb of the dialyser. For further information relating to the parenteral use of iron, see Iron Dextran, p. 2075.3.

References.

1. Lyseng-Williamson KA, Keating GM. Ferric carboxymaltose: a review of its use in iron-deficiency anaemia. *Drugs* 2009; 69: 739–56.
2. Moore RA, *et al.* Meta-analysis of efficacy and safety of intravenous ferric carboxymaltose (Ferinject) from clinical trial reports and published trial data. *BMC Blood Disord* 2011; 11: 4. Available at: http://www.biomedcentral.com/content/pdf/1471-2326-11-4.pdf (accessed 11/04/12)

Hypersensitivity. Rash is common after injection of ferric carboxymaltose, but urticaria, pruritus, and anaphylactoid reactions are stated to be less so. For a discussion of whether dextran-free preparations may be safer than iron dextran, see p. 2076.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Ferinject; ***Austria***: Ferinject; ***Belg.***: Injectafer; ***Cz.***: Ferinject; ***Denm.***: Ferinject; ***Fin.***: Ferinject; ***Fr.***: Ferinject; ***Ger.***: Ferinject; ***Gr.***: Ferinject; ***Irl.***: Ferinject; ***Israel***: Ferinject; ***Neth.***: Ferinject; ***Norw.***: Ferinject; ***Port.***: Ferinject; ***Singapore***: Ferinject; ***Spain***: Ferinject; ***Swed.***: Ferinject; ***Switz.***: Ferinject; ***UK***: Ferinject; ***USA***: Injectafer.

Ferric Pyrophosphate

Difosfato férrico; Férrico, pirofosfato; Iron Pyrophosphate; Пирофосфат Железа.
$Fe_4(P_2O_7)_3$=745.2
CAS — 10058-44-3.
UNII — QK8899250F.

Profile

Ferric pyrophosphate is given orally as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Incremin Iron; ***India***: Incremin; ***Mex.***: Incremin Con Hierro; ***USA***: Vitafol; Vitalize.

Ferritin

Ferritina; Ферритин.

Profile

Ferritin is the major iron storage protein of vertebrates, found mainly in the liver, spleen, intestinal mucosa, and bone marrow and consisting of a soluble protein shell (apoferritin) with a core of crystalline ferric hydroxyphosphate complex. It has been given orally as a source of iron (p. 2073.1) in iron-deficiency anaemias (p. 2073.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Ferrivax; ***Port.***: Profer; ***Spain***: Ferroprotina; Kilor; Profer; Syron.

Ferrocholinate *(rINN)*

Ferrocholinatum; Ferrocolinato; Феррохолинат.
$C_{11}H_{20}FeNO_9.2H_2O$=402.2
CAS — 1336-80-7.
UNII — LWI5ZJ8WVL.

Profile

Ferrocholinate is a chelate prepared by reacting equimolar quantities of freshly precipitated ferric hydroxide with choline dihydrogen citrate. It is given orally as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Spain***: Podertonic.

Multi-ingredient Preparations. ***India***: Alcezyme; Atpro; Avpro; C Haem; Caslop; Haemoprotex; Hemral; Irex-12 Tonic; Irobex Irona; Medifer; Nutra; Osprovit.

Ferrous Ascorbate

Ferroso, ascorbato; Железа Аскорбат.
$C_{12}H_{14}FeO_{12}$=406.1
CAS — 24808-52-4.
ATC — B03AA10.
ATC Vet — QB03AA10.

Profile

Ferrous ascorbate is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in usual doses of up to 1.47 g daily (equivalent to about 200 mg of iron daily).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Ascofer; ***India***: Aloha-XT DPS; Fericos-XT.

Multi-ingredient Preparations. ***Austria***: China-Eisenwein†; ***India***: Aloha-XT; Ascofit; Ascoliza; Barocal Forte; C-Rich; Cariz-XT; Corus-FA; CPink; Ep-Iron Fol; Ev-Syl-XT; Faroo-XT; Farris; Febate; Fephar; Feriena; Ferisym-XT; Ferolact; Ferolact; Feronia-XT; Feropic-XT; Ferosig; Ferulic; Fesu-XT; Fezon; Pezys-XT; Fresco; HB-Ron; Hemacor; Huntred-Z; Huntred; I-Fol; Ifyasco-Z; Iolebate; Ircor-FA; Irofur; Iromax; Irosol; Irosol; Irus; Levifer; Litron-XT; Nid-XT.

Ferrous Aspartate

Ferroso, aspartato; Железа Аспартат.
$C_8H_{12}FeN_2O_8.4H_2O$=392.1
ATC — B03AA09.
ATC Vet — QB03AA09.
UNII — Z56D82TX8V.

Profile

Ferrous aspartate is a source of iron (p. 2073.1) used in dietary supplements. It is given orally in a usual dose of 112 mg daily (equivalent to about 16 mg of iron daily). Higher doses were formerly given in the treatment of iron-deficiency anaemia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fin.***: Spartocine†; ***USA***: FE Aspartate.

Ferrous Chloride

Ferroso, cloruro; Железа Хлорид.
iron (II) chloride tetrahydrate.
$FeCl_2.4H_2O$=198.8
CAS — 7758-94-3 (anhydrous ferrous chloride); 13478-10-9 (ferrous chloride tetrahydrate).
ATC — B03AA05.
ATC Vet — QB03AA05.
UNII — S3Y25PHP1W.

Profile

Ferrous chloride is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in a usual dosage of about 350 to 700 mg daily in divided doses (equivalent to about 100 to 200 mg of iron daily).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Fer UCB; ***Pol.***: Hemofer; ***Switz.***: Ferrascorbin†.

Multi-ingredient Preparations. ***Switz.***: Ferrascorbin†.

Ferrous Fumarate

Demir Fumarat; Eisen(II)-fumarat; Ferrofumaraatti; Ferrofumarat; Ferrosi Fumaras; Ferroso, fumarato; Fumaran

železnatý; Fumarate ferreux; Geležies(II) fumaratas; Vas(II)-fumarát; Железа Фумарат.
$C_4H_2FeO_4$=169.9
CAS — 141-01-5.
ATC — B03AA02.
ATC Vet — QB03AA02; QB03AD02.
UNII — RSL48BRY0Q.

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

Ph. Eur. 8: (Ferrous Fumarate). A fine, reddish-orange or reddish-brown powder. Slightly soluble in water; very slightly soluble in alcohol. Store in airtight containers. Protect from light.

USP 36: (Ferrous Fumarate). A reddish-orange to red-brown, odourless powder, which may contain soft lumps that produce a yellow streak when crushed. Slightly soluble in water; very slightly soluble in alcohol. Its solubility in dilute hydrochloric acid is limited by the separation of fumaric acid.

Profile

Ferrous fumarate is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in usual doses of up to 600 mg daily (equivalent to about 200 mg of iron daily); doses of up to 1.2 g daily (equivalent to about 400 mg of iron daily) may be used if necessary.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ferrous fumarate 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 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Hemofer; Hemoferrol; *Austria*: Ferretab; Ferrobet; *Canad.*: Neo-Fer; Palafer; *Cz.*: Ferronat†; *Fr.*: Aloferal; Fumafer; *Ger.*: Ferrum Hausmann; Rulofer N; *Gr.*: Chrofer; *Hung.*: Feroglobin-B12; *Indon.*: Fercee; *Irl.*: Fersaday†; Galfer; *Mex.*: Biofuroso; Croferron; Fernadin; Ferro-Terapina; Ferval; Fumavit; Gestaferron; Medifer†; *Norw.*: Nycoplus Neo-Fer; *Rus.*: Heferol (Хеферол); *Singapore*: Iron Beacons; *Swed.*: Erco-Fer†; *Switz.*: Ferrum Hausmann; Lufer†; *Thai.*: Cebrin-Fe; F-Tab; Femarate; Ferdek; Fermasian; Fermate; I-RON; *Turk.*: Feramat; *UK*: Fersaday; Fersamal†; Galfer; *USA*: Femiron; Ferretts; Ferro-Dok; Hemocyte; Nephro-Fer†; Vitron-C; *Venez.*: Ferol; Ferroce.

Multi-ingredient Preparations. *Arg.*: Anemidox-Ferrum; Anemidox-Solutab; Ferretab Compuesto; Ferrocebrina; Hemofer Folic; Hierro Folico; *Austral.*: Bio Iron; Extralife PMS-Care†; Iron Max; Iron Plus; *Austria*: Ferretab Comp; *Belg.*: Gestiferrol; *Braz.*: Betozone†; Folix-Mater†; Iloban; *Canad.*: Ferro-C with B Complex; Formula C 36†; Liv-Gd; Neo-Fer CP; Palafer CP; *Chile*: Confer; Fercovit; Ferranim; Ferro Vitaminico†; Folifer; Orlon; *Cz.*: Feroglobin B_{12}; Ferretab Comp; Merz Spezial†; *Denm.*: Jern C; *Gr.*: Dicalets-M; *Hong Kong*: Fortifer; *Hung.*: Merz Spezial; *India*: Adfe-C; Adfe; Adifer-Z; Agion; Alamin-Fez; Anemidox; Astyfer-Z; Astyfer; Autrin; Aviton; Avpro; Blosyn; Blush; Calcefol; Calhem Plus; Calpro ZE; Capsovit; Chemofer-12; Choice; Cromofer-OD; Cromofer-Z; Deferon; Dumasules-Z; Dumasules; Elferri-Z; Enzofer-TR; Facicap; Fe-Z; Febex; Fekair; Femicontin; Fenna; Feritol; Ferozinc; Ferrimin; Ferritop; Ferro Hepatine; Ferrogen-Z; Ferrogen; Fezocaps; Fleefer; Globac-Z; Glohem TR; Haem Up-Z; Haem-Up Gems; Haematinga; Haemglow-Z; Haemglow; Haemplus; Hamozen-Z; HB Plus; HB-Act; HB-Norm; Hembran Plus; Hemfast; Hemforte; Hemofer-Z; Hemprovit-Fe; Hemral; Hemsi; Hemsyneral-TD; Hepasules-F; Hepasules†; Hepatoglobine†; Idiglobin; Irex-12; Ironate; Ironeed; Liton-Z; Livogen Captab; Livogen-Z; Medifer; Mefol; Myglo; Nid-XT; Nodyfer; Ossofez; Oxyglobin; Siderfol; Softeron-Z; Softeron; *Indon.*: Bioferron; Bionemi; Calmin-AF; Dasabion; Emineton; Ferobion; Hemafort; Hemarate CE†; Hemobion; Lactacin; Natabion; Nichobion; Nonemi; Nufagrabion-GM; Nufagrabion; Odiron-C†; Prenamia; Prenatin-DF; Prohelic; Rejuvan†; Solvitral; Solvitron; Veroscan; Vitachol; Vitalex; Vitamam 2; Vitamam 3; Vitonal; *Irl.*: Galfer FA; Givitol†; *Israel*: Folex; Foric; *Malaysia*: Ferrovit†; *Mex.*: Autrin; Dialeli AF; Ferro Grin†; Ferrotemp; Pumarol†; Yemifer-HE; *Philipp.*: Anemicon Plus; Anixon; Appebon with Iron; Azul; Beniforte; Blush; Charlize; Comvit FA; Essenfer; Femme; Fer-Essence; Fergesol; Ferlette; Feronerv; Ferosal; Ferroplex; Ferrovit; Foramefer; Fortifer FA; Fortifer; Fumiron + B; Harvifer; Hemarate; Hemobion; Hemovin; Heralink; Hi-Smart Teens; Iroplex; Macrobee with Iron; Micropil Plus; Molvite-OB; Multispec-E; Mulvitron; Nakaron; Natalbes; TLC Vita-OB; Trev-Iron Plus; Trev-Iron; TriHEMIC; Trust Pill; Usanatal; Zoiron; *Rus.*: Ferretab Comp (Ферретаб Комп); Merz Spezial Dragees (Специальное Драже Мерц); *S.Afr.*: Autrin†; Neurotone; Pregamal; *Singapore*: Iron Melts; Odiron-C; Wanse; *Spain*: Cinfavit Complex; Folliferron; *Switz.*: Duofer Fol; Duofer; *Thai.*: Adnemic-F; Biocalron; Boracap; FB Fer†; FBC Plus; FBC; Fer-200†; Percalmin; Ferli-6; Ferosix; Perplus-B; Ferrocine; Ferropro; Ferrovit; Foli-C; Hemarate†; Hemolax†; Intricon; Obimin-AZ; Polycolvit; Polyvit; Vita-Cal; *Turk.*: Ferrozinc; Vi-Fer; *UK*: Galfer FA; Meterfolic; Pregaday; *Ukr.*: Hemsyneral-TD (Гемсинерал-ТД)†; Little Friend (Маленькие Друзья)†; Merz Special Dragees (Специальное Драже Мерц); Pregnalac (Прегналак)†; Pregnavit (Прегнавит); Ranferon-12 (Ранферон-12); Vimifor Multivitamin with Beta-Carotene (Віміфор Мультивітамін з Бета-каротином)†; Vitrum Prenatal (Витрум Пренатал); *USA*: ABC to Z; Albafort; Berocca Plus; Caltrate + Iron & Vitamin D; Certagen; Chromagen FA; Chromagen Forte; Chromagen†; Contrin; Diatx Fe; Estrostep Fe; Femcon Fe; Ferotrinsic; Ferrogels Forte; Fetrin; Formula B Plus; Fumatinic†; Geriot; Gevral T; Hem Fe; Hematinic Plus; Hematinic; Hemocyte Plus; Hemocyte-F; Junel Fe; Livitrinsic-f†; Lo Minastrin Fe; Loestrin Fe; Minastrin 24 FE; Multifol; Parvlex; Pronemia Hematinic; Repliva†; Tandem Plus; Tandem; Thera Hematinic; Theragenerix-H; Tilia Fe; Tolfrinic; Tri-Legest; TriHEMIC; Trinsicon†; Vitafol-OB; Vitafol; Wymzya Fe; Yelets; Zenchent Fe; Zodeac; *Venez.*: Cobalfer; Fefol; Ferroliver; Ferronorm; Folifer B-12; Hepafol con B-12; Vitnatal.

Pharmacopoeial Preparations
BP 2014: Ferrous Fumarate and Folic Acid Tablets; Ferrous Fumarate Capsules; Ferrous Fumarate Oral Suspension; Ferrous Fumarate Tablets;
USP 36: Ferrous Fumarate and Docusate Sodium Extended-release Tablets; Ferrous Fumarate Tablets.

Ferrous Gluceptate

Ferroso, gluceptato; Ferrous Glucoheptonate; Glucoheptonato ferroso.
$Fe(C_7H_{13}O_8)_2$=506.2
CAS — 25126-38-9.
UNII — 13809H6DVG.

Profile

Ferrous gluceptate is given orally as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Unifer.

Multi-ingredient Preparations. *Arg.*: Egestan Hierro; *Spain*: Normovite Antianemico.

Ferrous Gluconate

E579; Eisen(II)-Gluconat; Ferroglukonaatti; Ferroglukonat; Ferrosi gluconas; Ferrosi Gluconas Hydricus; Ferroso, gluconato; Geležies(II) gliukonatas; Gluconate ferreux; Glukonan železnatý hydrát; Vas(II)-glükonát; Železa(II) glukonian; Железа Глюконат.
Iron (II) di(D-gluconate).
$C_{12}H_{22}FeO_{14}.xH_2O$
CAS — 299-29-6 (anhydrous ferrous gluconate); 12389-15-0 (ferrous gluconate dihydrate).
ATC — B03AA03.
ATC Vet — QB03AA03.
UNII — U1B111423Z.

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

Chin. and *US* specify the dihydrate.

Ph. Eur. 8: (Ferrous Gluconate). A greenish-yellow to grey powder or granules. It contains not less than 11.8% and not more than 12.5% of ferrous iron calculated with reference to the dried substance. Freely but slowly soluble in water producing a greenish-brown solution, more readily soluble in hot water; practically insoluble in alcohol. A 10% solution in water has a pH of 4.0 to 5.5 three to four hours after preparation. Protect from light.

USP 36: (Ferrous Gluconate). A yellowish-grey or pale greenish-yellow, fine powder or granules having a slight odour resembling that of burnt sugar. Soluble 1 in 5 of water; practically insoluble in alcohol. A 5% solution in water is acid to litmus. Store in airtight containers.

Profile

Ferrous gluconate is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in doses of up to 1.8 g daily (equivalent to up to 210 mg of iron daily).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ferrous gluconate 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 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Losferron; *Belg.*: Losferron; *Canad.*: Novo-Ferrogluc†; *Chile*: Glucoferro K; *Cz.*: Losferron†; *Denm.*: Fexin†; *Ger.*: Eisen-Sandoz†; Ferrum Verla; Floradix mit Eisen; Losferron; Rulofer G†; Vitaferro†; *Gr.*: Viofer; *Israel*: Ferro-Nes; Ferro; Ferronal; *Ital.*: Auxofer†; Bioferal; Bioglufer; Blustark†; Crom; Cromatonferro; Effegyn; Emoxiron†; Eritropiu; Ferro Complex; Ferrogyn; Gloros; Glucoferro; Losferron; Megafer; Monoferro†; Prontoferro; Sidervim; Sustemial; *Neth.*: Losferron; *Norw.*: Fexin†; *Pol.*: Ascofer; *Port.*: Bioferro; Hemototal; *Rus.*: Ferronal (Ферронал)†; *Spain*: Losferron; *Swed.*: Fexim†; *Switz.*: Lufer†; *Turk.*: Losferron; *Ukr.*: Megaferin (Мегаферин)†; *USA*: Ferate Tabs; Fergon; *Venez.*: Salfer; Yisafer.

Multi-ingredient Preparations. *Canad.*: Floradix Formula; Floradix Tab†; Floravit†; Floravit; Liv-Gd; *Chile*: Prenavit; *Fr.*: Alpharegul Femme; Tot'Hema; *Ger.*: Floradix Eisen-Folsaure; Floradix Krauterblut†; *Hung.*: Floradix; *India*: Ampiro; Beetone; Deferon; Elferri; Pacicap; Febex; Ferrocin C B12 Plus; Fezee; Gynae-CVP; Gystat; Haemglow; Hemiphos; Hemolex; Hepp-Tone; Infaglobin; Ironate; JP Tone; Livogen Hemtonic; Marvita; Mefol; Mulmin Plus; Mulmin; Myglo; Mynberrys Compound; Osteoz-FR; *Indon.*: Adfer; Biosanbe; Diabion; Emibion; Habebion†; Inbion; Maltiron; Muveron; Neogobion; Opibion; Pronita; Sangobion; Sangobion; Sangofer; Sangovitin†; Solvitron; Suprabion; Suprabion; Tropifer; Vitabion; *Ital.*: Ergon; Ferromina; *Malaysia*: Opibion; Sangobion; *Philipp.*: Sangobion; Sangobion; *Pol.*: Additiva Ferrum†; *Port.*: Tot'Hema; *Rus.*: Tot'Hema (Тотема); *Singapore*: Chitosano; Hemacaps†; Hemoplex; Neogobion; Opibion; Sangobion; *Switz.*: Duofer Fol; Duofer; Ferrascorbin†; *Thai.*: Ferro-Be-Sian†; Ferromin; Glufer-C†; Sangobion†; *Turk.*: Ferro-Vital†; *UK*: Floradix; Foresight Iron Formula; *Ukr.*: Tot'Hema (Тотема); *USA*: Compete; Iromin-G; *Venez.*: Bioglobina.

Homoeopathic Preparations. *Ger.*: HanoOxygen E.

Pharmacopoeial Preparations
BP 2014: Ferrous Gluconate Tablets;
USP 36: Ferrous Gluconate Capsules; Ferrous Gluconate Elixir; Ferrous Gluconate Tablets.

Ferrous Glycine Sulfate

Aminoacetosulfato ferroso; Demir Glisin Sülfat; Ferroglycini Sulfas; Ferroglycinsulfat; Ferroglysiinisulfaatti; Ferroso de glicina, sulfato; Ferrous Aminoacetosulphate; Ferrous Glycine Sulphate; Железа Глицин Сульфат.
CAS — 14729-84-1.
ATC — B03AA01.
ATC Vet — QB03AA01.

Profile

Ferrous glycine sulfate is a chelate of ferrous sulfate and glycine used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in a usual dose containing the equivalent of 100 mg of iron daily; up to about 300 mg daily has been used in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Neutrofer Neonatal; Neutrofer; *Chile*: Cheltin; *Denm.*: Glycifer; Niferex; *Fin.*: Obsidan; Spartofer; *Ger.*: Ferro sanol duodenal; Ferro Sanol; *Gr.*: Ferro Sanol; *Hong Kong*: Ferro Sanol; *Irl.*: Plesmet†; *Ital.*: Niferex; *Norw.*: Niferex; *Port.*: Niferex; *Spain*: Ferbisol; Ferro Sanol; Glutaferro; *Swed.*: Niferex; *Switz.*: Ferro sanol; *Turk.*: Ferro Sanol; *USA*: Gentle Iron; *Venez.*: Herronduo.

Multi-ingredient Preparations. *Arg.*: Anemidox Ultra; *Braz.*: Neutrofer Folico; *Chile*: Cheltin Folic; Pre Mat; *Fin.*: Obsidan comp; *Ger.*: Ferro sanol comp; Ferro sanol gyn; *India*: Astyfer; Fecontin-F; Fecontin-Z†; Fereg-F; Fereg-Z; Ferinova; Fezocar; Glyciron; Hemfer-A; Hemfer; Hemfer; Hemocare; Hemocare; Mighty; *Turk.*: Ferro Sanol B; *UK*: Florisene; *USA*: Repliva†; *Venez.*: Herrongyn.

Ferrous Iodide

Ferrous Iodine; Iron Diiodide.
FeI_2=309.7
CAS — 7783-86-0.
ATC — B03AA11.
ATC Vet — QB03AA11.
UNII — F5452U54PN.

Profile

Ferrous iodide has been used as a source of iron (p. 2073.1) and iodine (p. 2336.3).

Homoeopathy

Ferrous iodide has been used in homoeopathic medicines under the following names: Eisenjodid; Eisenjodür; Ferr-i.; Ferrum iodatum; Ferrum jodatum; Iodide of iron; Jodeisen.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austria*: Lymphomyosot; *Cz.*: Lymphomyosot; *Fr.*: Aurum Complexe No 38†; *Ger.*: Lymphomyosot N; Lymphomyosot; Rufebran thyreo†; Thyreo-Injektopas; *Hung.*: Lymphomyosot; *S.Afr.*: Lymphomyosot; *Switz.*: Regenaplex Nr. 25c; *Ukr.*: Lymphomyosot (Лімфоміозот); Lymphomyosot N (Лімфоміозот Н).

Ferrous Lactate

ES85; Ferroso, lactato; Iron Lactate; Молочнокислое Железо.

$C_6H_{10}FeO_6.3H_2O$=288.0

CAS — 5905-52-2 (anhydrous ferrous lactate); 6047-24-1 (ferrous lactate trihydrate).

UNII — 5JU4C2L5A0 (ferrous lactate); IEP4081R5X (ferrous lactate trihydrate).

Profile

Ferrous lactate is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Dan Zhu (丹珠); La Ke Fei (拉克菲); Tie Xin (貼鑫); You Ni Xue (尤尼雪); *S.Afr.*: Ferro Drops L; *Spain*: Cromatonbic Perro.

Multi-ingredient Preparations. *Austria*: Anthozym†; *Pol.*: Multivitamol; *Ukr.*: Gerovital Dr. Theiss (Геровитал Др. Тайсс); Multivitamol Dr Theiss (Мультивитамол Др. Тайсс).

Ferrous Oxalate

Ferroso, oxalato; Ferrum Oxalicum Oxydulatum; Iron Protoxalate; Protoxalato de hierro; Железа Оксалат.

$C_2FeO_4.2H_2O$=179.9

CAS — 516-03-0 (anhydrous ferrous oxalate); 6047-25-2 (ferrous oxalate dihydrate).

UNII — DZP4YV3ICV.

Profile

Ferrous oxalate has been used as a source of iron (p. 2073.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Disulone.

Ferrous Succinate

Ferroso, succinato; Железа Сукцинат.

$C_4H_4FeO_4$=171.9

CAS — 10030-90-7.

ATC — B03AA06.

ATC Vet — QB03AA06.

UNII — 8T8ZYK7N91.

Profile

Ferrous succinate is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in doses of up to about 600 mg daily (equivalent to up to about 200 mg of iron daily).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ferrous succinate 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 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ferdromaco; *China*: Su Li Fei (速力菲); *Fr.*: Inofer; *Ger.*: Ferrlecit 2.

Multi-ingredient Preparations. *India*: Hematrine; *USA*: Iron Complex.

Ferrous Sulfate

Demir Sülfat; Eisen(II)-Sulfat; Ferreux (Sulfate); Ferrosi Sulfas; Ferrosi sulfas heptahydricus; Ferroso, sulfato; Ferrosulfaattiheptahydraatti; Ferrosulfatheptahydrat; Ferrous Sulphate; Ferrum Sulfuricum Oxydulatum; Geležies(II) sulfatas heptahidratas; Iron (II) Sulphate Heptahydrate; Iron Sulphate; Síran železnatý heptahydrát; Sulfate ferreux heptahydraté; Sulfato de hierro; Sulfato de hierro (II) heptahidrato; Vas(II)-szulfát; Železa(II) síarczan; Железа Сульфат.

$FeSO_4.7H_2O$=278.0

CAS — 7720-78-7 (anhydrous ferrous sulfate); 7782-63-0 (ferrous sulfate heptahydrate).

ATC — B03AA07.

ATC Vet — QB03AA07; QB03AD03.

UNII — 39R4TAN1VT.

NOTE. Crude ferrous sulfate is known as Green Vitriol or Green Copperas.

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

Swiss also includes ferrous sulfate sesquihydrate.

Ph. Eur. 8: (Ferrous Sulfate Heptahydrate). A light green crystalline powder or bluish-green crystals, efflorescent in air. It is oxidised in moist air, becoming brown. Freely soluble in water; very soluble in boiling water; practically insoluble in alcohol. A 5% solution in water has a pH of 3.0 to 4.0. Store in airtight containers.

USP 36: (Ferrous Sulfate). Pale bluish-green, odourless, crystals or granules. It is efflorescent in dry air and oxidises readily in moist air to form brownish-yellow basic ferric sulfate. Soluble 1 in 1.5 of water and 1 in 0.5 of boiling water; insoluble in alcohol. A 10% solution in water is acid to litmus, having a pH of about 3.7. Store in airtight containers.

Dried Ferrous Sulfate *(USAN)*

Dried Ferrous Sulphate; Exsiccated Ferrous Sulphate; Ferreux (sulfate) desséché; Ferrosi sulfas desiccatus; Ferrosi Sulfas Exsiccatus; Ferroso desecado, sulfato; Sulfato ferroso seco.

CAS — 13463-43-9.

UNII — 2IDP3X9OUD (anhydrous ferrous sulfate); RIB009B0VW (dried ferrous sulfate).

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

Ph. Eur. 8: (Ferrous Sulfate, Dried). Hydrated ferrous sulphate deprived of part of its water of hydration by drying. A greyish-white powder which is oxidised in moist air, becoming brown. It contains 86.0 to 90.0% of $FeSO_4$. Slowly but freely soluble in water, very soluble in boiling water; practically insoluble in alcohol. A 5% solution in water has a pH of 3.0 to 4.0. Store in airtight containers.

USP 36: (Dried Ferrous Sulfate). A greyish-white to buff-coloured powder consisting primarily of ferrous sulfate monohydrate with varying amounts of ferrous sulfate tetrahydrate. It contains 86.0 to 89.0% of $FeSO_4$. Slowly soluble in water; insoluble in alcohol.

Profile

Ferrous sulfate is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally; the dried form is often used in solid dosage forms and the heptahydrate in liquid dosage forms. Usual doses of dried ferrous sulfate are up to 600 mg daily (equivalent to 180 to 195 mg of iron daily, this figure being somewhat variable depending on the purity and water content of the salt).

Ferrous sulfate oxidised with nitric and sulfuric acids yields ferric subsulfate solution, also known as Monsel's solution, which has been used as a haemostatic.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ferrous sulfate 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 07/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Eurofer; Factofer; Feklon; Fer-In-Sol; Ferricol; Ferrocebrina; Ferromas; Ferromotion; Hemofer; Hemoferrol; Iberol; Medifer; Siderblut; TGI; *Austral.*: Ferro-Gradumet; Ferrograd C; *Austria*: Aktiferrin; Ferro-Gradumet; Tardyferon; *Belg.*: Fero-Grad; Fero-Gradumet; Tardyferon; *Braz.*: Cimefer; Fer-In-Sol; Ferronil; Perrosol†; Ferrototal; Iberol; Ironfer†; Sulfer Plus†; Sulferbel; Sulfergan Composto; Sulferro†; Sulferrol; Vitafer; *Canad.*: Fer-In-Sol; Perodan; Ferofate†; Novo-Perrosulfate†; Slow-Fe; *Chile*: Fer-In-Sol; Ferrigot; *Cz.*: Aktiferrin; Sorbifer; Tardyferon; *Denm.*: Ferro; *Fin.*: Duroferon; Retafer; *Fr.*: Fer AP-HP; Fero-Grad vitamine C; Timoferol; *Ger.*: Aktiferrin N†; Ceferro; Dreisafer; Eisentabletten; Eryfer; Ferrogamma; Floradix Eisen; Haemoprotect; Hamatopan; Kendural C; Plastufer†; Plastulen†; Tardyferon; *Gr.*: Cooperfer; Fer-In-Sol; Microfer; Resoferon; Tardyferon; *Hong Kong*: Ferasul†; Ferisan†; Iron-200; Super-Fe†; *Hung.*: Aktiferrin; Ferro-Gradumet; Sorbifer; Tardyferon; *India*: Perich; *Indon.*: Sulfas Ferrosus; *Irl.*: Feospan; Fer-In-Sol; Ferrograd C; Ferrograd; *Israel*: Ferro-Gradumet; Slow-Fe†; Tardyferon; *Ital.*: Fer-In-Sol; Ferrograd C; Ferrograd; *Malaysia*: Retafer; *Mex.*: Biofenor; Fer-In-Sol; Perifer; Forcil†; Hemobion; Valdefer; *Neth.*: Fero-Gradumet; Ferrograd; Protiferron; *Norw.*: Duroferon; Ferromax; Nycoplus Ferro-Retard; *NZ*: Ferro-Gradumet; Ferrograd C; *Philipp.*: Brisofer; Feosol; Feovit†; Fer-In-Sol; Perglobin; Perosal; Sorbifer; United Home Fersulfate Iron; *Pol.*: Ferro-Gradumet†; Hemofer; Sorbifer; Tardyferon; *Port.*: Ferro-Gradumet; Tardyferon; *Rus.*: Aktiferrin (Актиферрин); Ferro-Gradumet (Феррогрядумет); Ferroplex (Ферроплекс); Hemofer (Гемофер); Sorbifer (Сорбифер); Tardyferon (Тардиферон); *S.Afr.*: Fero-Grad†; Ferro Drops; Fesofor†; *Spain*: Fero-Gradumet; Tardyferon; *Swed.*: Duroferon; *Switz.*: Aktiferrin; Ferro-Gradumet; *Thai.*: Fer-In-Sol†; Ferrotabs; Kidiron; Pediron; *Turk.*: Oroferon; Tardyferon; *UAE*: Kdiron; *UK*: Feospan; Ferrograd C; Ferrograd; Ironorm; *Ukr.*: Aktiferrin (Актиферрин); Aktiferrin (Актиферрин); Sorbifer (Сорбифер); Tardyferon (Тардиферон); *USA*: Enfamil Fer-In-Sol; Fe^{50}; Feosol; Fer-gen-sol†; Fer-Iron; Feratab†; Fero-Grad; Ferrous Drops; Irospan; Slow-Fe; *Venez.*: Fer-In-Sol.

Multi-ingredient Preparations. *Arg.*: Bifidosa; Cistidac; Factofer B12; Fefol; Ferro Folic; Ferrogalfol; Hierro Plus†; Iberol; Rubiron; Sideralce; Tardyferon; Vifortol Prenatal; *Austral.*: Fefol; FGF Tabs; Irontonat†; *Austria*: Aktiferrin Compositum; Ferrograd Fol; Ferrum-Quarz; Kephalodoron; Tardyferon-Fol; *Braz.*: Betozone†; Cobaldoze†; Combiron; Dobiron; Ferrocomplex; Ferroplex; Ferrotrat; Iberin Folico; Iberol; Novofer; Paratonico†; Sulfato Ferroso Composto; Vitonico; *Canad.*: Pediavit Select; Slow-Fe Folic†; *Chile*: Acomir con hierro†; Ferranem; Ferromalt; Iberol Folico†; Iberol†; *China*: Yi Yuan Sheng (益源生); *Cz.*: Aktiferrin Compositum; Ferro-Folgamma; Tardyferon-Fol; *Fr.*: Oligobiane Fe-Cu; Tardyferon B$_9$; Tardyferon; Thalamag fer B$_9$; *Ger.*: Eryfer comp†; Ferro-Folgamma; Ferro-Folsan; Hamatopan F; Kendural-Fol-500†; Plastulen Duo†; Tardyferon-Fol; *Gr.*: Feofol; Fero-Folic; Gyno-Tardyferon; *Hong Kong*: Iberet-Folic†; Iberet†; *Hung.*: Ferro-Folgamma; Ferrograd Folic; Neo-Ferro Folgamma; Tardyferon-Fol; *India*: Cofol; Conviron Forte; Conviron-TR; Durovit-Fez; Durovit; Elferri-TR; Fefol-Z; Fefol; Feonat-Z; Feonat; Ferobid-Z; Ferritop-SR; Ferro-Plan Kit; Ferrochelate-Z; Fersolate-CM; Ferz; Fesofor-Z; Fesovit; Fesovit; Festo-TR; Feton-Z-TR; Fezee; Haem-F; HB-Plan Kit; Hb-Rich 300; Iberol†; Iberol; Irex-TR; Ironifol-Z; Irosoft; JP Tone-TR†; Maxiferon; Mulmin-P; Plastules B-12; Protone; *Indon.*: Befozi; Iberet-Folic; Iberet; *Irl.*: Fefol; Ferrograd Folic; *Israel*: Aktiferrin-F; Ferrograd Folic; Foliferrin; Slow-Fe Folic†; Tardyferon B9†; *Ital.*: Ferrograd Folic; *Malaysia*: Aktiferrin-F†; Iberet-Folic; *Mex.*: Alpharexin†; Ferro Folico; Hemoinfant; Iberet†; Iberol†; Orafer Comp; Tardyferon-Fol; *NZ*: Ferrograd Folic; *Philipp.*: Ameciron; Appebon with Iron; Appetason; Appetason; Appetite OB; Appetite with Iron; Cuteplex; Drexabion OB; Dupharon; Femina; Ferlin; Ferlin; Perosal; Ferro-Folsan Plus†; Foralivit; Hanizyn; Heltine; Hemiron; IBC; Iberet-Folic; Iberet; Imefer; Irobon; Magniferron; Mediferron-Vita; Meganerv-E; Micron-C; Molvite with Iron; Natalac FeFol; Propan with Iron; Regeron-E Plus; Terraferron; *Pol.*: Ferrograd Folic†; Hemofer P†; Tardyferon-Fol; *Port.*: Fefolato; Ferrograd Folico; Folifer; Tardyferon-Fol; *Rus.*: Aktiferrin Compositum (Актиферрин Композитум); Biovital (Биовитал); Penules (Фенюльс); Penules Zinc (Фенюльс Цинк); Ferro-Folgamma (Ферро-Фольгамма); Ferrohematogen (Феррогематоген); Ferrovit (Ферровит); Gyno-Tardyferon (Гино-тардиферон); Hematogen C (Гематоген С); Hematogen C Vita (Гематоген С Вита); Hematogen Nova (Гематоген Новый); *S.Afr.*: Dr Williams Pink Pills†; Fefol-Vit†; Fefol†; Fero-Folic; Ferrous Sulphate Compound†; Foliglobin; *Singapore*: Aktiferrin-P†; Perbeaplex; Iberet-Folic; Iberet; *Spain*: Bialfer; *Switz.*: Aktiferrin-P†; Fero-Folic; Gyno-Tardyferon; *Kendural*; Tardyferon; *Thai.*: Ferro-BC; Iberet; Temaron; *Turk.*: Gyno-Tardyferon; Gynoferon; Natabec†; *UAE*: Folicron; *UK*: Fefol; Ferrograd Folic; Ironorm; *Ukr.*: Penules (Фенюльс)†; Fersinol-Z (Ферсинол-З); Gyno-Tardyferon (Гино-Тардиферон); *USA*: Aqua Ban Plus; Fero-Folic; Generet; Slow Fe with Folic Acid; *Venez.*: Ferro-Folic; Ferroce B12; Iberol C.

Homoeopathic Preparations. *Cz.*: Ferrum Homaccord†; *S.Afr.*: Kephalodoron†; *UK*: Bidor.

Pharmacopoeial Preparations

BP 2014: Ferrous Sulphate Tablets; Paediatric Ferrous Sulphate Oral Solution; Prolonged-release Ferrous Sulphate Tablets;
USP 36: Ferric Subsulfate Solution; Ferrous Sulfate Oral Solution; Ferrous Sulfate Syrup; Ferrous Sulfate Tablets.

Ferrous Tartrate

Ferrosi Tartras; Ferroso, tartrato; Железа Тартрат.

$C_4H_4FeO_6.2½H_2O$=249.0

CAS — 2944-65-2 (anhydrous ferrous tartrate).

ATC — B03AA08.

ATC Vet — QB03AA08.

UNII — ZRW631PTZD.

Profile

Ferrous tartrate has been used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Denm.*: Ferroplex-frangula.

Ferumoxytol *(USAN)*

Code 7228, Ферумокситол.
CAS — 1309-38-2.
UNII — CLH5FT6412 (ferumoxytol non-stoichiometric magnetite).

Uses and Administration

Ferumoxytol is a superparamagnetic iron oxide that is coated with a low-molecular-weight semisynthetic carbohydrate, polyglucose sorbitol carboxymethyl ether. It is used as a source of iron for the treatment of iron-deficiency anaemia (p. 2073.2) in patients with chronic kidney disease. The dose is expressed in terms of elemental iron. An initial dose of 510 mg is given by intravenous injection at a rate of up to 30 mg/second. A second dose of 510 mg is given 3 to 8 days later. In patients receiving haemodialysis, ferumoxytol is given after at least one hour of haemodialysis has been completed and once the blood pressure is stable. Haematological response to therapy should be assessed at least one month after the second dose of ferumoxytol. Patients with persistent or recurrent iron-deficiency anaemia may receive further doses of ferumoxytol. Ferumoxytol may potentially be used as a contrast medium in magnetic resonance imaging (p. 1580.1).

References.
1. Spinowitz BS, *et al.* The safety and efficacy of ferumoxytol therapy in anemic chronic kidney disease patients. *Kidney Int* 2005; **68**: 1801–7.
2. Li W, *et al.* Lower extremity deep venous thrombosis: evaluation with ferumoxytol-enhanced MR imaging and dual-contrast mechanism—preliminary experience. *Radiology* 2007; **242**: 873–81.
3. Neuwelt EA, *et al.* The potential of ferumoxytol nanoparticle magnetic resonance imaging, perfusion, and angiography in central nervous system malignancy: a pilot study. *Neurosurgery* 2007; **60**: 601–11.
4. Spinowitz BS, *et al.* Ferumoxytol for treating iron deficiency anemia in CKD. *J Am Soc Nephrol* 2008; **19**: 1599–1605.
5. Singh A, *et al.* Safety of ferumoxytol in patients with anemia and CKD. *Am J Kidney Dis* 2008; **52**: 907–15.
6. Provenzano R, *et al.* Ferumoxytol as an intravenous iron replacement therapy in hemodialysis patients. *Clin J Am Soc Nephrol* 2009; **4**: 386–93.
7. Schwenk MH. Ferumoxytol: a new intravenous iron preparation for the treatment of iron deficiency anemia in patients with chronic kidney disease. *Pharmacotherapy* 2010; **30**: 70–9.

Adverse Effects and Precautions

As for Iron Dextran, p. 2076.1

Haematological response to ferumoxytol therapy should be monitored regularly. It should not be used in patients with evidence of iron overload or to treat anaemia not caused by iron deficiency.

The results of magnetic resonance imaging may be altered by ferumoxytol therapy, and the effects may persist for up to 3 months after the last dose.

Hypersensitivity. Ferumoxytol has not been directly compared with other intravenous iron preparations in terms of its safety profile. For a discussion of whether dextran-free preparations may be safer than iron dextran, see p. 2076.2.

Pharmacokinetics

Peak plasma concentrations of ferumoxytol occur about 20 minutes after intravenous injection. Plasma elimination half-life is about 15 hours. Ferumoxytol is not removed by haemodialysis.

References.
1. Landry R, *et al.* Pharmacokinetic study of ferumoxytol: a new iron replacement therapy in normal subjects and hemodialysis patients. *Am J Nephrol* 2005; **25**: 400–10.
2. Pai AB, *et al.* Plasma pharmacokinetics of two consecutive doses of ferumoxytol in healthy subjects. *Clin Pharmacol Ther* 2010; **88**: 237–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Feraheme; *Neth.*: Rienso; *Norw.*: Rienso; *Switz.*: Rienso; *UK*: Rienso; *USA*: Feraheme.

Folic Acid *(BAN, rINN)*

Acide Folique; Ácido fólico; Acidum Folicum; Folacin; Fólico, ácido; Folik Asit; Folinsyre; Folio rūgštis; Folsäure; Folsav; Folsyra; Foollhappo; Kwas foliowy; Kyselina listová; PGA; Pteroylglutamic Acid; Pteroylmonoglutamic Acid; Vitamin B_9; Vitamin B_{11}; Фолиевая Кислота.

N-[4-[(2-Amino-4-hydroxypteridin-6-ylmethylamino)benzoyl]-L-(+)-glutamic acid.
$C_{19}H_{19}N_7O_6$=441.4
CAS — 59-30-3 (folic acid); 6484-89-5 (sodium folate).
ATC — B03BB01.
ATC Vet — QB03BB01.
UNII — 935E97BOY8.

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

Ph. Eur. 8: (Folic Acid). A yellowish or orange crystalline powder. Practically insoluble in water and in most organic solvents. It dissolves in dilute acids and in alkaline solutions. Protect from light.

USP 36: (Folic Acid). A yellow, yellow-brownish, or yellowish-orange, odourless crystalline powder. Very slightly soluble in water; insoluble in alcohol, in acetone, in chloroform, and in ether. It readily dissolves in dilute solutions of alkali hydroxides and carbonates; soluble in hot, 3N hydrochloric acid and in hot, 2N sulfuric acid; soluble in hydrochloric acid and in sulfuric acid, yielding pale yellow solutions. Protect from light.

Uses and Administration

Folic acid is a member of the vitamin B group. Folic acid is reduced in the body to tetrahydrofolate, which is a coenzyme for various metabolic processes including the synthesis of purine and pyrimidine nucleotides, and hence in the synthesis of DNA; it is also involved in some amino-acid conversions, and in the formation and utilisation of formate. Deficiency, which can result in megaloblastic anaemia (p. 2109.1), develops when the dietary intake is inadequate (as in malnutrition), when there is malabsorption (as in sprue), increased utilisation (as in pregnancy or conditions such as haemolytic anaemia), increased loss (as in haemodialysis), or as a result of the use of folate antagonists and other drugs that interfere with normal folate metabolism (see Interactions, p. 2066.2).

Folic acid is used in the treatment and prevention of the folate deficiency state. It does not correct folate deficiency due to dihydrofolate reductase inhibitors; calcium folinate (p. 2067.1) is used for this purpose, but see Antineoplastic Toxicity, below. Folic acid is also used in women of child-bearing potential and pregnant women to protect against neural tube defects in their offspring. This is discussed in more detail in Neural Tube Defects, p. 2064.3.

For the **treatment** of folate-deficient megaloblastic anaemia it is recommended in the UK that folic acid is given orally in doses of 5 mg daily for 4 months; up to 15 mg daily may be necessary in malabsorption states. Continued oral dosage with folic acid 5 mg every 1 to 7 days may be necessary in chronic haemolytic states such as thalassaemia major or sickle-cell anaemia, depending on the diet and rate of haemolysis; similar doses may be necessary in some patients receiving renal dialysis in order to prevent deficiency.

In the USA the usual recommended therapeutic dose for folate deficiency is oral folic acid 0.25 to 1 mg daily until a haematopoietic response has been obtained, although some patients require higher doses, especially in malabsorption states. The usual maintenance dose is 400 micrograms daily.

For doses in children, see below.

In the **prophylaxis** of megaloblastic anaemia of pregnancy, the usual dose is 500 micrograms daily in the UK.

For women of child-bearing potential at high risk of having a pregnancy affected by neural tube defect, the dose of folic acid is 4 or 5 mg daily starting before pregnancy (in the USA the recommendation is 4 weeks before) and continued through the first trimester. For other women of child-bearing potential the dose is 400 micrograms daily.

Folic acid may also be given by intramuscular, intravenous, or subcutaneous injection as the sodium salt.

Administration in children. The *BNFC* suggests the following oral doses of folic acid for children:

Folate supplementation in neonates
- preterm neonates: 50 micrograms once daily *or* 500 micrograms once weekly, given from 2 weeks of age until full-term corrected age is reached

Folate-deficient megaloblastic anaemia
- neonate to 1 year: initially 500 micrograms/kg daily (maximum 5 mg) for up to 4 months; up to 10 mg daily may be required in those aged from 1 month with malabsorption states
- 1 to 18 years: use adult doses, see above

Haemolytic anaemia, metabolic disorders
- 1 month to 12 years: 2.5 to 5 mg daily
- 12 to 18 years: 5 to 10 mg daily

Prophylaxis of folate deficiency in dialysis
- 1 month to 12 years: 250 micrograms/kg (maximum 10 mg) daily
- 12 to 18 years: 5 to 10 mg daily

For doses of folic acid used to prevent methotrexate adverse effects in juvenile idiopathic arthritis, see below.

Antineoplastic toxicity. Folinic acid does not require reduction by dihydrofolate reductase to its active form, and is used to reduce the toxicity of high-dose methotrexate antineoplastic therapy (folinic acid rescue, see p. 2067.1). In patients with mucosal or gastrointestinal adverse effects associated with the much lower weekly doses of methotrexate used in the treatment of autoimmune diseases such as rheumatoid arthritis or juvenile idiopathic arthritis, a weekly oral dose of folic acid has been used to reduce the frequency of adverse effects. Such supplementation, although widely favoured, particularly in the USA,[1] remains somewhat controversial, as some consider it may reduce the efficacy of methotrexate.[2] Nonetheless, although unlicensed in the UK, the following oral doses of folic acid have been suggested, usually given at least 24 hours after the methotrexate dose:

BNF
- adult over 18 years: 5 mg once weekly

BNFC
- 2 to 18 years: 1 mg daily or 5 mg once weekly

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2. Khanna D, *et al.* Reduction of the efficacy of methotrexate by the use of folic acid: post hoc analysis from two randomized controlled studies. *Arthritis Rheum* 2005; **52**: 3030–8.

Cardiovascular disease. Epidemiological studies indicate that individuals with a low serum folate are at increased risk of fatal coronary heart disease,[1] and that those with a high intake of folate,[2] or folic acid and vitamin B_6,[3] from vitamin supplements or food, are at lower risk of ischaemic heart disease or stroke. Vitamin deficiency, especially folic acid deficiency, is a common cause of hyperhomocysteinaemia.[4,5] Elevated blood-homocysteine concentrations may be an independent risk factor for atherosclerosis (p. 1250.2) and ischaemic heart disease (p. 1254.2), venous thrombosis (p. 1274.1), and stroke (p. 1269.2).[4-8] Whether hyperhomocysteinaemia directly causes cardiovascular disease, as concluded by a meta-analysis,[9] or is a possible marker of increased vascular risk,[10] remains controversial.[11,12]

Folic acid reduces blood-homocysteine concentrations;[13-15] vitamin B_{12}, but not B_6, may have an additional effect.[14] The higher the baseline blood-homocysteine concentration, or the lower the baseline value of folate,[14] the greater the effect of folate supplements; reductions were similar with daily doses from 0.5 to 5 mg of folic acid,[14] although a randomised study[15] found greater effects with a daily 2-mg dose compared with a dose of 200 micrograms. A meta-analysis concluded that a daily dose of 800 micrograms or more was needed to achieve maximum reductions in homocysteine concentrations.[16]

Results of studies assessing cardiovascular risk versus folate intake have been variable. Although some have found the risk of hypertension,[17] or stroke[18] to be lower in patients with higher folate intakes (dietary or via supplementation), and there are suggestions that endothelial function is improved by folate supplementation,[19,20] others have reported no association between intake and cardiovascular risk.[21,22] A large open-label study[23] found that, while folic acid supplementation significantly reduced plasma homocysteine concentrations, it did not reduce recurrence of cardiovascular events in patients with stable coronary artery disease. (Most patients had been treated with lipid-lowering therapy, and the authors stated that this might have overshadowed any potential beneficial effects of folic acid.) Similarly, a randomised controlled study, the Vitamin Intervention for Stroke Prevention (VISP) study,[24] found that high daily doses of folic acid, vitamin B_6 and vitamin B_{12} modestly decreased total homocysteine concentrations compared with low daily doses, but had no treatment effect on recurrent stroke, myocardial infarction, or death. Three further large controlled studies (HOPE-2, NORVIT, and WENBIT) also found no significant beneficial effect of treatment with folic acid plus vitamin B_{12} and/or vitamin B_6 on cardiovascular disease risk, despite adequate homocysteine-lowering effects;[25-27] such therapy was even suggested to be harmful.[25] Results from meta-analyses have been conflicting; one[28] concluded that folic acid supplementation could effectively reduce the risk of stroke in patients without a history of stroke, whereas others found no reduction in the risk of cardiovascular events, stroke, or all-cause mortality in patients at risk of, or with pre-existing, cardiovascular disease given folic acid, vitamin B_6, and vitamin B_{12} (alone or in combination)[29] or in patients with pre-existing cardiovascular or renal disease given folic acid with or without additional B vitamins.[30] However, exclusion of the VISP study from the latter meta-analysis led to a significant protective effect of folic acid supplementation on stroke.[30]

Results of other ongoing studies are considered necessary before definite conclusions can be drawn as to the so-called

'homocysteine hypothesis' of atherothrombotic vascular disease; while some recommend against routine treatment,[4,31,32] others consider homocysteine-lowering treatment in high-risk patients to be justified.[33,34] A meta-analysis[35] of observational studies indicated that the relationship between hyperhomocysteinaemia and ischaemic heart disease and stroke risk in healthy individuals might not be as strong as had previously been suggested, with stronger associations found in retrospective studies than in prospective studies. The lack of effect in some studies also prompted the suggestion that homocysteine may be a biological marker of cardiovascular disease risk rather than a modifiable cause.[27] The American Heart Association has stated[7] that, until the results of more controlled studies become available, routine testing of plasma-homocysteine concentrations cannot be justified; all patients should, however, be encouraged to consume the recommended dietary allowance (RDA) of folate, vitamin B_6 and vitamin B_{12}.

Daily treatment with oral folic acid, vitamin B_6, and vitamin B_{12} significantly decreased restenosis and target-vessel revascularisation after percutaneous coronary angioplasty.[36] In contrast, in another study[37] folic acid, vitamin B_6, and vitamin B_{12}, increased restenosis and target-vessel revascularisation. The studies differed in dosage regimen, patient population, lesion length, and procedure used,[38,39] but the strong proliferative effect of folate on neointimal growth may exceed the positive effect of lowering homocysteine concentrations,[40] and it has been stated[36] that these vitamins should not be routinely used in patients receiving coronary stents.

Patients with renal impairment develop hyperhomocysteinaemia as a result of delayed elimination and altered metabolism; the prevalence of plasma homocysteine levels greater than 15 micromoles/L has been reported to be 80 to 90% in dialysis patients, compared with 5% in the general population. In haemodialysis patients with moderate to severe hyperhomocysteinaemia, intravenous folinic acid 10 mg three times weekly has been reported to dramatically decrease homocysteine concentrations, although normal levels of homocysteine were not attained.[41] In a small study in renal transplant recipients with hyperhomocysteinaemia, vitamin B_6 was effective in reducing post-methionine-loading plasma homocysteine concentrations, and folic acid plus vitamin B_{12} was effective in lowering fasting plasma-homocysteine concentrations. The authors concluded that all three of these B-group vitamins may have a role in reducing atherosclerotic outcomes in this patient group.[42]

There has been some suggestion that folic acid supplementation during pregnancy may reduce rates of congenital heart defects in infants. Although the dose-effect relationship between folic acid intake and congenital heart defects remains unclear, an analysis[43] of the prevalence of severe congenital heart defects before and after food fortification with folic acid (below), reported a 6.2% decrease per year in birth prevalence after the introduction of a fortification programme in Canada; birth prevalence did not change in the 8 years before fortification.

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Deficiency states. Reviews of the use of folic acid in conditions associated with folate deficiency.

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Food fortification. Mandatory fortification of foods with folic acid has caused much controversy. Some advocate this measure as prevention against neural tube defects (below) and there is some suggestion it may also prevent other birth defects such as congenital heart defects (see Cardiovascular Disease, p. 2063.3). Others remain concerned about folic acid supplementation masking vitamin B_{12} deficiency (p. 2066.1) or having possible carcinogenic effects (p. 2065.3).

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Hearing loss. Epidemiological studies have suggested an association between homocysteine and folate concentrations and hearing status. A 3-year controlled study in a country without folic acid food fortification found that supplementation slowed the decline in age-related hearing loss. Further studies were considered necessary to confirm these findings.[1]

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Mental function. For a discussion of the effects of folate supplementation on cognitive function and depression, see Mental Function, p. 2046.3.

Neural tube defects. Failure of the fetal neural tube to fuse normally during the first 4 weeks of pregnancy may result in one of several congenital defects. These include *anencephaly* (absence of the brain and cranial vault) and *spina bifida* (failure of the vertebrae to fuse).[1,2] The latter ranges from spina bifida occulta, where neurological abnormalities are rare, to meningocoele or meningomyelocoele, where the meninges, or meninges and spinal cord, herniate outwards through the vertebral defect and which may be associated with hydrocephalus and paralysis of the lower limbs and sphincters.

The reasons for this failure in normal development are not well understood and appear to include both environmental and genetic factors. The risk is increased in certain geographical areas, and in the offspring of parents with previous children who had neural tube defects, or of parents who themselves suffer from the condition.[1]

A defect in the methylenetetrahydrofolate reductase gene has been identified, which is estimated to occur in about 5 to 15% of white populations, and appears to result in an increased requirement for folates, and an increased risk of recurrent early pregnancy loss and neural tube defects.[3,4] Since the 1960s there has been some evidence that the mother's folate status was significant, and in the early 1980s two groups published evidence for claims that oral folic acid, with or without other vitamins, in the period around conception, reduced the incidence of neural tube defect in the offspring of mothers who had previously borne children with the defect.[5,6]

Although criticised on several grounds, the conclusions of these studies were borne out by a large multicentre study initiated by the UK Medical Research Council (MRC).[7] This study was terminated early because of overwhelming evidence that folic acid 4 mg daily taken from before conception until the twelfth week of gestation by women with a history of a previous pregnancy affected by a neural tube defect reduced the incidence of such defect by about two-thirds. Other studies and systematic reviews have since confirmed the benefits of supplementation.[8-10] Multivitamins alone (A, D, B_1, B_2, nicotinamide, B_6, and C) did not demonstrate a similar benefit.

Prevention of recurrence. In the light of the MRC study, it is recommended in the UK that in couples with spina bifida or a history of previous offspring with neural tube defect, all those women who may become pregnant should receive folic acid 5 mg daily (in the absence of a commercially-available 4-mg dosage form) until the twelfth week of pregnancy.[11] In the USA, recommendations are 4 mg of folic acid daily from at least 4 weeks before conception through the first 3 months of pregnancy.[12] It must be borne in mind that only about 60 to 70% of neural tube defects appear to be folate-sensitive, and parents should be counselled appropriately. Similar doses of folic acid have been recommended for women in intermediate- to high-risk categories for neural tube defects in Canada.[13]

The investigators in the MRC study acknowledged that a 4-mg dose may not be optimal, and both early[3,6] and later[14] studies imply that much lower doses of folic acid may reduce the risk of recurrence, but this has yet to be clearly shown. Furthermore, the optimum length of time that supplements should be given to these women before conception is unknown.

Prevention of occurrence. First occurrences of neural tube defects account for about 95% of cases, and there are obvious public health implications if the benefits of folate in mothers known to be at risk can be extended to the general population. A study in Hungary[15] indicated that folic acid 800 micrograms daily with multivitamins, taken for at least one month before conception and until the third month of gestation decreased the incidence of first occurrence of neural tube defects. A case control study in the USA[16] (where the normal incidence of neural tube defect is much lower than Hungary) suggested that a periconceptional folic acid intake of as little as 400 micrograms daily reduced the occurrence of the disorder by 60%.

With such results in mind the US Public Health Service has recommended that all women of child-bearing age who are capable of pregnancy should receive folic acid 400 micrograms daily.[1,17] A subsequent review by the US Preventive Services Task Force suggested that the dose of folic acid should be slightly higher at 400 to 800 micrograms daily.[18] Care should be taken to keep folate consumption below 1 mg daily except under medical supervision.[1,17] Such universal coverage would allow for the problem of unplanned pregnancies but would be difficult to achieve, other than by fortification of dietary staples with folate.

Food fortification has therefore been adopted in the USA, at a level of 140 micrograms of folic acid per 100 g of cereal-grain product. While this amount will probably be insufficient to provide maximum reduction in the incidence of neural tube defects,[19,20] there is some evidence of benefit,[21] and it was chosen to minimise the risk of masking vitamin B_{12} deficiency in the elderly.[22] Efforts to increase the use of folic acid supplements in women of child-bearing potential are still advocated. In Canada, where food fortification has been associated with a significant reduction in neural tube defects,[23] similar recommendations have been made.[13]

In the UK, the current recommendation is that all women planning a pregnancy should take an extra 400 micrograms of folic acid daily before conception and during the first 12 weeks of pregnancy, bringing the average folate intake to about 600 micrograms daily.[11] In unplanned pregnancies, supplementation should begin as soon as pregnancy is suspected. Some, however, consider this amount to be too low.[24] As in the USA, food fortification has been considered, and the Committee on Medical Aspects of Food and Nutrition Policy (COMA) concluded that universal fortification of flour at 240 micrograms of folic acid per 100 g in food would significantly reduce the number of neural tube defects.[25] In May 2007, the UK Food Standards Agency agreed that mandatory fortification be introduced. However, there are concerns about possible carcinogenic effects (see Carcinogenicity, below) and results of further studies are awaited. Debate has continued as to the amount, if any, of fortification necessary.[24,26-31] The UK Scientific Advisory Committee on Nutrition reconfirmed[32] the COMA recommendation for fortification of flour but said that further consideration should be given to the amount and form of folate used and also called for better monitoring of vitamin B_{12} in those aged 65 and over. There has also been a renewed call for fortification of foods in Europe,[33-36] and Australia and New Zealand,[37,38] as issuing recommendations on folic acid use has not led to a substantial decrease in the incidence of neural tube defects, and efforts have not reached all the target population. Certainly, mandatory food fortification with folic acid has been shown to dramatically decrease the incidence of neural tube defects in Canada,[39] Chile,[40] and the USA.[21,41,42] Fears of masking vitamin B_{12} deficiency appear to have not been borne out (see Vitamin B_{12} Deficiency, p. 2066.1).

Patients receiving antiepileptic drugs are at increased risk of neural tube defect and it has been suggested that folic acid supplementation for such patients should be at the level used for prevention of recurrence,[43] i.e. 4 or 5 mg daily.

The mechanism by which folic acid protects against neural tube defects is unknown, but various theories have been postulated including a positive effect in promoting neural tube closure,[44] or a selective abortifacient effect on affected fetuses (terathanasia),[45] although the latter has been disputed.[46] There is some evidence that low maternal vitamin B_{12} concentrations are an independent risk factor for neural tube defects,[47,48] perhaps indicating a role for methionine synthase in their aetiology, and suggesting that additional supplementation with cobalamins may be warranted, or that methionine supplements could be investigated as an alternative to folic acid.[49,50] Some suggest that hyperhomocysteinaemia may be a cause of some neural tube defects and that they may be due to an inborn error of folate and/or homocysteine metabolism; furthermore, a dietary deficiency may trigger a genetic predisposition towards the development of neural tube defects.[2] Interestingly, the results from the Hungarian programme[51,52] and from other studies[53-55] suggest that multivitamin supplements (including folic acid) may also reduce the occurrence of other congenital abnormalities. Maternal folate deficiency has also been associated with an increased risk of adverse birth outcomes, apart from neural tube defects, such as preterm delivery, low infant birthweight, and fetal growth retardation.[56]

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Osteoporosis. Treatment with folate and vitamin B_{12} can reduce elevated plasma homocysteine concentrations and may subsequently decrease the risk of osteoporosis and hip fracture, see Osteoporosis, under Vitamin B_{12}, p. 2109.3.

Prophylaxis of malignant neoplasms. For reference to suggestions that folate supplements may be associated with reduced risk of certain cancers, see p. 2047.3. However, folic acid may have dual modulatory effects on carcinogenesis, see Carcinogenicity, below.

Adverse Effects

Folic acid is generally well tolerated. Gastrointestinal disturbances and hypersensitivity reactions have been reported rarely.

Hypersensitivity. A woman had 3 episodes of hypersensitivity, including anaphylaxis, on exposure to synthetic folic acid. Intradermal testing with folic acid solution was positive and a blinded challenge to folic acid solution led to widespread urticaria. Sensitisation to folic acid may have occurred after supplementation with vitamin B, at which time she had recurrent episodes of urticaria. The patient appeared to tolerate dietary folates, and the authors suggested that foods fortified with folic acid be clearly labelled.[1]

1. Smith J, *et al.* Recurrent anaphylaxis to synthetic folic acid. *Lancet* 2007; 370: 652.

Precautions

Folic acid should never be given alone or with inadequate amounts of vitamin B_{12} for the treatment of undiagnosed megaloblastic anaemia, since folic acid may produce a haematopoietic response in patients with a megaloblastic anaemia due to vitamin B_{12} deficiency without preventing aggravation of neurological symptoms. This masking of the true deficiency state can lead to serious neurological damage, such as subacute combined degeneration of the spinal cord (see also Vitamin B_{12} Deficiency, p. 2066.1).

Breast feeding. Folic acid is excreted into breast milk. No adverse effects have been seen in breast-fed infants whose mothers were receiving folic acid, and the American Academy of Pediatrics considers that it is therefore usually compatible with breast feeding.[1]

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 06/01/06)

Carcinogenicity. Follow-up data from a large study of folate supplementation suggested a greater risk of death due to breast cancer in those women randomised to high doses; the association was not statistically significant and further studies were considered necessary.[1] In contrast, other studies suggest a reduced risk of some cancers with folate supplementation, see Prophylaxis of Malignant Neoplasms, p. 2047.3. A large study found that folic acid supplementation did not reduce colorectal adenoma risk; evidence for an increased risk of adenomas with supplementation was equivocal.[2]

Animal studies suggest that folic acid may have dual modulatory effects on carcinogenesis, depending on dose and timing of supplementation. Folate deficiency may inhibit, whereas supplementation may promote, the progression of established neoplasms. In normal tissue, however, folate deficiency can predispose towards neoplastic transformation and modest amounts of folate may suppress tumour development; supraphysiological doses may enhance tumour progression.[3,4] Thus, use of folate before the existence of preneoplastic lesions may prevent tumour development, whereas use once early lesions are established appears to increase tumorigenesis.[5] However, determining the presence of preneoplastic foci in the general population is almost impossible.[4] Given the tendency for cancer patients to consume more supplements than healthy subjects, the possibility of adverse effects of folic acid on cancer progression, recurrence, and metastasis should be borne in mind, and research on folate supplementation among patients with cancer is needed.[5]

Careful monitoring of the long-term effects of folic acid food fortification (p. 2064.2) is also advised,[3,4] and some have advocated against mandatory fortification on this basis.[6] Population-based observations[7] in Canada and the USA noted a temporal association between the introduction of folic acid fortification programmes and increased rates of colorectal cancer in North America. Although the explanation for the increase is unclear, improvements in cancer screening and higher intakes of folic acid may play a part. After reviewing the data regarding folic acid and the risk of cancer, the Scientific Advisory Committee on Nutrition[8] considered that although there are uncertainties, they still supported the recommendation for mandatory

fortification of flour in the UK, with controls to limit excessive folic acid intake. These included the restriction of voluntary fortification, and further guidance for at-risk population groups on the use of folic acid supplements: an intake from supplements not to exceed 200 micrograms daily is recommended in those with a history of colorectal adenomas, and in those aged over 50 years as the risk of developing colorectal cancer increases after this age.

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Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies folic acid 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 07/10/11)

Vitamin B_{12} deficiency. The issue of fortification of food with folic acid to reduce the number of infants born with neural tube defects (see p. 2064.3) has created debate[1-7] on the amount of fortification and on the risks of masking vitamin B_{12} deficiency, particularly in the elderly. As mentioned in Precautions, p. 2065.3, folic acid should not be used in megaloblastic anaemia due to vitamin B_{12} deficiency, because it will not prevent the neurological manifestations of this deficiency, and may delay the diagnosis. Masking of vitamin B_{12} deficiency has been noted with daily doses of folic acid of 5 mg, but it is generally considered that very low doses do not have this effect. It has also been stated that folic acid may precipitate the neurological manifestations of vitamin B_{12} deficiency; however, a review of the evidence suggests this is unlikely.[8]

Nevertheless, concerns regarding neurological effects of vitamin B_{12} deficiency in the elderly have led to adoption of a level of folic acid fortification in the USA that is accepted not to provide optimum protection against neural tube defects, but that it is hoped will minimise any risks.[9] It has been suggested that fortification with vitamin B_{12} as well might also be a solution.[10-12] While some studies of food fortification show no evidence of a deterioration in vitamin B_{12} status in elderly patients,[13,14] there is concern[12,15] that individuals may be consuming folic acid in excess of the upper limit of 1 mg daily (see under UK and US Recommended Dietary Intake, below). Because several countries in the Americas fortify flour, but at varying levels, a technical consultation was convened by the Pan American Health Organization, the March of Dimes, and the CDC, in order to develop guidelines on fortification.[15] It was recommended[16] that all women of reproductive age consume 400 micrograms daily of synthetic folic acid in addition to dietary intake; a minimum additional intake of 200 micrograms daily of folic acid from fortified foods was proposed. A target mean intake of 1 microgram daily of vitamin B_{12} from food fortification was recommended in countries where data are consistent with vitamin B_{12} deficiency; this amount was considered sufficient since, unlike dietary sources of vitamin B_{12}, synthetic vitamin B_{12} is highly bioavailable.

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16. Allen LH, *et al.* Recommended levels of folic acid and vitamin B_{12} fortification: conclusions. *Nutr Rev* 2004; **62** (suppl): S62–S66.

Interactions

Folate deficiency states may be produced by drugs such as antiepileptics, oral contraceptives, antituberculous drugs, alcohol, glucarpidase, and folic acid antagonists such as methotrexate, pyrimethamine, triamterene, trimethoprim, and sulfonamides. In some instances, such as during methotrexate or antiepileptic therapy, replacement therapy with folinic acid or folic acid may become necessary in order to prevent megaloblastic anaemia developing; folate supplementation has reportedly decreased serum-phenytoin concentrations in a few cases (see Vitamins, p. 545.2) and there is a possibility that such an effect could also occur with barbiturate antiepileptics.

Antiepileptic-associated folate deficiency is discussed further under Effects on the Blood in Phenytoin, p. 540.2.

References.
1. Lambie DG, Johnson RH. Drugs and folate metabolism. *Drugs* 1985; **30**: 145–55.

Pharmacokinetics

Folic acid is rapidly absorbed from the gastrointestinal tract, mainly from the duodenum and jejunum. Dietary folates are stated to have about half the bioavailability of crystalline folic acid. The naturally occurring folate polyglutamates are largely deconjugated, and then reduced by dihydrofolate reductase in the intestines to form 5-methyltetrahydrofolate, which appears in the portal circulation, where it is extensively bound to plasma proteins. Folic acid given therapeutically enters the portal circulation largely unchanged, since it is a poor substrate for reduction by dihydrofolate reductase. It is converted to the metabolically active form 5-methyltetrahydrofolate in the plasma and liver.

The principal storage site of folate is the liver; it is also actively concentrated in the CSF.

Folate undergoes enterohepatic circulation. Folate metabolites are eliminated in the urine and folate in excess of body requirements is excreted unchanged in the urine. Folate is distributed into breast milk. Folic acid is removed by haemodialysis.

Human Requirements

Body stores of folate in healthy persons have been reported as being between 5 to 10 mg, but may be much higher. In the UK about 150 to 200 micrograms of folate daily is considered a suitable average intake for all healthy persons except women of child-bearing potential and pregnant women who require additional folic acid to protect against neural tube defects in their offspring (see p. 2064.3). In the US the recommended dietary allowance is 400 micrograms of dietary folate equivalents (see below) in both men and women. Folate is present, chiefly combined with several L(+)-glutamic acid moieties, in many foods, particularly liver, kidney, yeast, and leafy green vegetables. The vitamin is readily oxidised to unavailable forms and is easily destroyed during cooking.

UK and US recommended dietary intake. In the UK dietary reference values (see p. 2046.1) have been published for folate.[1] In the USA recommended dietary allowances (RDAs) had been set, and were reviewed[2] under the programme to set Dietary Reference Intakes (see p. 2046.1). Differing amounts are recommended for infants and children of varying ages, for adult males and females, and for pregnant and lactating women. In the UK the Reference Nutrient Intake (RNI) for adult males and females is 200 micrograms daily and the Estimated Average Requirement (EAR) is 150 micrograms daily. In the USA the RDA is expressed in terms of dietary folate equivalents (DFEs) where 1 microgram DFE is equivalent to 1 microgram folate from natural sources, 0.5 micrograms of a folic acid supplement taken on an empty stomach, or 0.6 micrograms of folic acid from fortified food or as a supplement taken with meals. An RDA of 400 micrograms DFE daily for adult men and women has been set; the EAR is 320 micrograms DFE daily and the tolerable upper intake level is 1 mg daily.

Folate requirements are increased during pregnancy; an RNI of 300 micrograms daily has been suggested for pregnant women in the UK and an RDA of 600 micrograms daily in the USA. In view of the value of folate in preventing neural tube defects, it is now recommended that women planning a pregnancy receive supplemental folic acid before conception and during the first trimester (see Neural Tube Defects, p. 2064.3). To increase the intake in women of child-bearing age, folic acid fortification (p. 2064.2) of grain-based foods has been adopted in the USA, and advocated in other countries including the UK. However, there remains some debate over the appropriate level of fortification to optimise prevention of neural tube defects and to minimise the risks of possible carcinogenicity, or of masking underlying vitamin B_{12} deficiency in the elderly (see Carcinogenicity and Vitamin B_{12} deficiency, p. 2065.3 and above, respectively).

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acifol; Anemidox Folico; Anfolic; Arisfolic; Azolac Folico; Bernafolic; Biolfolic; Coflic; Conacid; Dupofol; Edulsan Folic†; Egestan Folico; Folacina; Folaport; Foliagen; Folimax; Folinemic; Galfol; Gynofol; Livifol; *Medifol*; Nexovital Folico; *Ronfolic*; *Sojar* Folico; *Suprafol*; *Austral.*: Megafol; *Austria*: Folsan; *Belg.*: Folavit; *Braz.*: Afopic; Endofolin; Enfol; Femme Folico; Folacin; Folantine; Folifolin; Folital; Folonin; Hipofol; Materfolic Neo Folico; Pre-Folic; *Canad.*: Novo-Folacid; *Chile*: Folacid; Folifemin; Folisanin; Folvit; Miliser; *China*: Mei Tian Fu (美天福); Pa Lai Xin (帕莱欣); Si Li An (斯利安); *Denm.*: Folimet; *Fin.*: Foliver; Folvite; *Fr.*: Speciafoldine; *Ger.*: DreisaFol; Fol Injekt†; Fol Lichtenstein†; Folarell; Folcur†; Folgamma Mono†; Folsan; Folverlan; Gravi-Fol†; Lafol†; *Gr.*: Filicine; Folidex; *Hong Kong*: Uni-Folic†; *Hung.*: Feroglobin-B12; Folsav; Huma-Folacid; *India*: Afol; B-9; B-Fol; C-Fol; Chewfol; Cobal Forte; Cufol; Elfol; F-5; FA; Facitab; Ferich; Fericos-XT; FH-12; Flolica-OD; Fol-B; Fol; Folacin; Folaid; Folat; Folbit; Foldivit; Folet; Folib; Folicare; Foliday; Foliden; Folimac; Follmust; Folistar; Folitas; Folix; Foliz; Folneu; Folson; Folvite; Foly; Forich; Ptol; Globin; Ingafol; Lik; Momfol; Neofol; Nicofer-F; Nutrilic; Rubraplex; Vitafol; *Indon.*: Anelat; Folac; Folacite; Folacom; Folas; Folavit; Folaxin; Nufolic; *Irl.*: Clonfolic; Preconceive; *Israel*: Foli; *Ital.*: Fertifol; Folidex; Folina; Folingrav; Serengrav; *Mex.*: AF; Folivital; Materfol; Prinac Ac†; *Norw.*: Nycoplus Folsyre; *Philipp.*: Enhansid; Folacid; Folart; Foleq; Foliage; Folicard; Folicare; Folinc; Folisure; Maxifol; Purifol; *Pol.*: Acifolik; Folacid; Folifem; Folik; Folimin†; Folovit; *Port.*: Acfol; Dozefol; Folicil; Folidex; Fovital; *Rus.*: Folacin (Фолацин); Mamifol (Мамифол); *Spain*: Acfol; Bialfoli; Zolico; *Swed.*: Folacin; Folvidon; *Switz.*: Andreafol; Drossafol; Fertifol; Folvite; *Thai.*: Cebrin-Fe; F-Min; Foliamin; Folicare†; Folimed; Folivit; *Turk.*: Folbiol; *UAE*: Folicum; *UK*: Folicare; Lexpec; Preconceive; *Ukr.*: Folacin (Фолацин); Tifol (Тифол); Vitrum Folicum (ВитрумФоликум); *USA*: Folvite; *Venez.*: Afoklin; Folac.

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

Pharmacopoeial Preparations

BP 2014: Ferrous Fumarate and Folic Acid Tablets; Folic Acid Injection; Folic Acid Tablets;

USP 36: Folic Acid Injection; Folic Acid Tablets; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Tablets; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Folinic Acid *(BAN)*

Citrovorum Factor; Folínico, ácido; Leucovorin; Фолиновая Кислота.

5-Formyltetrahydropteroylglutamic acid; *N*-[4-(2-Amino-5-formyl-5,6,7,8-tetrahydro-4-hydroxypteridin-6-ylmethylamino)benzoyl]-L(+)-glutamic acid.

$C_{20}H_{23}N_7O_7$=473.4

CAS — 58-05-9.

UNII — QS7319DVLP.

Calcium Folinate *(BANM, rINN)*

Calcii Folinas; Calcii Folinas Hydricus; Calcium, folinate de; Calcium Folinate-SF; Calcium Leucovorin; Calciumfolinat; Folinate de Calcium; Folinato cálcico; Kalcio folinatas; Kalciumfolinat; Kalcium-folinát; Kalcium-folinát hydrát; Kalsiumfolinaatti; Kalsiyum Folinat; Kalsiyum Lökovorin; Leucovorin Calcium; NSC-3590; Кальция Фолинат.

The calcium salt of folinic acid (1:1).

$C_{20}H_{21}CaN_7O_7$=511.5

CAS — 1492-18-8 (anhydrous calcium folinate); 41927-89-3 (calcium folinate pentahydrate); 6035-45-6 (calcium folinate pentahydrate).
ATC — V03AF03.
ATC Vet — QV03AF03.
UNII — RPR1R4C0P4.

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

Chin. includes the pentahydrate ($C_{20}H_{21}CaN_7O_7$, $5H_2O$ = 601.6).

Ph. Eur. 8: (Calcium Folinate). A white or light yellow, amorphous or crystalline, hygroscopic powder. Sparingly soluble in water; practically insoluble in alcohol and in acetone. A 2.5% solution in water has a pH of 6.8 to 8.0. Store in airtight containers. Protect from light.

USP 36: (Leucovorin Calcium). A yellowish-white or yellow, odourless, powder. Very soluble in water; practically insoluble in alcohol. Protect from light.

Incompatibility. Calcium folinate and fluorouracil, with or without 5% glucose, were incompatible when mixed in various ratios and stored in PVC containers at various temperatures.[1]

1. Trissel LA, *et al.* **Incompatibility of fluorouracil with leucovorin calcium or levoleucovorin calcium.** *Am J Health-Syst Pharm* 1995; **52:** 710–15.

Calcium Levofolinate (BAN, rINN)

Calcii Levofolinas; Calcii levofolinas pentahydricus; Kalcio levofolinatas; Kalciumlevofolinat; Kalcium-levofolinát pentahydrát; Kalcium-levofolinát-pentahidrát; Kalciumlevofolinat-pentahydrat; Kalsiumlevofolinaatti; Kalsiumlevofolinaattipentahydraatti; Levofolinate; Lévofolinate calcique pentahydraté; Lévofolinate de Calcium; Levofolinato de calcio; Levoleucovorin Calcium (USAN); Кальция Левофолинат.

The calcium salt of the isomer of *S*-folinic acid (1:1).
$C_{20}H_{21}CaN_7O_7,5H_2O$=601.6
CAS — 80433-71-2 (anhydrous calcium levofolinate).
ATC — V03AF04.
ATC Vet — QV03AF04.
UNII — 778XL6VBS8.

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

Ph. Eur. 8: (Calcium Levofolinate Pentahydrate). A white or light yellow, amorphous or crystalline, hygroscopic powder. Slightly soluble in water; practically insoluble in alcohol and in acetone. A 0.8% solution in water has a pH of 7.5 to 8.5. Store in airtight containers. Protect from light.

Sodium Folinate

Dinatrium folinat; Disodium folinate (BANM); Natrium folinat; Натрия Фолинат.
$C_{20}H_{21}N_7O_7Na_2$=517.4
CAS — 42476-21-1 (monosodium folinate).
ATC — V03AF06.
ATC Vet — QV03AF06.
UNII — 4MXU9LJS4Q.

Uses and Administration

Folinic acid is the 5-formyl derivative of tetrahydrofolic acid, the active form of folic acid. Folinic acid is used principally as an antidote to folic acid antagonists, such as methotrexate (p. 826.3), which block the conversion of folic acid to tetrahydrofolate by binding the enzyme dihydrofolate reductase. It does not block the antimicrobial action of folate antagonists such as trimethoprim or pyrimethamine, but may reduce their haematological toxicities. It is also used as an adjunct to fluorouracil in the treatment of colorectal cancer.

Folinic acid is given as calcium or sodium folinate, although doses are stated in terms of folinic acid. 1.08 mg of anhydrous calcium folinate, 1.27 mg of calcium folinate pentahydrate, or 1.09 mg of sodium folinate are each equivalent to about 1 mg of folinic acid. Calcium folinate can be given orally, by intramuscular injection, by intravenous infusion, or by intravenous injection; Intravenous injections should be given over several minutes because of their calcium content; the maximum recommended rate is equivalent to folinic acid 160 mg/minute. It has been recommended that oral doses should not be greater than 25 to 50 mg, since absorption is saturable. Calcium levofolinate, the active laevo-isomer, is used similarly to calcium folinate; it is given in doses half those recommended for the racemic form. Sodium folinate is given by intravenous injection or infusion; sodium levofolinate is used similarly.

In cases of inadvertent **overdosage of a folic acid antagonist**, folinic acid should be given as soon as possible and preferably within the first hour. Doses equal to or greater than the dose of *methotrexate* have been recommended. Alternatively it has been stated that for large doses or overdoses of methotrexate, calcium folinate may be given by intravenous infusion in a dose equivalent to 75 mg of folinic acid within 12 hours, followed by 12 mg intramuscularly every 6 hours for 4 doses. Although *vincristine* is not a folic acid antagonist, folinic acid has also been proposed for some manifestations of vincristine toxicity overdosage—see p. 883.2.

Folinic acid is used with high-dose methotrexate antineoplastic therapy to reduce the toxicity of the methotrexate (**'folinic acid rescue'**; 'calcium leucovorin rescue'). Calcium folinate rescue is necessary when *methotrexate* is given at doses exceeding 500 mg/m² and should be considered with methotrexate doses of 100 to 500 mg/m². It may sometimes be considered in patients who have received lower doses.

Dosage and duration of folinic acid rescue must be adapted according to the methotrexate regimen and the patient's ability to clear the antineoplastic; many antineoplastic regimens include appropriate rescue protocols. In general, UK licensed product information recommends that the first dose of calcium folinate is the equivalent of 15 mg folinic acid (6 to 12 mg/m²) to be given 12 to 24 hours (usually the latter) after the beginning of methotrexate infusion. The same dose is given every 6 hours for 24 hours, initially by intramuscular injection or intravenous injection or infusion, but switching to the oral form after one or more parenteral doses. At the end of this time (48 hours after the start of the original methotrexate infusion) the residual methotrexate concentration should be measured. If this is *less* than a threshold concentration of 0.5 micromoles/litre, the same dose is continued usually for a further 48 hours. If it is *greater* than this value, further calcium folinate dosages should be adapted according to methotrexate concentration as follows, and given every 6 hours for a further 48 hours or until the serum-methotrexate concentration falls below 0.05 micromoles/litre (i.e. one-tenth of the threshold concentration):

- serum methotrexate > 0.5 micromoles/litre: calcium folinate equivalent to 15 mg/m² folinic acid
- serum methotrexate > 1 micromole/litre: calcium folinate equivalent to 100 mg/m² folinic acid
- serum methotrexate > 2 micromoles/litre: calcium folinate equivalent to 200 mg/m² folinic acid

The dose of sodium folinate in rescue therapy is also based on serum-methotrexate concentrations (as measured 24 to 30 hours after beginning methotrexate):

- serum methotrexate 0.01 to 1.5 micromoles/litre: sodium folinate equivalent to 10 to 15 mg/m² folinic acid every 6 hours for 48 hours
- serum methotrexate 1.5 to 5 micromoles/litre: sodium folinate equivalent to 30 mg/m² folinic acid every 6 hours until methotrexate concentration is less than 0.05 micromoles/litre
- serum methotrexate > 5 micromoles/litre: sodium folinate equivalent to 60 to 100 mg/m² folinic acid every 6 hours until methotrexate concentration is less than 0.05 micromoles/litre

In patients who have received doses of methotrexate below 100 mg, and in whom rescue therapy is considered appropriate, oral doses of folinic acid 15 mg every 6 hours for 48 to 72 hours may suffice.

In addition, measures to ensure the prompt excretion of methotrexate (maintenance of high urine output and alkalinisation of urine) are integral parts of rescue treatment. Renal function should be monitored daily.

To prevent *trimetrexate* toxicity, folinic acid is given during treatment and for 72 hours after the last trimetrexate dose. A usual dose is folinic acid 20 mg/m² given every 6 hours, either orally or by intravenous injection over 5 to 10 minutes; daily doses are adjusted according to toxicity. In trimetrexate toxicity (such as may occur when folinic acid has not been given with high trimetrexate doses), intravenous folinic acid can be given after trimetrexate has been stopped, in a dose of 40 mg/m² every 6 hours for 3 days.

For *trimethoprim* toxicity, folinic acid 3 to 10 mg daily is given intravenously or intramuscularly after the drug is stopped, until blood counts recover.

For *pyrimethamine* toxicity (such as may occur with prolonged low-dose therapy or with high doses), folinic acid 5 to 50 mg daily intravenously or intramuscularly is given during treatment, and adjusted according to blood counts.

Folinic acid is also used **with fluorouracil** to enhance the cytotoxic effect in advanced colorectal cancer. Both high-dose regimens (typically doses of folinic acid 200 mg/m², followed by fluorouracil) and low-dose regimens (20 mg/m²) have been used—for details, see Uses and Administration of Fluorouracil, p. 795.3. Sodium folinate has been used in similar doses. It may also be given at a dose equivalent to folinic acid 500 mg/m² by intravenous infusion over 2 hours. An intravenous injection of fluorouracil 600 mg/m² is given one hour after the start of the folinate infusion. Alternatively, a continuous infusion of fluorouracil 2.6 g/m² is given for 24 hours after the sodium folinate dose. Treatment is given weekly for 6 weeks, and may then be repeated after a 2-week interval; the number of cycles depends on the response of the tumour.

Folinic acid, like folic acid, is effective in the treatment of folate-deficient **megaloblastic anaemia** (see p. 2109.1). Oral doses of 15 mg daily have been suggested. If given intramuscularly a dose of up to 1 mg daily has been recommended on the grounds that higher doses have not been proven to be any more effective. It is unsuitable for megaloblastic anaemia secondary to vitamin-B_{12} deficiencies.

Cardiovascular disease. For a report of the use of intravenous folinic acid to reduce levels of homocysteine in haemodialysis patients, see Cardiovascular Disease, under Folic Acid, p. 2063.3.

Deficiency states. Cerebral folate deficiency has been defined as any neurological syndrome associated with low CSF concentrations of 5-methyltetrahydrofolate, the active metabolite of folic acid.[1-3] Neurodevelopmental disorders have been associated with this deficiency, manifest as irritability, sleep disturbances, cerebellar ataxia, spastic paraplegia, dyskinesia, epileptic seizures, and speech difficulties. Dramatic improvements in some symptoms have been noted with oral folinic acid;[1,2,4] 0.5 to 1 mg/kg folinic acid daily has been used.[1] Analysis of CSF folate metabolites is recommended for patients presenting with movement disorders, mental retardation, or autism.[2,4]

1. Ramaekers VT, Blau N. **Cerebral folate deficiency.** *Dev Med Child Neurol* 2004; **46:** 843–51.
2. Hansen FJ, Blau N. **Cerebral folate deficiency: life-changing supplementation with folinic acid.** *Mol Genet Metab* 2005; **84:** 371–3.
3. Gordon N. **Cerebral folate deficiency.** *Dev Med Child Neurol* 2009; **51:** 180–2.
4. Moretti P, *et al.* **Cerebral folate deficiency with developmental delay, autism, and response to folinic acid.** *Neurology* 2005; **64:** 1088–90.

HIV infection and AIDS. Calcium folinate has been used to reduce the toxicity of pyrimethamine and trimethoprim in patients with HIV infection. However, oral calcium folinate given to patients with AIDS receiving co-trimoxazole for the treatment of pneumocystis pneumonia was associated with a higher rate of therapeutic failure and a decrease in survival and did not reduce the frequency of dose-limiting co-trimoxazole toxicity.[1] Calcium folinate also did not reduce the toxicity of co-trimoxazole being used for the primary prophylaxis of PCP.[2] Vitamin B_{12} and folinic acid supplementation in patients with HIV infection did not prevent or reduce zidovudine-induced myelosuppression.[3]

1. Safrin S, *et al.* **Adjunctive folinic acid with trimethoprim-sulfamethoxazole for Pneumocystis carinii pneumonia in AIDS patients is associated with an increased risk of therapeutic failure and death.** *J Infect Dis* 1994; **170:** 912–17.
2. Bozzette SA, *et al.* **The tolerance for zidovudine plus thrice weekly or daily trimethoprim-sulfamethoxazole with and without leucovorin for primary prophylaxis in advanced HIV disease.** *Am J Med* 1995; **98:** 177–82.
3. Falguera M, *et al.* **Study of the role of vitamin B_{12} and folinic acid supplementation in preventing hematologic toxicity of zidovudine.** *Eur J Haematol* 1995; **55:** 97–102.

Adverse Effects

Occasional hypersensitivity, including anaphylactic reactions, has been reported; pyrexia has occurred rarely after injections. Gastrointestinal disturbances, insomnia, agitation, and depression have been reported rarely, after high doses.

Precautions

As for Folic Acid, p. 2065.3.

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

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

As for Folic Acid, p. 2066.2.

Folinic acid should not be used with a folic acid antagonist such as methotrexate unless the intention is to nullify the effect of the antagonist. It should not be given within 2 hours of a dose of glucarpidase, see p. 1555.2. Folinic acid enhances the toxicity, as well as the antineoplastic action, of fluorouracil, especially on the gastrointestinal tract.

Antineoplastics. For the suggestion of an interaction between *capecitabine* and intracellularly retained folate when capecitabine was given after a regimen of fluorouracil and folinic acid, see Administration, under Capecitabine, p. 758.1.

Pharmacokinetics

Calcium folinate is well absorbed after oral and intramuscular doses and, unlike folic acid (p. 2066.2), is rapidly converted to biologically active folates. The oral absorption of calcium folinate is saturable, with a bioavallability of about 97% for a 25 mg dose, 75% for 50 mg, and 37% for 100 mg. Peak plasma concentrations of folinic acid occur about 10 minutes after an intravenous dose; systemic availability is similar with intramuscular doses but peak serum concentrations are lower. Sodium folinate is considered to be bioequivalent to calcium folinate. Folate is concentrated in the liver and CSF although distribution occurs to all body tissues. The major metabolite of folinic acid is 5-methyl-tetrahydrofolic acid which is mainly produced in the liver and intestinal mucosa. The total terminal half-life of the active metabolites of parenteral calcium folinate is about 6 hours. Folates are mainly excreted in the urine, with small amounts in the faeces.

References.
1. McGuire BW, *et al.* Pharmacokinetics of leucovorin calcium after intravenous, intramuscular, and oral administration. *Clin Pharm* 1988; 7: 52–8.
2. Wolfrom C, *et al.* Pharmacokinetic study of methotrexate, folinic acid and their serum metabolites in children treated with high-dose methotrexate and leucovorin rescue. *Eur J Clin Pharmacol* 1990; 39: 377–83.
3. Zittoun J, *et al.* Pharmacokinetic comparison of leucovorin and levokeucovorin. *Eur J Clin Pharmacol* 1993; 44: 569–73.
4. Mader RM, *et al.* Pharmacokinetics of rac-leucovorin vs [S]-leucovorin in patients with advanced gastrointestinal cancer. *Br J Clin Pharmacol* 1994; 37: 243–8.
5. Schmitz JC, *et al.* Disposition of folic acid and its metabolites: a comparison with leucovorin. *Clin Pharmacol Ther* 1994; 55: 501–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Asovorin; Elvefocal†; Estroquin; Folinfabra; Leucocalcin; Novizet; Rontafort†; *Austria*: POLI-Cell†; Sodiofolin†; *Belg.*: Elvorine; Folina-Cell†; Levofolic; Rescuvolin; VoriNa; *Braz.*: Fauldleuco; Folicorin; Glencovorin; Legifol CS; Levorin; Prevax; Tecnovorin; Tevafolin; *Canad.*: Folacal; *Chile*: Covorit; *China*: Ai Jie Kang (爱捷康); Ai Ru Xi (爱汝昔); Antrex (安迪希); Fu Neng (福能); Gai Er Qing (盖尔青); Kang Da Li Ping (康达利平); Kang Lai Er (康莱尔); Li Lei Te (力雷特); Likelin (立可林); Lu Wei Fen (路维芬); Ou Li (欧力); Quefuli (瑰呋力); Rescuvolin (惠仁复林); Shiming (世明); Si Min Le (司敏乐); Tong Ao (阿奥); Ya Fu Xin (亚复欣); *Cz.*: Levofolic; VoriNa; *Denm.*: Isovorin; *Fin.*: Antrex; Isovorin; Levofolic; *Fr.*: Elvorine; Folinoral; Lederfoline; Osfolate†; *Ger.*: Axifolin; Bendafolin; DeGalin; FOLI-Cell; Haemato-folin; Lederfolat; Neofolin†; Oncofolic; Rescuvolin; Ribofolin; Ribosofol; VoriNa; *Gr.*: Buateron; Calcifolin; Calcivoran; Claro; Durofolin; Esvorin; Fedolen; Folical; Foliment; Folinacid; Folinato; Folivoran; Folmigor; Foxolin; Isovorin; Levofolic; Lizocalcio; Osimol; Refolinon; Reotan; Rescuvolin; Sanficinate; Sanovein; Veravorin; Vivalcid; Zamenit; Zenemia; *Hong Kong*: Calciumfolinat; *Hung.*: VoriNa†; *India*: Biovorin; Cafonate; CCM; Covorin; Dalisol; Fastovorin; Leucorin; Lucal; Nyrin; *Indon.*: Rescuvolin; *Irl.*: Folicid; Lederfolin†; Sodiofolin; VoriNa; *Israel*: Calciumfolinat; *Ital.*: Calcifolin; Calfolex; Calinat†; Citofolin; Divifolin; Ecofol; Folanemin; Folaren; Foliben; Folidar; Lederfolin; Levofolene; Osfolato; Sanifolin; Sulton; Tonofolin; *Jpn*: Uzel; *Malaysia*: Nyrin†; Rescuvolin; *Mex.*: Dalisol†; Ifavor†; Medsavorina; Precileudin; *Neth.*: Ebefolin†; Rescuvolin; Ribofolin†; VoriNa; *Norw.*: Isovorin†; *Philipp.*: Folinoxan†; Litacor; Lovorin; Rescuvolin; VoriNa; *Pol.*: Levofolic; *Port.*: FOLI-Cell; Folinovo; Isovorin; Lederfoline; Levofolic; Medifolin; Raycept; Sodiofolin; VoriNa†; *Rus.*: Natriofoline (Натриофолин); *S.Afr.*: Isovorin; Rescuvolin; *Singapore*: Nyrin; Rescuvolin; *Spain*: Cromatonbic Folinico; Folaxin; Folidan†; Isovorin; Lederfolin; Sodiofolin†; *Swed.*: Isovorin; *Thai.*: Cafonate; Dalisol; Folina†; Rescuvolin; *Turk.*: Antrex†; Rescuvolin; *UK*: Isovorin; Refolinon; Sodiofolin; *USA*: Pusilev; *Venez.*: Leuconolver.

Multi-ingredient Preparations. *Gr.*: Pysiofol; Legofolin; *Ital.*: Carfosid; Emopon; Eparmefolin; Ferritin Complex; Ferrofolin; Hepa-Factor; Linfofiu; *Rus.*: Feriatum Fol (Ферлатум Фол); *Turk.*: Komfer Fol.

Pharmacopoeial Preparations
BP 2014: Calcium Folinate Injection; Calcium Folinate Tablets;
USP 36: Leucovorin Calcium Injection; Leucovorin Calcium Tablets.

Folitixorin *(rINN)*

Folitixorina; Folitixorine; Folitixorinum; 5,10-Methylenetetrahydrofolate; 5,10-Methylenetetrahydrofolic acid; Tetrahydromethylenefolate; Фолитиксорин.

N-[4-[[(6a*RS*)-3-Amino-1-oxo-1,4,5,6,6a,7-hexhydroimidazo[1,5-f]pteridin-8(9*H*)-yl]benzoyl]-L-glutamic acid.

$C_{20}H_{23}N_7O_6$=457.4.

CAS — 3432-99-3.

UNII — 0SXY5ET48B.

Profile

Folitixorin is an active metabolite of folinic acid. It is under investigation for use with fluorouracil in the treatment of pancreatic cancer and metastatic colorectal cancer.

Fructose

Azúcar de fruta; D-Fructosa; Fructosa; D-Fructose; Fructosum; Fruit Sugar; Fruktoosi; Fruktos; Fruktosa; Fruktoze; Fruktóz; Fruktoza; Laevulose; Laevulosum; Levulosa; Levulose; Фруктоза.

D-(-)-Fructopyranose.

$C_6H_{12}O_6$=180.2

CAS — 57-48-7.

ATC — V06DC02.

ATC Vet — QV06DC02.

UNII — 6YSS42VSEV (fructose); XY6UN3QB6S (high fructose corn syrup).

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

USNF includes High Fructose Corn Syrup.

Ph. Eur. 8: (Fructose). A white or almost white, crystalline powder with a very sweet taste. Very soluble in water; soluble in alcohol.

USP 36: (Fructose). Colourless crystals or a white crystalline powder. Is odourless and has a sweet taste. Freely soluble in water; soluble 1 in 15 of alcohol and 1 in 14 of methyl alcohol.

USNF 31: (High Fructose Corn Syrup). A sweet, nutritive saccharide mixture prepared as a clear, aqueous solution from high-glucose-equivalent corn starch hydrolysate by the partial enzymatic conversion of glucose to fructose, using an insoluble glucose isomerase enzyme preparation. It is available in two types, 42% and 55%, based on fructose content. Store in airtight containers.

Uses and Administration

Fructose is sweeter than sucrose or sorbitol. It is used as a sweetener in foods for diabetics (although it is not clear it offers any advantage over sucrose); in the UK it has been advised that the intake of fructose be limited to 25 g daily in persons with diabetes mellitus.

Fructose has been used as an alternative to glucose in parenteral nutrition but its use is not recommended because of the risk of lactic acidosis. Use by intravenous infusion in the treatment of severe alcohol poisoning is also no longer recommended.

Solutions of fructose with glucose have been used in the treatment of nausea and vomiting (p. 1811.3) including vomiting of pregnancy. Fructose is also used as a dissolution enhancer and tablet diluent in pharmaceuticals.

Pain. Oral fructose solution was considered to be as effective as oral glucose solution (p. 2069.3) in alleviating mild pain in neonates.[1]

1. Akçam M. Oral fructose solution as an analgesic in the newborn: a randomized, placebo-controlled and masked study. *Pediatr Int* 2004; 46: 459–62.

Adverse Effects

Large oral doses of fructose may cause flatulence, abdominal pain, and diarrhoea. Lactic acidosis and hyperuricaemia may follow intravenous infusions; fatalities have occurred.

Effects on metabolism. Fructose may increase serum concentrations of uric acid, especially in those with existing *hyperuricaemia* or gout. A large cohort study found that consumption of fructose was associated with an increased risk of gout in men. Fructose-rich fruits or fruit juice may also increase the risk.[1] It has been pointed out that fructose intake has increased in the USA, where soft drinks are usually sweetened with high fructose corn syrup (also known as isoglucose), whereas elsewhere they tend to be sweetened with sucrose.[2] The potential adverse metabolic effects of dietary fructose intake on *serum lipids*, and whether such intake is associated with the metabolic syndrome and a disproportionate risk of hyperlipidaemia, obesity, and consequent diabetes mellitus has been repeatedly reviewed,[3-10] although definitive evidence seems to be lacking.

1. Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ* 2008; 336: 309–12.
2. Underwood M. Sugary drinks, fruit, and increased risk of gout. *BMJ* 2008; 336: 285–6.
3. Bray GA. Fructose: should we worry? *Int J Obes (Lond)* 2008; 32 (suppl 7): S127–S131.
4. Angelopoulos TJ, *et al.* The effect of high-fructose corn syrup consumption on triglycerides and uric acid. *J Nutr* 2009; 139: 1242S–1245S.
5. Johnson RJ, *et al.* Hypothesis: could excessive fructose intake and uric acid cause type 2 diabetes? *Endocr Rev* 2009; 30: 96–116.
6. Schaefer EJ, *et al.* Dietary fructose and glucose differentially affect lipid and glucose homeostasis. *J Nutr* 2009; 139: 1257S–1262S.
7. Dolan LC, *et al.* Evidence-based review on the effect of normal dietary consumption of fructose on development of hyperlipidemia and obesity in healthy, normal weight individuals. *Crit Rev Food Sci Nutr* 2010; 50: 53–84.
8. Bray GA. Soft drink consumption and obesity: it is all about fructose. *Curr Opin Lipidol* 2010; 21: 51–7.
9. Tappy L, Lê KA. Metabolic effects of fructose and the worldwide increase in obesity. *Physiol Rev* 2010; 90: 23–46.
10. Stanhope KL, Havel PJ. Fructose consumption: recent results and their potential implications. *Ann N Y Acad Sci* 2010; 1190: 15–24.

Hypersensitivity. Urticaria associated with the ingestion of certain foods by a patient was found to be caused by D-psicose, a minor constituent of the sweetener, high-fructose syrup.[1]

1. Nishioka K, *et al.* Urticaria induced by D-psicose. *Lancet* 1983; ii: 1417–18.

Precautions

Fructose should not be given to patients with hereditary fructose intolerance.

It should be given with caution to patients with impaired kidney function or severe liver damage.

Intravenous administration. Reiterations of the view that the use of intravenous infusions containing fructose and sorbitol, which remained popular in some countries, should be abandoned.[1,2] Not only could they lead to life-threatening build-up of lactic acid, they had led to fatalities in patients with undiagnosed hereditary fructose intolerance.

1. Collins J. Time for fructose solutions to go. *Lancet* 1993; 341: 600.
2. CSM/MCA. Reminder: fructose and sorbitol containing parenteral solutions should not be used. *Current Problems* 2001; 27: 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 21/07/08)

Pharmacokinetics

Fructose is absorbed from the gastrointestinal tract but more slowly than glucose. It is metabolised more rapidly than glucose, mainly in the liver where it is phosphorylated and a part is converted to glucose; other metabolites include lactic acid and pyruvic acid. Although the metabolism of fructose is not dependent on insulin, and insulin is not considered necessary for its removal from the blood, glucose is a metabolic product of fructose and requires the presence of insulin for its further metabolism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Feng Hai Neng (丰海能); Gan Le Li (甘乐力); Hu Chuan (护川); Pu Li Kang (普利康); Wei Bei Xian (韦贝仙); Xing Ya (星雅); *Hung.*: Fructosol; *Ital.*: Fructan; Fructofin; Fructosil.

Multi-ingredient Preparations. *Arg.*: Azodac; High Energy; *Braz.*: Biofructose; Caviamina†; Dramin B6 DL; Energivit; Energoplex; Enervit; Frutoplex; Frutovena; Neo Cebetil; *Canad.*: Pediatric Electrolyte; *China*: Bu Rui De (布瑞得); Peng Hai Ping (丰海平); Ganruining (甘瑞宁); Hai Si Wei (海斯维); Nai Neng (耐能); Rui Qin Yuan (瑞泰源); Ying Fan Shu (英凡舒); *Fr.*: Filigel†; *India*: Maxoza; *Indon.*: Gastro-Ad†; Trifluid; *Irl.*: Rehidrat†; *Israel*: Peptical; *Ital.*: Api Baby; Eparema-Levul; Liozim; Litostop; Nerex; Nutrigel; The Ginseng King†; *Jpn*: Trifluid; Triparen; *USA*: Emetrol; Formula EM; Nausatrol; Nausetrol.

Pharmacopoeial Preparations
BP 2014: Fructose Infusion;
USP 36: Fructose and Sodium Chloride Injection; Fructose Injection.

Gleptoferron *(BAN, USAN, rINN)*

Gleptoferrón; Gleptoferronum; Iron Heptonate; Гептоферрон.

$C_7H_{14}O_8(C_6H_{10}O_5)_nFeOOH$

CAS — 57680-55-4.

ATC Vet — QB03AC91.

UNII — 898723IQHQ.

Profile

Gleptoferron is a macromolecular complex of ferric hydroxide and dextran-glucoheptonic acid. It is used for iron-deficiency anaemia in veterinary medicine. It is given by intramuscular injection.

Glucose

Glucosa; Glukoz; Glukoza; Глюкоза; Декстроза.

ATC — B05CX01; V04CA02; V06DC01.

ATC Vet — QB05CX01; QV04CA02; QV06DC01.

Anhydrous Glucose

Anhydrous Dextrose; Dextrosa anhidra; Dextrosum Anhydricum; Gliukozė, bevandenė; Glucosa anhidra; D-Glucose; Glucose anhydre; Glucosum; Glucosum anhydricum; Glukoosi, vedetön; Glukos, vattenfri; Glukosa; Glukoza bezvodna; Vízmentes glükóz; Безводная Глюкоза.

D-(+)-Glucopyranose.

$C_6H_{12}O_6$=180.2

CAS — 50-99-7.

UNII — 5SL0G7R0OK (anhydrous dextrose); IY9XDZ35W2 (dextrose).

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

Some pharmacopoeias include anhydrous glucose and/or glucose monohydrate as separate monographs whereas others permit the anhydrous and/or monohydrate under a single monograph.

Ph. Eur. 8: (Glucose, Anhydrous). A white or almost white, crystalline powder with a sweet taste. Freely soluble in water; sparingly soluble in alcohol.

The BP 2014 directs that when Glucose Intravenous Infusion is required as a diluent for official injections or intravenous infusions, Glucose Intravenous Infusion 5% should be used.

USP 36: (Dextrose). It contains one molecule of water of hydration or is anhydrous. Colourless crystals or white, crystalline or granular powder. It is odourless and has a sweet taste. Soluble 1 in 1 of water and 1 in 100 of alcohol; very soluble in boiling water; soluble in boiling alcohol.

Glucose Monohydrate

Dekstroz Monohidrat; Dextrosa monohidrato; Dextrosum Monohydridicum; Gliukozė monohidratas; D-Glucosa monohidrato; Glucosa monohidrato; Glucose-Monohydrat; D-Glucose Monohydrate; Glucose monohydraté; Glucosum monohydricum; Glukoosimonohydraatti; Glukosa monohydrát; Glukosmonohydrat; Glükóz-monohidrát; Glycosum; Grape Sugar; Глюкоза Моногидрат.

D-(+)-Glucopyranose monohydrate.

$C_6H_{12}O_6.H_2O$=198.2

CAS — 5996-10-1 (glucose monohydrate); 14431-43-7 (glucose monohydrate); 8027-56-3 (liquid glucose).

UNII — IY9XDZ35W2 (dextrose); LX22YL083G (dextrose monohydrate).

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

Some pharmacopoeias include anhydrous glucose and/or glucose monohydrate as separate monographs whereas others permit the anhydrous and/or monohydrate under a single monograph.

Eur. includes Glucose, Liquid and Glucose, Liquid, Spray-dried. *USNF* includes Dextrose Excipient, Liquid Glucose, Corn Syrup, and Corn Syrup Solids.

Ph. Eur. 8: (Glucose Monohydrate; Glucose BP 2014). A white or almost white crystalline powder with a sweet taste. Freely soluble in water; sparingly soluble in alcohol.

Ph. Eur. 8: (Glucose, Liquid). A clear, colourless, or brown viscous liquid containing a mixture of glucose, oligosaccharides, and polysaccharides obtained by hydrolysis of starch, in aqueous solution. It contains not less than 70.0% of dry matter. Miscible with water. It may partly or totally solidify at room temperature, liquefying again on heating to 50 degrees.

Ph. Eur. 8: (Glucose, Liquid, Spray-dried). A white or almost white, slightly hygroscopic powder or granules. Freely soluble in water.

USP 36: (Dextrose). It contains one molecule of water of hydration or is anhydrous. Colourless crystals or white, crystalline or granular powder. It is odourless and has a sweet taste. Soluble 1 in 1 of water and 1 in 100 of alcohol; very soluble in boiling water; soluble in boiling alcohol.

USNF 31: (Dextrose Excipient). A sugar usually obtained by hydrolysis of starch. It contains one molecule of water of hydration. Colourless crystals or white, crystalline or granular powder. Freely soluble in water; very soluble in boiling water; slightly soluble in alcohol; sparingly soluble in boiling alcohol.

USNF 31: (Liquid Glucose). It is obtained by incomplete hydrolysis of starch; it consists chiefly of glucose, dextrins, maltose, and water. It is a colourless or yellowish, thick, syrupy, odourless or nearly odourless liquid. Miscible with water; sparingly soluble in alcohol.

USNF 31: (Corn Syrup). An aqueous solution of saccharides obtained by partial hydrolysis of edible corn starch by food grade acids and/or enzymes. It contains not less than 20% reducing sugar content (dextrose equivalent) expressed as D-glucose, calculated on the dried basis. A clear, white to light yellow, viscous liquid. Miscible in all proportions with water. Store in airtight containers.

USNF 31: (Corn Syrup Solids; Dried Glucose Syrup). A dried mixture of saccharides obtained by partial hydrolysis of edible corn starch by food grade acids and/or enzymes. It contains not less than 20% reducing sugar content (dextrose equivalent) expressed as D-glucose, calculated on the dried basis. A sweet, white to light yellow powder or granules. Soluble in water. Store in airtight containers at a temperature of 8 degrees to 15 degrees.

Uses and Administration

Glucose, a monosaccharide, is given orally or by intravenous infusion in the treatment of carbohydrate and fluid depletion. It is the preferred source of carbohydrate in parenteral nutrition regimens (p. 2044.1) and is used in oral rehydration solutions (p. 1780.1) for the prevention and treatment of dehydration due to acute diarrhoeal diseases (p. 1805.2).

Glucose is also used in the treatment of hypoglycaemia (see below) and is given orally in the glucose tolerance test as a diagnostic aid for diabetes mellitus (see p. 458.3).

The way in which the strengths of glucose solutions for intravenous use are expressed varies in different countries. Glucose Intravenous Infusion (BP 2014) may be prepared from either anhydrous glucose or glucose monohydrate but the potency is expressed in terms of anhydrous glucose whereas Dextrose Injection (USP 36) is prepared from glucose monohydrate and potency is expressed in terms of the monohydrate. Anhydrous glucose 900 mg is equivalent to about 1 g of glucose monohydrate. Thus, the term glucose 5% may represent, depending on origin, either 50 g/litre of anhydrous glucose (equivalent to about 55 g/litre of glucose monohydrate) or 50 g/litre of glucose monohydrate (equivalent to about 45 g/litre of anhydrous glucose). As the manner in which such preparations are referred to in the medical literature is sometimes ambiguous, it has not always been possible to state clearly in *Martindale* whether the strengths of glucose solutions mentioned relate to the anhydrous or hydrated form; however, in *Martindale*, unless otherwise specified, glucose injection is a 5% solution to distinguish it from more concentrated forms. For many practical purposes it is probably less important to know the exact way in which the strength of a given concentration is expressed than to avoid confusion between completely different strengths such as 5, 10, and 50% as the more concentrated forms are associated with particular adverse effects and precautions.

Solutions of glucose in water are iso-osmotic with blood at a concentration of anhydrous glucose 5.05% or glucose monohydrate 5.51%. Glucose solution 5% is therefore the strength often employed for fluid depletion; it may be given via a peripheral vein. Glucose solutions with a concentration greater than 5% are hyperosmotic and are generally used as a carbohydrate source; a 50% solution is often used in the treatment of severe hypoglycaemia (but see also Hypoglycaemia, below). Hyperosmotic solutions should generally be given via a central vein although the *American Hospital Formulary Service* suggests that concentrations up to 10% may be given via a large peripheral vein, with the injection site alternated daily if possible. In the emergency treatment of hypoglycaemia it may be necessary to use a peripheral vein but the solution should be given slowly; a suggested rate for glucose 50% in such circumstances is 3 mL/minute.

The dose of glucose is variable and is dependent on individual patient requirements; serum-glucose concentrations may need to be carefully monitored. The maximum rate of glucose utilisation has been estimated to be about 500 to 800 mg/kg per hour.

Strongly hyperosmotic glucose solutions (25 to 50%) have also been given to reduce cerebrospinal pressure see Raised Intracranial Pressure, (p. 1271.3) and cerebral oedema caused by delirium tremens or acute alcohol intoxication (see p. 1734.1) although they do not appear to be widely used. Glucose solution (25 to 50%) has also been used as a sclerosing agent in the treatment of varicose veins (p. 2564.1) and as an irritant to produce adhesive pleuritis in the management of pleural effusions and pneumothorax. Liquid glucose is used as a sweetener, binder, or granulating and coating agent in pharmaceuticals.

Ectopic pregnancy. Ectopic pregnancy is now recognised at earlier stages as a result of improved diagnostic techniques. Surgery remains the mainstay of treatment, but although conservative surgical techniques may be used in an attempt to preserve fertility, nonsurgical methods have been increasingly investigated. The best established therapy is with methotrexate (p. 823.3), but hyperosmolar glucose solutions have also been used. Local instillation of 5 to 20 mL of glucose 50% into the gestational sac (salpingocentesis) has been described.[1] It was reported to be more effective than expectant management of early tubal pregnancy[2] but another study was stopped because of a higher failure rate with glucose than local methotrexate.[3]

1. Nanofsky JG, *et al.* Ultrasound-guided injection of ectopic pregnancy. *Clin Obstet Gynecol* 1999; **42**: 39–47.
2. Lang PFJ, *et al.* Laparoscopic instillation of hyperosmolar glucose vs. expectant management of tubal pregnancies with serum hCG≤2500 mIU/mL. *Acta Obstet Gynecol Scand* 1997; **76**: 797–800.
3. Sadan O, *et al.* Methotrexate versus hyperosmolar glucose in the treatment of extrauterine pregnancy. *Arch Gynecol Obstet* 2001; **265**: 82–4.

Glycogen storage disease type I. Starch may be a more acceptable alternative to glucose in the control of the hypoglycaemia of type I glycogen storage disease, see p. 2095.3.

Haemodialysis-induced cramp. Suggestions that haemodialysis-induced cramps (p. 1779.3) are due to hypovolaemia are supported by the efficacy of volume expansion with hypertonic solutions in the management of such cramps. Intravenous infusion of 50 mL of glucose 50% solution has been used as an effective alternative to infusion of sodium chloride or mannitol.[1,2]

1. Milutinovich J, *et al.* Effect of hypertonic glucose on the muscular cramps of hemodialysis. *Ann Intern Med* 1979; **90**: 926–8.
2. Canzanello VJ, *et al.* Comparison of 50% dextrose water, 25% mannitol, and 23.5% saline for the treatment of hemodialysis-associated muscle cramps. *Trans Am Soc Artif Intern Organs* 1991; **37**: 649–52.

Hyperkalaemia. Insulin, together with glucose to prevent hypoglycaemia, is given to stimulate the cellular uptake of potassium in the emergency treatment of moderate to severe hyperkalaemia (p. 1777.1). Usually, 50 mL of glucose 50% is given.

Hypoglycaemia. Glucose is used to correct insulin-induced hypoglycaemia, as discussed on p. 484.3, either orally or by infusion of a hypertonic solution (20 or 50%). Glucose 5 or 10% may be used but larger volumes are required. Although 50% glucose solution has been generally used to correct hypoglycaemia in children, some consider that so concentrated a solution is associated with unacceptable morbidity and possible mortality, and that it should be replaced by the 10% solution for this purpose.[1] The *BNFC* recommends use of 5 mL/kg of glucose 10% intravenous infusion, given with care and through a large-gauge needle into a large vein; it states that a 50% solution of glucose should not be used, as it is very viscous and hypertonic. A 5 or 10% solution is used to prevent the hypoglycaemia associated with insulin infusion for the treatment of diabetic ketoacidosis, once blood-glucose concentrations have fallen to an acceptable level (see Diabetic Emergencies, p. 465.3).

1. Winrow AP, *et al.* Paediatric resuscitation: don't use 50% dextrose. *BMJ* 1993; **306**: 1612.

Myocardial infarction. The value of a glucose, insulin, and potassium combination in patients with myocardial infarction has been investigated (see p. 482.3).

Pain. Oral glucose solution or spray has been used similarly to sucrose solution (p. 2097.1) to alleviate mild pain in neonates,[1-6] and there is some suggestion it may be more effective than topically applied local anaesthetic, or an opioid.[6,7]

Glucose solutions have been injected for prolotherapy (the local injection of irritant solutions to stimulate proliferation)[8,9] in the management of painful musculoskeletal conditions such as low back pain[9] and groin strain.[10] The value of such treatment has been disputed.

1. Skogsdal Y, *et al.* Analgesia in newborns given oral glucose. *Acta Paediatr Scand* 1997; **86**: 217–20.
2. Carbajal R, *et al.* Randomised trial of analgesic effects of sucrose, glucose, and pacifiers in term neonates. *BMJ* 1999; **319**: 1393–7.
3. Carbajal R, *et al.* Crossover trial of analgesic efficacy of glucose and pacifier in very preterm neonates during subcutaneous injections. *Pediatrics* 2002; **110**: 389–93.
4. Akçam M, Örmeci AR. Oral hypertonic glucose spray: a practical alternative for analgesia in the newborn. *Acta Paediatr* 2004; **93**: 1330–3.
5. Thyr M, *et al.* Oral glucose as an analgesic to reduce infant distress following immunization at the age of 3, 5 and 12 months. *Acta Paediatr* 2007; **96**: 233–6.
6. Axelin A, *et al.* Oral glucose and parental holding preferable to opioid in pain management in preterm infants. *Clin J Pain* 2009; **25**: 138–45.
7. Gradin M, *et al.* Pain reduction at venipuncture in newborns: oral glucose compared with local anesthetic cream. *Pediatrics* 2002; **110**: 1053–7.
8. Rabago D, *et al.* A systematic review of prolotherapy for chronic musculoskeletal pain. *Clin J Sport Med* 2005; **15**: 376–80.
9. Dagenais S, *et al.* Prolotherapy injections for chronic low-back pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 23/06/08).
10. Topol GA, *et al.* Efficacy of dextrose prolotherapy in elite male kicking-sport athletes with chronic groin pain. *Arch Phys Med Rehabil* 2005; **86**: 697–702.

Adverse Effects and Precautions

Intravenous glucose solutions (particularly hyperosmotic solutions, which also have a low pH) may cause local pain, vein irritation, and thrombophlebitis, and tissue necrosis if extravasation occurs. Some of these reactions may be due to degradation products present after autoclaving or to poor

technique in giving the solution. Intravenous infusion can lead to fluid and electrolyte disturbances including hypokalaemia, hypomagnesaemia, and hypophosphataemia. Prolonged or rapid infusion of large volumes of isosmotic solutions may cause oedema or water intoxication; conversely, prolonged or rapid use of hyperosmotic solutions may result in dehydration as a consequence of the induced hyperglycaemia.

The use of hyperosmotic glucose solutions is contra-indicated in patients with anuria, intracranial or intraspinal haemorrhage, and in delirium tremens where there is dehydration. They should be used with caution in patients with diabetes mellitus, as rapid infusion can lead to hyperglycaemia, as well as in those with malnutrition, thiamine deficiency, carbohydrate intolerance, sepsis, shock, or trauma.

It has been suggested that glucose solutions should not be used after acute ischaemic strokes as hyperglycaemia has been implicated in increasing cerebral ischaemic brain damage and in impairing recovery.

Glucose solutions should not be given through the same infusion equipment as whole blood as haemolysis and clumping can occur.

Pregnancy. Glucose solutions are commonly used as hydrating fluids and as vehicles for other drugs. If given during labour it has been suggested that the glucose load on the mother may lead to fetal hyperglycaemia, hyperinsulinaemia, and acidosis, with subsequent neonatal hypoglycaemia and jaundice.[1,2] Others[3] have found no evidence of such an effect, especially if the fetus is well-oxygenated,[4] and note that the number of patients included in such reports is often small and the selection criteria not homogeneous.

A placebo-controlled study[5] in healthy women scheduled for termination of pregnancy at mid-gestation found that giving 100 g of oral glucose 1 hour before termination had no adverse effect on fetal acid–base levels. Fetuses with malformations had been excluded. However, the authors cautioned that, at higher maternal glucose concentrations (as may be found in pregnant diabetics), changes consistent with fetal metabolic acidosis might occur, and that the glucose tolerance test might also be hazardous to fetuses with growth retardation. Late reactions to the acute glucose load could not be studied.

1. Kenepp NB, *et al.* Fetal and neonatal hazards of maternal hydration with 5% dextrose before cesarean section. *Lancet* 1982; i: 1150–2.
2. Singhi S, *et al.* Hazards of maternal hydration with 5% dextrose. *Lancet* 1982; ii: 335–6.
3. Piquard F, *et al.* Does fetal acidosis develop with maternal glucose infusion during normal labor? *Obstet Gynecol* 1989; 74: 909–14.
4. Cerri V, *et al.* Intravenous glucose infusion in labor does not affect maternal and fetal acid-base balance. *J Matern Fetal Med* 2000; 9: 204–8.
5. Weissman A, *et al.* Effect of the 100-g oral glucose tolerance test on fetal acid-base balance. *Prenat Diagn* 2003; 23: 281–3.

Stroke. Hyperglycaemia may be caused by physiological stress during ischaemic stroke, and this worsens cerebral ischaemic damage and impairs recovery. During cerebral ischaemia, cellular hypoxia causes a shift from aerobic to anaerobic metabolism of glucose leading to intracellular lactic acidosis, which is toxic to the cell. Hyperglycaemia provides more glucose for anaerobic metabolism, further worsening intracellular acidosis. Blood-glucose concentrations should therefore be monitored and hyperglycaemia avoided or treated. Glucose infusions should not be used routinely after ischaemic stroke, unless specifically indicated. Hypoglycaemia must also be avoided and for patients who do require glucose, it should be given by continuous infusion, avoiding large infusions or boluses that can cause hyperglycaemia.[1]

1. Wass CT, Lanier WL. Glucose modulation of ischemic brain injury: review and clinical recommendations. *Mayo Clin Proc* 1996; 71: 801–12.

Thiamine deficiency. Wernicke's encephalopathy (p. 2103.3) may be precipitated by giving intravenous glucose to thiamine-deficient patients.[1,2]

1. Watson AJ, *et al.* Acute Wernickes encephalopathy precipitated by glucose loading. *Ir J Med Sci* 1981; 150: 301–3.
2. Koguchi K, *et al.* Wernicke's encephalopathy after glucose infusion. *Neurology* 2004; 62: 512.

Pharmacokinetics

Glucose is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations of glucose occur about 40 minutes after oral doses in hypoglycaemic patients. It is metabolised via pyruvic or lactic acid to carbon dioxide and water with the release of energy. All body cells are capable of oxidising glucose and it forms the principal source of energy in cellular metabolism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Glucolin; Glucotem; Kissimin; Nutrosa; *Canad.*: Dextroject; Glucodex; *Cz.*: Ardeanutrisol G; *Fin.*: Glucosteril; Selutrio; *Ger.*: Accu-Chek Dextrose OGT; Glucosteril; *Hung.*: Isodex; *Indon.*: Infusan D; Otsu-D5; Wida; *Ital.*: Energen; *Pol.*: Maltan; *Port.*: Glucosada; Glucosado; Glucosteril; *Rus.*: Glucosteril (Глюкостерил); Rheopolyglukin (Реополиглюкин); *Spain*: Aptroserum Glucosado; Flebobag Glucosada†; Fleboflex Glucosada†; Fleboplast Glucosada†; Freeflex Glucosa; Glucocemin; Glucosmon†; Meinvenil Glucosa†; Plast Apyr Glucosado; Suero Glucosado; *Swed.*: Perfadex; *UK*: Dextrogel; GlucoGel; Rapilose; *USA*: Dex4 Glucose; Glutose; Insulin Reaction.

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

Homoeopathic Preparations. *Ger.*: NeyArthrosome (Revitorgan-Dilution)†.

Pharmacopoeial Preparations
BP 2014: Compound Glucose, Sodium Chloride and Sodium Citrate Oral Solution; Glucose Infusion; Glucose Irrigation Solution; Potassium Chloride and Glucose Infusion; Potassium Chloride, Sodium Chloride and Glucose Infusion; Sodium Chloride and Glucose Infusion;
Ph. Eur.: Anticoagulant Acid-Citrate-Glucose Solutions (ACD); Anticoagulant Citrate-Phosphate-Glucose Solution (CPD);
USNF 31: Dextrose Excipient; Liquid Glucose;
USP 36: Alcohol in Dextrose Injection; Anticoagulant Citrate Dextrose Solution; Anticoagulant Citrate Phosphate Dextrose Adenine Solution; Anticoagulant Citrate Phosphate Dextrose Solution; Bretylium Tosylate in Dextrose Injection; Bupivacaine Hydrochloride in Dextrose Injection; Dextran 40 in Dextrose Injection; Dextran 70 in Dextrose Injection; Dextrose and Sodium Chloride Injection; Dextrose Injection; Dobutamine in Dextrose Injection; Dopamine Hydrochloride and Dextrose Injection; Half-strength Lactated Ringer's and Dextrose Injection; Lactated Ringer's and Dextrose Injection; Lidocaine Hydrochloride and Dextrose Injection; Multiple Electrolytes and Dextrose Injection Type 1; Multiple Electrolytes and Dextrose Injection Type 2; Multiple Electrolytes and Dextrose Injection Type 3; Multiple Electrolytes and Dextrose Injection Type 4; Potassium Chloride in Dextrose and Sodium Chloride Injection; Potassium Chloride in Dextrose Injection; Potassium Chloride in Lactated Ringer's and Dextrose Injection; Ringer's and Dextrose Injection; Sodium Chloride and Dextrose Tablets; Tetracaine Hydrochloride in Dextrose Injection.

Glucose-1-phosphate

Cori Ester; α-D-Glucopyranose-1-phosphate; α-Glucose-1-Phosphoric Acid; Glucose-1-(dihydrogen Phosphate). α-D-Glucopyranose 1-(dihydrogen phosphate).

$C_6H_{13}O_9P$=260.1

CAS — 59-56-3 (glucose-1-phosphate); 18822-82-7 (arginine glucose-1-phosphate); 6997-09-7 (calcium glucose-1-phosphate); 17364-14-6 (monosodium glucose-1-phosphate); 56401-20-8 (disodium glucose-1-phosphate).

UNII — CIX3U01VAU.

NOTE. The name Arginil has been used to denote arginine glucose-1-phosphate.

Profile

Glucose-1-phosphate is an intermediate in both the synthesis and utilisation of glycogen and has been used as a source of glucose (p. 2068.3) and organic phosphorus. The sodium and calcium salts have been used as dietary supplements and the arginine salt has been used in liver disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Phocytan; *Ital.*: Glu-Phos.

Glutamic Acid *(USAN, rINN)*

Acide Glutamique; Ácido glutámico; Acidum Glutamicum; E; E620; Glu; L-Glutamic Acid; Glutámico, ácido; Glutamiinihappo; Glutaminic Acid; Glutaminsäure; Glutaminsav; Glutaminsyra; Glutamo rūgštis; Kwas glutaminowy; Kyselina glutámová; Глутаминовая Кислота.

L-(+)-2-Aminoglutaric acid.

$C_5H_9NO_4$=147.1

CAS — 56-86-0.

UNII — 3KX376GY7L (L-glutamic acid); 61LJ05I15S (DL-glutamic acid).

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

Ph. Eur. 8: (Glutamic Acid). A white or almost white, crystalline powder or colourless crystals. Freely soluble in boiling water; slightly soluble in cold water; practically insoluble in alcohol, in acetic acid, and in acetone. Protect from light.

USP 36: (Glutamic Acid). Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Glutamic Acid Hydrochloride *(rINNM)*

Acide Glutamique, Chlorhydrate de; Acidum Glutamicum Hydrochloridum; Aciglumin; Glu Hydrochloride; Glutámico, hidrocloruro del ácido; Hidrocloruro del ácido glutámico; Глутаминовой Кислоты Гидрохлорид.

L-(+)-2-Aminoglutaric acid hydrochloride.

$C_5H_9NO_4$.HCl=183.6

CAS — 138-15-8.

ATC — A09AB01.

ATC Vet — QA09AB01.

UNII — M0C2SP444T.

Pharmacopoeias. In *Ger.* Also in *USNF*.

USNF 31: (L-Glutamic Acid, Hydrochloride). A white, crystalline powder. Soluble 1 in about 3 of water; almost insoluble in alcohol and in ether. Solutions are acid to litmus. Protect from light.

Glutamine *(USAN, rINN)*

Gln; Glutamina; L-Glutamina; L-Glutamine; Glutaminum; Levoglutamida; Levoglutamide; Lévoglutamide; Levoglutamidum; Q; Левоглутамид.

L-Glutamic acid 5-amide; L-(+)-2-Aminoglutaramic acid.

$C_5H_{10}N_2O_3$=146.1

CAS — 56-85-9.

ATC — A16AA03.

ATC Vet — QA16AA03.

UNII — 0RH81L854J.

Pharmacopoeias. In *Ger.*, *Jpn*, and *US*.

USP 36: (Glutamine). White crystals or crystalline powder Soluble in water; practically insoluble in alcohol and in ether. Store at a mean temperature not exceeding 25 degrees.

Profile

Glutamic acid is a non-essential amino acid which is degraded readily in the body to form glutamine (levoglutamide). Glutamic acid and glutamine are used as dietary supplements. The dipeptides *N* (2)-L-alanyl-L-glutamine (Ala-Gln) and glycyl-L-glutamine (Gly-Gln) are used similarly.

Glutamic acid hydrochloride, which releases hydrochloric acid in the stomach, has been used in the symptomatic treatment of achlorhydria or hypochlorhydria in usual oral doses of 250 to 750 mg with meals.

A glutamine-based oral suspension is under investigation for the treatment of oral mucositis.

Antineoplastic toxicity. Oral glutamic acid has been used in the reduction of vincristine neurotoxicity (see Administration Error, p. 883.2).

Oral supplementation with glutamine may also have a role in alleviating the diarrhoea associated with irinotecan (see Effects on the Gastrointestinal Tract, p. 813.2).

A glutamine-based oral suspension is under investigation for the treatment of oral mucositis associated with cancer chemotherapy (p. 732.1). In breast cancer patients with moderate to severe oral mucositis glutamine reduced both the incidence and severity of the mucositis.[1] A literature review[2] reported variable results with glutamine supplementation for chemotherapy-induced mucositis, but stated that higher doses may be beneficial.

Oral glutamine was found to be of no benefit in alleviating myalgias or arthralgias associated with paclitaxel therapy.[3]

1. Peterson DE, *et al.* Randomized, placebo-controlled trial of Saforis for prevention and treatment of oral mucositis in breast cancer patients receiving anthracycline-based chemotherapy. *Cancer* 2007; 109: 322–31.
2. Savarese DMF, *et al.* Prevention of chemotherapy and radiation toxicity with glutamine. *Cancer Treat Rev* 2003; 29: 501–13.
3. Jacobson SD, *et al.* Glutamine does not prevent paclitaxel-associated myalgias and arthralgias. *J Support Oncol* 2003; 1: 274–8.

Parenteral and enteral nutrition. Evidence that glutamine is involved in the regulation of muscle protein synthesis maintenance of gut mucosal barrier function, and possibly enhanced immunological response has led to studies on supplementation with glutamine or more stable peptide derivatives in parenteral and enteral nutrition regimens for patients with injury and infection.[1] Although non-essential under normal circumstances, many consider glutamine to be a conditionally essential amino acid in patients with catabolic disease.[2,3]

Supplementation of parenteral nutrition regimens with glutamine has been shown to reduce clinical infection in patients who have undergone bone marrow transplantation[4] or who have suffered multiple trauma.[5] Improved survival has been reported among intensive-care patients given parenteral feeds supplemented with glutamine,[6] although a larger study found it difficult to show a benefit.[7] A systematic review,[8] including these studies, inferred that seriously ill patients, with gastrointestinal failure and

receiving parenteral nutrition, should receive glutamine supplements for at least 6 days and at a dose of greater than 200 mg/kg daily, in order to derive maximum benefit. Low plasma glutamine concentration upon admission to an intensive-care unit was considered to be an independent risk factor for mortality, and it has been suggested that plasma concentrations be used as an indicator for glutamine supplementation.[10]

In patients undergoing major uncomplicated surgery on the lower gastrointestinal tract, a significantly better postoperative nitrogen balance was achieved in those whose total parenteral nutrition regimen had been supplemented with about 20 g daily of glutamine coupled with alanine (L-alanyl-L-glutamine) (equivalent to about 12 g daily of glutamine) when compared with a control group.[11] Others[12] have shown that supplementation of total parenteral nutrition solutions with a glutamine dipeptide (glycyl-L-glutamine), in quantities equivalent to 230 mg/kg of glutamine daily, prevented the increased intestinal permeability and atrophic changes in the intestinal mucosa associated with unsupplemented solutions. Supplementation of total parenteral nutrition with α-ketoglutarate or a dipeptide, ornithine-α-ketoglutarate, reduced muscle protein depletion in one study,[13] suggesting that this may be a more physiological way of providing glutamine. Although recognising that clinical benefit in terms of infectious complications remained to be established, a review[14] of the use of ornithine-α-ketoglutarate stated that supplementation in the elderly improved clinical outcome in chronic malnutrition, by increasing appetite and body-weight gain and improving healing.

1. Sacks GS. Glutamine supplementation in catabolic patients. *Ann Pharmacother* 1999; 33: 348–54.
2. Kelly D, Wischmeyer PE. Role of L-glutamine in critical illness: new insights. *Curr Opin Clin Nutr Metab Care* 2003; 6: 217–22.
3. Mellis GC, *et al.* Glutamine: recent developments in research on the clinical significance of glutamine. *Curr Opin Clin Nutr Metab Care* 2004; 7: 59–70.
4. Ziegler TR, *et al.* Clinical and metabolic efficacy of glutamine-supplemented parenteral nutrition after bone marrow transplantation: a randomized, double-blind, controlled study. *Ann Intern Med* 1992; 116: 821–8.
5. Houdijk APJ, *et al.* Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. *Lancet* 1998; 352: 772–6.
6. Griffiths RD, *et al.* Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. *Nutrition* 1997; 13: 295–302.
7. Goeters C, *et al.* Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. *Crit Care Med* 2002; 30: 2032–7.
8. Powell-Tuck J, *et al.* A double blind, randomised, controlled trial of glutamine supplementation in parenteral nutrition. *Gut* 1999; 45: 82–8.
9. Novak F, *et al.* Glutamine supplementation in serious illness: a systematic review of the evidence. *Crit Care Med* 2002; 30: 2022–9.
10. Wernerman J. Glutamine and acute illness. *Crit Care* 2003; 9: 279–85.
11. Stehle P, *et al.* Effect of parenteral glutamine peptide supplements on muscle glutamine loss and nitrogen balance after major surgery. *Lancet* 1989; i: 231–3.
12. van der Hulst RRWJ, *et al.* Glutamine and the preservation of gut integrity. *Lancet* 1993; 334: 1363–5.
13. Wernerman J, *et al.* α-Ketoglutarate and postoperative muscle catabolism. *Lancet* 1990; 335: 701–3.
14. Blonde-Cynober F, *et al.* Use of ornithine α-ketoglutarate in clinical nutrition of elderly patients. *Nutrition* 2003; 19: 73–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glutamic acid hydrochloride as not porphyrinogenic: it may be used as a drug of first choice and no precautions are needed. Glutamine is not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Actyn-Myosyn; Alglutamin; Dipeptiven; *Austria*: Dipeptiven; Neuroglutamin; *Braz.*: Glutafora; *Chile*: Dipeptiven; *China*: An Kai Shu (安凯舒); Chong Tai (重太); Dipeptiven (力太); Pei Er Ji (培尔吉); Shi Lin (施林); Xin Kun Chang (欣坤畅); Xin Mai Lin (新麦林); Zhong Xin Tai (仲新太); Zi Wei (自维); *Cz.*: Adamin-G; Dipeptiven; *Denm.*: Dipeptiven; *Fin.*: Dipeptiven; Hypochylin; *Fr.*: Dipeptiven; *Ger.*: Dipeptamin; Glutamin; Gluti-Agil mono; Pepsaletten N†; *Gr.*: Aminol; Dipeptiven; Glutamol; *Hong Kong*: Dipeptiven; *Hung.*: Dipeptiven; *India*: Convales; Elemune; *Indon.*: Dipeptiven; Glutrop; *Irl.*: Adamin-G†; Dipeptiven; *Israel*: Dipeptiven; *Ital.*: Dipeptiven; Glutaven; *Malaysia*: Dipeptiven†; *Mex.*: Dipeptiven; *Neth.*: Dipeptiven; *Norw.*: Dipeptiven; *NZ*: Dipeptiven; *Pol.*: Dipeptiven; *Port.*: Dipeptiven; *Rus.*: Dipeptiven (Дипептивен); *S.Afr.*: Dipeptiven; *Singapore*: Dipeptiven; *Spain*: Dipeptiven; *Swed.*: Dipeptiven; Hypochylin; *Switz.*: Dipeptiven; *Thai.*: Dipeptiven; *Turk.*: Dipeptiven; *UK*: Dipeptiven; *Ukr.*: Dipeptiven (Дипептивен); *USA*: NutreStore.

Multi-ingredient Preparations. *Arg.*: Levoglutil Vitaminado; Memorex Vital; Normoprost Compuesto; Tuaplex; *Austral.*: Aspartatol†; Digestive Zyme†; Mindac; *Braz.*: Glutavigon; Libiplus; Memoriol B6; Nutrimaiz SM; Organoneuro Cerebral; *Canad.*: Digest; *Chile*: Dynamisan; Glutacyl Vitaminado; Hexalectol; *China*: Gu Ao (谷奥); Pu Luo Si Tai (普罗司泰); She Lan (舍兰); Zi Mo (兹末); *Fr.*: Bouillet; Phakan†; ProstaSecurA; Vita-Dermacide; Xal; YSE Glutamique†; *Ger.*: Leferdivin†; *Gr.*: Tonotil-N; *Hong Kong*: Esafosfina Glutammica; *Hung.*: Glutarsin E; Reergin; *India*: Actovit; Ameco; Aminos; Aminut; Aneudox-12; B-Banc Bavitam; Bcom-L; Betaneuron OD; Dayvital; Dipeptiven; Florablend; Glubex-Z; Glubex-Z; Glutammune; Glutazene; Kabimmune; Lycobel; Mecze-FL; Medineuron; Miol; Neuratab B6; Neurogard; Orovit; Orovit; Orovit; *Indon.*: Asten; Cerebrofort AA+DHA; Cerebrofort Gold; Cerebrovit Senior; Cerebrovit X-Cel; Curbexon; Erpha Livita; Fortelysin†; Hemaviton Stamina Plus; Kuminta; Lanavision Plus; Pediagrow; Prefit; Proseval; Provital Plus; Provital; Stamino; Zamel; *Ital.*: Acutil Fosforo; Fosfaserin; Fosfo Plus; Glutamin Fosforo; Memovit B12; Selene; *Jpn*: Azulemin; Azulene.Glutamine; Manamin GA; Mesadorin S; Podonin-S; Ruefrien; Sedagaston; Towazuren; Youzuren S; *Mex.*: Bigenol†; Glutacalcio; *Philipp.*: Catarstat; Glutaphos; Spasmo-Canulase; *Pol.*: Naturapia Prostata†; *Port.*: Cebrotex Forte†; Espasmo Canulase†; Fosgluten Super Reforcado; Relavit Fosforo; *Rus.*: Eltacin (Элтацин); *S. Afr.*: Lentogesic Spasmo-Canulase†; *Singapore*: Glutamine Plus; NutraMX; Provital; *Spain*: Agudil†; Dynamin; Fosgluten Reforzado†; Nucleserina; Tebetane Compuesto; *Switz.*: Spasmo-Canulase; Tonoglutal; Vitasprint B12; Vitasprint Complex†; *Turk.*: Pepzan; Seldiyet; *Ukr.*: Fakovit (Факовит)†; Quadevit (Квадевит); *USA*: Panplex 2-Phase; Sunnie; Tyler Prenatal; *Venez.*: Glutapak-R; Glutapak.

Homoeopathic Preparations. *Ger.*: NeyGeront Vitalkapsein A.

Glycine *(rINN)*

Ácido aminoacético; Acidum Aminoaceticum; Aminoacetic Acid; Aminoättiksyra; Aminoetikkahappo; E640 (glycine or glycine sodium); G; Glicin; Glicina; Glicinas; Glicocola; Glicolol; Glicyna; Gly; Glycin; Glycinum; Glycocoll; Glysiini; Sucre de Gélatine; Глицин.

$C_2H_5NO_2$=75.07

CAS — 56-40-6.

ATC — B05CX03.

ATC Vet — QB05CX03.

UNII — TE7660XO1C.

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

Ph. Eur. 8: (Glycine). A white or almost white crystalline powder. It exhibits polymorphism. Freely soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 5.9 to 6.4.

USP 36: (Glycine). A white, odourless crystalline powder. Soluble 1 in 4 of water at 25 degrees, 1 in 2.6 at 50 degrees, 1 in 1.9 at 75 degrees, and 1 in 1.5 at 100 degrees; soluble 1 in 1254 of alcohol; very slightly soluble in ether. Its solutions are acid to litmus.

Uses and Administration

Glycine is a non-essential aliphatic amino acid. It is used as a dietary supplement.

Glycine is sometimes used with antacids in the treatment of gastric hyperacidity. It is also used as an ingredient of some aspirin preparations with the object of reducing gastric irritation. Glycine powder has been used as a debriding and polishing agent for dental hygiene.

Sterile solutions of glycine 1.5% in water, which are hypotonic and non-conductive, are used as urogenital irrigation solutions during certain surgical procedures, particularly transurethral resection of the prostate.

Glycine hydrochloride has also been used.

Adverse Effects and Precautions

Systemic absorption of glycine irrigation solutions can lead to disturbances of fluid and electrolyte balance and cardiovascular and pulmonary disorders (see below).

Glycine irrigation should be used cautiously in patients with hepatic impairment since any absorption and consequent metabolism may cause hyperammonaemia. The possible effects on fluid and electrolyte balance warrant cautious use in patients with cardiopulmonary or renal dysfunction; glycine irrigation is contra-indicated in anuric patients.

Systemic absorption. Absorption of glycine irrigation solution during surgical procedures can cause disturbances of the circulatory and nervous systems.[1-3] Often seen after transurethral resection of the prostate, these symptoms and signs have been referred to as the transurethral resection syndrome,[1] although they have also been described after other urological or gynaecological surgical procedures.[4,5] Hyponatraemia and glycine toxicity are thought to be responsible for the clinical manifestations.[1,2,5]

Symptoms and signs include chest pains, hypertension, hypotension, bradycardia, anuria, dyspnoea, nausea, vomiting, restlessness, confusion, apprehension, irritability, headache, and seizures.[1,3-5] Chills, diarrhoea, and abdominal pain have also been reported,[1] as have visual disturbances and blindness.[3,6] Myocardial infarction,[7,8] coma, and death may occur.[5,7]

Absorption may occur rapidly, through the intravascular route, or, more rarely, slowly via extravascular absorption.[1,2,4] Extravasation should be suspected when abdominal pain and swelling are apparent.[4,9] Ethanol has been added to the irrigation fluid, and ethanol breath tests performed regularly during procedures in order to detect and monitor absorption.[1,2,4,9] However, the syndrome has still occurred despite monitoring;[9] awareness of the pattern of ethanol changes and clinical symptoms associated with extravascular as well as intravascular absorption are considered essential.[4,9]

1. Olsson J, *et al.* Symptoms of the transurethral resection syndrome using glycine as the irrigant. *J Urol (Baltimore)* 1995; 154: 123–8.
2. Tauzin-Fin P. Complication des liquides d'irrigation à base de glycocolle: le syndrome de résorption. *Therapie* 2002; 57: 48–54.
3. Radziwill AJ, *et al.* Visual disturbances and transurethral resection of the prostate: the TURP syndrome. *Eur Neurol* 1997; 38: 7–9.
4. Hahn RG. Transurethral resection syndrome after transurethral resection of bladder tumours. *Can J Anaesth* 1995; 42: 69–72.
5. Siddiqui MA, *et al.* Glycine irrigant absorption syndrome following cystoscopy. *Clin Nephrol* 1996; 45: 365–6.
6. Kard A, Erkin Y. Transient blindness following hysteroscopy. *J Int Med Res* 2003; 31: 152–5.
7. Byard RW, *et al.* Glycine toxicity and unexpected intra-operative death. *J Forensic Sci* 2001; 46: 1244–6.
8. Hahn RG, Persson P-G. Acute myocardial infarction after prostatectomy. *Lancet* 1996; 347: 335.
9. Hahn RG. Life-threatening transurethral resection syndrome despite monitoring of fluid absorption with ethanol. *Eur J Anesthesiol* 1995; 12: 431–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Titralac; *Fr.*: Derm Hydralin; Hydralin Gyn; *Hong Kong*: Gyn-Hydralin; Titralac†; *NZ*: Titralac; *Rus.*: Prostatilen (Простатилен); *S.Afr.*: Titralac†; *Thai.*: Glycine-Tur; *Ukr.*: Glicised (Глицисед-кмп).

Multi-ingredient Preparations. *Arg.*: Cicatrex Biotic; Glicocalcio; Normoprost Compuesto; Novo Benitol; Synapsys; *Austral.*: Cal Alkyline†; Cicatrin†; *Austria*: Centramin; *Braz.*: B-Vesil†; Cicatrene; *Canad.*: Antacid 2†; *Chile*: Dolotol 12; *China*: BiFu (比孚); Bo Luo Ni (博罗尼); Gan Mu Shu (甘木舒); Gan Wei Xin (甘维欣); Gan You Lin (感佑林); Jun Qiang (君强); Kang Er Ning (康尔宁); LiWeiEr (里威尔); Neo-Minophagen C (美能); Neo-Minophagen C (美能); NuoHao (诺豪); Pu Luo Si Tai (普罗司泰); Ruo Jing (若菁); Shu Kang Lin (抒康林); Tuo Di (妥迪); Wei Suan Su (卫算苏); Wei Yi Xing (卫伊兴); XinKang (昕康); Ye Xin (业欣); Yi Nuo Wei (依诺维); Yi Xin (易新); YouNiDi (尤尼迪); *Fr.*: Derm'Intim; Phakan†; ProstaSecurA; Pruriced; *Gr.*: Titralac; *India*: Astyfer-Z; Astyfer; Biospirin; Cotaryl; Fe-Z; Ferro Hepatine; *Indon.*: Aviter; IsoCal; Viusid; *Irl.*: Cicatrin†; *Ital.*: Cicatrene; Detoxicon; Digestivo Antonetto; Omegadin Plus; *Mon.*: Magnesium Glycocolle Lafarge; *Philipp.*: Catarstat; *Pol.*: Naturapia Prostata†; *Port.*: Cicatrin; *Rus.*: Eltacin (Элтацин); *S.Afr.*: Cicatrin†; *Spain*: Tebetane Compuesto; Tulgrasum Cicatrizante; *Switz.*: Cicatrex; DAM Antacidum†; *Thai.*: Genquin; *Ukr.*: Fakovit (Факовит)†; Medichronal (Медихронал); Oko-Health (Око-хелс).

Used as an adjunct in: *Austral.*: Cardiprin; Disprin Direct; *Cz.*: Godasal; *Ger.*: Godamed; *Gr.*: Junior Algon; *Hong Kong*: Cardiprin; Glyprin; *India*: Aspisol; *Indon.*: Contrexyn; Inzanat†; Minigrip; Proxime; *Ital.*: Aspiglicina; *Malaysia*: Cardiprin; Glyprin; *Pol.*: Alka-Prim; Asprocard†; Asprocol; *Rus.*: Alka-Prim (Алька-Прим); *Singapore*: Cardiprin; Glyprin; *Spain*: Okaldol con Cafeína; Okaldol; *Thai.*: Caparin; Cardiprin; *Ukr.*: Alka-Prim (Алька-Прим); Godasal (Годасал).

Pharmacopoeial Preparations

BP 2014: Glycine Irrigation Solution;
USP 36: Glycine Irrigation.

Halibut-liver Oil

Aceite de hígado de fletán; Aceite de Hígado de Hipogloso; Heilbuttleberöl; Ol. Hippoglossi; Oleum Hippoglossi; Oleum Jecoris Hippoglossi; Палтусовый Печёночный Жир.

CAS — 8001-46-5.

UNII — QMX76ZL97M.

Pharmacopoeias. In *Br.*

BP 2014: (Halibut-liver Oil). The fixed oil extracted from the fresh or suitably preserved liver of the halibut species belonging to the genus *Hippoglossus*. It contains not less than 30 000 units of vitamin A activity per g. Wt per mL 0.915 to 0.925 g. A pale to golden yellow liquid with a fishy, but not rancid, odour and taste. Practically insoluble in alcohol; miscible with chloroform, with ether and with petroleum spirit. Store in well-filled containers. Protect from light.

Profile

Halibut-liver oil is used as a means of giving vitamins A (p. 2098.3) and D (p. 2112.3); the proportion of vitamin A to vitamin D is usually greater in halibut-liver oil than in cod-liver oil (p. 2056.3). It is usually given in capsules.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Pancutan Base†.

Multi-ingredient Preparations. *Arg.*: Eryteal; Klorane Bebe Eryteal; Pancutan; *Austria*: Nuri-Kapseln†; Vitawund; *Chile*: Hipoglos; Mintaglos; Nistaglos; *Port.*: Halibut.

Pharmacopoeial Preparations
BP 2014: Halibut-liver Oil Capsules.

Histidine *(BAN, USAN, rINN)*

H; His; Histidiini; Histidin; Histidina; Histidinas; L-Histidine; Histidinum; Hisztidin; NSC-137773; Гистидин.
L-2-Amino-3-(1*H*-imidazol-4-yl)propionic acid.
$C_6H_9N_3O_2$=155.2
CAS — 71-00-1.
UNII — 4QD397987E.

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

Ph. Eur. 8: (Histidine). Colourless crystals or a white or almost white crystalline powder. Soluble in water; very slightly soluble in alcohol. Protect from light.

USP 36: (Histidine). White, odourless crystals. Soluble in water; very slightly soluble in alcohol; insoluble in ether. pH of a 2% solution in water is between 7.0 and 8.5.

Histidine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de histidina; Histidiinihydrokloridimonohydraatti; Histidina, hidrocloruro; Histidine (chlorhydrate d') monohydraté; Histidine, Chlorhydrate de; Histidine Monohydrochloride; Histidin-hydroklorid monohydrát; Histidinhydrokloridmonohydrat; Histidini Hydrochloridum; Histidini Hydrochloridum Monohydricum; Histidinium Chloride; Histidino hidrochloridas monohidratas; Histydyny monochlorowodorek; Hisztidin-hidroklorid-monohidrát; Гистидина Гидрохлорид.
L-Histidine hydrochloride monohydrate.
$C_6H_9N_3O_2.HCl.H_2O$=209.6
CAS — 645-35-2 (anhydrous histidine hydrochloride).
UNII — 1D5Q932XM6 (anhydrous histidine hydrochloride); X573657P6P (histidine hydrochloride monohydrate).

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

Ph. Eur. 8: (Histidine Hydrochloride Monohydrate). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 3.0 to 5.0. Protect from light.

Profile

Histidine is a basic amino acid that is essential for infant growth and which may be essential for some other groups, such as patients with uraemia. Histidine and histidine hydrochloride are used as dietary supplements.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Enhance for Men; *Fr.*: Bion Restore; *India*: Astyfer-Z; Astyfer; Astyfer; Doloral; *Phi-lipp.*: Biomix.

Honey

Bal; Clarified Honey; Gereinigter Honig; Honig; Honung; Hunaja; Madu; Med; Medus; Mel; Mel Depuratum; Mel Despumatum; Miel; Miel Blanc; Miel purificada; Purified Honey; Strained Honey; Měd.
UNII — Y9H1V576FH (honey); Z9305QFA72 (dandelion honey); W44S7N2P8P (rape honey).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Honey; Mel). It is produced by bees (*Apis mellifera*) from the nectar of plants or from secretions of living parts of plants, which the bees collect, transform by combining with specific substances of their own, deposit, dehydrate, store, and leave in the honey comb to ripen and mature. If the bee has been exposed to treatment to prevent or cure diseases or to any substance intended for preventing, destroying, or controlling any pest, unwanted species of plants or animals, appropriate steps are taken to ensure that the levels of residues are as low as possible. It is an almost white to dark brown, viscous liquid which may be partly crystalline.

USNF 31: (Purified Honey). It is obtained by purification of honey from the comb of the bee, *A. mellifera* and all subspecies of *A. mellifera*. The honey is extracted by centrifugation, pressure, or other suitable procedures. Specific gravity 1.400 and 1.435 at 20 degrees. Store in airtight containers. It is not intended for infants under one year of age unless it is free from *Clostridium* spp.

Profile

Honey, which contains about 70 to 80% of glucose and fructose, is used as a demulcent and sweetening agent, especially in linctuses and cough mixtures (see Cough p. 1651.2). Preparations containing honey are used in the management of skin ulcers, wounds, and burns.

Contamination. Honey has been identified as a source of *Clostridium botulinum* spores and thus recommendations have been made that honey should not be given to infants under 1 year because of the risk of causing infant botulism.[1,2]

Honey produced from certain species of *Rhododendron* plants has been found to contain grayanotoxins. Grayanotoxin I is responsible for honey poisoning, manifest as bradycardia, cardiac arrhythmias, hypotension, gastrointestinal disturbances, dizziness, loss of consciousness, blurred vision, chills, cyanosis, sweating, and salivation.[3,4] Convulsions have also been reported.[4]

1. Arnon SS, *et al.* Honey and other environmental risk factors for infant botulism. *J Pediatr* 1979; 94: 331–6.
2. Tanzi MG, Gabay MP. Association between honey consumption and infant botulism. *Pharmacotherapy* 2002; 22: 1479–83.
3. Özhan H, *et al.* Cardiac emergencies caused by honey ingestion: a single centre experience. *Emerg Med J* 2004; 21: 742–4.
4. Dilber E, *et al.* A case of mad honey poisoning presenting with convulsion: intoxication instead of alternative therapy. *Turk J Med Sci* 2002; 32: 361–2.

Cough. Honey has a long history of use in the management of cough (p. 1651.2), particularly in children, but as with many traditional cough remedies, evidence of its value is largely lacking.[1,2]

1. Mulholland S, Chang AB. Honey and lozenges for children with non-specific cough. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 10/06/10).
2. Oduwole O, *et al.* Honey for acute cough in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 10/06/10).

Wounds. Anecdotal reports and traditional usage dating back to ancient Egypt suggest that honey may be of some value as a wound dressing (p. 1690.1). Its antibacterial properties are attributed both to high osmolality and the liberation of hydrogen peroxide, but may vary with the source:[1-4] in Europe, some of the best activity has been seen with lime-flower honey.[2] Manuka honey (p. 2550.1) has been found to have high concentrations of methylglyoxyl, which correspond to a greater antibacterial activity *in vitro* than other honeys.[5] Sterilised manuka honey was reported to heal a leg ulcer infected with meticillin-resistant *Staphylococcus aureus*,[6] although a randomised open-label study found no evidence that dressings impregnated with manuka honey improved the healing of venous leg ulcers at 12 weeks compared with usual care.[7] However, a systematic review[8] concluded that there was no evidence of benefit from adjuvant use of honey with compression dressings in the treatment of leg ulcers. In a preliminary study, honey obtained from the tea plant (see Xanthine-containing Beverages, p. 2648.2) significantly reduced the incidence of grade 3 and 4 radiation-induced oral mucositis.[9]

A group from India[10] has reported that the properties of honey offer a potentially simple and cheap means of preserving skin grafts in developing countries, with 100% uptake of reconstituted grafts stored for up to 6 weeks and 80% uptake of those stored for 7 to 12 weeks. In comparison with sulfadiazine silver, occlusive honey dressings were also found to be more effective for the treatment of superficial partial thickness thermal burns,[11] and systematic reviews[8,12] have tended to confirm its benefits in aiding the healing of burns.

However, concern has been expressed since honey may contain not only chemical contaminants but clostridial spores (see also above), and it has been suggested[2] that to be medically acceptable, honey must be sterile, residue-free, and of measured antibacterial activity.

Sugar has been used similarly to honey in treating wounds (see p. 2097.2).

1. Greenwood D. Honey for superficial wounds and ulcers. *Lancet* 1993; 341: 90–1.
2. Postmes T, *et al.* Honey for wounds, ulcers, and skin graft preservation. *Lancet* 1993; 341: 756–7.
3. Molan PC. Re-introducing honey in the management of wounds and ulcers - theory and practice. *Ostomy Wound Manage* 2002; 48: 28–40.
4. Booth S. Are honey and sugar paste alternatives to topical antiseptics? *J Wound Care* 2004; 13: 31–3.
5. Mavric E, *et al.* Identification and quantification of methylglyoxal as the dominant antibacterial constituent of Manuka (Leptospermum scoparium) honeys from New Zealand. *Mol Nutr Food Res* 2008; 52: 483–9.
6. Natarajan S, *et al.* Healing of an MRSA-colonized, hydroxyurea-induced leg ulcer with honey. *J Dermatol Treat* 2001; 12: 33–6.
7. Jull A, *et al.* Honey as Adjuvant Leg Ulcer Therapy trial collaborators. Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. *Br J Surg* 2008; 95: 175–82.
8. Jull AB, *et al.* Honey as a topical treatment for wounds. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 10/06/10).
9. Biswal BM, *et al.* Topical application of honey in the management of radiation mucositis: a preliminary study. *Support Care Cancer* 2003; 11: 242–8.
10. Subrahmanyam M. Storage of skin grafts in honey. *Lancet* 1993; 341: 6–4.
11. Subrahmanyam M. A prospective randomised clinical and histologic study of superficial burn wound healing with honey and silver sulfadiazine. *Burns* 1998; 24: 157–61.
12. Wijesinghe M, *et al.* Honey in the treatment of burns: a systematic review and meta-analysis of its efficacy. *N Z Med J* 2009; 122: 47–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Antibacterial Honey Barrier†; Medihoney Antibacterial Wound Gel; *Ger.*: Infecto-Honey; *India*: Crack Free; *Indon.*: SanoSkin Melladerm Plus; *Ital.*: Oramil; *Neth.*: Natterman Melrosum; *Rus.*: Gepton (Гептрош); Kriomelt (Криомелт); *UK*: Medihoney Antibacterial Wound Gel; Mesitran.

Multi-ingredient Preparations. *Arg.*: Expectosan Hierbas y Miel; Farinop; Laxiruela; *Braz.*: Expectomel; Melagriao; Melxi; Pectoral Martel; *Canad.*: Honey Blend Herbal Cough Syrup; Mielcol†; *Chile*: Fray Romano; Jarabe Palto Compuesto con Miel Adulto; Jarabe Palto Compuesto con Miel Infantil†; Mielax; Mielito; Paltomiel Plus; Paltomiel; Paltomiel; Propolkit; Propolkit; Pulmosina; Timuss-Kit; *Fr.*: Aromadetox†; Aromavital; Aromazen†; Feromiel†; Olioseptil Gorge-Larynx; Olioseptil Gorge-Larynx; Pharyndol; Pharyndol; Taido; *Ger.*: InfectoHoney Alginat†; *Hung.*: Doppelherz Energie Tonikum N; *India*: Britesite; Evaren; Honitus; Kofarest-H; Moiste; *Indon.*: Bio-Strath; Pectum; Sirec; *Irl.*: Lemsip Dry Cough; Venos Honey & Lemon; *Ital.*: Alvear con Ginseng; Apiserum con Telergon 1-; Bebimix†; Bioton; Bron 6; Faringel; Liozim; Nepiros; Nerex; Nutrigel; The Ginseng King†; *NZ*: Robitussin Honey Cough-; *Pol.*: Babicum; Melis-Tonic; *Rus.*: Bronchicum Husten (Бронхикум Сироп от Кашля)†; Doppelherz Energotonic (Доппельгерц Энерготоник); Evalar (Эвалар); Kliophyt (Клиофит); Prostopine (Простопин); *S.Afr.*: Choats Extract of Lettuce Cough Mixture†; Enzian Anaemodoron Drops†; *Singapore*: Arkopharma Propolis Spray; *Spain*: Novogumil; *UK*: Adult Meltus for Chesty Coughs & Catarrh; Beehive Balsam; Buttercup Syrup (Honey and Lemon flavour); Feroglobin; Herb and Honey Cough Elixir; Honey & Molasses; Jackson's Lemon Linctus; Jackson's Troublesome Coughs; Lemsip Cough & Cold Dry Cough; Lockets Medicated Linctus; Lockets; M & M; Meltus Expectorant; Meltus Honey & Lemon; Potters Children's Cough Pastilles; Potters Gees Linctus; Regina Royal Five; Sanderson's Throat Specific Throaties Pastilles; Venos Honey & Lemon Zubes Honey & Lemon; *Ukr.*: Huato Pills (Болюсы Хуато); *Venez.*: Jengimiel Sabila; Jengimiel; Jengimiel; Viusid.

Homoeopathic Preparations. *Chile*: Drosemiel; *UK*: Fragador.

Invert Sugar

Azúcar invertido; Инвертный Сахар.
CAS — 8013-17-0.
ATC — C05BB03.
ATC Vet — QC05BB03.
UNII — ED959S6ACY (maize invert sugar).

Pharmacopoeias. *Br.* and *US* include preparations of invert sugar.

Profile

Invert sugar is an equimolecular mixture of glucose and fructose which may be prepared by the hydrolysis of sucrose with a suitable mineral acid such as hydrochloric acid. Invert sugar has similar actions and uses to those of glucose (p. 2068.3) and fructose (p. 2068.2). It has been used as a 10% solution as an alternative to glucose in parenteral nutrition but, as with fructose, such use cannot be recommended.

A syrup of invert sugar is used as a stabilising agent when mixed with suitable proportions of sucrose-based syrup it will help to prevent crystallisation of the sucrose.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Fructodex.

Multi-ingredient Preparations. *Hung.*: Doppelherz Energie Tonikum N; *Rus.*: Doppelherz Energotonik (Доппельгерц Энерготоник); *S.Afr.*: Emex; *USA*: Travert.

Pharmacopoeial Preparations
BP 2014: Invert Syrup;
USP 36: Invert Sugar Injection; Multiple Electrolytes and Invert Sugar Injection Type 1; Multiple Electrolytes and Invert Sugar Injection Type 2; Multiple Electrolytes and Invert Sugar Injection Type 3.

Iron

Demir; Eisen; Fer; Ferro; Ferrum; Hierro; Ijzer; Järn; Rauta; Železo; Żelazo; Железо.

Fe=55.845.

CAS — 7439-89-6.

UNII — E1UOL152H7.

Pharmacopoeias. *Eur.* (see p. vii) includes a form for homoeopathic preparations.

Ph. Eur. 8: (Iron for Homoeopathic Preparations; Ferrum ad Praeparationes Homoeopathicae). A fine, blackish-grey powder, without metallic lustre, obtained by reduction or sublimation. Practically insoluble in water and in alcohol; it dissolves with heating in dilute mineral acids.

Uses and Administration

Iron is an essential constituent of the body, being necessary for haemoglobin formation and for the oxidative processes of living tissues. Iron deficiency results in defective erythropoiesis and anaemia. Iron and iron salts should only be given for the treatment or prophylaxis of iron-deficiency anaemias (see below). They should not be given for the treatment of other types of anaemia except where iron deficiency is also present. Iron-deficiency anaemias respond readily to iron therapy but the underlying cause of the anaemia should be determined and treated.

The preferred route for giving iron is oral, usually as soluble ferrous salts which are better absorbed than ferric salts. The usual adult dose for the treatment of iron-deficiency anaemia is 100 to 200 mg of iron daily in divided doses. The usual adult prophylactic dose is about 60 to 120 mg of iron daily. For doses in children, see Administration in Children, below. Therapy is generally continued until haemoglobin concentrations reach normal values, which may take some weeks, and then for a further 3 months or more to restore body-iron stores.

Further information concerning the dosage of iron salts and compounds used is provided in the individual monographs; this information, however, tends to reflect the amounts of iron contained in different salts or available commercial preparations and therefore, in some instances, may not be within the general range of iron dosages as quoted above.

The iron content of various iron salts is tabulated in Table 1, below.

Modified-release dosage forms of iron are claimed to result in reduced gastrointestinal adverse effects and have the advantage of once-daily dosage. The preparations are designed to release the iron gradually along the gut but in some instances the iron may not be released until the preparation reaches a part of the gut where absorption is poor thus resulting in sub-optimal dosing.

Iron can also be given parenterally in circumstances where oral therapy cannot be undertaken and such use is typified by iron dextran (see p. 2075.3).

Administration in children. Iron is given orally to children to treat and prevent iron-deficiency anaemia (see below). There are various recommendations for children's doses but up to 2 mg/kg of iron three times daily for treatment and 1 to 2 mg/kg (usually to a maximum of 30 mg) daily for prophylaxis has been used.

Administration in the elderly. Patients over 80 years of age with iron-deficiency anaemia (below) were randomised to elemental iron therapy in daily doses of 15 mg, 50 mg (as liquid ferrous gluconate), or 150 mg (as tablets of calcium ferrous citrate) and treated for 2 months.[1] Serum haemoglobin and ferritin concentrations increased significantly in all patients, without significant differences between the 3 doses. The authors concluded that, while these results may not apply to patients with iron deficiency due to malabsorption, chronic disease, or untreated *Helicobacter pylori* infection, low-dose therapy is an effective option for elderly patients with iron-deficiency anaemia, in whom the adverse effects of iron could cause considerable morbidity and impaired compliance. Younger patients could also probably be treated effectively with low-dose iron therapy.

1. Rimon E, *et al.* Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. *Am J Med* 2005; 118: 1142–7.

Table 1. Approximate amounts of different iron salts that supply 60 mg of elemental iron.

Iron salt	Amount
Ferrous ascorbate (anhydrous)	437 mg
Ferrous aspartate (tetrahydrate)	422 mg
Ferrous chloride (tetrahydrate)	214 mg
Ferrous fumarate (anhydrous)	183 mg
Ferrous gluconate (dihydrate)	518 mg
Ferrous succinate (anhydrous)	185 mg
Ferrous sulfate (dried)	186 mg
Ferrous sulfate (heptahydrate)	300 mg

The symbol † denotes a preparation no longer actively marketed

Anoxic seizures. Reductions in the frequency of breath-holding episodes in children treated with iron,[1] and especially in those with iron-deficiency anaemia,[2,3] suggest that there might be a relationship between reflex anoxic seizures (p. 1311.3) and iron deficiency.[4] A systematic review[5] confirmed the apparent benefit of iron supplementation (5 mg/kg daily of elemental iron for 16 weeks) in reducing frequency and severity of attacks, particularly in children with iron-deficiency anaemia, in whom there appeared to be a trend to parallel improvements in breath-holding and haemoglobin values.

1. Daoud AS, *et al.* Effectiveness of iron therapy on breath-holding spells. *J Pediatr* 1997; 130: 547–50.
2. Mocan H, *et al.* Breath holding spells in 91 children and response to treatment with iron. *Arch Dis Child* 1999; 81: 261–2.
3. Pedersen KW, Knudsen FU. Skal børn med affektkramper behandles med jern? *Ugeskr Laeger* 2004; 166: 2789–91.
4. Hannon DW. Breath-holding spells: waiting to inhale, waiting for systole, or waiting for iron therapy? *J Pediatr* 1997; 130: 510–12.
5. Zeherner AA, *et al.* Iron supplementation for breath-holding attacks in children. Available in The Cochrane Database of Systematic Reviews: Issue 5. Chichester: John Wiley; 2010 (accessed 09/06/10).

Cough. In a small study[1] of 19 patients, iron supplementation with ferrous sulfate successfully reduced the cough associated with ACE inhibitors (see p. 1285.3). The authors hypothesised that this effect was due to the inhibition by iron of nitric oxide synthase. However, there are some concerns[2] about the effect of giving a nitric oxide synthase inhibitor to hypertensive patients, as it has been found to increase blood pressure in *animal* studies.

1. Lee S-C, *et al.* Iron supplementation inhibits cough associated with ACE inhibitors. *Hypertension* 2001; 38: 166–70.
2. Lev L Rian AJJT. Iron supplementation in ACE inhibition as a treatment for cough: is it really inoffensive? *Hypertension* 2001; 38: e38.

Iron-deficiency anaemia. The iron content of the body is normally kept constant by regulation of the amount absorbed to balance the amount lost. If loss is increased, and/or intake inadequate, a negative iron-balance may lead by degrees to depletion of body iron stores, iron deficiency, and eventually to anaemia. Iron requirements are increased during infancy, puberty, pregnancy, and during menstruation, and iron-deficiency anaemias are most common in women and children; the most common cause in adult males and postmenopausal women is blood loss, usually from the gastrointestinal tract.

Iron deficiency usually results in a microcytic, hypochromic anaemia, but the diagnosis of iron deficiency should be confirmed, if there is any doubt, by measurement of serum ferritin, erythrocyte protoporphyrin, or total iron binding capacity (transferrin). Iron therapy can begin once deficiency is confirmed, but the underlying cause of the deficiency should still be sought and treated.

Treatment. The prevention and control of iron-deficiency anaemias has been reviewed.[1-4] Almost all iron-deficiency anaemias respond readily to treatment with iron. The treatment of choice is an oral ferrous salt (ferrous iron is better absorbed than ferric iron).[1] Many iron compounds have been used for this purpose, but do not offer any real advantage over the simple ferrous fumarate, gluconate, or sulfate salts. The usual adult dose is sufficient of these salts to supply about 100 to 200 mg of elemental iron daily (for the elemental iron content of various iron salts, see Table 1, above), with the aim of increasing haemoglobin concentrations by about 1 g/litre daily or about 20 g/litre every 3 weeks.[1] Haemoglobin response is greatest in the first few weeks of therapy and is proportional to the severity of the original anaemia. Once haemoglobin concentrations have risen to the normal range, iron therapy should be continued for a further 3 months to aid replenishment of iron stores.[1,3] For the view that low-dose iron therapy may be as effective as higher doses, see Administration in the Elderly, above.

Oral iron has been given with agents such as ascorbic acid to enhance iron absorption, and modified-release preparations have been used in patients intolerant of ordinary formulations of iron but the *BNF* considers them to have no therapeutic advantage.

Failure to respond to oral iron after about 3 weeks of therapy may be indicative of non-compliance, continued blood loss with inadequate replacement of iron, malabsorption, wrong diagnosis, or other complicating factors, and the treatment should be reassessed.

Parenteral iron therapy is rarely indicated, may produce severe adverse effects, and should be reserved for patients who are genuinely intolerant of oral iron, persistently non-compliant,[3] who have gastrointestinal disorders exacerbated by oral iron therapy, continuing blood loss too severe for oral treatment to provide sufficient iron, or for those unable to absorb iron adequately from the gastrointestinal tract. Patients with chronic renal failure on haemodialysis (and some on peritoneal dialysis) require regular iron. US guidelines[5] suggest that intravenous use is preferred in haemodialysis patients, but that iron may be given either intravenously or orally in predialysis and peritoneal dialysis patients. The most common parenteral forms are iron dextran, iron sorbitol, iron sucrose, and sodium ferric gluconate complex.

Exceptionally, in patients with profound anaemia, blood transfusion may be necessary to restore dangerously low concentrations of haemoglobin. This may be the case, for example, in cases of worsening angina or severe coexisting pulmonary disease.[1] However, transfusion should always be avoided if possible.

Prophylaxis. Prophylaxis may be desirable in some groups at risk of iron deficiency and consequent anaemia, and may include therapy with oral iron supplements, measures to improve dietary iron intake, fortification of food staples, or control of infection. For the possible problems associated with iron supplementation in those who are not deficient, see Effects in Non-deficient Subjects, under Precautions, p. 2074.3.

WHO[2] recommends that universal supplementation of iron and folic acid should be implemented for pregnant women, starting as soon as possible after gestation starts and continuing for the rest of the pregnancy. WHO also recommends that where anaemia prevalence is above 40%, women of child-bearing age and lactating women should be given 3 months of iron and folic acid supplementation. However, the US Preventive Services Task Force has reviewed the subject of iron supplementation during pregnancy,[6] and concluded that there was insufficient evidence for or against routine supplementation.[7] A systematic review[8] found that weekly or daily antenatal iron supplementation, with or without folic acid, was effective at preventing anaemia and iron deficiency at term, although data on maternal and neonatal adverse outcomes such as low birth-weight, preterm birth, or postpartum haemorrhage were limited. Adverse effects, particularly haemoconcentration, (Hb greater than 130 g/litre) were associated with the use of iron; the authors considered that current preventative antenatal iron doses for use in developing countries appeared to be excessive. However, antenatal iron supplements may help reduce neonatal mortality in developing countries; a study[9] carried out in rural China found that antenatal iron and folic acid increased the duration of gestation, reduced preterm delivery, and reduced early neonatal mortality compared with folic acid alone. Antenatal micronutrients (supplementation with 15 minerals and vitamins including folic acid and a lower dose of iron) increased birth-weight compared with folic acid alone, but did not affect early neonatal mortality.

Iron supplementation is accepted in menorrhagia, after gastrectomy, and in the management of low birth-weight infants such as the premature. Iron deficiency in infants and children may result in developmental delay or impairment of cognitive function.[2] Breast feeding should be encouraged during the first year of life.[1] WHO has suggested[2] that low birth-weight infants be given universal supplementation. Where the diet does not include foods fortified with iron or where anaemia prevalence is above 40%, iron supplementation should be given to all children between 6 and 23 months of age; for children aged 24 months and above, a 3-month course of iron supplementation should be given where the anaemia prevalence is above 40%.

The usual prophylactic dose in adults suggested by WHO is about 60 mg of elemental iron daily (see also Uses and Administration above). Doses of about 2 mg/kg of elemental iron daily (up to 30 mg) have been suggested for prophylaxis in children (see also Administration in Children, above).

Dietary measures, such as addition of vitamin-C-rich foods, or other enhancers of iron absorption including iron in the form of haem (found in meat or fish) to the diet, control of parasitic infections such as hookworm (which are responsible for considerable occult blood loss), and malaria prophylaxis are particularly important for the general community in developing countries. Fortification of food staples poses technical problems as iron salts react with food components and may produce rancidity or other undesirable changes on storage. Nonetheless, wheat or maize flour, rice, and milk products have been fortified in some countries, and consideration has also been given to fortification of salt or sugar.

1. Provan D. Iron deficiency anaemia. In: Provan D, ed. *ABC of clinical haematology*. 2nd ed. London: BMJ Books, 2003: 1–4.
2. WHO. *Iron deficiency anaemia assessment, prevention, and control: a guide for programme managers*. Geneva: WHO, 2001. Available at: http://www.who.int/entity/nutrition/publications/en/ida_assessment_prevention_control.pdf (accessed 11/07/06)
3. British Society of Gastroenterology. Guidelines for the management of iron deficiency anaemia (issued May 2005). Available at: http://www.bsg.org.uk/pdf_word_docs/iron_def.pdf (accessed 09/11/05)
4. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. *Lancet* 2007; 370: 511–20.
5. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in adults. *Am J Kidney Dis* 2006; 47 (suppl 3): S16–S85. Correction. *ibid.*; 48: 518. Also available at: http://www.kidney.org/professionals/KDOQI/guidelines_anemia/index.htm (accessed 04/12/06)

6. US Preventive Services Task Force. Routine iron supplementation during pregnancy: review article. *JAMA* 1993; 270: 2848–54.
7. US Preventive Services Task Force. Routine iron supplementation during pregnancy: policy statement. *JAMA* 1993; 270: 2846–8.
8. Peña-Rosas JP, Viteri FE. Effects and safety of preventive oral iron or iron+folic acid supplementation for women during pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 05/02/10).
9. Zeng L, *et al.* Impact of micronutrient supplementation during pregnancy on birth weight, duration of gestation, and perinatal mortality in rural western China: double blind cluster randomised controlled trial. Abridged version: *BMJ* 2008; 337: 1211–15. Full version: http://www.bmj.com/cgi/reprint/337/nov07_4/a2001 (accessed 16/03/09) Correction. *ibid.* a2522.

Restless legs syndrome. Iron deficiency is present in about a quarter of people with restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2), particularly older people, and serum ferritin concentrations are inversely correlated with the severity of symptoms. Iron may have a role in the pathophysiology of the disorder, and treatment of iron deficiency may reduce symptoms.[1]

1. Medcalf P, Bhatia KP. Restless legs syndrome. *BMJ* 2006; 333: 457–8.

Adverse Effects

The astringent action of **oral** iron preparations sometimes produces gastrointestinal irritation and abdominal pain with nausea and vomiting. These irritant adverse effects are usually related to the amount of elemental iron taken rather than the type of preparation. Other gastrointestinal effects may include either diarrhoea or constipation. Adverse effects can be reduced by giving it with or after food (rather than on an empty stomach) or by beginning therapy with a small dose and increasing gradually. Modified-release products are claimed to produce fewer adverse effects but this may only reflect the lower availability of iron from these preparations. Oral liquid preparations containing iron salts may blacken the teeth and should be drunk through a straw. The faeces of patients taking iron salts may be coloured black.

The adverse effects associated with iron given **parenterally** are described under iron dextran (see p. 2076.1).

Since absorbed iron is conserved by the body, **iron overload**, with increased storage of iron in various tissues (haemosiderosis), may occur as a result of excessive or mistaken therapy, especially parenteral therapy. Patients with pre-existing iron storage or absorption diseases are also at risk.

Acute iron **overdosage** can be divided into four stages.

- In the first phase, which occurs up to 6 hours after oral ingestion, gastrointestinal toxicity, notably vomiting and diarrhoea, predominates. Other effects may include cardiovascular disorders such as hypotension, metabolic changes including acidosis and hyperglycaemia, and CNS depression ranging from lethargy to coma. Patients with only mild to moderate poisoning do not generally progress past this first phase.
- The second phase, which is not always seen, may occur at 6 to 24 hours after ingestion and is characterised by a temporary remission or clinical stabilisation.
- In the third phase, 12 to 48 hours after ingestion, gastrointestinal toxicity recurs together with shock, metabolic acidosis, severe lethargy or coma, hepatic necrosis and jaundice, hypoglycaemia, coagulation disorders, oliguria or renal failure, and possible myocardial dysfunction.
- The fourth phase may occur several weeks after ingestion and is characterised by gastrointestinal obstruction and possibly late hepatic damage.

Relatively small amounts of iron may produce symptoms of toxicity. It has been stated that more than the equivalent of 20 mg/kg of iron could lead to some symptoms of toxicity and that toxicity is likely with doses containing more than the equivalent of about 60 mg/kg of iron; the equivalent of 200 to 250 mg/kg iron is considered potentially fatal. Serum-iron concentrations have also been used as an indication of the severity of overdosage, see below.

Effects on the cardiovascular system. For a suggestion that iron overload may contribute to ischaemic heart disease, see Effects in Non-deficient Subjects, below.

Effects on growth. Iron supplementation in iron-replete children has been reported to adversely affect their growth—see Effects in Non-deficient Subjects, below.

Hypersensitivity. Oral iron supplements have been associated with hypersensitivity reactions; reports to Health Canada have included anaphylaxis and skin reactions such as rash, pruritus, urticaria, oedema, and photosensitivity.[1]

1. Health Canada. Oral iron supplements: skin reactions and other hypersensitivity reactions. *Can Adverse React News* 2010; 20 (3): 4–5. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/bulletin/carn-bcei_v20n3-eng.pdf (accessed 02/12/13)

Iron overload. Because the body lacks a mechanism for the excretion of excess iron, abnormally high absorption or repeated blood transfusion will result in iron overload (p. 1545.2), leading eventually to haemochromatosis. The consequences of haemochromatosis include pigment deposition in skin and other organs, mild liver dysfunction, endocrine dysfunction (failure of the adolescent growth spurt, hypogonadism, sometimes diabetes and hypothyroidism), and heart disease (pericarditis, heart failure, and arrhythmias). If unchecked, the iron build-up can lead to death, mainly through heart failure or arrhythmia. Where iron overload is due to increased absorption, phlebotomy is the treatment of choice; however, if phlebotomy is not tolerated or in patients who are transfusion-dependent (as in β-thalassaemia—see p. 1124.1) treatment with iron chelators such as desferrioxamine is used to retard accumulation.

Treatment of Adverse Effects

In treating acute iron poisoning, speed is essential to reduce absorption of iron from the gastrointestinal tract. Activated charcoal is ineffective, but whole bowel irrigation should be considered in those who have ingested the equivalent of more than 20 mg/kg of elemental iron within 6 hours of presentation. Serum-iron concentrations may be an aid to estimating the severity of poisoning. Although these do not always correlate well with symptoms, the UK Poisons Information Service considers that concentrations taken about 4 hours after ingestion generally indicate the severity of poisoning as follows:

- less than 3 micrograms/mL, mild poisoning
- 3 to 5 micrograms/mL, moderate poisoning
- more than 5 micrograms/mL, severe poisoning

Peak iron concentrations occur about 4 to 6 hours after ingestion.

Chelation therapy with desferrioxamine (p. 1544.1) can be considered for moderate to severe poisoning, and is guided by iron concentrations and symptoms. Iron concentrations should be measured when the patient presents, before chelation therapy is started. In patients with severe poisoning and symptoms such as coma or shock, desferrioxamine is given without waiting for the results of iron measurements. Desferrioxamine may also be considered in patients who are symptomatic and have a iron concentration above 5 micrograms/mL within 6 hours of ingesting more than 20 mg/kg iron. In asymptomatic patients with severe poisoning, those with moderate poisoning, or those presenting more than 6 hours after ingestion, further measurements of iron concentration determine the need for chelation.

Other measures include symptomatic management and treatment for metabolic acidosis (p. 1775.2). Haemodialysis does not remove iron efficiently but may be useful in acute renal failure to help remove the iron-desferrioxamine complex.

Maternal treatment of iron overdose should be as for the non-pregnant patient.

General references.

1. Proudfoot AT, *et al.* Management of acute iron poisoning. *Med Toxicol* 1986; 1: 83–100.
2. Mann KV, *et al.* Management of acute iron overdose. *Clin Pharm* 1989; 8: 428–40.
3. Mills KC, Curry SC. Acute iron poisoning. *Emerg Med Clin North Am* 1994; 12: 397–413.
4. Pine JS. Iron poisoning. *Curr Probl Pediatr* 2000; 30: 71–90.

Overdosage. References highlighting the specific problem of iron overdose in children.[1–4] Child-resistant packaging and warning labels may be helpful in reducing the problem.

1. Anonymous. Iron-containing drugs and supplements: accidental poisoning. *WHO Drug Inf* 1995; 9: 159–60.
2. Fitzpatrick R, Murray V. Iron toxicity: dietary supplements. *Pharm J* 1996; 256: 666.
3. CSM/MCA. Oral iron supplements: accidental overdose may be fatal in children. *Current Problems* 2001; 27: 14. Also available at: http://www.mhra.gov.uk/home/Idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 08/11/05)
4. Singhi SC, *et al.* Acute iron poisoning: clinical picture, intensive care needs and outcome. *Indian Pediatr* 2003; 40: 1177–82.

Overdosage in pregnancy. Limited data on the treatment of iron overdose in pregnancy from the UK National Teratology Information Service, suggested that treatment with desferrioxamine should not be withheld if clinically indicated.[1-3] Most pregnancies had a normal outcome. A literature review[4] of iron overdose in pregnant women found that women with peak serum-iron concentrations greater than or equal to 4 micrograms/mL were more frequently symptomatic, but that there was no relationship between peak iron level and frequency of spontaneous abortion, preterm delivery, congenital anomalies, or perinatal or maternal death. However, women with stage 3 iron toxicity, defined as those manifesting with hepatic, renal, or cardiac failure, were more likely to spontaneously abort, deliver preterm, or die.

1. McElhatton PR, *et al.* The consequences of iron overdose and its treatment with desferrioxamine in pregnancy. *Hum Exp Toxicol* 1991; 10: 251–9.
2. McElhatton PR, *et al.* Outcome of pregnancy following deliberate iron overdose by the mother. *Hum Exp Toxicol* 1993; 12: 579.
3. McElhatton PR, *et al.* The outcome of pregnancy following iron overdose by the mother. *Br J Clin Pharmacol* 1998; 45: 212P–213P.
4. Tran T, *et al.* Intentional iron overdose in pregnancy—management and outcome. *J Emerg Med* 2000; 18: 225–8.

Precautions

Iron compounds should not be given to patients receiving repeated blood transfusions or to patients with anaemias not produced by iron deficiency unless iron deficiency is also present. Oral and parenteral iron therapy should not be used together. Care should be taken in patients with iron-storage or iron-absorption diseases such as haemochromatosis, haemoglobinopathies, or existing gastrointestinal diseases such as inflammatory bowel disease, intestinal strictures and diverticulae.

Liquid preparations containing iron salts should be well diluted with water and swallowed through a straw to prevent discoloration of the teeth.

Effects in non-deficient subjects. There has been concern about the potential consequences of iron supplementation in individuals and groups who are not actually iron-deficient. Apart from the suggestion that certain populations may be at somewhat increased risk of microbial *infection* after supplementation (see Infections, below), there is some evidence that supplementation in children without iron deficiency may *retard their growth*.[1,2] It has also been proposed that iron may be associated with *ischaemic heart disease*, by modifying low-density lipoprotein in ways which increase its atherogenic potential and by sensitising the myocardium to ischaemic injury.[3,4] However, conclusions of a cohort study[5] and a systematic review[6] did not support any correlation between iron status and coronary heart disease. There is some suggestion that an excess of iron may be *carcinogenic*;[7,8] conclusive studies are lacking.

1. Idjradinata P, *et al.* Adverse effect of iron supplementation on weight gain of iron-replete young children. *Lancet* 1994; 343: 1252–4.
2. Dewey KG, *et al.* Iron supplementation affects growth and morbidity of breast-fed infants: results of a randomized trial in Sweden and Honduras. *J Nutr* 2002; 132: 3249–55.
3. Burt MJ, *et al.* Iron and coronary heart disease: iron's role is undecided. *BMJ* 1993; 307: 575–6.
4. Sullivan JL. Iron and coronary heart disease: iron makes myocardium vulnerable to ischaemia. *BMJ* 1993; 307: 1066–7.
5. Sempos CT, *et al.* Serum ferritin and death from all causes and cardiovascular disease: the NHANES II Mortality Study. *Ann Epidemiol* 2000; 10: 441–8.
6. Danesh J, Appleby P. Coronary heart disease and iron status: meta-analyses of prospective studies. *Circulation* 1999; 99: 852–4.
7. Deugnier Y. Iron and liver cancer. *Alcohol* 2003; 30: 145–50.
8. Huang X. Iron overload and its association with cancer risk in humans: evidence for iron as a carcinogenic metal. *Mutat Res* 2003; 533: 153–71.

INFECTIONS. Iron is not only an essential element for humans but is also essential for many micro-organisms. Thus, it has been suggested that persons with either adequate iron stores or iron overload may provide optimum conditions for microbial growth and therefore be susceptible to an increased incidence and severity of infection; conversely, iron-deficiency anaemia may offer some protection against infections. The topic has been reviewed[1,2] and although there is no evidence that small amounts of iron supplements or iron-fortified food in normal people will render them more prone to infection[3] there is some evidence that in populations with a high prevalence of endemic infectious disease such as malaria, iron therapy may be followed by a higher incidence of infectious complications or by a flare-up of existing low-grade disease. Therefore, the routine use of iron supplements in such communities has been questioned,[4,5] although an increasing number of studies failed to show a detrimental effect.[6-10] A subsequent systematic review[11] concluded that, while iron supplementation slightly increases the risk of developing diarrhoea, it has no apparent harmful effect on the overall incidence of infectious illnesses in children. More recently, a controlled study found that supplementation with iron and folic acid increased the risk of severe illness and death in pre-school children in a population with high rates of malaria. The authors concluded that, while iron-deficient children can benefit from supplementation in the presence of active prophylaxis and treatment of malaria, supplementation in non-deficient subjects might be harmful.[12] Data conflict on the association between parenteral iron and infection in dialysis patients; some consider that treatment with parenteral iron should be avoided during active infection.[13,14]

1. Hershko C, *et al.* Iron and infection. *BMJ* 1988; 296: 660–4.
2. Oppenheimer SJ. Iron and its relation to immunity and infectious disease. *J Nutr* 2001; 131 (suppl): 616S–633S.
3. Bullen JJ, Ward CG. Iron and infection. *BMJ* 1988; 296: 1539.
4. Oppenheimer SJ, *et al.* Iron supplementation increases prevalence and effects of malaria: report on clinical studies in Papua New Guinea. *Trans R Soc Trop Med Hyg* 1986; 80: 603–12.

5. Smith AW, *et al.* The effects on malaria of treatment of iron-deficiency anaemia with oral iron in Gambian children. *Ann Trop Paediatr* 1989; 9: 17–23.
6. Harvey PWJ, *et al.* The effect of iron therapy on malarial infection in Papua New Guinean schoolchildren. *Am J Trop Med Hyg* 1989; 40: 12–18.
7. Boele van Hensbroek M, *et al.* Iron, but not folic acid, combined with effective antimalarial therapy promotes haematological recovery in African children after acute falciparum malaria. *Trans R Soc Trop Med Hyg* 1995; 89: 672–6.
8. van den Hombergh J, *et al.* Does iron therapy benefit children with severe malaria-associated anaemia? A clinical trial with 12 weeks supplementation of oral iron in young children from the Turiani Division, Tanzania. *J Trop Pediatr* 1996; 42: 220–7.
9. Menendez C, *et al.* Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. *Lancet* 1997; 350: 844–50.
10. Mebrahtu T, *et al.* Low-dose daily iron supplementation for 12 months does not increase the prevalence of malarial infection or density of parasites in young Zanzibari children. *J Nutr* 2004; 134: 3037–41.
11. Gera T, Sachdev HPS. Effect of iron supplementation on incidence of infectious illness in children: systematic review. *BMJ* 2002; 325: 1142.
12. Sazawal S, *et al.* Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. *Lancet* 2006; 367: 133–43.
13. Brewster UC, Perazella MA. Intravenous iron and the risk of infection in end-stage renal disease patients. *Semin Dial* 2004; 17: 57–60.
14. Maynor L, Brophy DF. Risk of infection with intravenous iron therapy. *Ann Pharmacother* 2007; 41: 1476–80.

Interference with diagnostic tests. Although studies *in vitro* found that iron (ferrous sulfate) caused a false-positive result in the Hemoccult test for blood in faeces, this did not occur *in vivo* in persons receiving oral iron therapy.[1-3] An explanation for the difference in these findings was that hydrogen peroxide in the Hemoccult developer converted ferrous ions in solution to ferric ions, which caused oxidation in the test, whereas *in vivo* the iron was probably eliminated in the faeces in the form of non-reactive insoluble iron precipitates.[2]

1. Kulbaski MJ, *et al.* Oral iron and the Hemoccult test: a controversy on the teaching wards. *N Engl J Med* 1989; 320: 1500.
2. McDonnell M, Eita G. More on oral iron and the Hemoccult test. *N Engl J Med* 1989; 321: 1684.
3. Anderson GD, *et al.* An investigation into the effects of oral iron supplementation on in vivo Hemoccult stool testing. *Am J Gastroenterol* 1990; 85: 558–61.

Porphyria. Erythropoietic protoporphyria was exacerbated by oral iron therapy in 4 patients;[1] a further patient had a variable reaction to iron, being able to tolerate it on some occasions but suffering from exacerbation of porphyria on others.[2] Intravenous iron precipitated porphyria cutanea tarda in one patient on haemodialysis.[3]

The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, offers classifications and recommendations for various iron preparations — see Ferrous Fumarate (p. 2061.1), Ferrous Gluconate (p. 2061.2), Ferrous Succinate (p. 2062.1), Ferrous Sulfate (p. 2062.2), and Iron Sucrose (p. 2078.2).

1. Milligan A, *et al.* Erythropoietic protoporphyria exacerbated by oral iron therapy. *Br J Dermatol* 1988; 119: 63–6.
2. McClements BM, *et al.* Erythropoietic protoporphyria and iron therapy. *Br J Dermatol* 1990; 122: 423–6.
3. McKane W, *et al.* Porphyria cutanea tarda precipitated by intravenous iron in a haemodialysis patient. *Nephrol Dial Transplant* 2001; 16: 1936–8.

Interactions

Iron salts are not well absorbed orally, and food may further impair their absorption.

Compounds containing calcium and magnesium, including antacids and mineral supplements, and bicarbonates, carbonates, oxalates, or phosphates, may impair the absorption of iron by the formation of insoluble complexes. Zinc salts may also decrease the absorption of iron. The absorption of both iron salts and tetracyclines is diminished when taken together orally. If treatment with both drugs is required, a time interval of about 2 to 3 hours should be allowed between them. A suitable interval is also advised if an iron supplement is needed in patients given trientine. Iron is chelated by acetohydroxamic acid, reducing the absorption of both. Iron should not be given with dimercaprol as toxic complexes may form.

The response to iron may be delayed in patients receiving systemic chloramphenicol.

Some agents, such as ascorbic acid and citric acid, may actually increase the absorption of iron.

In addition to those already mentioned, iron salts can also decrease the absorption of other drugs and thus reduce their bioavailability and clinical effect. Drugs so affected include cefdinir, bisphosphonates, entacapone, fluoroquinolones, levodopa, methyldopa, mycophenolate mofetil, and penicillamine. Iron salts may reduce the efficacy of levothyroxine (p. 2342.1).

Interactions with parenteral iron are mentioned under Iron Dextran, p. 2077.1.

Reviews.

1. Campbell NRC, Hasinoff BB. Iron supplements: a common cause of drug interactions. *Br J Clin Pharmacol* 1991; 31: 251–5.

Pharmacokinetics

Iron is irregularly and incompletely absorbed from the gastrointestinal tract, the main sites of absorption being the duodenum and jejunum. Absorption is aided by the acid secretion of the stomach and by some dietary acids (such as ascorbic acid) and occurs more readily when the iron is in the ferrous state or is part of the haem complex (haem-iron). Absorption is also increased in conditions of iron deficiency or in the fasting state but is decreased if the body stores are overloaded. Normally only about 5 to 15% of the iron ingested in food is absorbed.

Most absorbed iron is bound to transferrin and transported to the bone marrow where it is incorporated into haemoglobin; the remainder is contained within the storage forms, ferritin (p. 2060.2) or haemosiderin, or as myoglobin, with smaller amounts occurring in haem-containing enzymes or in plasma bound to transferrin.

Only very small amounts of iron are excreted as the majority released after the destruction of the haemoglobin molecule is re-used. This conservation of body iron, and lack of an excretory mechanism for excess iron, is the reason for the development of iron overload with excessive iron therapy or repeated transfusions.

General references.

1. Harju E. Clinical pharmacokinetics of iron preparations. *Clin Pharmacokinet* 1989; 17: 69–89.

Human Requirements

The body contains about 4 g of iron most of which is present as haemoglobin.

Apart from haemorrhage, iron is mainly lost from the body in the faeces, urine, from skin, and sweat, but the total loss is very small. Iron is also lost in small amounts in breast milk and in menstrual blood. In healthy men and postmenopausal women the loss is replaced by the absorption of about 1 mg of iron daily; about 1.5 to 2 mg needs to be absorbed daily by premenopausal women. In childhood and adolescence, the need is proportionately greater because of growth. Iron absorption is variable but is usually between 5 and 15% and therefore a dietary allowance containing the equivalent of about 10 mg of iron daily is usually sufficient for men and postmenopausal women; up to 15 mg daily may be necessary for premenopausal women with normal menstrual blood losses; some authorities recommend higher amounts or supplements during pregnancy. For further details concerning dietary requirements, see below and for a discussion of prophylactic iron given during pregnancy, see Iron-deficiency Anaemia, under Uses and Administration, p. 2073.2.

Good dietary sources of haem-iron are animal products such as meat and fish; non-haem-iron is also found in animal products and in vegetable products such as legumes and some leafy vegetables, but some vegetable products with a high iron content also contain phosphates or phytates which inhibit absorption by the formation of unabsorbable complexes.

UK and US recommended dietary intake. In the UK, dietary reference values (DRV)[1] and in the USA, recommended dietary allowances (RDA)[2] have been published for iron.

In the UK the estimated average requirement (EAR) for adult males and postmenopausal females is 6.7 mg daily and the reference nutrient intake (RNI) is 8.7 mg daily; for premenopausal females, but without heavy menstrual blood losses, the EAR and RNI are 11.4 and 14.8 mg daily respectively. Amounts for infants, children, and adolescents, which are proportionately higher than those for adults, are also given. No increase is considered necessary during pregnancy or lactation.[1]

In the USA the RDA for adult males and postmenopausal females is 8 mg daily and that for premenopausal women is 18 mg. The tolerable upper intake level is 45 mg daily. Amounts for infants, children, and adolescents, again proportionately higher than for adults, are also provided. The RDA for pregnant women is 27 mg daily. An RDA of 9 mg for lactating adult women has been estimated from the EAR of non-menstruating women plus the average iron content of human milk.[2]

The Food and Agriculture Organization of the United Nations and the WHO have together published guidelines concerning iron requirements and these take into account many factors including bioavailability of iron in the diet.[3]

For the definitions of DRV, EAR, RNI, and RDA, see under Vitamins, p. 2046.1.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. FAO/WHO. *Requirements of vitamin A, iron, folate and vitamin B_{12}: report of a joint FAO/WHO expert consultation*. Rome: Food and Agriculture Organization of the United Nations, 1988.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Myrafer; *Canad.*: Gento-Iron†; *Hong Kong*: Hausmann Ferrum†; *India*: Biofer; Eleron; Evaglow; Fegem; Fejet-IV; Ferisan-S; Feritin; Ferium; Feriz; Fesafe; Folinal Plus; HB Fast; Orofer; Phosfomin Iron; *Indon.*: Ferromia†; *Israel*: Ferrocal; *Ital.*: Profer; *Jpn*: Ferromia; *Malaysia*: Ferrocyte; *Mex.*: Unifer; *Singapore*: Ferrocyte; *Thai.*: Ferrocyte†; *USA*: EZFE; Icar; iFerex; Ircon; ProFe; Wee Care.

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

Homoeopathic Preparations. *Austral.*: Hangover Relief; *Austria*: Dalektro; *Canad.*: Formula FA 224†; *Chile*: Ikoplex No 2; *Cz.*: Ferrum Homaccord†; *Fr.*: Ferrum Complexe No 29; *Ger.*: Conva-cyl Ho-Len-Complex; Cranio-cyl Ho-Len-Complex; Delto-cyl Ho-Len-Complex; Nuxal comp; *Neth.*: Biodoron; Emvita 11; Geovita.

Pharmacopoeial Preparations

USP 36: Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Iron Dextran

Complejo de hierro dextrano; Demir Dekstran; Hierro dextrano; Iron-Dextran Complex; Железо-Декстрановый Комплекс.

CAS — 9004-66-4.

ATC Vet — QB03AB90; QB03AC90.

UNII — 9SHR524N2M.

Pharmacopoeias. *Br.*, *Chin.*, and *US* include injections.

BP 2014: (Iron Dextran Injection). A sterile colloidal solution containing a complex of ferric hydroxide and dextrans of weight average molecular weight between 5000 and 7000. It contains 4.75 to 5.25% of iron and 17.0 to 23.0% of dextrans. pH 5.2 to 6.5.

USP 36: (Iron Dextran Injection). A sterile colloidal solution of ferric hydroxide in complex with partially hydrolysed dextran of low molecular weight. It may contain not more than 0.5% of phenol as a preservative. pH 5.2 to 6.5.

Uses and Administration

Iron dextran is given by injection, and should be used only in the treatment of proven iron-deficiency anaemia (p. 2073.2) where oral therapy is ineffective or impracticable.

For iron-deficiency anaemia, total dosage is calculated according to the haemoglobin concentration and body-weight of the patient; allowance is also made for additional iron to replenish iron stores. Iron dextran injection is usually supplied with a table from which the recommended dose can be obtained for patients of different weights and haemoglobin (Hb) status. There may be variations between countries in the doses obtained from such tables. Doses can also be calculated from various formulas. A typical formula used for a preparation containing the equivalent of 50 mg/mL of iron is:

$$\text{Dose in mL} = [0.0442 \times \text{body-weight (kg)} \times [\text{desired Hb level (g/100 mL)} - \text{measured Hb level}]] + (0.26 \times \text{body-weight})$$

In adults, the calculated lean body-weight should normally be used in this formula rather than the actual body-weight. Note that doses obtained from tables or the above formulas are for iron-deficiency anaemia, and are not suitable for iron replacement for simple blood loss.

Before starting therapy, some licensed product information recommend a **test** dose via the intended route with observation for adverse reactions, but see Hypersensitivity (p. 2076.2) for a discussion of the value of such doses.

The total dose requirement may be given as a series of **intramuscular** injections daily or once or twice weekly. It is given by deep intramuscular injection into the upper outer quadrant of the buttock; to prevent leakage along the injection track, the subcutaneous tissue is drawn to one side before the needle is inserted. Before the first therapeutic dose, a test dose may be given and the patient observed for at least 1 hour: a dose of 0.5 mL (25 mg) has been suggested.

Thereafter, up to 2 mL (100 mg) may be given daily until the required dose is reached.

Iron dextran is also given **intravenously** either by total-dose infusion (TDI) or as divided injections. US licensed product information recommends that a test dose of 25 mg is given before the first therapeutic dose and that the patient is observed for at least 1 hour; if no adverse reactions occur within that time, the remainder of the initial dose may be given. In the UK, the first portion of every dose is given more slowly than the remainder of the dose, during which time the patient is observed for adverse reactions; recommendations for the rate at which this is done may vary in different countries.

In total-dose infusion, the total dose calculated according to the haemoglobin concentration (as outlined above) is given by slow intravenous infusion in about 500 mL of sodium chloride 0.9% or glucose 5%; sodium chloride may be preferable because of the reduced incidence of thrombophlebitis. The first 25 mg of iron should be infused over 5 to 15 minutes. UK licensed product information recommends that if no adverse reaction has occurred during this time the rate of infusion may be increased progressively to 45 to 60 drops/minute; the infusion usually takes 4 to 6 hours.

For divided intravenous use, the total dose is also calculated according to the haemoglobin concentration. In the UK, the usual recommended dosage schedule is 100 to 200 mg of iron given 2 or 3 times weekly until the total dose has been given. It may be given diluted in 10 to 20 mL of sodium chloride 0.9% or glucose 5%; the first 25 mg of iron is given slowly over 1 to 2 minutes. If no adverse reactions occur within 15 minutes, the remaining portion of the dose is given. Alternatively, 100 to 200 mg may be diluted in 100 mL of sodium chloride 0.9% or glucose 5%; the first 25 mg of iron is given over 15 minutes and if no adverse reactions occur during this time, the remaining portion of the infusion is given at a rate of not more than 100 mL in 30 minutes. In the USA, the injection may be given undiluted at a rate not exceeding 50 mg iron (1 mL) per minute; maximum daily doses are similar to those given for intramuscular injection.

For use in children, see Administration in Children, below.

Administration in children. In some countries, including the USA, iron dextran is licensed in children from 4 months of age to treat iron-deficiency anaemia (p. 2073.2) when oral therapy is not possible or ineffective. The total dose is calculated according to the haemoglobin concentration and body-weight of the child. Licensed product information usually contains a table with doses for patients of different weights and haemoglobin status. A formula can also be used to calculate the dose; an example is given in Uses and Administration, p. 2075.3.

Iron dextran is usually given as a series of daily deep intramuscular injections until the required dose is reached, but it may also be given as a series of daily slow intravenous injections. A total dose intravenous infusion may be used in some countries. Before starting therapy, some licensed product information recommend a test dose given via the intended route and the child observed for adverse reactions, but see Hypersensitivity (below) for a discussion of the value of such doses. The following test doses have been suggested according to body-weight:

- less than 10 kg: 0.2 mL (10 mg)
- 10 to 20 kg: 0.3 mL (15 mg)
- over 20 kg: 0.5 mL (25 mg), as for adults

Provided no untoward reaction occurs a therapeutic dose may then be given. If a test dose is not given, the first portion of every dose is administered more slowly than the remainder, and the patient observed for adverse effects.

When giving iron dextran as a series of divided intravenous or intramuscular injections, the following daily doses have been suggested as a maximum, according to body-weight, continued until the total dose has been given:

- under 5 kg: 0.5 mL (25 mg)
- 5 up to 10 kg: 1 mL (50 mg)
- 10 kg or more: as for adults, p. 2075.3

Adverse Effects and Treatment

Severe anaphylactoid reactions may occur with iron dextran and fatalities have been reported. It is therefore recommended that it be given where there are facilities for the emergency treatment of such reactions and that certain precautions be observed; the value of a test dose has been questioned (see Precautions, below for further details).

Rapid intravenous use may be associated with vascular flushing and hypotension. Thrombophlebitis may occur at the site of injection, although the incidence can be reduced by giving iron dextran in sodium chloride 0.9% rather than glucose 5%. Intramuscular injection is associated with local reactions, pain, and staining at the site of injection; leakage along the injection track may occur unless the proper technique is used (see Uses and Administration, p. 2075.3). Cardiovascular effects such as chest pain or tightness, shock, myocardial infarction, hypertension, tachycardia, bradycardia, and arrhythmias may occur with either route. Rashes, urticaria, purpura, and pruritus have been reported. Other reactions include gastrointestinal disturbances, haematuria, dyspnoea, and taste disturbance.

Patients may also have delayed reactions 1 to 2 days after injection of iron dextran, such as backache, arthralgia, myalgia, lymphadenopathy, chills, fever, paraesthesia, dizziness, malaise, headache, nausea, and vomiting.

Overdose of parenteral iron is unlikely to be associated with any acute manifestations. Unwarranted parenteral iron therapy will result in iron overload and excess storage of iron (haemochromatosis) in the long term. The consequences of this include liver and endocrine dysfunction and heart disease (see Iron Overload, p. 2074.2), and possibly an increased risk of infection (see Infections, under Precautions for Iron, p. 2074.3). Iron overload may require chelation therapy with desferrioxamine (p. 1544.1).

Intramuscular injection of iron complexes such as iron dextran has resulted in sarcomas at the injection site in *animals*. There is some evidence that this may occur in humans.

Incidence of adverse effects. For information about the incidence of adverse effects and comparison of the safety profiles of different intravenous iron products, see Hypersensitivity, below.

Effects on the blood. A 1-year-old girl with Down's syndrome and iron-deficiency anaemia was given 3 intramuscular injections of iron dextran over 6 days (to a total of 30 mg/kg). Pancytopenia, which developed subsequently, reappeared when challenged with iron dextran. Tests indicated an allergic pathogenesis for the pancytopenia.[1] For further discussion of hypersensitivity reactions to iron dextran, see under Hypersensitivity, below.

Thrombocytopenia has also been reported after iron dextran[2] and iron sucrose[3] therapy.

1. Hurvitz H, *et al.* Pancytopenia caused by iron-dextran. *Arch Dis Child* 1986; 61: 194–6.
2. Go RS, *et al.* Thrombocytopenia after iron dextran administration in a patient with severe iron deficiency anemia. *Ann Intern Med* 2000; 132: 925.
3. Taskapan H, *et al.* Transient severe thrombocytopenia in a patient on CAPD after intravenous iron administration. *Perit Dial Int* 2003; 23: 408–9.

Hypersensitivity. The Boston Collaborative Drug Surveillance Program monitored consecutively 32 812 medical inpatients. Drug-induced anaphylaxis occurred in 1 of 169 patients given iron dextran (route not stated).[1] An investigation of 481 persons given a total of 2099 intravenous injections of iron dextran found 3 life-threatening immediate anaphylactoid reactions; 8 severe delayed reactions were also observed, and many reactions of a less serious nature.[2] In a more recent series,[3] 10 of 573 patients had anaphylactoid reactions after intravenous iron dextran. Other serious reactions included 1 case of cardiac arrest, and 3 cases of dyspnoea, hypertension, or chest pain.

Licensed product information may recommend a test dose before giving a full therapeutic dose (see Uses and Administration, p. 2075.3); however, hypersensitivity reactions have still occurred when doses were previously tolerated, and the EMA does not consider a test dose a reliable way to predict how the patient will respond.[4] A desensitisation protocol has been used successfully in a patient who reacted to the test dose[5] and in a patient with a previous life-threatening reaction to iron infusion;[6] methylprednisolone 50 mg was given intravenously at 13 hours, 7 hours, and 1 hour before iron dextran, and diphenhydramine 50 mg and ephedrine 25 mg were given intramuscularly 1 hour before infusion. Dextran 1 (p. 1137.3) was given just before the iron dextran infusion. Approximately 2 g of iron was then given over a period of about 4 days.

It is not clear whether hypersensitivity to iron dextran is due to the dextran or the iron component.[7-9] When compared with lower molecular-weight iron dextran, a higher molecular-weight iron dextran was reported to be associated with significantly higher rates of adverse reactions,[8,10,11] including fatalities and anaphylactoid reactions;[10] some have called for the use of high-molecular-weight iron dextran to be abandoned.[12] Reviews[7,9,13,14] suggest that parenteral dextran-free iron compounds such as iron sucrose or sodium ferric gluconate complex may be safer alternatives to iron dextran. Iron sucrose has been reported to be well tolerated in patients previously intolerant to iron dextran, sodium ferric gluconate complex, or both.[15,16] Iron sucrose was considered to have the most favourable safety profile when compared with iron dextran and sodium ferric gluconate;[14] a comparison of adverse reaction rates found that iron sucrose and sodium ferric gluconate had much lower rates of adverse effects than iron dextran or ferumoxytol.[17] However, adverse reactions have still been reported in patients treated with dextran-free preparations,[9,18] and some have challenged the view that they are safer than iron dextran.[19,20]

In a report of a lupus-like disorder associated with use of iron dextran,[21] the illness resolved with appropriate treatment but recurred on rechallenge.

Due to the risk of severe hypersensitivity reactions, use of intravenous iron products is restricted during pregnancy, see Pregnancy, p. 2077.1.

For discussion of pancytopenia believed to have an underlying allergic pathogenesis, see Effects on the Blood, above.

1. Porter J, Jick H. Drug-induced anaphylaxis, convulsions, deafness, and extrapyramidal symptoms. *Lancet* 1977; i: 587–8.
2. Hamstra RD, *et al.* Intravenous iron dextran in clinical medicine. *JAMA* 1980; 243: 1726–31.
3. Fishbane S, *et al.* The safety of intravenous iron dextran in hemodialysis patients. *Am J Kidney Dis* 1996; 28: 529–34.
4. EMA. New recommendations to manage the risk of allergic reactions with intravenous iron-containing medicines (issued 28th June. 2013). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC500144874.pdf (accessed 02/12/13)
5. Monaghan MS, *et al.* Safe administration of iron dextran to a patient who reacted to the test dose. *South Med J* 1994; 87: 1010–12.
6. Hickman MA, *et al.* Successful administration of iron dextran in a patient who experienced a life threatening reaction to intravenous iron dextran. *Ann Allergy Asthma Immunol* 2000; 84: 262–3.
7. Fishbane S. Safety in iron management. *Am J Kidney Dis* 2003; 141 (suppl): S18–S26.
8. McCarthy JT, *et al.* Adverse events in chronic hemodialysis patients receiving intravenous iron dextran—a comparison of two products. *Am J Nephrol* 2000; 20: 455–62.
9. Fishbane S, Kowalski EA. The comparative safety of intravenous iron dextran, iron saccharate, and sodium ferric gluconate. *Semin Dial* 2000; 13: 381–4.
10. Chertow GM, *et al.* On the relative safety of parenteral iron formulations. *Nephrol Dial Transplant* 2004; 19: 1571–5.
11. Auerbach M, *et al.* Clinical update: intravenous iron for anaemia. *Lancet* 2007; 369: 1502–4.
12. Auerbach M, Rodgers GM. Intravenous iron. *N Engl J Med* 2007; 357: 93–4.
13. Silverstein SB, Rodgers GM. Parenteral iron therapy options. *Am J Hematol* 2004; 76: 74–8.
14. Coppol E, *et al.* A comparative look at the safety profiles of intravenous iron products used in the hemodialysis population. *Ann Pharmacother* 2011; 45: 241–7.
15. Charytan C, *et al.* Safety of iron sucrose in hemodialysis patients intolerant to other parenteral iron products. *Nephron Clin Pract* 2004; 96: c63–c66.
16. Haddad A, *et al.* Use of iron sucrose in dialysis patients sensitive to iron dextran. *Saudi J Kidney Dis Transpl* 2009; 20: 208–11.
17. Baille GR. Comparison of rates of reported adverse events associated with i.v. iron products in the United States. *Am J Health-Syst Pharm* 2012; 69: 310–20.
18. Saadeh CE, Srkalovic G. Acute hypersensitivity reaction to ferric gluconate in a premedicated patient. *Ann Pharmacother* 2005; 39: 2124–7.
19. Eichbaum Q, *et al.* Is iron gluconate really safer than iron dextran? *Blood* 2003; 101: 3756–7.
20. Auerbach M, Al Talib K. Low-molecular weight iron dextran and iron sucrose have similar comparative safety profiles in chronic kidney disease. *Kidney Int* 2008; 73: 528–30.
21. Oh VMS. Iron dextran and systemic lupus erythematosus. *BMJ* 1992; 305: 1000.

Overdosage. A 29-year-old woman was given 32 mL iron dextran (*Imferon*) intravenously. Twenty-four hours later she developed muscle cramps, bilateral frontal headaches, with subsequent neck stiffness, and marked opisthotonia with photophobia.[1] The haemoglobin concentration did not rise after the infusion of iron which indicated there had been no iron deficiency. Thus, abnormally high concentrations of free iron had followed the iron therapy and this free iron was able to cross into the CSF and was responsible for the meningitic symptoms.

1. Shuttleworth D, *et al.* Meningism due to intravenous iron dextran. *Lancet* 1983; ii: 453.

Precautions

Iron dextran is contra-indicated in patients with severe liver damage or acute kidney infection. It is also contra-indicated in persons with a history of hypersensitivity to the preparation. Teratogenicity has been found in non-anaemic *animals* given the equivalent of about three times the maximum human dose and its use is restricted in pregnancy (see p. 2077.1).

Additionally, iron dextran should be given with caution to patients with a history of allergic disorders or asthma and in these patients the intramuscular, and not the intravenous, route should be used. Patients with rheumatoid arthritis may develop worsening of symptoms when given iron dextran intravenously. Patients with other inflammatory disorders may be at increased risk of delayed reactions. Large doses of iron dextran by infusion may lead to serum discoloration; this should not be mistaken as evidence of haemolysis. Oral iron salts should be stopped before giving parenteral iron.

Intravenous iron preparations should only be given when resuscitation facilities are available to treat allergic reactions immediately. Some licensed product information recommend a test dose before a full therapeutic dose (see Uses and Administration p. 2075.3), but see Hypersensitivity (above) for a discussion of the value of such doses.

Patients should be kept under observation for at least 30 minutes after intravenous doses.

Iron dextran formulated with phenol as a preservative is intended to be given by the intramuscular route only.

Pregnancy. Severe hypersensitivity reactions to intravenous iron products used during pregnancy can put both the mother and unborn child at risk, and the EMA recommends treatment should be confined to the second or third trimesters, provided the benefit outweighs the risk to the unborn child.[1]

1. EMA. New recommendations to manage the risk of allergic reactions with intravenous iron-containing medicines (issued 28th June, 2013). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC500144874.pdf (accessed 02/12/13)

Interactions

As for Iron, p. 2075.1.

Enalapril. Enalapril may possibly potentiate the adverse systemic reactions seen with intravenous iron therapy.[1]

1. Rolla G, *et al.* Systemic reactions to intravenous iron therapy in patients receiving angiotensin-converting enzyme inhibitor. *J Allergy Clin Immunol* 1994; 93: 1074–5.

Pharmacokinetics

After intramuscular injection iron dextran is absorbed primarily through the lymphatic system: most is absorbed after 3 days and the remainder over 3 to 4 weeks. A variable portion may become fixed in the muscle for several weeks or months. After intravenous infusion, iron dextran is taken up by the cells of the reticuloendothelial cells, particularly in the liver and spleen. The reticuloendothelial cells gradually separate iron from the iron-dextran complex; the distribution and elimination of iron is described on p. 2075.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cosmofer; Fexiron; Intrafer; Yectafer; *Austria*: Cosmofer; *Belg.*: Fercayl; *Canad.*: DexIron; Infufer; *China*: CosmoFer (科莫菲); *Denm.*: Cosmofer; *Fin.*: Cosmofer; *Fr.*: Ferrisat; *Ger.*: Cosmofer†; *Gr.*: Cosmofer; Ironate; Multiferrum; *India*: Ferri; Imferon; *Indon.*: Cosmofer; Hibiron†; *Irl.*: Cosmofer; *Mex.*: Driken†; Ferrocel; Ferroin; Hidex; Irondex; *Neth.*: Cosmofer; *Norw.*: Cosmofer; *Philipp.*: Cosmofer; *Port.*: Cosmofer; *S.Afr.*: Cosmofer; *Spain*: Cosmofer; *Swed.*: Cosmofer; *Switz.*: Ferrum Hausmann; *Thai.*: Cosmofer; Unodex; *Turk.*: Cosmofer; *UK*: Cosmofer; *Ukr.*: Ferrolecum (Ферролек); *USA*: DexFerrum; INFeD; *Venez.*: Cosmofer.

Multi-ingredient Preparations. *Arg.*: Yectafer Complex; *India*: Imferon P-12.

Pharmacopoeial Preparations
BP 2014: Iron Dextran Injection;
USP 36: Iron Dextran Injection.

Iron Phosphate

Ferri Phosphas; Ferric Phosphate; Iron Orthophosphate; Железа Фосфат.
$FePO_4$=150.8
CAS — 10045-86-0.
UNII — N6BAA189V1.

Pharmacopoeias.

Br. includes forms for homoeopathic preparations.

BP 2014: (Hydrated Iron(II) and Iron(III) Phosphate for Homoeopathic Preparations). A mixture of hydrated iron(II) phosphate and iron(III) phosphate and some hydrated oxides of iron. It contains not less than 16.0% of Fe^{2+}, equivalent to not less than 47.9% of $Fe_3(PO_4)_2$, $8H_2O$ = 501.6. A slate blue amorphous powder. Insoluble in water; soluble in hydrochloric acid. Protect from light.

BP 2014: (Hydrated Iron(III) Phosphate for Homoeopathic Preparations). It consists of $FePO_4.4H_2O$ = 222.9. A yellow to pale ochre powder. Insoluble in water; soluble in dilute mineral acids. Protect from light.

Profile

Iron phosphate is used as a source of iron in food supplements. It is also used as a molluscicide and is an ingredient in some fertilisers.

Homoeopathy

Iron phosphate has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Celloids IP 82†.

Multi-ingredient Preparations. *Austral.*: Celloid Compounds Magcal Plus†; Celloid Compounds Sodical Plus†; Duo Celloids CPIP†; Duo Celloids PCIP†; Duo Celloids PPIP†; Duo Celloids SPIP†; Hemidisc; Irontona†; Prosta Balance; Vitatona†.

Homoeopathic Preparations. *Austral.*: Earache Relief†; Pain & Fever Relief; Respatona Sore Throat; *Austria*: Aflubin; China Med Complex; Ferrum Phosphoricum comp; Globuli gegen Fieber und Grippe Nr 1; Globuli gegen Grippe; Metavirulent; Osanit Zahnungskugelchen; Proagil; Rheuma; Zahnkugelchen; *Canad.*: Artis-Heel†; Biochemic Phosphates; Calms Forte; Calnor†; Camilia; Combinaison†; Comp-Drops 5 Expectorant†; Den 141†; Diamite; Drosera Complex; Drosera Plex†; Earache; Homeovox; Hylands Bioplasma; Hylands Formula CF; Hylands Formula NT; Ikoplex 11 Digestion Aid†; Ikoplex 21†; Kids' Earache; Melange†; Minerals+; Nerve Tonic; Nuage Bioplasma†; Rexorubia†; Ton 1 Complex†; *Chile*: Ikoplex No 11; Ikoplex No 18; Ikoplex No 19; Ikoplex No 21; Ikoplex No 22; Ikoplex No 23; Ikoplex No 7; Ikoplex No 8; Influk; *Cz.*: Drosetux; Ferrum Homaccord†; Homeovox; *Fr.*: Aconitum Compose†; Boripharm No 1†; Drosera Compose; Drosetux; Homeovox; Infludo; Ipeca Compose; Jenoverine†; Kalium Phosphoricum Complexe No 100; Rexorubia; Selenium Complexe No 99; Silicea Complexe No 11; *Ger.*: Arthriplex; Cefasinu; Drufusan N†; Drufusan; Ferrum phosphoricum comp; Grippe-Gastreu S R6; Immunorell; Infifer N; metavirulent; Naranotox comp; Naranotox; Osanit; phono Gripp; Poly-Arthrisan M; Pulmosan Infekt; Ranocalcin HM; Refesan T; Secale-Gastreu; Sinfrontal; toxi-loges; *Hung.*: Aflubin; Drosetux; Homeovox; *Neth.*: Auriculite; Grippe-Gastreu R6; Hemorrolite; Homeovox; Jenoverine†; Kind 0-3 Chamodent; Kind 0-6 Kinditherm; Oteel H; Rhodolith-Gastreu R46; Rhumeel; *Port.*: Homeovox; *Rus.*: Aflubin (Афлубин); Anabar (Анабар); Homeovox (Гомеовокс); *S.Afr.*: Ferrum Phos Comp†; *Switz.*: Drosetux; Homeovox; Influaforce†; Lithiumeel; metavirulent; Omida comprimes homeopathiques pour la gorge; Regenaplex Nr 41a; Rheuma-Heel; Sinfrontal; Sinusin; *UK*: Fragador; New Era Elasto; *Ukr.*: Aflubin (Афлубин); Dentokind (Дентокинд); Dr Theiss Gripp Drops (Капли От Гриппа Др. Тайсс)†; Homeovox (Гомеовокс); *USA*: Preferred Remedies Cold & Flu.

Iron Polymaltose

Demir III Hidroksit Polimaltoz; Ferromaltose; Ferrum Polyisomaltose; Hierro polimaltosa; Железа (III) Гидроксид Полимальтозат.
UNII — UMS219H89V.

Profile

Iron polymaltose is a complex of ferric hydroxide and isomaltose. It is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in usual doses containing the equivalent of 100 mg of iron daily although up to 300 mg daily has been given in some countries. It is also given parenterally, the total dose being calculated and given by intravenous infusion or, preferably, as a series of intramuscular injections containing the equivalent of up to 200 mg of iron in a single day; injections are usually given only every few days. For further information relating to the parenteral use of iron, see Iron Dextran, p. 2075.3.

Iron isomaltoside 1000 is a complex of ferric iron and isomaltosides derived from the low-molecular-weight dextran fraction dextran 1 (p. 1137.3) that is given intravenously; it is used similarly to iron polymaltose for iron-deficiency anaemia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ferranin; Maltofer; Siderblut Poli; Siderblut; Vitalix; *Austral.*: Ferrosig; Ferrum H; *Braz.*: Endofer; Noripurum; Ultrafer; *Chile*: Ferium; Ferroral; Ferzun; Hemoval; Maltofer; *Cz.*: Ferrum†; Maltofer; *Denm.*: Monofer; *Fin.*: Maltofer; Monofer; *Ger.*: Ferrum Hausmann; *Gr.*: Antianem; Dextrifer; Feralice; Ferrata; Ferrobest; Ferrum Hausmann; Hemafer; Hydrofer-3; Monofer; Plus-Fer; Veltifer; *Hong Kong*: Ferrum Hausmann; *Hung.*: Maltofer; *India*: Carbiran; Ferich; Fericip; Ferid; Ferigil; Feritas; Ferium; Ferocid; Feron; Ferose; Ferro Hepatine; Ferron; Ferst; Feton; Gilfer; Globiron; Haemarange; Hbron; Hemglo; Hemsub; Malto-Mix; Maltofer; Mumfer; Orofer; *Indon.*: Maltofer; *Irl.*: Ferrum Hausmann; Monover; *Israel*: Ferripel; *Ital.*: Intrafer; *Malaysia*: Maltofer; Saferon; *Mex.*: Ferranina; *Neth.*: Monofer; *Norw.*: Monofer; *NZ*: Ferrosig; Ferrum H; *Pol.*: Ferrum Lek; *Port.*: Ferrum Hausmann; Maltofer; *Rus.*: Fenules Complex (Фенюльс Комплекс); Ferri (Ферри); Ferrum Lek (Феррум Лек); Maltofer (Мальтофер); *S.Afr.*: Ferrimed; *Singapore*: Ferrum Hausmann; *Spain*: Monoferro; *Swed.*: Monofer; *Switz.*: Maltofer; *Thai.*: Eurofer-Iron; Ferium; *Turk.*: Ferifer; Ferimax; Ferlos; Ferrum Hausmann; Maltofer; Santafer; Solufer; Veltifer; *UK*: Monofer; *Ukr.*: Fenules Baby (Фенюльс)†; Ferrum Lek (Феррум); Ferumbo (Ферумбо); Maltofer (Мальтофер); *Venez.*: Intafer; Maltofer.

Multi-ingredient Preparations. *Arg.*: Ferranin Complex; Hierro Dupofol†; Isis Fe; Maltofer Fol; Siderblut Complex; Siderblut Folic; Tenvic; Vitalix Complex; *Braz.*: Noripurum Folico; Noripurum Vitaminado; *Chile*: Ferroral Fol; Maltofer Fol Plus; Maltofer Fol†; *Cz.*: Maltofer Fol; *Gr.*: Dextrifer-Fol; Ferrum Fol Hausmann; Hemafer fol; *Hong Kong*: Eurofer; Maltofer Fol; *Hung.*: Maltofer Fol; *India*: Biofer; Carbofen; Carzin-IPC; Cheri; Facer; Fefa; Fegem; Femed; Femed; Fered; Ferich; Fericip; Feritas; Peritin; Ferium-C; Ferium; Ferom Grow; Feron; Ferose; Ferrasia; Ferro; Ferro; Ferronova; Ferrum Fol; Ferst; Feton; Folinal Plus; Globac-PM; Globiron; Glowcarb; Growell-PM; Hbron; Hem; Hemglo; Hemsub; Hepofer; Infer-Z; Ironifol; Irozys; Mumfer-Z; Mumfer; New-Feripro; Orofer Kit; *Indon.*: Peritrin; Maltofer Fol; *Irl.*: Ferrum Fol; *Israel*: Ferrifol; Tiptipot Ferripel + D; *Malaysia*: Eurofer; Maltofer; Saferon; *Mex.*: Ferranina Complex; Ferranina Fol; Ironfol; *Philipp.*: Eurofer; Orofer; Restor; *Port.*: Ferrum Fol; Maltoferfol†; *Rus.*: Biofer (Биофер); Ferri-Fol (Ферри-Фол); Maltofer Fol (Мальтофер Фол); *S.Afr.*: Ferrimed; *Singapore*: Eurofer†; Floron; *Switz.*: Maltofer Fol; *Thai.*: Eurofer; Orofer; *Turk.*: Ferlos; Ferrum Hausman Fort; Maltofer Fol; Santafer Fort; *Ukr.*: Maltofer Fol (Мальтофер Фол); *Venez.*: Intafer; Intaferfol; Maltoferfol.

Iron Sorbitol

Astra-1572; Demir Sorbitol; Hierro sorbitol; Iron Sorbitex (USAN); Iron-Sorbitol-Citric Acid Complex; Сорбитоловое Железо.
CAS — 1338-16-5.
ATC Vet — QB03AC03.

Pharmacopoeias. *US* includes an injection.

USP 36: (Iron Sorbitex Injection). A sterile solution of a complex of iron, sorbitol, and citric acid that is stabilised with the aid of dextrin and an excess of sorbitol. pH 7.2 to 7.9.

Profile

Iron sorbitol is a complex of ferric iron, sorbitol, and citric acid that has been given by deep intramuscular injection in the treatment of iron-deficiency anaemia (p. 2073.2); like iron dextran (p. 2076.1) its use is potentially hazardous and it should only be used where oral therapy is ineffective or impracticable.

Iron sorbitol should not be given intravenously.

Effects on the heart. Severe cardiac complications, including complete AV block, ventricular tachycardia, and atrial or ventricular fibrillation have occurred with iron sorbitol, and have sometimes proved fatal.

Of 3 patients with the malabsorption syndrome treated with intramuscular injections of iron sorbitol,[1] 2 died; in one, findings were consistent with anaphylaxis but in the other cardiac toxicity was considered to be due to a direct effect. In the third patient direct cardiac toxicity was also implicated. In another report,[2] a patient developed cardiac arrhythmia after his seventh injection of iron sorbitol. He was found to have a low serum concentration of alpha-tocopherol, supposed by the authors to be caused by the patient's malabsorption syndrome. This had apparently predisposed the patient to arrhythmia by contributing to myocardial cell sensitivity to lipid peroxidation, which is catalysed by ferrous ions. Insufficient alpha-tocopherol to scavenge the free radicals generated by the iron could also have led to loss of myocardial fatty acids, thereby disturbing membrane function. It was suggested that iron sorbitol was a less stable form of iron than iron dextran, and should be given with extreme caution to patients with malabsorption and low levels of alpha-tocopherol.

1. Kathunen P, *et al.* Reaction to iron sorbitol injection in three cases of malabsorption. *BMJ* 1970; 2: 521–2.
2. Lindvall S, *et al.* Alpha-tocopherol and cardiac toxicity of iron. *Scand J Haematol* 1980; 25: 331–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Jecktofer; *Turk.*: Jectofer†.

Multi-ingredient Preparations. *India*: Ferimax; Jectocos Plus.

Pharmacopoeial Preparations
USP 36: Iron Sorbitex Injection.

Iron Succinyl-Protein Complex

Demir III Protein Süksinat; Ferro Proteinsuccinilato; Hierro succinil-proteína, complejo de; Iron Proteinsuccinylate; ITF-282; Proteinsuccilinato de hierro; Железа Протеин Сукцинилат.
CAS — 93615-44-2.
ATC — B03AB09.
ATC Vet — QB03AB09.

Profile

Iron succinyl-protein complex is a source of iron (p. 2073.1) used for iron-deficiency anaemia (p. 2073.2). It is given orally in doses of up to 1.6 g daily (equivalent to up to 80 mg of iron daily).

References.
1. Köpcke W, Sauerland MC. Meta-analysis of efficacy and tolerability data on iron proteinsuccinylate in patients with iron deficiency anemia of different severity. *Arzneimittelforschung* 1995; 45: 1211–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Perplex; *Chile*: Fisiofer; Legofer; *China*: Perplex (蒂普利); *Cz.*: Perplex; *Gr.*: Pysiofer; Legofer; *India*: Perplex; *Ital.*: Feriatum; Perplex; Pernexin; Proteoferrina†; Rekord Ferro; Stratofer; *Mex.*: Ferxal; *Pol.*: Feroplex; *Port.*: Fervit; Fetrival; Legofer; *Rus.*: Feriatum (Фериатум); *Spain*: Ferplex; Ferrocur; Lactoferrina; *Turk.*: Ferplex; Komfer.

Multi-ingredient Preparations. *Gr.*: Pysiofol; Legofolin; *India*: Ferolact; *Ital.*: Ferrofolin; *Rus.*: Feriatum Fol (Фериатум Фол); *Turk.*: Ferplex Fol; Komfer Fol.

Iron Sucrose *(BAN, USAN)*

Demir Sükroz; Eisenzucker; Ferri oxidum saccharatum; Ferric Hydroxide Sucrose; Ferric Oxide, Saccharated; Ferrique (oxyde) sucré; Ferrum Oxydatum Saccharatum; Hierro sacarosa; Iron (III) hydroxide-sucrose complex; Iron Saccharate; Oxyde de Fer Sucré; Saccharated ferric oxide; Saccharated Iron Oxide; XI-921; Железа Оксид Сахарат.

CAS — 8047-67-4.
ATC — B03AB02; B03AC02.
ATC Vet — QB03AB02; QB03AC02.
UNII — FZ7NYF5N8L.

Pharmacopoeias. In *Swiss*.

Br. and *US* include an injection.

BP 2014: (Iron Sucrose Injection). A sterile colloidal solution containing a complex of iron(III) hydroxide with sucrose of average molecular weight between 34 000 and 60 000. It contains 1.90 to 2.10% w/v of iron (Fe) and 27.0 to 33.0% w/v of sucrose. pH 10.5 to 11.0.

USP 36: (Iron Sucrose Injection). A sterile, colloidal solution of ferric hydroxide in complex with sucrose in water for injection. Sodium hydroxide may be added to adjust the pH. It contains no antimicrobial agent, chelating agent, dextran, gluconate, or other added substances. pH 10.5 to 11.1 at 20 degrees. It is intended for intravenous use only. When given by intravenous infusion, it should be diluted with 0.9% sodium chloride injection to a concentration of 0.5 to 2.0 mg of elemental iron/mL. Do not allow to freeze.

Uses and Administration

Iron sucrose is used as a source of iron (p. 2073.1) for adults with iron-deficiency anaemia (p. 2073.2), including those with chronic kidney disease. It is given when oral iron therapy is ineffective or impractical, by slow intravenous injection, or intravenous infusion; when used in haemodialysis patients, it may be given into the venous limb of the dialyser. The dose is calculated according to body-weight and iron deficit. In the UK, the maximum single dose must not exceed 200 mg of iron given not more than three times weekly. The dose is split if the total necessary dose exceeds the maximum single dose. The dose may be given undiluted at a rate of 20 mg/minute. Alternatively, it is diluted to a minimum concentration of 1 mg/mL in sodium chloride 0.9% and given at a rate not exceeding 50 mL per 15 minutes.

In the USA, for patients with chronic kidney disease and on haemodialysis, a dose of 100 mg may be given per consecutive haemodialysis session, either undiluted as a slow intravenous injection over 2 to 5 minutes, or diluted in up to 100 mL sodium chloride 0.9% and infused over at least 15 minutes. For peritoneal dialysis patients, two infusions of 300 mg over 1.5 hours are given 14 days apart, followed by an infusion of 400 mg over 2.5 hours 14 days later. The doses are diluted in a maximum of 250 mL of sodium chloride 0.9%. For patients with chronic kidney disease but not on dialysis, a dose of 1 g is given over a 14-day period, as a 200 mg slow undiluted intravenous injection over 2 to 5 minutes on 5 separate occasions within this time. Iron sucrose has also been given orally.

Anaemia of chronic renal failure. References.
1. Charytan C, *et al.* Efficacy and safety of iron sucrose for iron deficiency in patients with dialysis-associated anemia: North American clinical trial. *Am J Kidney Dis* 2001; 37: 300–7.
2. Stoves J, *et al.* A randomized study of oral vs intravenous iron supplementation in patients with progressive renal insufficiency treated with erythropoietin. *Nephrol Dial Transplant* 2001; 16: 967–74.
3. Chandler G, *et al.* Intravenous iron sucrose: establishing a safe dose. *Am J Kidney Dis* 2001; 38: 988–91.
4. Blaustein DA, *et al.* The safety and efficacy of an accelerated iron sucrose dosing regimen in patients with chronic kidney disease. *Kidney Int* 2003; (suppl): S72–S77.
5. Charytan C, *et al.* Safety of iron sucrose in hemodialysis patients intolerant to other parenteral iron products. *Nephron Clin Pract* 2004; 96: 63–6.
6. Leijn E, *et al.* Intravenous iron supplementation in children on hemodialysis. *J Nephrol* 2004; 17: 423–6.
7. Aronoff GR, *et al.* Iron sucrose in hemodialysis patients: safety of replacement and maintenance regimens. *Kidney Int* 2004; 66: 1193–8.
8. Van Wyck DB, *et al.* The United States Iron Sucrose (Venofer) Clinical Trials Group. A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. *Kidney Int* 2005; 68: 2846–56.
9. Hollands JM, *et al.* Safety of high-dose iron sucrose infusion in hospitalized patients with chronic kidney disease. *Am J Health-Syst Pharm* 2006; 63: 731–4.

Iron-deficiency anaemia. A treatment protocol consisting of alternate day iron sucrose infusions was reported to be well tolerated and effective in improving haemoglobin concentrations in patients with iron deficiency anaemia (and without severe chronic kidney disease).[1]

1. Wall GC, Pauly RA. Evaluation of total-dose iron sucrose infusions in patients with iron deficiency anemia. *Am J Health-Syst Pharm* 2008; 65: 150–3.

Adverse Effects, Treatment, and Precautions

For parenteral iron, see Iron Dextran, p. 2076.1. Iron sucrose injection is strongly alkaline and must not be given subcutaneously or intramuscularly. UK (but not US) licensed product information contra-indicates its use in patients with a history of asthma, eczema, anaphylaxis, or other allergic disorders.

Effects on the blood. For a report of thrombocytopenia associated with iron sucrose, see under Iron Dextran, p. 2076.2.

Hypersensitivity. For a discussion of whether iron sucrose may be a safer alternative to iron dextran, see p. 2076.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies iron sucrose 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 07/10/11)

Pharmacokinetics

Iron sucrose is rapidly cleared from the plasma after intravenous injection with a terminal half-life of about 6 hours. A competitive exchange of iron takes place from the iron sucrose complex to the iron-binding protein transferrin. About 5% of a dose is eliminated via the kidneys in the first 4 hours after a dose.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dixafer; Energavit; Ferive; Ferricrine†; Sucrox; Venofer; *Austral.*: Venofer; *Austria*: FerMed; Venofer; *Belg.*: Venofer; *Canad.*: Venofer; *Chile*: Cheltin IV; Encifer; Rafofer; Sucrox; Venofer; *China*: Venofer (维乐福); *Cz.*: Ferion; FerroLogic; Ferrum†; Venofer; *Denm.*: Venofer; *Fin.*: Venofer; Venotrix; *Fr.*: Fer Actavis; Fer Mylan; Fer Sandoz; Venofer; *Ger.*: FerMed; Venofer; *Gr.*: Alvofer; Anemifer; Dextrifer-S; Faremio; Felix; Ferrinemia; Ferroprol; Ferrovin; Hemafer-S; Intrafer; Ironcrose; Nephroferol; Reoxyl; Sucro-Fer; Sucroven; Veniron; Venofer; *Hong Kong*: Venofer; *Hung.*: Venofer; *India*: Aviron; Encifer; Evron; Farris; Ferocorp; Ferosig; Feshia; Fesu; Fezza-S; Hemilift; Icor; Intrafer; Ircor; Irofer; Isest; Litron; Microfer; Nicofer; Omron; *Indon.*: Nefrofer; Venofer; *Irl.*: FerroLogic; Venofer; *Israel*: Fermed; Ferrovin; Venofer; *Ital.*: Ferrum Hausmann; Venofer; *Malaysia*: Venofer; *Mex.*: Venoferrum; *Neth.*: Ferracin; FerroLogic; Venofer; *Norw.*: Venofer; *NZ*: Venofer; *Philipp.*: Encifer; Feron; Ferrofer; Venofer; *Pol.*: Ferion; Venofer; *Port.*: Referen; Venofer; *Rus.*: Venofer (Венофер); *S.Afr.*: Venofer; *Singapore*: Venofer; *Spain*: Feriv; FerMed; Venofer; *Swed.*: Venofer; *Switz.*: Venofer; *Thai.*: Encifer; Fe-Back; Ferrofer; Venofer; *Turk.*: Ferroven; Inferose; Sukrofer; Venofer; *UAE*: Feromax; *UK*: Venofer; *USA*: Venofer; *Venez.*: Venofer.

Multi-ingredient Preparations. *India*: Corus; Feristar.

Pharmacopoeial Preparations
BP 2014: Iron Sucrose Injection;
USP 36: Iron Sucrose Injection.

Isoleucine *(BAN, USAN, rINN)*

I; Ile; Isoleucin; Isoleucina; L-Isoleucine; Isoleucinum; Isoleusiini; Izoleucin; Izoleucinas; Изолейцин.

L-2-Amino-3-methylvaleric acid.

$C_6H_{13}NO_2$=131.2
CAS — 73-32-5.
UNII — 04Y7590D77.

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

Ph. Eur. 8: (Isoleucine). A white or almost white, crystalline powder or flakes. Sparingly soluble in water; slightly soluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Isoleucine). White, practically odourless crystals Soluble in water; slightly soluble in hot alcohol; insoluble in ether. pH of a 1% solution in water is between 5.5 and 7.0

Profile

Isoleucine is a branched-chain aliphatic amino acid that is an essential constituent of the diet. It is used as a dietary supplement. It is also an ingredient of several preparations that have been promoted for disorders of the liver.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ger.*: Falkamin; *Ital.*: Isobranch Isoram; Sargenor Sport†.

Isomalt *(BAN)*

Bay-I-3930; E953; Isomalta; Isomalti; Isomaltitol; Isomaltum; Izomalt; Izomaltas; Palatinit; Изомальт.

CAS — 64519-82-0.
UNII — S870P55O2W.

NOTE. The name Isomaltitol has also been applied to 6-*O*-α-D-glucopyranosyl-D-glucitol.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Isomalt). A mixture of 6-*O*-α-D-glucopyranosyl-D-glucitol ($C_{12}H_{24}O_{11}$ = 344.3) and 1-*O*-α-D-glucopyranosyl-D-mannitol dihydrate ($C_{12}H_{24}O_{11},2H_2O$ = 380.3) and neither of the two components is less than 3%, calculated with reference to the anhydrous substance. A white or almost white powder or granules. Freely soluble in water; practically insoluble in dehydrated alcohol.

USNF 31: (Isomalt). 6-*O*-α-D-Glucopyranosyl-D-glucitol (1,6-GPS) and 1-*O*-α-D-glucopyranosyl-D-mannitol (1,1-GPM), and neither of the two components is less than 3.0% of the mixture, calculated on the anhydrous basis.

Profile

Isomalt is a sugar alcohol (polyol) used as a bulk sweetener in foods. It is noncariogenic with about half the sweetness of sucrose. The ingestion of large quantities may produce flatulence and have a laxative effect.

Metabolism. Isomalt is partly metabolised in the small intestine to glucose, mannitol, and sorbitol and the remaining isomalt is completely metabolised by the flora of the large intestine.[1] The Australian manufacturers have commented that the hydrolysis and absorption is minimal and does not significantly affect blood-sugar or insulin concentrations; they consider isomalt to be suitable for use by diabetic patients.[2]

1. FAO/WHO. Evaluation of certain food additives and contaminants: twenty-ninth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser* 733 1986. Available at: http://libdoc.who.int/trs/WHO_TRS_733.pdf (accessed 20/03/09)
2. Barnes JA. Martindale and isomalt. *Aust J Pharm* 1994; 75: 183.

Lactose

Azúcar de la leche; Lactosa; Lactosum; Laktoosi; Laktos; Laktosa; Laktozė; Laktóz; Laktoza; Lattosio; Milk Sugar; Saccharum Lactis; Лактоза.

CAS — 63-42-3 (anhydrous lactose); 5989-81-1 (lactose monohydrate); 10039-26-6 (lactose monohydrate, cyclic); 64044-51-5 (lactose monohydrate, open form).
UNII — J2B2A4N98G (lactose); 3SY5LH9PMK (anhydrous lactose); EWQ57Q8I5X (lactose monohydrate).

Description. Lactose is a disaccharide obtained from the whey of milk. It may exist in a number of distinct forms depending upon the crystallisation and drying processes employed. The forms can vary in the contents of crystalline and amorphous lactose, the amounts of α-lactose (*O*-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose) and β-lactose (*O*-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose), and in their hydration states. The α-form of lactose exists in either the anhydrous ($C_{12}H_{22}O_{11}$ = 342.3) or monohydrate ($C_{12}H_{22}O_{11},H_2O$ = 360.3) state whereas the β-form exists only in the anhydrous state. Commercial lactose is mainly the α-monohydrate.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *Viet*. Also in *USNF*. Some pharmacopoeias include separate monographs for anhydrous lactose and lactose monohydrate.

Ph. Eur. 8: (Lactose, Anhydrous). It is β-lactose or a mixture of α-lactose and β-lactose. A white or almost white, crystalline powder. Freely but slowly soluble in water; practically insoluble in alcohol.

Ph. Eur. 8: (Lactose Monohydrate; Lactose BP 2014). It is the monohydrate of α-lactose. It may be modified as to its physical characteristics and may contain varying propor-

tions of amorphous lactose. A white or almost white, crystalline powder. Freely but slowly soluble in water; practically insoluble in alcohol. Store in airtight containers.

USNF 31: (Anhydrous Lactose). It is β-lactose or a mixture of α- and β-lactose. It is a white or almost white powder. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers.

USNF 31: (Lactose Monohydrate). It is a natural disaccharide, obtained from milk, which consists of one glucose and one galactose moiety. It may be modified as to its physical characteristics, and may contain varying proportions of amorphous lactose. It is a white, free-flowing powder. Freely, but slowly soluble in water; practically insoluble in alcohol. Store in airtight containers.

Uses and Administration

Lactose, the carbohydrate component of milk, is less sweet than sucrose.

Lactose is widely used as an excipient in pharmaceutical manufacturing. In the production of capsules or tablets it may be used as a diluent, bulking agent, or filler, and in powders as a bulking agent. Lactose is also used as a carrier for drugs in dry powder inhalers. Characteristics such as particle size or flow characteristics make different grades of lactose suitable for different applications.

Adverse Effects and Precautions

Lactose intolerance occurs due to a deficiency of the intestinal enzyme lactase. Ingestion of lactose by patients with lactase deficiency leads to a clinical syndrome of abdominal pain, diarrhoea, distension, and flatulence; symptoms may also occur in persons without such a deficiency who have ingested excessive amounts of lactose.

Lactose is contra-indicated in patients with galactosaemia, the glucose-galactose malabsorption syndrome, or lactase deficiency.

Lactose intolerance. Reviews of lactose intolerance.[1-3] The capacity of the infant intestine to produce lactase, the enzyme responsible for digesting lactose, is retained into adulthood only by a minority of the world's population, mostly in those of north European descent; in Africa and Asia more than 90% of the population are lactase deficient. Because of the ubiquity of lactose in the diet and the consequent frequency of abdominal symptoms, attempts have been made to treat lactose intolerance by dietary exclusion (which need not be complete since lactase deficiency is rarely absolute). An alternative is enzyme replacement therapy with β-galactosidase from micro-organisms (see Tilactase, p. 2631.2), but the role of such therapy has yet to be fully determined. The findings of one study[4] suggested that, in adults with lactose intolerance, the use of lactose-digestive aids is unnecessary if lactose intake is limited to the equivalent of 240 mL of milk or less daily.

There has been concern that lactose might be contaminated with protein from milk, and it has been recommended that children with cow's milk allergy avoid lactose-containing foods. However, a small study[5] found that children allergic to cow's milk could still tolerate lactose.

For the use of soya in infants intolerant to cow's milk, see Food Intolerance, p. 2093.2.

1. Anonymous. Lactose intolerance. *Lancet* 1991; 338: 663–4.
2. Vesa TH, *et al.* Lactose intolerance. *J Am Coll Nutr* 2000; 19 (suppl): 165S–175S.
3. Heyman MB. Committee on Nutrition. Lactose intolerance in infants, children, and adolescents. *Pediatrics* 2006; 118: 1279–86.
4. Suarez FL, *et al.* A comparison of symptoms after the consumption of milk or lactose-hydrolysed milk by people with self-reported severe lactose intolerance. *N Engl J Med* 1995; 333: 1–4.
5. Plocchi A, *et al.* Clinical tolerance to lactose in children with cows' milk allergy. *Pediatrics* 2003; 112: 359–62.

Pharmacokinetics

Lactose is hydrolysed by lactase in the small intestine to glucose and galactose, which are then absorbed.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Novo-Plus†.

Multi-ingredient Preparations. *Fr.*: Tavag†; *Hung.*: Genia; *India*: Osmowin.

Leucine *(BAN, USAN, rINN)*

α-Aminoisocaproic Acid; L; Leu; Leucin; Leucina; Leucinas; L-Leucine; Leucinum; Leucyna; Leusiini; Лейцин.

L-2-Amino-4-methylvaleric acid.

$C_6H_{13}NO_2$=131.2

CAS — 61-90-5.

UNII — GMW67QNF9C.

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

Ph. Eur. 8: (Leucine). A white or almost white, crystalline powder or shiny flakes. Sparingly soluble in water; practically insoluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Leucine). White, practically odourless crystals. Sparingly soluble in water; insoluble in ether. pH of a 1% solution in water is between 5.5 and 7.0.

Profile

Leucine is a branched-chain aliphatic amino acid that is an essential constituent of the diet. It is used as a dietary supplement. It is also an ingredient of several preparations that have been promoted for disorders of the liver.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Revitalose; *Ger.*: Falkamin; *Ital.*: Isobranch; Isoram; Sargenor Sport†.

Lutein

E161(b); Xanthophyll; Лютеин.

(3*R*,3′*R*,6′*R*)-β,ε-Carotene-3,3′-diol.

$C_{40}H_{56}O_2$=568.9

CAS — 127-40-2.

UNII — X72A60C9MT.

Pharmacopoeias. In *US*.

US. also includes Lutein Preparation.

USP 36: (Lutein). A red crystalline powder. Soluble in dehydrated alcohol, in dichloromethane, and in ethyl acetate; partially soluble in hexane. Store at 8 degrees to 15 degrees in tightly-sealed, airtight containers. Protect from light and oxygen.

Profile

Lutein is a naturally occurring carotenoid that has been investigated for its supposed role in a number of conditions including age-related macular degeneration (p. 880.2), cataracts, cardiovascular disease, and cancer.

Lutein is also used as a colouring agent.

References.

1. Mares-Perlman JA, *et al.* The body of evidence to support a protective role for lutein and zeaxanthin in delaying chronic disease: overview. *J Nutr* 2002; 132 (suppl): 518S–524S.
2. Granado F, *et al.* Nutritional and clinical relevance of lutein in human health. *Br J Nutr* 2003; 90: 487–502.
3. Trumbo PR, Ellwood KC. Lutein and zeaxanthin intakes and risk of age-related macular degeneration and cataracts: an evaluation using the Food and Drug Administration's evidence-based review system for health claims. *Am J Clin Nutr* 2006; 84: 971–4.
4. Cho E, *et al.* Prospective study of lutein/zeaxanthin intake and risk of age-related macular degeneration. *Am J Clin Nutr* 2008; 87: 1837–43.
5. Roberts RL, *et al.* Lutein and zeaxanthin in eye and skin health. *Clin Dermatol* 2009; 27: 195–201.
6. Carpentier S, *et al.* Associations between lutein, zeaxanthin, and age-related macular degeneration: an overview. *Crit Rev Food Sci Nutr* 2009; 49: 313–26.
7. Berson EL, *et al.* Clinical trial of lutein in patients with retinitis pigmentosa receiving vitamin A. *Arch Ophthalmol* 2010; 128: 403–11.
8. Stringham JM, *et al.* The influence of dietary lutein and zeaxanthin on visual performance. *J Food Sci* 2010; 75: R24–R29.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Y-Lut.

Multi-ingredient Preparations. *Arg.*: Ocuvite DM; Ocuvite Omega3; Vitalux Plus; *Austral.*: For Eyes; Multi+Vision; Radiance; *Canad.*: ICaps Lutein and Zeaxanthin; Visionex; *Chile*: Vision Tabs; *Fr.*: Anti-oxydant 200; Bion 3 Seniors; Blue Berry; Corvitec; Difravision; Lero Pervulane; Macula; Naturophta Macula; Phytosolaire†; PreserVision; Reti-Nat†; Sun Vue; Trioptec; Visioprev; Vitalux Plus; Vitareds†; Vitrecor; *Hong Kong*: Icaps; Ocuvite; Visionex†; *India*: Absolut; Calorex; Dayvital; Ecome-LY; Elgrape; Elnutra-M; Elnutra; GV-24; I-Lute; I-Site; I-Zen; Imunolife; Izeal; L-Bex; Leclub; Lutamin; Lutivit; Luvion; Lycocare; Lycoden-M; Lycodric; Lycofact Plus; Lycominvit; Lyconerve; Lycosta; Lycozin; Lytox; Macuchek; Multivite Vision; Multizac; Natoz; Nervijen-D; Nislutin; Ocugold; One-Up; Optivision; Optivite; Orymax; Orymax; Oxired-L; Oxy-V; Oxyeye; *Indon.*: Ervision; Eyebright; Eyevit; Kapset; Lubire; Lutevision Extra; Lutevision†; Lutevit; Lycoxy; Matoflam; Matovit AX; Matovit Fifty; Natureyes; nutrivision; Nuvision; Ocu-V; Ocugard; Oculex; Oculex; Optha-LL; Optimax Plus; Optimax; Oxypen; Proview; Reticopen; Retivit Plus; Retivit; Retop; Seltifort Gold; Vita-Vision; Vitalux Plus; Vitanox; *Irl.*: Ocuvite†; *Israel*: Multivitamin; Opti-Safe Areds; Opti-Safe†; Quantum; Vitalux Plus; *Ital.*: AMD; Assist; Astar; Berart; Connivea; Euretin Duo; Ginkoret; Macvit; Meralut; PML Crono; Preservision Luteina; Troca Vit; Visu Q10; Visu-len; Visu-ton; VisuQ10; Vitalux Plus; *Malaysia*: Eurobio Bio-Vizmax; Visionex†; Vitalux Plus; *Mex.*: Drusen; Icaps; Optivision; Snelvit; Vitalux Plus; *Philipp.*: Havitall; iiCare; Nutricap; Nutrof†; Nutrotal; Polynerv-E with lecithin; *Port.*: Ever-Fit Dermo; Fortal Vision; *Rus.*: Complivit Oftalmo (Компливит Офтальмо); Multimax (Мультимакс); Multimax for Eyes (Мультимакс Для Глаз); *Singapore*: Essentials†; I-Vite; i-Vitein; Icaps; Nutrivision†; Ocuvite Adult 50+; Ocuvite Lutein; Optibiol; PreserVision; Visionex†; Visionex; Vitalux Plus; *Thai.*: Icaps†; Ocuvite; Vitalux Plus; *Turk.*: Per-Vital; *UK*: Icaps; Vitalux Plus; *Ukr.*: Centrum with Lutein (Центрум С Лютеином); Multimax (Мультимакс); Ocuvite Complete (Окювайт Комплит); Ocuvite Lutein Forte (Окювайт Лютеин форте); Oko-Health (Око-хелс); Optix (Оптикс); Optix Forte (Оптикс Форте); Perfectil Plus (Перфектил Плюс); Vitrum Foreyes (Витрум Форайз); Vitrum Foreyes Forte (Витрум Форайз Форте); *USA*: Alive Mens Energy; Alive Once Daily Womens 50+ Ultra Potency; Alive Womens 50+; Cardio Tone; Certavite Senior with Antioxidant Nutrients; Clinical Nutrients 50-Plus Men; Corvita; Corvite Free; Daily Betic Fitness Tabs for Men; Fitness Tabs for Women; MacuTrition; Nutravance; Ocuvite Eye + Multi; Preservision Eye Vitamin; Preservision Lutein; REQ49+; *Venez.*: Vilox; Vitalux Plus; Vitavision.

Pharmacopoeial Preparations

USP 36: Lutein Capsules.

Lysine *(BAN, USAN, rINN)*

K; Lisina; Lys; L-Lysine; Lysinum; Лизин.

L-2,6-Diaminohexanoic acid.

$C_6H_{14}N_2O_2$=146.2

CAS — 56-87-1.

ATC — B05XB03.

ATC Vet — QB05XB03.

UNII — K3Z4F929H6.

Pharmacopoeias. In *Ger.* as the monohydrate.

Lysine Acetate *(BANM, rINNM)*

Acetato de lisina; Lisina, acetato de; Lizino acetatas; Lizyny octan; Lys Acetate; Lysiiniasetaatti; Lysinacetat; Lysin-acetát; Lysine, Acétate de; L-Lysine Monoacetate; Lysini acetas; Лизина Ацетат.

L-2,6-Diaminohexanoic acid acetate.

$C_6H_{14}N_2O_2C_2H_4O_2$=206.2

CAS — 57282-49-2.

UNII — TTL6G7LIWZ.

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

Ph. Eur. 8: (Lysine Acetate). A white or almost white, crystalline powder or colourless crystals. It exhibits polymorphism. Freely soluble in water; very slightly soluble in alcohol. Protect from light.

USP 36: (Lysine Acetate). White, odourless crystals or crystalline powder. Freely soluble in water.

Lysine Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de lisina; Lisina, hidrocloruro de; Lizin-hidroklorid; Lizino hidrochloridas; Lys Hydrochloride; Lysiinihydrokloridi; Lysine, chlorhydrate de; L-Lysine Monohydrochloride; Lysin-hydrochlorid; Lysinhydrochlorid; Lysin-hydroklorid; Lysini Hydrochloridum; Лизина Гидрохлорид.

L-2,6-Diaminohexanoic acid hydrochloride.

$C_6H_{14}N_2O_2$,HCl=182.6

CAS — 657-27-2.

UNII — JNJ23Q2COM.

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

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

USP 36: (Lysine Hydrochloride). A white, odourless powder. Freely soluble in water.

Profile

Lysine is a basic amino acid that is an essential constituent of the diet. Lysine acetate and lysine hydrochloride are used as dietary supplements.

Lysinuric protein intolerance. For mention of the use of lysine to correct lysine deficiency in lysinuric protein intolerance, see Hyperammonaemia, under Citrulline, p. 2056.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ai Xin Wei (爱欣威); An Wan Tong (安万彤); Bao Lin (包林); Beiyuan (倍援); Ci Xing (慈星); Gan Luo (甘络); Hai Jing Wu (海京吴); He An Si (荷安斯); Jun Ao (君傲); Lai An (莱安); Lang De (朗德); Li Da An (力达安); Lu Wei Tong (路维彤); Nuo Lai Xin (诺莱欣); Pi Luo

Tong (铵洛彤); Pu Le Kang (普乐康); Rui Shi Kang (瑞适康); Sai Luo Su (赛络苏); Shu Lang (舒朗); Si Pu Ti (思普提); Si Li Jia (思力加); Tai Di Te (泰迪特); Tai Li Xing (泰利星); Tian Yi An (恬亦安); Wei Sai Lai (威赛来); Xinjielin (新杰林); Ya Shu (雅抒); Yi Ning Shi (怡宁适); Yifu (亿复); You Ni Ming (尤尼明); Zhen Tong (镇通); Zhi Mai Xin (智迈欣).

Multi-ingredient Preparations. *Arg.*: Cistidac; Feronat†; Kiddi; Latlas Fresh; Latlas; *Austral.*: Accomin†; C Pal†; Calporo†; Incremin Iron; Lyp-Sine; Once Daily Mens Multi; Once Daily Womens Multi; Womens One-a-Day Multi; *Braz.*: Betozone†; Buclimax†; Calcifluol; Carnabol; Ferrotrat B12 Plus; Gaballon; Glucal B12†; Pharmaton Kiddi; Profol; Propan; Suplevit; Trimetabol†; *Chile*: Chicovit Pharmaton; Orodina; Peracon; Tonval†; *China*: Diweijia (迪维佳); Kiddi (冠迪); Cz.: Kiddi Pharmaton†; *Fr.*: Curasten†; Revitalose; Sarvit a la lysine†; Stimuplexe†; Surfortan; *Gr.*: Beceton; Issobevit; Set-Vit; Upsaton; Vivacton; *Hong Kong*: Appezym; Bioviter; Calibo Calcium†; Champs C with Lysine; Champs M with Lysine; Conbo-BC†; Digezym; Kiddi Pharmaton†; Lysinevita†; Macro M†; Nutroplex with Iron & Lysine; Pantamin MV†; Tricavita†; Vi-Daylin with Lysine; Vita-Bo Calcium†; Vita-Bo Multivitamins†; Vitacymin Syrup with Lysine†; *Hung.*: Epavir; *India*: Abiphos; Absolut; Acmic-S; Actioner; Adrovit; Alcevit; Almal-Z; Aminocal 500; Aminocal; Anvital DPS; Arical; Arogyme; Asiplex; Astyfer-Z; Astyfer; Astyfer; Atovit; Aviton; Avm; Avpro; B Com; B-12; Bcom-L; Beco-Red-12; Betadex-12; Beth-P; Bethadoxin-12; Bethadoxin-P; Betonin-AST; Bevon; Bioferum Forte; Bonforte; C-Haem; C-Lysin; Cadbe; Calcefol; Calcila; Calcila; Calme; Calmix; Calnet; Calsal Plus; Calsat; Calsure; Caltac; Calvit-L; Cecal; Cherrytone; Cinred; Compicare; Cuplex-L; Cydine; Cypee; Cyprowal; Delvit; Diakair; Dicalciiplex; ECD3; Elferri Plus; Enerjex; Eugadine Lysine; Extrafer; Facicap; Familykair; Fe-Z; Ferrimin; Ferrisun; Perritop Iron; Ferrochelate; Fibrotin; Forcal; Fortical; Fortox; Full-365; G-Calvit; G-Vit; Gromet-Z; Gromin; HB-Orange; Hemral; Hemsi; Hepachol; Ibelac; Ifycal-D3; Incremin; Inpro; Intabion; Irex-12 Tonic; Irona; Ironate; Irosol; Karibe; Kelcer; Kidicare; Kudamin; Lephos; Litcal; Liton; Livobion; Livobion; Logical; Lycal; Lycoden-M; Lycosta; Lycozin; Lysicon-V c Zinc; Lysicon-V; Lysoplex; M-Cal; Marvita; Meconerv; Medifer; Merical; Mexivit; Mincovit; Minero; Minitone Plus; Miproten; Momkair; Moreage; Multiphar; Mumcal; Mvimin; N-Care; N-Rich; Nervic; Nervion; Nestosule-MV; Neuragen; Neurobex; New Viminta; Nitical; Nor-B; Nucal; Nutra; Ob-Cal; Orovit; Ospical; Oxired; Oxitra; Pedic; Phosfomin; Polybion; Protone; Sioplex Lysine; Tonoferon; *Indon.*: Abdelyn; Adebion; Adelysin; Alsine; Anabion Plus DHA; Anabion; Apialys; Asedas; Becombion Extra Lysine; Biokid†; Biolysin Smart; Biolysin; Bionutrion; Biostrum; Calcidol; Calostrum; Cavital; Champs C with Lysine; Champs M with Lysine; Corovit; Curmunos; Curviplex; Elkana; Erpha Livita; Perobion; Perofort; Feroglobin; Fitkom; Fortelysin†; Growee; Igastrum Plus; Imustrum; Incremin with Iron†; Kiddi Pharmaton; Kolivit; Kuminta; Likurmin; Lisovit; Lybex; Lycalvit; Lysmin Plus; Lysmin; Lytacur; Lyvit; Mulsanol; Muveron; Osimax; Pediagrow; Pedilis; Picavit; Prefit; Prokids; Provital Plus; Provital; RaVita; Seltifort Kids; Solvita Baby; Solvita Plus; Truvit; Vialyn; Vidaylin L; Vidoran Plus; Viferron; Xanda; Zamel; *Irl.*: Kiddi Pharmaton†; *Israel*: Kiddi; *Ital.*: Rinotrofina C; *Malaysia*: Appeton; Junior Citrex; Kiddi Pharmaton; Nutroplex with Iron & Lysine†; Proviton; Shine Cutie; Shine Junior Multivitamin; Shine Multivitamin Plus†; Vi-Daylin; *Mex.*: Aminoyodarsencal; Convifer con Hierro; Corpotasin CL; Incremin Con Hierro; Infavit; Integrovin; Kiddi Pharmaton; Medox ABC; Rocavit; Vita-Bel†; Vivioptal; *NZ*: Incremin with Iron; *Philipp.*: Appebon with Iron; Appebon; Appetason; Appetite Plus; Appetite with Iron; Bio-Termin Plus with Lecithin; Biomix; Bomvital; Brighser; Ceegeefer†; Celer C; Celermin†; Chlorvytol†; Crevytin†; Dreamvite; Ener A Plus; Enersel; Enouvim; EZ-Grow; Perlette; Flexivit; Healthy Kidz; Heltine Plus; Hi-Smart Teens; Hi-Smart; Incremin; Jagaplex; K-A Plus; Kiddi Pharmaton; Kiddie Estamin; Kiddirel; Leginsol Vita; Lexivit; Lysadam Plus; Macrobee with Lysine; Medgivit; Mediferron-Vita; Medifortan; Megavit; Memorx IQ Plus; Molvite with Iron; Multigen; Multigrow; Nerveplex; Nutrazinc Nutri 10; Nutricaire; Nutrigrow Plus; Nutrigrow†; Nutrigrow; Nutrivita; Nutroplex with Iron & Lysine; Onevit; Optigrow; Pediafortan Forte-GB; Pediafortan Forte; Provital; Pryce-Kidz; Regeron Vita with Chlorella; Regeron Vita; Rejuvon; Restor; Revicon Forte (Improved); Siglaton Plus; Strevit; Supplemin-C; Syplex; TLC Vita; Tropicee Plus; Ultravit-TL; United American Tiki Tiki Star; Vigorvit; Visymplex Plus; Vita SL Plus; Vita SL with lecithin†; Vita SL; Vitakids; Vitalivin-E Reformulated†; Vitaplex; Vitazinc Z-Vita; *Port.*: Belisina†; Tonice; *Rus.*: Feroglobin-B12 (Фероглобин-B12); *S.Afr.*: Activex 40 Plus†; Clusivol; *Singapore*: Appelin-B12; Belvea Liquid Health Calcium; Champs C with Lysine†; Champs M†; Growee†; NutraMX; Pharmaton Kiddi; Provital; Vitaton Gold; Vitaton; *Spain*: Malandil; Pranzo; Tomevit†; *Switz.*: Pharmaton Kiddi Vita; *Thai.*: Kiddi Pharmaton; Nutroplex Lysine; Osmo; Patarvit; Syn-O-Vits; Vitakid; *UK*: Feroglobin; Florisene; *Ukr.*: Cardonat (Кардонат); Energin (Энергин); Kiddi Pharmaton (Кидди Фарматон); Rotavit Royal (Ротавит Ройял); Trimetabol (Триметабол); Vitrum Beauty Elite (Витрум Бьюти Элит); *USA*: Biotect Plus; Herpetrol; Jets; Klorvess; Klorvess; Vitalize; *Venez.*: Vitisival.

Pharmacopoeial Preparations
USP 36: Lysine Hydrochloride Tablets.

Magnesium Fluoride

Фторид Магния.
MgF_2=62.30.
CAS — 7783-40-6.
UNII — 5N014C7IWU.

Profile

Magnesium fluoride is used as a fluoride supplement (see Sodium Fluoride, p. 2089.2) for the prevention of dental caries. Magnesium fluoride is also used as a source of magnesium.

Homoeopathy

Magnesium fluoride has been used in homoeopathic medicines under the following names: Magnesia Fluorata; Magnesium Fluoratum; Magnesia Fluoricum.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Total Magnesiano.

Multi-ingredient Preparations. *Arg.*: Total Magnesiano con Vitamina C; Total Magnesiano Limon; Total Magnesiano Sport; Total Magnesiano; Total Magnesiano; *Spain*: Magnesium Pyre; Magnogene.

Homoeopathic Preparations. *Ger.*: Maflurell; *Hung.*: Toxex.

Maize Oil

Aceite de maíz; Corn Oil; Huile de Maïs; Kukoricamagolaj; Kukuřičný olej; Kukurūzų aliejus; Maïs, huile de; Maissiõljy; Majsolja; Maydis Oleum; Ol. Mayd.; Olej kukurydziany; Oleum Maydis; Кукурузное Масло; Маисовое Масло.
CAS — 8001-30-7.
UNII — 8470G57WFM.

Pharmacopoeias. In *Chin.*, *Eur* (see p. vii), and *Jpn*. Also in *USNF*.

Ph. Eur. 8: (Maize Oil, Refined; Maydis Oleum Raffinatum). The refined fatty oil obtained from the seeds of *Zea mays*. A clear, light yellow or yellow oil. Practically insoluble in water and in alcohol; miscible with dichloromethane and with petroleum spirit (b.p.: 40 degrees to 60 degrees). Store at a temperature not exceeding 25 degrees. Protect from light.

USNF 31: (Corn Oil). The refined fixed oil obtained from the embryos of *Zea mays* (Gramineae). A clear, light yellow, oily liquid having a faint characteristic odour. Slightly soluble in alcohol; miscible with chloroform, with ether, with petroleum spirit, and with benzene. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Profile

Maize oil is a fixed oil with a high content of unsaturated acids, and has been used to replace saturated acids in the diets of patients with familial hypercholesterolaemia. It is also used as an oily vehicle in pharmaceutical formulations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Preservation; *USA*: Lipomul†.

Malt Extract

Extractum Bynes; Malta, extracto de; Экстракт Солода; Солодовый Экстракт.
UNII — R3NBG8914U (barley malt extract); 22P8DKP670 (barley malt syrup).

Profile

Malt extract contains 50% or more of maltose, with dextrin, glucose, and small amounts of other carbohydrates, and protein. It is prepared from malted grain of barley (*Hordeum distichon*, *H. vulgare*) or a mixture of this with not more than 33% of malted grain of wheat (*Triticum aestivum* or *T. turgidum*).

Malt extract has nutritive properties. It is chiefly used as a vehicle in preparations containing cod-liver oil (p. 2056.3) and halibut-liver oil (p. 2071.3). It is a useful flavouring agent for masking bitter tastes.

A product known as malt soup extract, obtained from barley grains, and containing 73% maltose with 12% other polymeric carbohydrates as well as small amounts of proteins, electrolytes, and vitamins, is sometimes used as a laxative.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Maltin; *USA*: Maltsupex.

Multi-ingredient Preparations. *Canad.*: Floradix Kindervital†; *Chile*: Ferromalt; *Fr.*: Effidigest; Galactogil; *Ger.*: Weleda Hustenelixier; *India*: Marvita; Sharkoferrol; Sharkomalt†; *Indon.*: Bio-Strath; *Jpn*: Hangebyakujutsutemmato; *S.Afr.*: Cough Elixir†.

Maltitol *(BAN)*

E965; Hydrogenated Maltose; D-Maltitol; Maltitoli; Maltitolis; Maltitolum; Maltosa hidrogenada; Мальтит.
α-D-Glucopyranosyl-1,4-D-glucitol.
$C_{12}H_{24}O_{11}$=344.3.
CAS — 585-88-6.
UNII — D65DG142WK.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Maltitol). A white or almost white, crystalline powder. Very soluble in water; practically insoluble in dehydrated alcohol.

USNF 31: (Maltitol). A white, crystalline powder. Very soluble in water; practically insoluble in dehydrated alcohol.

Maltitol Syrup

E965; Hydrogenated Glucose Syrup; Hydrogenated High Maltose-glucose Syrup; Jarabe de glucosa hidrogenada; Jarabe de glucosa hidrogenada con alto contenido en maltosa; Liquid Maltitol; Maltitol ciekły; Maltitol, flytande; Maltitol, jarabe de; Maltitol liquide; Maltitol roztok; Maltitol Solution; Maltitoli, nestemäinen; Maltitolum liquidum; Maltitszirup; Skystasis maltitolis; Мальтитный Сироп.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Maltitol Liquid). An aqueous solution of a hydrogenated, part hydrolysed starch, containing not less than 68.0% w/w and not more than 85.0% w/w of anhydrous substance composed of a mixture of mainly D-maltitol with D-sorbitol and hydrogenated oligo- and polysaccharides. It contains not less than 50.0% w/w of D-maltitol and not more than 8.0% w/w of D-sorbitol, both calculated with reference to the anhydrous substance. A clear, colourless, syrupy liquid. Miscible with water and with glycerol.

USNF 31: (Maltitol Solution). A water solution containing, on the anhydrous basis, not less than 50.0% of D-maltitol (w/w) and not more than 8.0% of D-sorbitol (w/w).

Nomenclature. Hydrogenated glucose syrup is a generic term encompassing products of widely varying composition and it was concluded that such products containing up to 90% of maltitol should more properly be called maltitol syrup.[1] This was subsequently amended to include products containing up to 98% maltitol.[2] Preparations containing a minimum of 98% of maltitol were assigned the title maltitol.

1. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-third report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 776* 1989. Available at: http://libdoc.who.int/trs/WHO_TRS_776.pdf (accessed 20/03/09)
2. FAO/WHO. Evaluation of certain food additives and contaminants: forty-first report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 837* 1993. Available at: http://libdoc.who.int/trs/WHO_TRS_837.pdf (accessed 20/03/09)

Profile

Maltitol and maltitol syrup are bulk sweeteners used in foods and pharmaceuticals. They are considered to be noncariogenic and about as sweet as sucrose. The ingestion of large quantities may produce flatulence and diarrhoea.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Singapore*: Arkopharma Propolis Spray.

Maltodextrin

Maltodekstriini; Maltodekstrinas; Maltodextrina; Maltodextrine; Maltodextrinum; Мальтодекстрин.
CAS — 9050-36-6.
UNII — 7CVR7L4A2D.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Maltodextrin). A mixture of glucose, disaccharides, and polysaccharides, obtained by the partial hydrolysis of starch. The degree of hydrolysis, expressed as dextrose equivalent (DE) is less than 20 (nominal value). A white or almost white, slightly hygroscopic powder or granules. Freely soluble in water.

USNF 31: (Maltodextrin). A nonsweet, nutritive saccharide mixture of polymers that consists of D-glucose units with a dextrose equivalent of less than 20. It is prepared by the partial hydrolysis of food grade starch with suitable acids and/or enzymes. White, hygroscopic powder or granules. Freely soluble or readily dispersible in water; slightly soluble to insoluble in dehydrated alcohol. pH of a 20% solution in water is between 4.0 and 7.0. Store in airtight containers at a temperature not exceeding 30 degrees and a relative humidity not exceeding 50%.

Profile

Maltodextrin, a glucose polymer (malto-oligosaccharide), is a source of carbohydrate often used in oral dietary supplements and tube feeding. It rapidly releases glucose in the gastrointestinal tract but because of the high average molecular weight of maltodextrin, solutions have a lower osmolarity than isocaloric solutions of glucose. Additionally, preparations based on maltodextrin and intended for dietary supplementation usually have a low electrolyte content and are free of other sugars such as fructose, galactose, lactose, and sucrose. Such preparations may be particularly useful in certain gastrointestinal disorders where malabsorption is a problem, in disaccharide intolerance (without isomaltose intolerance), and in acute and chronic hepatic and renal diseases where protein, mineral, and fluid restriction are often necessary.

Maltodextrin is also employed as a pharmaceutical excipient.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Carbohidrato 100; MC Modulo Calorico; Polimerosa; *Austral.*: Maxijul†; *Braz.*: Nidex; Oligossac; *Chile*: Modulo Calorico; *Cz.*: Fantomalt; *Fin.*: Fantomalt; *Hong Kong*: Fiber Basics; *Ital.*: Energen; Fantomalt; Maltovis; Nidex; *NZ*: Moducal; *Pol.*: Fantomalt; *Port.*: Fantomalt; *USA*: Moducal; *Venez.*: Fantomalt.

Multi-ingredient Preparations. *Arg.*: Hidro-Energy; Invisifiber; *Fr.*: Alhydrate†; Chondrosteo; Gumilk; Hydrigoz†; Pelvimag; Picolite; *Indon.*: L-Bio; *Ital.*: Combirice; Litostop; Selezime; *Venez.*: Glutapak-R; Glutapak; Hermesetas Gold; Modulo Calorico; Multidex.

Maltose

Maltobiose; Maltosa; D-Maltose; Мальтоза.

4-O-α-D-Glucopyranosyl-β-D-glucopyranose.

$C_{12}H_{22}O_{11}$=342.3

CAS — 69-79-4 (anhydrous maltose); 6363-53-7 (maltose monohydrate).

UNII — XJ659RV06F (maltose); 66Y63L379N (anhydrous maltose); DM477EE40D (maltose monohydrate).

Pharmacopoeias. *Jpn* includes the monohydrate. *USNF* permits the anhydrous and monohydrate forms.

USNF 31: (Maltose). It contains one molecule of water of hydration or is anhydrous. A white, odourless, crystalline powder that has a sweet taste. Freely soluble in water; very soluble in dehydrated alcohol; practically insoluble in ether; slightly soluble in methyl alcohol. pH of a 10% solution in water is between 3.7 and 4.7 (anhydrous form) and between 4.0 and 5.5 (monohydrate form).

Profile

Maltose, a disaccharide composed of two glucose molecules, is less sweet than sucrose. It is obtained from starch by hydrolysis with amylase. Maltose is often present with other sugars in mixtures used as carbohydrate sources. It is also used as a pharmaceutical excipient.

Adverse effects. Hyponatraemia developed after intravenous infusion of normal immunoglobulin in 10% maltose in a patient with acute renal failure after liver transplantation.[1] The effect, which recurred on each of four successive infusions, resembled that of hyperglycaemia and was thought to be due to accumulation of maltose and other osmotically active metabolites in the extracellular fluid.

1. Palevsky PM, *et al.* Maltose-induced hyponatremia. *Ann Intern Med* 1993; **118**: 526–8.

Precautions. Preparations that contain, or are metabolised to, maltose may interfere with the results from glucose tests (p. 2516.3). Overestimation of glucose results may mask hypoglycaemia, resulting in the inappropriate use of insulin.[1,2] The problem may also occur with icodextrin, which produces maltose as a metabolite (see Dialysis, p. 2059.2).

1. MHRA. Medical device alert: ref MDA/2007/058 issued 19 July 2007. Available at: http://www.mhra.gov.uk/PrintPreview/PublicationSP/CON2031807 (accessed 01/07/08)
2. FDA. Important safety information on interference with blood glucose measurement following use of parenteral maltose/parenteral galactose/oral xylose-containing products (issued November 2005 and updated). Available at: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm154213.htm (accessed 22/07/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Infumal; Martos; *Jpn*: Martos.

Multi-ingredient Preparations. *Indon.*: Hydromal; Potacol-R; *Jpn*: Actit; Potacol-R.

Pharmacopoeial Preparations

USNF 31: Liquid Glucose.

Manganese

Mangan; Manganèse; Manganeso; Manganum; Марганец.

Mn=54.938045

CAS — 7439-96-5.

UNII — H6EP7W5457 (manganese ion); 42Z2K6ZL8P (manganese).

Manganese Chloride

Manganeso, cloruro de; Марганца Хлорид.

$MnCl_2.4H_2O$=197.9

CAS — 7773-01-5 (anhydrous manganese chloride); 13446-34-9 (manganese chloride tetrahydrate).

UNII — 6YB4901Y90 (anhydrous manganese chloride); QQE170PANO (manganese chloride tetrahydrate).

Pharmacopoeias. In *US*.

USP 36: (Manganese Chloride). Large, irregular, pink, odourless, translucent crystals. Soluble in water and in alcohol; insoluble in ether. Store in airtight containers. pH of a 5% solution in water is between 3.5 and 6.0.

Manganese Gluconate

Manganèse, gluconate de; Manganeso, gluconato de; Mangangluconat; Mangani gluconas; Марганца Глюконат.

Bis(D-gluconato-O^1,O^2) manganese; Manganese D-gluconate.

$C_{12}H_{22}MnO_{14}$=445.2

CAS — 6485-39-8.

UNII — 9YY2F980SV (manganese gluconate); 7G09WJ8QIR (anhydrous manganese gluconate); 0O43J7044T (manganese gluconate dihydrate).

Pharmacopoeias. In *Eur.* (see p. vii), which allows either anhydrous or hydrated forms, and in *US*, which allows either anhydrous or the dihydrate.

Ph. Eur. 8: (Manganese Gluconate). A white or pale pink, slightly hygroscopic, crystalline powder. Soluble in water; practically insoluble in anhydrous ethanol; insoluble in dichloromethane. Store in non-metallic, airtight containers.

USP 36: (Manganese Gluconate).

Manganese Sulfate

Mangaanisulfaattimonohydraatti; Manganèse (sulfate de) monohydraté; Manganese Sulphate; Manganeso, sulfato de; Mangani Sulfas; Mangani Sulfas Monohydricum; Mangán(II)-szulfát-monohidrát; Mangano sulfatas; Mangansulfatmonohydrat; Manganu siarczan; Siran manganaty; Марганца Сульфат.

Manganese (II) sulphate monohydrate.

$MnSO_4.H_2O$=169.0

CAS — 7785-87-7 (anhydrous manganese sulfate); 10034-96-5 (manganese sulfate monohydrate); 10101-68-5 (manganese sulfate tetrahydrate).

UNII — W00LYS4T26 (manganese sulfate); IGA155S9H40 (anhydrous manganese sulfate).

Pharmacopoeias. In *Eur.* (see p. vii) and *US*. *Br.* and *Fr.* also include the tetrahydrate.

BP 2014: (Manganese Sulfate). The tetrahydrate occurs as pale pink, odourless or almost odourless, crystals or crystalline powder. Freely soluble in water; practically insoluble in alcohol.

Ph. Eur. 8: (Manganese Sulfate Monohydrate). It occurs as a pale pink, slightly hygroscopic, crystalline powder. Freely soluble in water; practically insoluble in alcohol.

USP 36: (Manganese Sulfate). The monohydrate occurs as pale red, slightly efflorescent crystals, or as a purple, odourless powder. Soluble in water; insoluble in alcohol. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Manganese is an essential trace element and small amounts of a salt such as the chloride or sulfate are sometimes added to solutions for TPN. Daily doses ranging from 150 to 800 micrograms (2.7 to 14.6 micromoles) of manganese have been suggested.

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

Manganese compounds or salts that have been used in therapeutics in addition to those mentioned above include manganese amino acid chelate, manganese dioxide, manganese gluconate, and manganese hydrogen citrate.

Administration in children. A manganese salt such as the chloride or sulfate may be added to parenteral feeds as a source of manganese in the prophylaxis and treatment of deficiency states in children. US licensed product information suggests 2 to 10 micrograms/kg (36 to 180 nanomoles/kg) of manganese daily for all children. In the UK, licensed product information suggests a daily dose of 1 microgram/kg (up to a maximum of 15 micrograms) of manganese for children weighing 40 kg or less, and adult doses in children over 40 kg (see above). A low-dose regimen of not more than 1 microgram/kg manganese daily has been recommended in children given long-term parenteral nutrition to avoid accumulation (see Accumulation, below).

Human requirements. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR) (see p. 2046.1) has been set for manganese although a safe intake for adults was believed to lie above 1.4 mg (26 micromoles) daily.[1] Similarly, in the USA a recommended dietary allowance has not been published, although an adequate intake has been estimated to be 2.3 mg daily for men and 1.8 mg daily for women.[2] A tolerable upper intake level of 11 mg daily has also been set.[2] WHO has not proposed a safe range of mean population intakes for manganese since neither intakes resulting in deficiency nor threshold toxicity levels have been established.[3] Diets high in unrefined cereals, nuts, leafy vegetables, and tea will be high in manganese.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. WHO. Manganese. In: *Trace elements in human nutrition and health*. Geneva: WHO, 1996; 163–7.

Adverse Effects and Precautions

Acute poisoning due to ingestion of manganese or manganese salts is rare. The main symptoms of chronic poisoning, either from injection or usually inhalation of manganese dust or fumes in air, include extrapyramidal effects which may be followed by progressive deterioration in the CNS. Parenteral manganese should be used cautiously in patients with reduced biliary excretion, especially in cholestatic liver disease. When the duration of total parenteral nutrition is likely to exceed 1 month, serum-manganese concentration and liver function should be checked before starting treatment and regularly during treatment; additives containing manganese should be stopped if serum-manganese concentrations are raised or cholestasis develops.

Accumulation. There are reports of cholestatic liver disease, and possibly changes in the basal ganglia, associated with hypermanganesaemia in children given long-term parenteral nutrition;[1,2] manganese accumulation may be secondary to impaired biliary excretion.[3] Manganese supplementation in such patients requires re-appraisal and whole blood manganese concentrations should be monitored regularly. A low-dose regimen of not more than 1 microgram/kg (18 nanomoles/kg) daily has been suggested,[2,3] a dose that was also recommended by the American Society for Parenteral and Enteral Nutrition.[4] Hypermanganesaemia and basal ganglia manganese deposition resolved over time in 2 children when the manganese dose in their parenteral nutrition was reduced.[5] Manganese accumulation in the basal ganglia has been seen in patients with liver cirrhosis,[6,7] and may be associated with parkinsonism[7-9] (for reference to the use of aminosalicylic acid in the treatment of manganese-induced parkinsonism, see p. 216.1). Concern has been expressed[10] at the high levels of manganese contained in infant formulas.

1. Reynolds AP, *et al.* Manganese in long term paediatric parenteral nutrition. *Arch Dis Child* 1994; **71**: 527–8.
2. Fell JME, *et al.* Manganese toxicity in children receiving long-term parenteral nutrition. *Lancet* 1996; **347**: 1218–21.
3. Beath SV, *et al.* Manganese toxicity and parenteral nutrition. *Lancet* 1996; **347**: 1773–4. Correction. *ibid.* **348**: 416.

4. Mirtallo J, *et al.* American Society for Parenteral and Enteral Nutrition. Safe practices for parenteral nutrition. *J Parenter Enteral Nutr* 2004; 28: S39–S70. Also available at: http://www.nutritioncare.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=574 (accessed 24/03/09)
5. Katritsa Y, *et al.* Long term outcome of brain manganese deposition in patients on home parenteral nutrition. *Arch Dis Child* 1998; 79: 263–5.
6. Krieger D, *et al.* Manganese and chronic hepatic encephalopathy. *Lancet* 1995; 346: 270–4.
7. Burkhard PR, *et al.* Chronic parkinsonism associated with cirrhosis. *Arch Neurol* 2003; 60: 521–8.
8. Zatta P, *et al.* The role of metals in neurodegenerative processes: aluminum, manganese, and zinc. *Brain Res Bull* 2003; 62: 15–28.
9. Lucchini RG, *et al.* From manganism to manganese-induced parkinsonism: a conceptual model based on the evolution of exposure. *Neuromolecular Med* 2009; 11: 311–21.
10. Hozyasz KK, Ruszczynska A. High manganese levels in milk-based infant formulas. *Neurotoxicology* 2004; 25: 733.

Pharmacokinetics

Absorption of manganese from the gastrointestinal tract is variable, ranging from 3 to 50%. There is some evidence that the amount absorbed decreases as intake increases, suggesting a homoeostatic response. In the circulation, manganese is bound to transmanganin, a beta-1-globulin. Manganese is stored in the brain, kidneys, pancreas, and liver. It is excreted in bile, and undergoes enterohepatic circulation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Micro Mn; *India*: Infladase Forte; *Israel*: Micro Mn; *USA*: Mangimin.

Multi-ingredient Preparations. *Arg.*: Gingeron; Glucobefol†; Ipri V Total; Krebs Plus; Senexon Plus; Tonovital Plus Antioxidante; *Austral.*: AB Ausbiobone; Accelerex; Bone Builder; Caltrate Plus; Joint Formula Advanced; Nutribone; *Braz.*: Ferrotrat B12 Plus; Olig-Trat; Xantinon B12; *Canad.*: Caltrate Plus; Fibroplex; Formula CDC; Procosa; *Chile*: Caprimida D Balance; Cicaplast; Larotabe; *Cz.*: Caltrate Plus; *Fr.*: Cicaplast; Kinesamine; Oligocure; Oligoderm†; Superoxylase; Tot'Hema; *Hong Kong*: Caltrate Plus; Procosa II†; *Hung.*: Dietet-In; Ferrocomp; Humet-R; Klimin; Multicomp; Obesmin; *India*: Actima; Antoxid; Aviton; Avpro; Avpro; B7 Plus; Beta-Sclerobion; Bonjo Aid; Calmix; Calsuper Forte; Carbosyl; Cartifix; Cartispan; Cartivit; Cartiwel; Cartiz; Casiop; Cool-Joint; Cosantin; D-Gard; Derantox; Eldervit-ZC; Elnutra; Elrox-AO; Evepearl-PMS; Exerge-HC; Exerge; Fabulae; Fejet; Ferrimin; Fersolate-CM; Flintoff; Free M; Freecad; Furtipil-L; GC Flex; Gencart; Geocal; Glortho Forte; Glucomade; Glucovit Plus; Haem Up; Haem-Up Gems; Haem-Up; Hemocare; Hemocare; I-Lute; Intecar; Iron-Gold; Ironate; Kefive Plus; Logical-M; Lytox; Macuchek; Maxiferon; Maxo-FE; Mexivit; Minigadine; Necare; Neogadine SG; Nervitone; Nicy Days; Nofro; Nutra; Orbone Forte; Orbone; Ostebon-M; Osteo-G; Osteoflex; Ostop; Ostovit; Oxidon; Oxipre; Oxy-V; Oxyban; Oxydex; Oxyeye; Oxyret; Oxyvit; Winofit; *Indon.*: Adfer; Artro Plus; Artro; Biosanbe; Calciviton; Caltron; Diabion; Emibion; Emineton; Eviprostat; Feroglobin; Fitbon Plus; Fripos; GCM; Habebion†; Hemafort; Inbion; Joint Care Plus; Joint Care; Jointace; Lavarix; Naturema; Neogobion; Nonemi; OA Forte; OA Plus; OA; Opibion; Osamin; Ossovit Plus; Oste; Ostela; Osteocal Plus; Osteoflam; Osteokom Forte; Osteokom; Osteonic; Osteor Plus; Osteor; Osteotin; Ostine; Osvion Plus; Pronita; Rebone; Rheumatin Forte; Rheumatin; Risteon; Sangobion; Sangofer; Sangovitin†; Solvitron; Steopor; Suprabion; Tonikum Bayer; Tonikum Bode; Tropifer; Viopor-M Forte; Viopor-M; Viopor; Viostin Com DS; Viostin Com; Viostin-X; Vioxyfm; Vioxy; Vitabion; Vitonal; *Irl.*: Caltrate Plus†; *Israel*: Mega Gluflex; *Ital.*: Saniquiet; Sterimar Mn; Vertiginkgo; *Malaysia*: Caltrate Plus; Opibion; *Mex.*: Actiman; *Norw.*: Tonipan†; *NZ*: Caltrate Plus; *Philipp.*: Caltrate Plus; Macrobee with Iron; Ruflex; Sangobion; *Pol.*: Biovital†; Caltrate Plus; *Port.*: Tot'Hema; *Rus.*: Calcemin (Кальцемин); Calcemin Advance (Кальцемин Адванс); Tot'Hema (Тотема); *S.Afr.*: Dr Williams Pink Pills†; Ferrous Sulphate Compound†; ProFLEX†; *Singapore*: Caltrate Plus; Eviprostat; Floron; Hemacaps†; Hemoplex; Multitrace-5; Neogobion; Opibion; Procosa II†; Sangobion; *Thai.*: Caltrate Plus; Calvin Plus; Glufer-C†; *Turk.*: Eser Metaller; Ultimate; *UK*: Calci-Plus; Caltrate Plus; Joint Action; Ostron; *Ukr.*: Calcemin (Кальцемин); Calcemin Advance (Кальцемин Адванс); Calcemin Silver (Кальцемин Сильвер); Tot'Hema (Тотема); Vimifor Multivitamin with Beta-Carotene (Віміфор Мультивітамін З Бета-каротином)†; Vitrum Osteomag (Витрум Остеомаг); *USA*: Antioxidant Formula; Caltrate Plus; Cro-Man-Zin; REQ49+; *Venez.*: Ocoxin; Vitalux.

Homoeopathic Preparations. *Austria*: Dalektro; *Canad.*: Formula DE 226†; Sinus Ease; Sinuspax†; *Fr.*: Silicea Complexe No 11; Sinuspax; Uranium Compose†; Voxpax; *Ger.*: Drufusan N†; NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†; *Switz.*: Sinuspax†.

Pharmacopoeial Preparations

USP 36: Calcium and Vitamin D with Minerals Tablets; Manganese Chloride for Oral Solution; Manganese Chloride Injection; Manganese Sulfate Injection; Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Medium-chain Triglycerides

Keskipitkäketjuiset tyydyttyneet triglyseridit; Triacylglyceroly středně nasycené; Triglicerídai, vidutinės grandinės; Triglicerídek, közepes szénláncú zsírsavaké; Triglicéridos de cadena media; Triglycerida saturata media; Triglycerider, medellångkedjiga; Triglycérides à chaîne moyenne; Среднецепочечные Триглицериды.

UNII — C9H2L21V7U.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Triglycerides, Medium-chain). The fatty acids are obtained from the oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* or from the dried endosperm of *Elaeis guineensis*. They consist of a mixture of triglycerides of saturated fatty acids, mainly of octanoic acid and of capric acid ($C_{10}H_{20}O_2$ = 172.3). They contain not less than 95% of saturated fatty acids with 8 and 10 carbon atoms. A colourless or slightly yellowish, oily liquid. Practically insoluble in water; miscible with alcohol, with dichloromethane, with petroleum spirit, and with fatty oils. Store in well-filled containers. Protect from light.

USNF 31: (Medium-Chain Triglycerides). They are obtained from the oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* or from the dried endosperm of *Elaeis guineensis*. They consist of a mixture of triglycerides of saturated fatty acids, mainly of octanoic acid and of capric acid ($C_{10}H_{20}O_2$ = 172.3). They contain not less than 95% of saturated fatty acids with 8 and 10 carbon atoms. A colourless or slightly yellowish, oily liquid. Practically insoluble in water; miscible with alcohol, with dichloromethane, with petroleum spirit, and with fatty oils. Store in airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Profile

Medium-chain triglycerides are used for enteral and parenteral nutrition (p. 2044.1) in conditions associated with malabsorption of fat, such as cystic fibrosis, enteritis, and steatorrhoea, and after intestinal resection. Medium-chain triglycerides are more readily hydrolysed than long-chain triglycerides and are not dependent upon biliary or pancreatic secretions for absorption from the gastrointestinal tract. They provide 35 kJ (8.3 kcal) per g. They do not provide essential fatty acids.

Medium-chain triglycerides have also been used as bases for pharmaceutical preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Teceeme; *Austral.*: Liquigen; MCT Oil; *Cz.*: MCT Oil; *Denm.*: MCT Oil; *Fin.*: Liquigen; MCT Olja; *Fr.*: Liquigen; *Gr.*: MCT Oil; *Hung.*: Structolipid†; *Irl.*: Liquigen†; *Israel*: MCT; *Ital.*: MCT; Mytic 810; *NZ*: Liquigen; MCT Oil; *Port.*: MCT Oil; *UK*: Alembicol D; Liquigen; MCT Oil; *USA*: MCT.

Multi-ingredient Preparations. *Arg.*: Lipofundin MCT/LCT-E†; Lipofundin MCT/LCT; Lipovenos MCT/LCT; *Austral.*: Caprilon; MCT Duocal†; SMOFlipid; Visine Professional†; *Austria*: Lipidem; Lipofundin mit MCT; SMOFlipid; Structolipid†; *Belg.*: Lipoplus; Medialipide; Nutriflex Lipid; *Chile*: Lipofundin MCT/LCT; Lipovenos MCT/LCT; *China*: Lipofundin MCT/LCT (力保脂宁); Lipovenoes (力能); Structolipid (力文); *Cz.*: Lipofundin MCT/LCT†; Lipoplus; Nutriflex Lipid; NuTRIflex Omega; SMOFKabiven; SMOFlipid; Structolipid; *Denm.*: Lipidem; Liquigen; MCT Duocal; Nutriflex Lipid; SMOFKabiven; SMOFlipid; Structolipid†; Vasolipid; *Fin.*: Lipophus; Nutriflex Lipid; SMOFKabiven; SMOFlipid; Structolipid; Vasolipid; *Fr.*: Lipidem; Liprocil; Medialipide; Mednutriflex Lipide G; Nutriflex Lipide†; Reanutriflex Lipide; Reanutriflex Omega; SMOFKabiven; SMOFlipid; Structolipide†; *Ger.*: Gleitgelen; Lipidem; Lipofundin MCT; Lipovenos MCT; Nutriflex Lipid; NuTRIflex Omega; SMOFKabiven; SMOFlipid; Visine Trockene Augen; *Gr.*: Lipofundin MCT/LCT; Lipoplus; SMOFKabiven; SMOFlipid; Structolipid; *Hong Kong*: Lipofundin MCT/LCT; Nutriflex Lipid; SMOFlipid; *Hung.*: Lipofundin MCT†; SMOFlipid; *India*: Celepid MCT-LCT; Lipofundin MCT/LCT; Nutrilex Lipid Peri; *Indon.*: Hepabion†; Lipimix; Lipofundin MCT/LCT†; Lipomed MCT/LCT; *Irl.*: Caprilon†; Lipidem; Lipofundin MCT/LCT†; Nutriflex Lipid; SMOFKabiven; SMOFlipid; Structolipid†; *Israel*: Lipofundin MCT/LCT; SMOFKabiven; SMOFlipid; *Ital.*: Caprilon; Dicovit DK; Dicovit; Lipidem; Lipimix; Lipofundin MCT; Liquigen; Nutriperi Lipid; Nutriplus Lipid; Nutrispecial Lipid; SMOFlipid; Structolipid; Visine Dry Eyes†; *Mex.*: Lipofundin MCT/LCT; *Neth.*: Lipofundin MCT/LCT†; Lipoplus; Nutriflex Lipid; SMOFKabiven; SMOFlipid; Structolipid; *Norw.*: Lipidem; Nutriflex Lipid; NuTRIflex Omega; SMOFKabiven; SMOFlipid; Structolipid†; Vasolipid; *NZ*: Structolipid; *Pol.*: Lipofundin MCT/LCT; SMOFKabiven; SMOFlipid; *Port.*: Lipofundina MCT/LCT; Lipoplus; Nutribraun; SMOFKabiven; SMOFlipid; Structolipid; *Rus.*: Lipofundin MCT/LCT (Липофундин MCT/ЛСТ); Lipoplus (Липоплюс); SMOFlipid (СМОФлипид); *S. Afr.*: Lipofundin MCT/LCT†; *Singapore*: Lipofundin MCT/LCT; *Spain*: Lipofundina MCT/LCT; Lipomix; Lipoplus; Nutriflex Lipid; NuTRIflex Omega; SMOFKabiven; SMOFlipid; Structolipid†; *Swed.*: Lipoplus; Nutriflex Lipid; SMOFKabiven; SMOFlipid; Structolipid; Vasolipid; *Switz.*: Lipofundin MCT/LCT; Lipoplus; Nutriflex Lipid; SmofKabiven; SMOFlipid; Structolipid; *Thai.*: Lipidem; Lipofundin MCT/LCT; Nutriflex Lipid; SMOFlipid; Structolipid†; *Turk.*: Lipofundin MCT/LCT; SMOFlipid; *UK*: Caprilon; Imuderm†; Lipidem; Lipofundin MCT/LCT; MCT Duocal; Nutriflex Lipid; NuTRIflex Omega; SMOFlipid; Structolipid; *Ukr.*: Lipofundin MCT/LCT (Липофундин MCT/ЛСТ); SMOFlipid (СМОФлипид); *Venez.*: Lipofundin MCT/LCT.

Molybdenum

Molibdeno; Molibdenum; Molybdán; Molybdène; Молибден.

Mo=95.96

UNII — 81AH48963U.

Ammonium Molybdate

Amonowy molibdenian; Molibdato de amonio; Молибдат Аммония; Молибденовокислый Аммоний.

Hexaammonium molybdate tetrahydrate.

$(NH_4)_6Mo_7O_{24}.4H_2O$=1236.0

CAS — 12054-85-2.

UNII — OGI154X474 (ammonium molybdate tetrahydrate); 21Y68J178E (anhydrous ammonium molybdate).

Pharmacopoeias. In *US*.

USP 36: (Ammonium Molybdate). Colourless or slightly greenish or yellowish crystals. Soluble in water; practically insoluble in alcohol. Store in airtight containers.

Sodium Molybdate

Molibdato de sodio; Molybdenan sodný dihydrát; Natrii Molybdas Dihydricus; Natrio molibdatas dihidratas; Nátrium-molibdenát-dihidrát; Natriummolybdaattidihydraatti; Natriummolybdatdihydrat; Sodium (molybdate de) dihydraté; Sodu molibdenian; Молибдат Натрия; Молибденовокислый Натрий.

$Na_2MoO_4.2H_2O$=242.0

UNII — 948QAQ08I1.

Pharmacopoeias. In *Eur.* (see p. vii). *Ger.* also includes a monograph for the anhydrous substance.

Ph. Eur. 8: (Sodium Molybdate Dihydrate). A white or almost white powder or colourless crystals. Freely soluble in water.

Uses and Administration

Molybdenum is an essential trace element and small amounts, in the form of ammonium molybdate or sodium molybdate, are sometimes added to solutions for TPN. A suggested dose is about 20 to 120 micrograms (0.2 to 1.2 micromoles) elemental molybdenum daily.

Ammonium molybdate is used in veterinary medicine to treat copper poisoning in sheep.

Human requirements. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR) (see p. 2046.1) has been set for molybdenum although a safe intake was believed to be between 50 and 400 micrograms (0.5 and 4 micromoles) daily for adults.[1] In the USA, the recommended dietary allowance is 45 micrograms daily for adults.[1] The tolerable upper intake level is 2 mg daily.[2] WHO make the suggestion that the adult basal requirement for molybdenum could be about 25 micrograms daily,[3] corresponding to approximately 400 nanograms/kg.

Foods contributing to dietary molybdenum include milk, beans, breads, and cereals; however, extreme regional variations occur in molybdenum contents of food crops due to soil differences.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. WHO. Molybdenum. In: *Trace elements in human nutrition and health*. Geneva: WHO, 1996; 144–54.

Adverse Effects

Very high intakes of molybdenum, and associated increases in xanthine oxidase activity, may result in hyperuricaemia, and possibly gout. Molybdenum intoxication may impair the utilisation of copper.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Molybdene Injectable†; *USA*: Molypen†.

Multi-ingredient Preparations. *Canad.*: T-OS; *Hung.*: Humet-R; *Thal.*: Ferrovit; *Ukr.*: Vimifor Multivitamin with Beta-Carotene (Вімівор Мультивітамін З Бета-каротином)†.

Pharmacopoeial Preparations

USP 36: Ammonium Molybdate Injection; Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Trace Elements Injection; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Nicotinamide Ascorbate *(BANM, rINNM)*

Ascorbato de nicotinamida; Niacinamide Ascorbate; Nicoscorbine; Nicotinamide, Ascorbate de; Nicotinamidi Ascorbas; Никотинамида Аскорбат.

$C_{12}H_{14}N_2O_7$=298.3.

CAS — 1987-71-9.

UNII — JTL8B7TVW7.

Profile

Nicotinamide ascorbate is a complex of nicotinamide (below) with ascorbic acid (p. 2110.3) that is used in multivitamin preparations. It has also been given with betaine glucuronate and diolamine glucuronate for liver disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hong Kong*: Jetepar†; *Malaysia*: Jetepar; *Philipp.*: Jetepar; *Singapore*: Jetepar†.

Nicotinic Acid *(BAN, rINN)*

375; Acide Nicotinique; Ácido nicotínico; Acidum nicotinicum; Kwas nikotynowy; Kyselina nikotinová; Niacin; Niacina; Nicotínico, ácido; Nicotinsäure; Nikotiinihappo; Nikotinik Asit; Nikotino rūgštis; Nikotinsäure; Nikotinsav; Nikotinsyra; Никотиновая Кислота.

Pyridine-3-carboxylic acid.

$C_6H_5NO_2$=123.1

CAS — 59-67-6.

ATC — C04AC01; C10AD02.

ATC Vet — QC04AC01; QC10AD02.

UNII — 2679MF687A.

NOTE. Some published sources use the term niacin as a generic term to include both nicotinic acid and nicotinamide.

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

Ph. Eur. 8: (Nicotinic Acid). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in boiling water and in boiling alcohol. It dissolves in dilute solutions of alkali hydroxides and carbonates. Protect from light.

USP 36: (Niacin). White crystals or crystalline powder, odourless or has a slight odour. Soluble 1 in 60 of water; freely soluble in boiling water, in boiling alcohol, and in solutions of alkali hydroxides and carbonates; practically insoluble in ether.

Nicotinamide *(BAN, rINN)*

Niacinamide; Nicotinamid; Nicotinamida; Nicotinamidum; Nicotinic Acid Amide; Nicotylamide; Nikotiinamidi; Nikotinamid; Nikotiniamidas; Nikotynamid; Vitamin B_3; Vitamin PP; Vitamina B_3; Vitamina PP; Никотинамид.

Pyridine-3-carboxamide.

$C_6H_6N_2O$=122.1

CAS — 98-92-0.

ATC — A11HA01.

ATC Vet — QA11HA01.

UNII — 25X51I8RD4.

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

Ph. Eur. 8: (Nicotinamide). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water and in dehydrated alcohol. A 5% solution in water has a pH of 6.0 to 7.5.

USP 36: (Niacinamide). A white crystalline powder, odourless or practically so. Soluble 1 in 1.5 of water, 1 in 10 of boiling water, and 1 in 5.5 of alcohol; soluble in glycerol. Its solutions are neutral to litmus. Store in airtight containers.

Uses and Administration

Nicotinic acid and nicotinamide, the form that occurs naturally in the body, are water-soluble vitamin B substances that are converted to nicotinamide adenine dinucleotide (nadide, p. 2567.1) and nicotinamide adenine dinucleotide phosphate (NADP). These coenzymes are involved in electron transfer reactions in the respiratory chain.

Nicotinic acid deficiency develops when the dietary intake is inadequate. Deficiency leads to the development of a syndrome known as pellagra, characterised by skin lesions, especially on areas exposed to sunlight, with hyperpigmentation and hyperkeratinisation. Other symptoms include diarrhoea, abdominal pain, glossitis, stomatitis, loss of appetite, headache, lethargy, and mental and neurological disturbances. Nicotinic acid deficiency may occur with other vitamin B-complex deficiency states, for example in alcoholism.

Nicotinic acid and nicotinamide are used in the treatment and prevention of **nicotinic acid deficiency**. Nicotinamide is preferred as it does not cause vasodilatation. They are usually given orally, the preferred route, but may also be given by the intramuscular route or by slow intravenous injection. Doses of up to 500 mg daily (of either compound) in divided doses have been recommended.

Nicotinic acid has been used for its **vasodilator** action in the treatment of a variety of disorders; its value is not considered to be established.

In high doses, nicotinic acid has beneficial effects on blood lipid profiles, and has been used, with dietary modification and often with other lipid regulating drugs, in **hyperlipidaemias** (see below). For the immediate-release preparations, an initial oral dose of 250 mg once daily is increased every 4 to 7 days until a dose of 1.5 to 2 g daily is reached or the desired effect is seen. If hyperlipidaemia is not controlled after 2 months at this dose, the dose can be increased at 2- to 4-week intervals to 3 g daily in 3 divided doses. Although US licensed product information suggests that doses up to 6 g daily may be required in some patients, the *National Heart, Lung, and Blood Institute* in the USA recommends a maximum dose of 4.5 g daily.

Alternatively, an initial dose of 500 mg at night has been given as a modified-release preparation and gradually increased according to response to a maintenance dose of 1 to 2 g at bedtime. The daily dose should not be increased by more than 500 mg in any 4-week period.

Topical nicotinamide is used in the treatment of mild to moderate inflammatory **acne** (see below), typically as a 4% gel applied twice daily.

Nicotinamide has been shown to inhibit the destruction of pancreatic beta cells *in vitro* and is therefore being investigated in the prevention and treatment of type 1 **diabetes mellitus** (see below).

Acne. Topical nicotinamide may be used in the treatment of inflammatory acne (p. 1682.2); nicotinamide 4% was as effective as clindamycin 1% when applied topically twice daily for 8 weeks.[1]

1. Shalita AR, *et al.* Topical nicotinamide compared with clindamycin gel in the treatment of inflammatory acne vulgaris. *Int J Dermatol* 1995; 34: 434–7.

Diabetes mellitus. Nicotinic acid can affect glucose tolerance and should be used with care in established diabetes (see Effects on Glucose Tolerance, p. 2084.1). However, the drug has been used successfully in patients with diabetes. In the prevention of diabetes mellitus (p. 460.3) nicotinamide has been reported to induce remission in patients with newly diagnosed type 1 diabetes mellitus and may delay the onset of disease.[1,2] However, a randomised study found modified-release nicotinamide at 1.2 g/m² daily (to a maximum of 3 g daily) to be ineffective in preventing the onset of diabetes mellitus in first-degree relatives of patients with the disease.[3] Nicotinic acid can also raise high-density lipoprotein (HDL)-cholesterol concentrations (see below);[4,5] changes in glucose tolerance were mild enough for the drug to be considered as an alternative to statins and fibrates in diabetic patients. For further discussion of the role of nicotinic acid in the management of dyslipidaemias in diabetic patients, see under Diabetes-associated Cardiovascular Disease, p. 463.3.

1. Elliott RB, Chase HP. Prevention or delay of type 1 (insulin-dependent) diabetes mellitus in children using nicotinamide. *Diabetologia* 1991; 34: 362–5.
2. Pozzilli P, *et al.* Meta-analysis of nicotinamide treatment in patients with recent-onset IDDM. *Diabetes Care* 1996; 19: 1357–63.
3. European Nicotinamide Diabetes Intervention Trial Group. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes. *Lancet* 2004; 363: 925–31.
4. Elam MB, *et al.* Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: a randomized trial. *JAMA* 2000; 284: 1263–70.
5. Grundy SM, *et al.* Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of Niaspan trial. *Arch Intern Med* 2002; 162: 1568–76.

Hyperlipidaemias. The first-line treatment for hyperlipidaemias remains dietary and lifestyle modification; where this fails, drug therapy may be considered (p. 1248.1). Nicotinic acid is reported to have a favourable effect on blood-lipid profiles, raising high-density lipoprotein (HDL)-cholesterol and lowering low-density lipoprotein (LDL)-cholesterol.[1-3] Nicotinic acid is used particularly in familial hypertriglyceridaemia, or in familial combined hyperlipidaemia when both triglyceride and cholesterol concentrations are similarly elevated. Nicotinic acid was less effective than lovastatin at reducing LDL-cholesterol in patients with primary hypercholesterolaemia, but more effective at increasing HDL-cholesterol; lovastatin was better tolerated.[4] A combination of nicotinic acid with lovastatin was found to be comparable to atorvastatin and more effective than simvastatin in reducing LDL-cholesterol, and more effective than either atorvastatin or simvastatin in increasing HDL-cholesterol, in a study of patients with dyslipidaemia.[5] Some have recommended that nicotinic acid be substituted for a statin to lower LDL-cholesterol when patients cannot tolerate a statin.[2] Combination therapy is recommended when the reduction in LDL-cholesterol is insufficient with statin monotherapy,[2,6] or when raising HDL-cholesterol would be beneficial,[7-9] as in patients with type 2 diabetes mellitus, or the metabolic syndrome.[8] The risk of muscle toxicity with this combination is not considered to be significantly different to that with statin monotherapy.[7,10] A combination preparation of nicotinic acid with laropiprant was developed in an attempt to reduce flushing, but this preparation was withdrawn when it was found to have no benefit over statin therapy and an increased risk of adverse effects.[11,12]

1. McKenney JM, *et al.* A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA* 1994; 271: 672–7.
2. McKenney J. Niacin for dyslipidemia: considerations in product selection. *Am J Health-Syst Pharm* 2003; 60: 995–1005.
3. McCormack PL, Keating GM. Prolonged-release nicotinic acid: a review of its use in the treatment of dyslipidaemia. *Drugs* 2005; 65: 2719–40.
4. Illingworth DR, *et al.* Comparative effects of lovastatin and niacin in primary hypercholesterolemia: a prospective trial. *Arch Intern Med* 1994; 154: 1586–95.
5. Bays HE, *et al.* Comparison of once-daily, Niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (The Advicor Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *Am J Cardiol* 2003; 91: 667–72.
6. Miller M. Niacin as a component of combination therapy for dyslipidemia. *Mayo Clin Proc* 2003; 78: 735–42.
7. McKenney J. New perspectives on the use of niacin in the treatment of lipid disorders. *Arch Intern Med* 2004; 164: 697–705.
8. Chapman MJ, *et al.* Raising high-density lipoprotein cholesterol with reduction of cardiovascular risk: the role of nicotinic acid—a position paper developed by the European Consensus Panel on HDL-C. *Curr Med Res Opin* 2004; 20: 1253–68.
9. Yim BT, Chong PH. Niacin-ER and lovastatin treatment of hypercholesterolemia and mixed dyslipidemia. *Ann Pharmacother* 2003; 37: 106–15.
10. Robinson JG. Management of complex lipid abnormalities with a fixed dose combination of simvastatin and extended release niacin. *Vasc Health Risk Manag* 2009; 5: 31–43.
11. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J* 2013; 34: 1279–91.
12. EMA. European Medicines Agency confirms recommendation to suspend Tredaptive, Pelzont and Trevaclyn: doctors should no longer prescribe these medicines and should review patients' treatment options (issued 18th January, 2013). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/01/WC500137453.pdf (accessed 03/12/13)

Pemphigus. Oral treatment with nicotinamide and a tetracycline[1-4] has controlled lesions in pemphigus and pemphigoid (p. 1687.1), including persistent pemphigoid gestationis,[5] and ocular cicatricial pemphigoid.[6]

1. Sawai T, *et al.* Pemphigus vegetans with oesophageal involvement: successful treatment with minocycline and nicotinamide. *Br J Dermatol* 1995; 132: 668–70.
2. Kolbach DN, *et al.* Bullous pemphigoid successfully controlled by tetracycline and nicotinamide. *Br J Dermatol* 1995; 133: 88–90.
3. Reiche L, *et al.* Combination therapy with nicotinamide and tetracyclines for cicatricial pemphigoid: further support for its efficacy. *Clin Exp Dermatol* 1998; 23: 254–7.
4. Goon ATJ, *et al.* Tetracycline and nicotinamide for the treatment of bullous pemphigoid: our experience in Singapore. *Singapore Med J* 2000; 41: 327–30.
5. Amato L, *et al.* Successful treatment with doxycycline and nicotinamide of two cases of persistent pemphigoid gestationis. *J Dermatol Treat* 2002; 13: 143–6.
6. Dragan L, *et al.* Tetracycline and niacinamide: treatment alternatives in ocular cicatricial pemphigoid. *Cutis* 1999; 63: 181–3.

Adverse Effects and Treatment

Nicotinic acid has a vasodilator action and when given orally or by injection in therapeutic doses it may cause flushing, a sensation of heat, faintness, and a pounding in the head. Flushing may be accompanied by tingling, itching, headache, dizziness, tachycardia, palpitations, dyspnoea,

sweating, chills, or oedema. These symptoms are transient and various strategies have been proposed to reduce them (see Incidence of Adverse Effects, below). Nicotinamide does not have a vasodilator action.

Other adverse effects that have been reported, especially after high doses of nicotinic acid, include dryness of the skin, pruritus, hyperpigmentation, rash, cramps, cough, diarrhoea, nausea and vomiting, anorexia, activation of peptic ulcer, eye disorders including cystoid macular oedema and toxic amblyopia, decrease in glucose tolerance, hyperglycaemia, and hyperuricaemia. Most of these effects subside on withdrawal of the drug. Nicotinic acid has been associated with abnormal liver function tests and jaundice. Increases in liver transaminases are generally reversible on stopping treatment. Hypophosphataemia, a reduction in platelet counts, prolongation of prothrombin time, arrhythmias, and hypersensitivity reactions including angioedema have also been reported. Insomnia, myalgia, and hypotension may occur.

Topical nicotinamide may cause dryness of the skin and, less frequently, pruritus, erythema, burning sensation, and irritation. Frequency of application should be reduced if these effects occur.

References.

1. Guyton JR, Bays HE. Safety considerations with niacin therapy. *Am J Cardiol* 2007; **99** (suppl 1): S22–S31.

Incidence of adverse effects. Nicotinic acid produces frequent adverse effects, but they are not usually serious, tend to decrease with time, and some can be minimised by following appropriate instructions for use.[1,2] Dermal and gastrointestinal reactions are most common. Truncal and facial flushing are reported in 90 to 100% of treated patients in large clinical studies; they appear to be prostaglandin-mediated and can be reduced with aspirin 75 mg or 325 mg given shortly before the nicotinic acid, or simply by giving nicotinic acid with food, and by starting therapy with a low dose and gradually increasing this. It may also help to avoid eating spicy foods or drinking hot drinks or alcohol at the same time as taking nicotinic acid. Flushing may be less common with modified-release formulations;[2] furthermore, an analysis of serious adverse events reported to the FDA suggested that the incidence of such effects (including effects on the liver) with modified-release preparations of nicotinic acid was about one-sixth of that with conventional formulations.[3]

1. Knodel LC, Talbert RL. Adverse effects of hypolipidaemic drugs. *Med Toxicol* 1987; **2**: 10–32.
2. American Society of Health-System Pharmacists. ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm* 1997; **54**: 2815–19.
3. Alsheikh-Ali AA, Karas RH. The safety of niacin in the US Food and Drug Administration adverse event reporting database. *Am J Cardiol* 2008; **101** (suppl): 9B–13B.

Effects on the eyes. Retrospective survey of hyperlipidaemic patients suggested that dry eyes (sicca syndromes), blurred vision, and swollen eyelids might be associated with nicotinic acid therapy in some patients.[1] The effects appeared to be dose-related and reversible. In 2 patients treatment was stopped because of symptoms suggestive of cystoid macular oedema. Other cases of nicotinic acid maculopathy have been reported.[2,3]

1. Fraunfelder FW, *et al.* Adverse ocular effects associated with niacin therapy. *Br J Ophthalmol* 1995; **79**: 54–6.
2. Callanan D, *et al.* Macular edema associated with nicotinic acid (niacin). *JAMA* 1998; **279**: 1702.
3. Spim MJ, *et al.* Optical coherence tomography findings in nicotinic acid maculopathy. *Am J Ophthalmol* 2003; **135**: 913–14.

Effects on glucose tolerance. Nicotinic acid can reduce glucose tolerance, and this may be problematic in patients with diabetes mellitus,[1,2] although it has been investigated in the prevention of diabetes mellitus (see p. 2083.2). A review[3] of the effects of nicotinic acid on glucose control in patients with dyslipidaemia found that, although it is recognised that it can increase blood glucose concentrations, the effects were typically minor (about 4 to 5%) when given at daily doses of 2.5 g or less. In most patients with type 2 diabetes mellitus changes in blood glucose concentrations could be managed by adjusting antidiabetic therapy, and the cardiovascular benefits of nicotinic acid treatment might outweigh the risks.

1. American Society of Health-System Pharmacists. ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm* 1997; **54**: 2815–19.
2. Kreisberg RA. Niacin: a therapeutic dilemma—"one man's drink is another's poison". *Am J Med* 1994; **97**: 313–16.
3. Goldberg RB, Jacobson TA. Effects of niacin on glucose control in patients with dyslipidemia. *Mayo Clin Proc* 2008; **83**: 470–8.

Effects on the liver. Hepatotoxicity may occur with nicotinic acid.[1-6] Significant elevations of liver enzymes are occasionally seen with nicotinic acid therapy. They are more common in patients given large dosage increases over short periods of time, and in patients treated with modified-release formulations. It has been suggested[7] that since effects on liver function may in some instances lead to hepatic failure and are more common with modified-release dosage forms the use of crystalline immediate-release preparations should be preferred, a view shared by other commentators.[8] However, although studies appear to confirm a more frequent association of hepatotoxicity with modified-release dosage forms[4,9,10] it should be borne in mind that these effects can also occur with the immediate-release preparations, especially at high doses. Some manufacturers of modified-release preparations have stated that cases of severe hepatotoxicity, including fulminant hepatic necrosis, have occurred when patients have substituted modified-release dosage forms for immediate-release crystalline preparations at equivalent doses. There is also a suggestion that not all modified-release preparations are alike in their effects.[11] For a study indicating a lower incidence of reported serious adverse effects in patients given modified-release rather than conventional formulations, see Incidence of Adverse Effects, above.

1. Henkin Y, *et al.* Rechallenge with crystalline niacin after drug-induced hepatitis from sustained-release niacin. *JAMA* 1990; **264**: 241–3.
2. Hodis HN. Acute hepatic failure associated with the use of low-dose sustained-release niacin. *JAMA* 1990; **264**: 181.
3. Etchason JA, *et al.* Niacin-induced hepatitis: a potential side effect with low-dose time-release niacin. *Mayo Clin Proc* 1991; **66**: 23–8.
4. Rader JI, *et al.* Hepatic toxicity of unmodified and time-release preparations of niacin. *Am J Med* 1992; **92**: 77–81.
5. Coppola A, *et al.* Niacin-induced hepatotoxicity: unusual presentations. *South Med J* 1994; **87**: 30–2.
6. Gavilán JC, *et al.* Hepatitis inducida por niacina. *Med Clin (Barc)* 2002; **118**: 558.
7. Palumbo PJ. Rediscovery of crystalline niacin. *Mayo Clin Proc* 1991; **66**: 112–13.
8. Kreisberg RA. Niacin: a therapeutic dilemma—"one man's drink is another's poison". *Am J Med* 1994; **97**: 313–16.
9. McKenney JM, *et al.* A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA* 1994; **271**: 672–7.
10. Gray DR, *et al.* Efficacy and safety of controlled-release niacin in dyslipoproteinemic veterans. *Ann Intern Med* 1994; **121**: 252–8.
11. Lavie CJ, Milani RV. Safety and side-effects of sustained-release niacin. *JAMA* 1994; **272**: 513–14.

Effects on the muscles. Myopathy has been noted with nicotinic acid.[1,2] Rhabdomyolysis has occurred when nicotinic acid was given with lovastatin (see Lipid Regulating Drugs, under Interactions of Simvastatin, p. 1495.3). However, an analysis of adverse events reported to the FDA with a combination of modified-release nicotinic acid and lovastatin suggested the incidence was no higher than with either drug alone, see Incidence of Adverse Effects, above.

1. Litin SC, Anderson CF. Nicotinic-acid associated myopathy: a report of three cases. *Am J Med* 1989; **86**: 481–3.
2. Gharavi AG, *et al.* Niacin-induced myopathy. *Am J Cardiol* 1994; **74**: 841–2.

Hyperuricaemia. Nicotinic acid decreases urinary excretion of uric acid, which may result in elevation of serum uric acid and exacerbation of pre-existing gout.[1]

1. American Society of Health-System Pharmacists. ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm* 1997; **54**: 2815–19.

Precautions

Liver function should be tested before starting treatment with nicotinic acid, every 6 to 12 weeks for the first year, and periodically thereafter. A persistent increase in transaminases of 3 or more times the upper limit of normal requires treatment to be stopped. Nicotinic acid should not be used in patients with significant hepatic impairment, and treatment should be closely monitored in those with jaundice or other hepato-biliary disorders. Modified-release preparations should not be substituted for equivalent doses of immediate-release crystalline nicotinic acid preparations, as cases of severe hepatotoxicity, including fulminant hepatic necrosis, have occurred.

Caution is required when using nicotinic acid in patients with active peptic ulcer disease or acute coronary syndrome, patients with or predisposed to gout, or in those who consume large amounts of alcohol. Nicotinic acid and its metabolites are excreted via the kidneys and caution is required in patients with renal impairment. Patients with diabetes mellitus should be monitored closely when taking nicotinic acid as increases in fasting blood glucose have occurred.

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

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

Although some evidence suggests that combinations of nicotinic acid and statins can be given safely (see Incidence of Adverse Effects, above), there may be an increased risk of myopathy or rhabdomyolysis (see Lipid Regulating Drugs, under Interactions of Simvastatin, p. 1495.3). Nicotinic acid may increase the requirements for insulin or oral hypoglycaemics. Aspirin may reduce the clearance of nicotinic acid. *In vitro* studies suggest that colestipol and colestyramine may reduce the availability of nicotinic acid, and some licensed product information recommends an interval of at least 4 to 6 hours between giving nicotinic acid and bile-acid binding resins.

Antiepileptics. For the effect of nicotinamide on *carbamazepine*, see Vitamins, p. 517.3.

Nicotine. A patient started to have flushing and dizziness after her usual doses of nicotinic acid when transdermal nicotine patches were added to her therapy.[1] She had experienced such reactions 3 years previously on starting nicotinic acid therapy, but not since, and it was suggested that on this occasion an interaction might have been responsible.

1. Rockwell KA. Potential interaction between niacin and transdermal nicotine. *Ann Pharmacother* 1993; **27**: 1283–4.

Pharmacokinetics

Nicotinic acid and nicotinamide are readily absorbed from the gastrointestinal tract after oral doses and widely distributed in the body tissues. Nicotinic acid appears in breast milk. The main route of metabolism is their conversion to *N*-methylnicotinamide and the 2-pyridone and 4-pyridone derivatives; nicotinuric acid is also formed. Small amounts of nicotinic acid and nicotinamide are excreted unchanged in urine after therapeutic doses; however the amount excreted unchanged is increased with larger doses.

References.

1. Pieper JA. Overview of niacin formulations: differences in pharmacokinetics, efficacy, and safety. *Am J Health-Syst Pharm* 2003; **60** (Suppl 2): S9–14.

Human Requirements

The daily human requirement of nicotinic acid, though not definitely known, is probably about 15 to 20 mg. Yeast, meat, fish, potatoes, legumes, and wholemeal cereals are good sources of nicotinic acid and nicotinamide. However they may be present in a bound, unabsorbable form in cereals, especially maize. Nicotinic acid can also be obtained from the conversion of tryptophan in the body, 60 mg of dietary tryptophan being considered equivalent to 1 mg of dietary nicotinic acid, so requirements are influenced by dietary protein intake and if protein intake is adequate there is little need for any preformed vitamin in the diet. There is generally little loss of nicotinic acid from foods during cooking.

UK and US recommended dietary intake. In the UK dietary reference values (see p. 2046.1) have been published for nicotinic acid[1] and in the USA recommended dietary allowances (RDAs) have been set.[2] In the UK the reference nutrient intake (RNI) is 6.6 mg niacin equivalent per 1000 kcal daily and the estimated average requirement (EAR) is 5.5 mg niacin equivalent per 1000 kcal daily for adult males and females. One niacin equivalent is equal to 1 mg of dietary nicotinic acid or 60 mg of dietary tryptophan. In the US the RDAs are also expressed in niacin equivalents and are 16 mg daily for adult males and 14 mg daily for adult females; the EAR is 12 mg daily in males and 11 mg daily in females. The tolerable upper intake level for adults is 35 mg daily.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: NB-3; Niaspan; *Austral.*: Papulex; *Austria*: Direktan; Niaspan; *Belg.*: Ucemine PP; *Braz.*: Acinic; Metri; Papuless; *Canad.*: Ni-Odan; Niaspan; *Chile*: Cotina; Niacex†; Niaspan; *China*: Ben Yue (本悦); Gao Zi Ke (高兹克); Niaspan (诺之平); Pu Fu Lin (普扶林); Rui Zhi (锐昔); Shu Cheng (舒成); Tian Xin Shuang (天新爽); *Fin.*: Niaspan†; *Fr.*: Niaspan†; Nicobion; Papulex; *Ger.*: Niaspan†; Nicobion†; *Gr.*: Nicotivit; *Hong Kong*: Niaspan; Nicocin†; *India*: Neasyn; Nialip; Nicocin; *Indon.*: Niacef; Niaspan; *Irl.*: Niaspan; Nicam; Pelzont†; *Israel*: Niaspan; *Ital.*: Niaspanor; *Mex.*: Hipocol; Nacro; Niaspan; Pepevit†; *Neth.*: Niaspan†; *Norw.*: Niaspan†; *Philipp.*: Niaspan; *Port.*: Niaspan; *Rus.*: Enduracin (Эндурацин); Vita-Iodurol (Вита-йодурол); *Singapore*: Niaspan; *Swed.*: Niaspan†; *Switz.*: Niaspan†; *Thai.*: Niaspan; Nicotabs; *Turk.*: Niascor; Niaspan; *UK*: Preederm; Niaspan†; Nicam; *USA*: Endur-acin; Niaspan; Slo-Niacin; *Venez.*: Niaspan.

Multi-ingredient Preparations. *Arg.*: Anemidox; Atomo Ordenador; Centella Asiatica Compuesta; Cordaptive; IP6; Proavenal Omegatopic; *Austral.*: Dynamo†; Papulex; Sunsense Anti Ageing Face; *Austria*: Pelzont†; Tredaptive†; *Belg.*: Tredaptive†; Trihistalex; *Braz.*: Cordaptive; Fortevit; Prutoplex; Prutovena; Sadol†; *Canad.*: Advicor†; Formula 7441†; Formula 7442†; Inner Shade†; Lipofactors & Niacin†; Nia-Plex; TBV; *Chile*: Becomplina Fuerte†; Benutrex 1000†; Cicapost; Effaclar AI; Exomega; Kerium Anticaspa Intensivo; Perfungol†; Proaven; Rodepan; Ureadin Forte; Ureadin Rx PS; Ureadin Rx RD; *China*: Kai Yu (凯瑜); Cz.: Pelzont†; Tredaptive†; Trevaclyn†; *Denm.*: Tredaptive†; *Fin.*: Neurovitan†; Vertipam†; *Fr.*: Actipur 3 en 1; Actipur Anti-imperfections; Actipur Stop; Dida; Papulex; Surelen†; Tone; Tredaptive†; Vita-Dermacide; *Ger.*: Eukalisan N†; Floradix Eisen-Folsaure; Floradix Kräuterblut†; Tredaptive†; *Gr.*: Collyre Vitaphakol; Suprin; Tredaptive†; Vertigo-Vomex; *Hong Kong*: Tredaptive†; *Hung.*: Dietet-in; Klimin; Obesmin; Paniverin†; *India*: Aclin; Acmic; Adifer-Z; Aglozyme; Alfariz; Aloederm; Altrazyme; Alvit; Aneudox-12; Aneudox-12; Atpro; Avas Plus; Avpro; B-12; CB-12; Clin-3; Clinicare; Clinmide; Clinsoft; Diligan; Ecobal; Efcoba Plus; Exomega; Facedin; Feast; Femcinol-A; Folcin-12 Combi; Folium; Folnet; Folvina; Fortox; Genprot; Globiron-Z; Hepa-Merz†; Hepasure; Hepawin; Kalzana; L-Bex; Lesstrol-N; Livogen; Livosil-B; Lornit; Mecona Plus; Mego-XL; Mericobal; Methoneuron-C; Methovit; N-Meedia; Neogadine SG; Neurophosphates†; Neurotrat; Neurotrat; Nicinal; Nicolin; Nisacne; Niyat; Nurokind Plus; Nurokind-More; Nutra; Nutrared; Nutrozyme; Oraflora; Ornipan; Pabatab-BZ; Sioneuron; *Indon.*: Ballin Q10; Biocholes†; Carni Plus; Cereton; Combiplex; Dansera; Dialac; Hemaviton Jreng; Kitotes†; Sangobion ActiFe; Sotens†; Tonikum Bayer; Vionin; Yeastafort; *Irl.*: Crampex; Effaclar AI; Effico; Quiet Life; Tredaptive†; Trevaclyn†; *Israel*: Babyzim; Tredaptive†; *Ital.*: AMD; Disepavit; Emopon; Epargriseovit; Epaviten; Folepar B12; Fosforilasi; Konorderm; Novostatin; Pineal; PML Crono; Solvobil†; Virman Plus; *Malaysia*: Dermaheal DeAkni; P-Trovite; *Mex.*: Cordaptive; *Mon.*: Monasens; Vitarutine; *Neth.*: Pelzont†; Tredaptive†; Trevaclyn†; *Norw.*: Tredaptive†; *NZ*: Tredaptive†; *Philipp.*: Hiruscar; Jetepar; Tredaptive†; *Pol.*: Dermilan; Pelzont†; Tredaptive†; Trevaclyn†; *Port.*: Cicapost; Pelzont†; Tredaptive†; Trevaclyn†; Ureadin Forte; *Rus.*: Cytoflavin (Цитофлавин); Doppelherz Ginseng Aktiv (Доппельгерц Женьшень Актив); Essliver Forte (Эссливер Форте); Lidevine (Лидевин); Multi-Tabs B-Complex (Мульти-Табс В-Комплекс); Nicospan (НИКОШПАН); Oftan Catachrom (Офтан Катахром); Remaxol (Ремаксол); Unienzyme с MPS (Юнизим с MTC); *Singapore*: Beafort; Beaplex; Erase; Ferbeaplex; Hiruscar; Papulex Isocorrexion; Papulex Oil-Free; Papulex; Tredaptive†; *Spain*: Depurativo Richelet†; Enofosforina Vigor†; Tredaptive†; *Swed.*: Tredaptive†; *Switz.*: Tredaptive†; *Thai.*: B-100 Complex; *Turk.*: Epargriseovit; *UK*: Crampex; Effico; Quiet Life; S.P.H.P.; Tredaptive†; Vitalux Plus; *Ukr.*: B-Complex Multi-Tabs (В-Комплекс Мульти-Табс)†; Cocarnit (Кокарнит); Cytoflavin (Цитофлавин); Decamevit (Декамевит); Fenules (Фенюль)†; Hepaforte (Гепафорте); Levasil (Левасил); Lidevin (Лидевин); Sedavit (Седавит); Vita-Iodurol (Вита-Йодурол)†; *USA*: Advicor; Integra F; NicAzel Forte; Nicomide†; REQ49+; Simcor; Trizel; VP-Zel.

Homoeopathic Preparations. *Ger.*: Infi-China; Infi-Symphytum; Infihepan.

Pharmacopoeial Preparations

BP 2014: Nicotinamide Tablets; Nicotinic Acid Tablets; Vitamins B and C Injection;

BPC 1973: Compound Vitamin B Tablets; Strong Compound Vitamin B Tablets;

USP 36: Niacin Extended-Release Tablets; Niacin Injection; Niacin Tablets; Niacinamide Injection; Niacinamide Tablets; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Olaflur *(BAN, USAN, rINN)*

Amine Fluoride 297; GA-297; Olaflurum; SKF-38095; Олафлур.

2,2′-(3-[*N*-(2-Hydroxyethyl)octadecylamino]propylimino) diethanol dihydrofluoride.

$C_{27}H_{60}F_2N_2O_3$=498.8

CAS — 6818-37-7.

ATC — A01AA03.

ATC Vet — QA01AA03.

UNII — 8NY9L8837D.

Profile

Olaflur is used as a source of fluoride (see Sodium Fluoride, p. 2089.2) in the prevention of dental caries. For a report of stomatitis considered to be due to olaflur, see Hypersensitivity, under Sodium Fluoride, p. 2091.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Pol.*: Fluormex; *Port.*: Elmex; Elmex.

Multi-ingredient Preparations. *Austria*: Elmex; Elmex; *Belg.*: Elmex; *Cz.*: Elmex; Elmex; *Fin.*: Elmex; Elmex; *Ger.*: Elmex; Elmex; Ledermix Fluorid; Multifluorid†; *Hung.*: Elmex; Elmex; *Israel*: Elmex; Elmex; Meridol; *Ital.*: Elmex; *Neth.*: Elmex; Elmex; *Pol.*: Elmex; Fluormex; *Switz.*: Elmex; Elmex; Paro aux fluorures d'amines Gelee.

Ornithine *(rINN)*

Orn; L-Ornithine; Ornithinum; Ornitina; α,δ-Diaminovaleric Acid; Орнитин.

L-2,5-Diaminovaleric acid.

$C_5H_{12}N_2O_2$=132.2

CAS — 70-26-8.

UNII — ES24N2IXA3.

Pharmacopoeias. *Ger.* includes Ornithine Aspartate and Ornithine Hydrochloride.

Profile

Ornithine is an aliphatic non-essential amino acid. It is used as a dietary supplement.

The aspartate, hydrochloride, and oxoglurate (ornithine ketoglutarate, see also Parenteral and Enteral Nutrition under Glutamic Acid, p. 2070.3) and phenylacetate have been used in various indications including the treatment of hyperammonaemia (p. 2049.3) and hepatic encephalopathy (p. 1808.2).

References.

1. Rapport L, Lockwood B. Ornithine ketoglutarate. *Pharm J* 2001; 266: 688–90.
2. Coudray-Lucas C, *et al.* Ornithine alpha-ketoglutarate improves wound healing in severe burn patients: a prospective randomized double-blind trial versus isonitrogenous controls. *Crit Care Med* 2000; 28: 1772–6.
3. Kircheis G, *et al.* Clinical efficacy of L-ornithine-L-aspartate in the management of hepatic encephalopathy. *Metab Brain Dis* 2002; 17: 453–62.
4. Blonde-Cynober F, *et al.* Use of ornithine alpha-ketoglutarate in clinical nutrition of elderly patients. *Nutrition* 2003; 19: 73–5.
5. Jalan R, *et al.* L-Ornithine phenylacetate (OP): a novel treatment for hyperammonemia and hepatic encephalopathy. *Med Hypotheses* 2007; 69: 1064–9.
6. Jiang Q, *et al.* L-Ornithine-l-aspartate in the management of hepatic encephalopathy: a meta-analysis. *J Gastroenterol Hepatol* 2009; 24: 9–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Hepa; Hepasan; *Braz.*: Hepa-Merz; *China*: Hepa-Merz (雅博司); Rui Gan (瑞甘); *Fr.*: Cetornan; Ornicetil†; *Ger.*: Hepa-Merz KT†; Hepa-Merz; Hepa-Vibolex; *Hong Kong*: Hepa-Merz; *Hung.*: Hepa-Merz; *India*: Alnalive; Analiv; Arosi; Biohep; Hep-Zo; Hepa-Merz; Hepacor; Hepagard; Hepastar; Hepawin; Hepaze; Hepoline; Intraliv; Longliv; Lorni-S; Lornit; Nitlor; Nitoliv; Olson; *Indon.*: Hepa-Merz; Hevtin†; Livola; *Ital.*: Ornil KGF; Ornil; *Mex.*: Hepa-Merz; *Philipp.*: Hepa-Merz; *Pol.*: Hepa-Merz; Hepatil†; *Rus.*: Hepa-Merz (Гепа-Мерц); Ornicetil (Орницетил); *Thai.*: Hepa-Merz; *Turk.*: Hepa-Merz; *Ukr.*: Hepa-Merz (Гепа-Мерц).

Multi-ingredient Preparations. *Braz.*: Ornitargin; *Fr.*: Actigess†; *Hong Kong*: Profile B Plus Fat Burner†; *India*: Alcohep; Analiv; Arosi: Biohep; Hepa-Merz†; Hepa-Merz; Hepalon; Hepan-L; Hepasure; Hepasure; Hepator; Hepawin Plus; Hepawin; Hepawin; Kayliv; Livbel; Livopill; Livtop; Lornit; Nitlor Plus; Ornilive; Ornipan; Ornipan; *Ital.*: Ipoazotal Complex; Somatron.

Pantothenic Acid *(BAN)*

Pantoténico, ácido; Vitamin B_5; Vitamina B_5; Пантотеновая Кислота; Витамин B5.

(+)-(*R*)-3-(2,4-Dihydroxy-3,3-dimethylbutyramido)propionic acid.

$C_9H_{17}NO_5$=219.2

CAS — 79-83-4 (D-pantothenic acid); 599-54-2 (DL-pantothenic acid).

ATC — A11HA31; D03AX04.

ATC Vet — QA11HA31; QD03AX04.

UNII — 19F5HK2737.

Calcium Pantothenate *(BANM, rINN)*

Calcii Pantothenas; Calcium, pantothénate de; Calciumpantothenat; Dextro Calcium Pantothenate; Kalcio pantotenatas; Kalciumpantotenat; Kalcium-pantotenát; Kalsiumpantotenaatti; Pantotenato de calcio; Pantothenan vápenatý; Pantothénate de Calcium; Wapnia pantotenian; Кальция Пантотенат.

$(C_9H_{16}NO_5)_2Ca$=476.5

CAS — 137-08-6 (calcium D-pantothenate); 6381-63-1 (calcium DL-pantothenate).

ATC — A11HA31; D03AX04.

ATC Vet — QA11HA31; QD03AX04.

UNII — 568ET80C3D (calcium D-pantothenate); 2KC899R47Q (calcium DL-pantothenate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.* *US* also has a monograph for Racemic Calcium Pantothenate.

Ger. also includes Sodium Pantothenate.

Ph. Eur. 8: (Calcium Pantothenate). A white or almost white, slightly hygroscopic powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution has a pH of 6.8 to 8.0. Store in airtight containers.

USP 36: (Calcium Pantothenate). The calcium salt of the dextrorotatory isomer of pantothenic acid. A white, odourless, slightly hygroscopic powder. Soluble 1 in 3 of water; practically insoluble in alcohol, in chloroform, and in ether; soluble in glycerol. Store in airtight containers.

USP 36: (Racemic Calcium Pantothenate). A mixture of the calcium salts of the dextrorotatory and laevorotatory isomers of pantothenic acid. The physiological activity of Racemic Calcium Pantothenate is about one-half that of Calcium Pantothenate. A white, slightly hygroscopic powder, having a faint characteristic odour. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether; soluble in glycerol. Its solutions are neutral or alkaline to litmus. Store in airtight containers.

Uses and Administration

Pantothenic acid is traditionally considered to be a vitamin B substance. It is a component of coenzyme A which is essential in the metabolism of carbohydrate, fat, and protein.

Deficiency of pantothenic acid is unlikely in man because of its widespread distribution in food.

Pantothenic acid has no accepted therapeutic uses in human medicine, though it has been given orally as a nutritional supplement, often as the calcium salt and usually with other vitamins of the B group.

Adverse Effects

Pantothenic acid is reported to be generally non-toxic.

Eosinophilia. A report of life-threatening eosinophilic pleuropericarditis associated with the use of biotin and pantothenic acid.[1] Symptoms resolved on stopping the vitamins.

1. Debourdeau PM, *et al.* Life-threatening eosinophilic pleuropericardial effusion related to vitamins B_5 and H. *Ann Pharmacother* 2001; 35: 424–6.

Pharmacokinetics

Pantothenic acid is readily absorbed from the gastrointestinal tract after oral doses. It is widely distributed in the body tissues and appears in breast milk. About 70% of pantothenic acid is excreted unchanged in the urine and about 30% in the faeces.

Human Requirements

Pantothenic acid is widely distributed in foods. Meat, legumes, and whole grain cereals are particularly rich sources; other good sources include eggs, milk, vegetables, and fruits.

UK and US recommended dietary intake. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR) has been set (see p. 2046.1) for pantothenic acid although an intake of 3 to 7 mg daily for adults was believed to be adequate.[1] Similarly, in the USA a recommended dietary allowance has not been published but an adequate intake for adults was believed to be 5 mg daily, increased to 6 mg in pregnancy and 7 mg during lactation.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline.* Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Pantonate†; *Denm.*: BiOrto Pantothensyre; *Ger.*: Kerato Biciron; *Mex.*: Span Plex†; *Rus.*: Zorex (Зорекс); *Switz.*: Pantothen.

Multi-ingredient Preparations. *Arg.*: Bifena; Cellskinlab Hydragel B5; Cidermex; Culuflex H†; Garcinia + Fucus; Guarana Diates†; Hairplus; Megaplus; Triconal; Valcatil Max; Valcatil Plus; Valeriana Relax Diates†; *Austral.*: Bio ACE Excell; Bio ACE; Otrivin

Saline Plus; Zn-A-C†; *Austria*: Pantogar; Priorin; *Belg.*: Sili-Met-San†; *Braz.*: Gaballon; Pantevit; Pantogar; *Canad.*: Femm†; Formula M†; *Chile*: Becomplina Puerte†; Foltene Research Anticaspa†; Hydragel B5 CKL; Hydrating B5 Gel†; Modane; *China*: Kai Yu (凯渝); *Fr.*: Forcapil; Modane; Navi Blef; *Ger.*: Pantovigar; Regepithel; *Hung.*: Forcapil; *India*: Acmic; Admine; All-G; Ameco; Efcoba Plus; Endruff; Livosil-B; Neurotrat; Nurokind-More; Pabatab-BZ; Sioneuron; *Indon.*: Aviter; Combiplex; Pantogar; Proimbus†; Provigor†; *Ital.*: Nuleron; Silisan; *Malaysia*: Vitamin C YSP; *Mex.*: Espaven; Modaton; Pantogar; *Mon.*: Cicaleine; *Philipp.*: B-Prime Plus; Korgivit-E†; Lungcaire Plus; *Rus.*: Multi-Tabs B-Complex (Мульти-Табс В-Комплекс); Pantovigar (Пантовигар); *Singapore*: Beafort; Pantogar; Vitamin C-500; *Spain*: Calcio 20 Complex†; Lacerdermol†; Lupidon; Pulmofasa; Tri Hacheminа†; *Switz.*: Cortifluid N; Decasept N†; Pantogar; Priorin N; *Turk.*: Pantogar; Pilo Cura; Priorin; *UK*: Pilfood; *Ukr.*: B-Complex Multi-Tabs (В-Комплекс Мульти-Табс)†; Penules (Фенюльс)†; Fitoval Capsules (Фитовал капсулы); Levasil (Левасил); Pantogar (Пантогар); Vimifor Multivitamin with Beta-Carotene (Вимифор Мультивитамин 3 Бета-каротином)†; Zorex (Зорекс); *USA*: REQ49+.

Pharmacopoeial Preparations

USP 36: Calcium Pantothenate Tablets; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Phenylalanine *(USAN, rINN)*

α-Aminohydrocinnamic Acid; F; Fenilalanin; Fenilalanina; Fenilalaninas; Fenylalanin; Fenyloalanina; Fenyylialanilni; Phe; Phenylalanin; L-Phenylalanine; Phénylalanine; Phenylalaninum; Фенилаланин.

L-2-Amino-3-phenylpropionic acid.

$C_9H_{11}NO_2$=165.2

CAS — 63-91-2.

UNII — 47ES017Y3R.

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

Ph. Eur. 8: (Phenylalanine). A white or almost white, crystalline powder, or shiny, white flakes. Sparingly soluble in water; very slightly soluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Phenylalanine). White, odourless crystals. Sparingly soluble in water; very slightly soluble in alcohol, in methyl alcohol, and in dilute mineral acids. pH of a 1% solution in water is between 5.4 and 6.0.

Profile

Phenylalanine is an aromatic amino acid that is an essential constituent of the diet. It is used as a dietary supplement.

Phenylalanine intake should be restricted in patients with phenylketonuria (see Amino Acid Metabolic Disorders, p. 2042.2).

Vitiligo. There is no totally effective treatment for vitiligo (localised hypopigmentation, p. 1687.2). Oral or topical photochemotherapy with psoralens is generally considered to be the best available treatment, but experimental therapy includes UVA phototherapy with phenylalanine. Use of phenylalanine in oral doses of up to 100 mg/kg with UVA/sunlight led to beneficial results in more than 90% of 200 patients with vitiligo.[1] Greatest benefit was noted in early disease, but prolonged use still induced repigmentation in long-standing cases. Repigmentation occurred mainly in areas rich in follicles. Such therapy is contra-indicated in phenylketonuria and in pregnancy.

Similarly a further open study reported responses in 94 of 149 patients receiving 50 to 100 mg/kg daily of phenylalanine plus twice weekly UVA treatment.[2] However, only 22% of responders had repigmentation in more than 60% of the affected area. Higher doses did not seem to be more effective than 50 mg/kg daily. Another group reported on 6 years of experience of treatment of vitiligo using 50 or 100 mg/kg daily of phenylalanine, with application of 10% phenylalanine gel and daily sun exposure.[3] Although not ideal, they considered the treatment useful, especially for its ability to rapidly repigment the face. The same group performed an open study, adding topical 0.025% clobetasol propionate, and ultraviolet exposure during autumn and winter; 65.5% of patients achieved 100% repigmentation on the face.[4]

1. Cormane RH, *et al.* Treatment of vitiligo with L-phenylalanine and light. *Br J Dermatol* 1986; 115: 587.
2. Siddiqui AH, *et al.* L-Phenylalanine and UVA irradiation in the treatment of vitiligo. *Dermatology* 1994; 188: 215–18.
3. Camacho F, Mazuecos J. Treatment of vitiligo with oral and topical phenylalanine: 6 years of experience. *Arch Dermatol* 1999; 135: 216–17.
4. Camacho F, Mazuecos J. Oral and topical L-phenylalanine, clobetasol propionate, and UVA/sunlight - a new study for the treatment of vitiligo. *J Drugs Dermatol* 2002; 2: 127–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fenilup.

Multi-ingredient Preparations. *Arg.*: Desgras; Posfovita; KLB6 Fruit Diet; *Fr.*: Revitalose.

Polysaccharide-Iron Complex

Polisacárido hierro, complejo.

Profile

Polysaccharide-iron complex is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in doses containing the equivalent of up to 300 mg of iron daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Ferricure; *Canad.*: Feramax; Triferexx; *China*: Hong Yuan Da (红源达); Niferex (力蜚能); *Hong Kong*: Niferex; *UK*: Niferex; *USA*: Duofer; Fe-Tinic†; Ferrex Plus; Ferrex; Myferon; Niferex; NovaFerrum 50; Nova-Ferrum Pediatric; Poly-Iron.

Multi-ingredient Preparations. *USA*: Fe-Tinic Forte; Ferrex Forte Plus†; Ferrex Forte; Ferrex PC; Hemocyte-P; Niferex Forte; Novaferrum 125; Nu-Iron V; Poly-Iron Forte; Tandem Plus; Tandem.

Proline *(BAN, USAN, rINN)*

P; Pro; Prolilni; Prolin; Prolina; Prolinas; L-Proline; Prolinum; Пролин.

L-Pyrrolidine-2-carboxylic acid.

$C_5H_9NO_2$=115.1

CAS — 147-85-3.

UNII — 9DLQ4CIU6V.

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

Ph. Eur. 8: (Proline). Fermentation product, extract or hydrolysate of protein. A white or almost white, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Proline). White, odourless crystals. Freely soluble in water and in dehydrated alcohol; insoluble in butyl alcohol, in ether, and in isopropyl alcohol.

Profile

Proline is a cyclic non-essential amino acid. It is used as a dietary supplement.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Calmobrul; *Port.*: Creme Laser Hidrante†.

Protein Hydrolysate

CAS — 9015-54-7.

Profile

Protein hydrolysates are produced by enzymatic, physical, or chemical hydrolysis of proteins from animal or vegetable sources. They contain mixtures of free amino acids and peptides of differing lengths (including dipeptides, tripeptides, other oligopeptides, and polypeptides) depending on the method of hydrolysis.

Protein hydrolysates have been used as a nitrogen source in preparations for enteral and parenteral nutrition (p. 2044.1). They have also been used in dietary supplements and in infant feeds, although their benefits are not established. Some protein hydrolysates (peptones) have been used as choleretics and as test meals to stimulate gastrin production. They have also been used as culture media for bacteria and other cells.

References.

1. Osborn DA, Sinn JKH. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 17/08/11).
2. Manninen AH. Protein hydrolysates in sports nutrition. *Nutr Metab (Lond)* 2009; 6: 38.
3. Schaafsma G. Safety of protein hydrolysates, fractions thereof and bioactive peptides in human nutrition. *Eur J Clin Nutr* 2009; 63: 1161–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Drenocol; *Austral*: Nutramigen†; *Canad.*: Alimentum; Colibyl†; *Chile*: Cholinogo-; *Hong Kong*: Pilfood; *India*: Alcezyme; Altone; Aminozym; Anzykair; Cydine; Cypee; Cyprowal; Genprot; Haemoprote; Hemocare; Hemocare; Hemprovit-Fe; Hepatoglobine†; Hepato-globine; Inpro; Kairase; Marpro-Z; Miproten; Neogadine S(; Nervitone; Newtrolax; Nodyfer; Osprovit; Oxyglobin; Prov; Santevini; *Israel*: Hydrolac; *Malaysia*: Alimentum; *Mex.*: Choi-bol; Peptochol; *S.Afr.*: Fissan; *Singapore*: Similac Alimentun; *Switz.*: Pil-Food; *UK*: Similac Alimentum; *USA*: Alimentun; Nutramigen; *Venez.*: Nutramigen.

Safflower Oil

Aceite de alazor; Aceite de cártamo; Carthame (huile de raffinée; Carthami Oleum Raffinatum; Dygminų aliejus rafinuotas; Saflorolja, raffinerad; Safloriõljy, puhdistettu Světlicový olej čištěný; Сафлоровое Масло.

ATC Herb — HB05BA5002 (Carthamus tinctorius: oil) HC10AW5003 (Carthamus tinctorius: oil).

UNII — 65UEH262IS.

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

Chin., *Eur.* (see p. vii), and *Jpn* include Safflower, the flowe of *Carthamus tinctorius*.

Ph. Eur. 8: (Safflower Flower; Carthami Flos). Dried flowe of *Carthamus tinctorius*. It contains not less than 1% of tot flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12}$=464.4 calculated with reference to the dried drug. Protect fro light.

Ph. Eur. 8: (Safflower Oil, Refined). The fatty oil obtaine from seeds of *Carthamus tinctorius* (type I) or from seeds o hybrids of *C. tinctorius* (type II), by expression and/o extraction followed by refining. Type II refined safflower o is rich in oleic acid. It may contain a suitable antoxidant. clear, viscous, yellow to pale yellow liquid. Relative densit about 0.922 (type I) and about 0.914 (type II). Practicall insoluble in alcohol; miscible with petroleum spirit (b.p.: 4 degrees to 60 degrees). Store in well-filled airtigh containers. Protect from light.

USP 36: (Safflower Oil). The refined fixed oil yielded fro the seed of *Carthamus tinctorius* (Compositae). A light yello oil. It thickens and becomes rancid on prolonged exposur to air. Insoluble in water; miscible with chloroform and wit ether. Store in airtight containers. Protect from light.

Profile

Safflower oil is the refined fixed oil obtained from the seed of the safflower, or false (bastard) saffron, *Carthamus tinctorius* (Compositae). It contains about 75% of linolei acid as well as various saturated fatty acids.

Safflower oil has similar actions and uses to those of soy oil, p. 2092.3. Emulsions containing a mixture of safflowe oil 5% and soya oil 5%, or 10% and 10% respectively, ar given as part of total parenteral nutrition regimens.

Adverse effects. For reference to the association of saf flower oil-based emulsion, as part of a parenteral nutritio regimen, with the development of sinus bradycardia, se Effects on the Cardiovascular System, under Soya Oi p. 2093.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Liposyn; Microlipic *India*: Dermamoist; *Indon.*: Baliin Q10; *Ital.*: Liposyn; *Mex*: *Liposyn*†; *Rus.*: Vitamax (Витамакс)†; Wantong Artipla (Вантуни Артиплас); *Singapore*: Life 2; *Turk.*: Liposyn†; *Ukr.* Energin (Энергин); Farcovit B12 (Фарковит B12)†; *USA*: Lipo syn II; Microlipid.

Selenium

Seléniam; Seleen; Seleeni; Selen; Selenas; Seleni; Selèni Selenij; Selenio; Selênio; Seleniu; Sélénium; Seleniwm; Selēns Selenyòm; Selenyum; Shellainium; Silinyu; Szelén; Ceneh Se=78.96.

UNII — H6241UJ22B.

Potassium Selenate

Selenato potásico; Селеновокислый Калий; Селенат Калия

K_2SeO_4=221.2

CAS — 7790-59-2.

UNII — 99798PU7ML.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Potassium Selenate). Colourless crystals or white crystalline powder. Freely soluble in water.

Selenious Acid

Kwas selenawy; Selenioso, ácido; Селенистая Кислота; Monohydrated selenium dioxide.
H_2SeO_3=129.0
CAS — 7783-00-8.
UNII — F6A27P4Q4R.

Pharmacopoeias. In *US.*

USP 36: (Selenious Acid). Store in airtight containers.

Selenium Dioxide

Selenious Anhydride; Selenium Oxide.
SeO_2=111.0
CAS — 7446-08-4.
UNII — 9N3UK29E57.

Selenomethionine

Selenium Methionine; Selenomethionin; L-Selenomethionine; Sélénométhionine.
(*S*)-2-Amino-4-(methylselenyl)butyric acid.
$C_5H_{11}NO_2Se$=196.1
CAS — 3211-76-5 (L-selenomethionine); 1464-42-2 (DL-selenomethionine).
UNII — 964MRR2PEL.

Pharmacopoeias. In *US.*

Sodium Selenate

AI3-10625; CCRIS 1259; Disodium Selenate; Natriumseleniat; NSC-378348; Selenato sódico; Sodium Selenium Oxide; Селеновокислый Натрий; Селенат Натрия.
Na_2SeO_4=188.9
CAS — 13410-01-0.
ATC — A12CE01.
ATC Vet — QA12CE01.
UNII — 5DQP25600A (sodium selenate); 0CJN4029EB (sodium selenate decahydrate).

Sodium Selenite

Natrii Selenis Pentahydricus; Natrio selenitas pentahidratas; Natriumseleniittipentahydraatti; Natriumselenitpentahydrat; Seleničitan sodný pentahydrát; Selenito sódico; Sodium (sélénite de) pentahydraté; Sodu selenin pięciowodny; Sodyum Selenit; Селенистокислый Натрий; Селенит Натрия.
$Na_2SeO_3.5H_2O$=263.0
CAS — 10102-18-8.
ATC — A12CE02.
ATC Vet — QA12CE02.
UNII — HIW548RQ3W (sodium selenite); 0WV4L961ZV (sodium selenite pentahydrate).

Pharmacopoeias. In *Eur.* (see p. vii). *BP(Vet)* includes anhydrous sodium selenite.

Ph. Eur. 8: (Sodium Selenite Pentahydrate). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers.

BP(Vet) 2014: (Sodium Selenite). A white to slightly greyish pink granular powder. Freely soluble in water; practically insoluble in alcohol and ether.

Uses and Administration

Selenium is an essential trace element. It is an integral part of the enzyme system glutathione peroxidase, which protects intracellular structures against oxidative damage. Deficiency of selenium has been associated with an endemic form of cardiomyopathy, Keshan disease, seen in certain areas of China. It has also been associated with Kaschin-Beck disease, an endemic osteoarthropathy, which causes a severe deformity of the joints. Selenium is present in foods mainly as the amino acids selenomethionine and selenocysteine and derivatives.

Selenious acid and its sodium salt, sodium selenite, are used as a source of selenium, especially for patients with deficiency states after prolonged parenteral nutrition. Suggested doses for addition to TPN range from 20 to 40 micrograms (0.25 to 0.5 micromoles) elemental selenium daily. Sodium selenate has also been used.

For doses added to parenteral nutrition for children, see Administration in Children, below.

For proven selenium deficiency that cannot be offset from food sources, selenium may be given orally, or by intramuscular or intravenous injection, usually in the form of sodium selenite pentahydrate, to provide doses of about 100 to 200 micrograms selenium daily; if necessary this can be increased to 500 micrograms daily.

Selenium and selenium salts have also been used in dietary supplements. Selenomethionine is thought to be more bioavailable than inorganic salts and has also been used; other organic selenium compounds that have been tried include methylselenocysteine (Se-methylselenocysteine; selenomethylselenocysteine).

Selenate and selenite salts are used for selenium deficiency states in veterinary medicine.

Action. References.
1. Rayman MP. The importance of selenium to human health. *Lancet* 2000; 356: 233–41.

Administration in children. Selenious acid or sodium selenite may be added to parenteral feeds as a source of selenium in the prophylaxis and treatment of deficiency states in children. US licensed product information suggests a dose of 3 micrograms/kg (38 nanomoles/kg) of selenium daily for all children. In the UK, licensed product information suggests 2 micrograms/kg (to a maximum of 30 micrograms) of selenium daily for children weighing 40 kg or less, and adult doses in children over 40 kg (see above).

In preterm neonates, low selenium plasma concentrations have been suggested to be a potential risk factor for neonatal respiratory disorders and retinopathy of prematurity. A systematic review[1] found that supplementation with selenium, either enterally or parentally, did not reduce the incidence of these complications, nor is it associated with improved survival. However, it is associated with benefit in terms of reduction in the number of episodes of late-onset sepsis in very preterm infants. There was evidence that recommended doses in this group might be inadequate for some populations.

1. Darlow BA, Austin NC. Selenium supplementation to prevent short-term morbidity in preterm neonates. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 18/02/09).

HIV infection and AIDS. A randomised controlled study found that oral supplementation with selenium 200 micrograms daily for 9 months suppressed the progression in HIV-1 viral load and provided indirect improvement of the CD4+ count.[1] For a study reporting increased CD4+ and CD8+ counts, but increased genital HIV-1 shedding with multivitamin plus selenium supplementation, see HIV Infection and AIDS, p. 2046.2.

1. Hurwitz BE, *et al.* Suppression of human immunodeficiency virus type 1 viral load with selenium supplementation: a randomized controlled trial. *Arch Intern Med* 2007; 167: 148–54.

Human requirements. In the UK dietary reference values (see p. 2046.1)[1] and in the USA recommended dietary allowances (RDA)[2] have been published for selenium.

In the UK the reference nutrient intake for adults is 75 and 60 micrograms daily for men and women respectively; values are also given for infants and children of varying ages and for lactating women. The UK report also noted that there was no convincing evidence that high intakes protected against cancer or cardiovascular disease; indeed, there was even some evidence that high intakes disturbed selenium homoeostasis and it was recommended that the maximum safe intake from all sources should be set at 450 micrograms daily for adult males. The Expert Group on Vitamins and Minerals[3] have since established a safe upper level (SUL) for selenium of 450 micrograms daily.

In the USA, the RDA for adult males and females is 55 micrograms daily, and again values are also given for infants and children as well as pregnant and lactating women. The tolerable upper intake level is 400 micrograms daily.[2]

WHO have recommended a lower limit of the safe range of population mean intakes of dietary selenium of 40 micrograms daily for adult males and 30 micrograms daily for adult females.[4] A maximum daily safe dietary selenium intake of 400 micrograms was suggested for adults.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO. 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin C, vitamin E, selenium, and carotenoids.* Washington DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309069351 (accessed 21/07/08)
3. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 10/11/05)
4. WHO. Selenium. In: *Trace elements in human nutrition and health.* Geneva: WHO, 1996: 105–22.

Prophylaxis of malignant neoplasms. Selenium supplementation did not protect against the development of new basal or squamous cell carcinomas of the skin in a study of patients with a history of these cancers.[1] Further follow-up data[2] showed a statistically significant increased risk of squamous cell carcinoma and of total non-melanoma skin cancer with selenium supplementation. However, analysis of secondary end-points at the first report indicated a reduced incidence of various other cancers in this study group.[1]

Subsequent study has suggested, in particular, an association between low selenium intake and the risk of prostate cancer; incidence was reduced by 63% in patients receiving the supplement.[3] Further follow-up confirmed this inverse association, but found that only men with low baseline selenium concentrations were likely to benefit.[4] Case-control studies have also reported that a higher selenium intake reduced the risk of advanced prostate cancer.[5,6] Higher pre-diagnostic selenium levels were associated with a lower risk of prostate cancer only for subjects with increased baseline prostate-specific antigen (PSA) concentrations (above 4 nanograms/mL). The authors hypothesised that selenium may slow tumour progression.[6] However, a large, randomised, controlled study[7] that used prostate cancer detection as the primary end-point, found no evidence of benefit with either selenium supplementation alone or selenium plus vitamin E, and prompted the suggestion that antoxidant supplements should not be recommended for preventing prostate cancer.[8] The possible value of selenium supplementation during conventional *treatment* of prostate cancer has also been reviewed.[9]

An inverse association between selenium concentrations and the risk of bladder cancer has been reported, although results from case-control studies are inconsistent. Controlled studies investigating the effect of selenium on bladder cancer recurrence and prognosis are planned.[10]

For a finding that selenium supplementation had no beneficial effect on overall mortality, see Effects on Mortality, below.

1. Clark LC, *et al.* Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: a randomized controlled trial. *JAMA* 1996; 276: 1957–63. Correction. *ibid.* 1997; 277: 1520.
2. Duffield-Lillico AJ, *et al.* Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial. *J Natl Cancer Inst* 2003; 95: 1477–81.
3. Clark LC, *et al.* Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *Br J Urol* 1998; 81: 730–4.
4. Duffield-Lillico AJ, *et al.* Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. *BJU Int* 2003; 91: 608–12.
5. Yoshizawa K, *et al.* Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst* 1998; 90: 1219–24.
6. Li H, *et al.* A prospective study of plasma selenium levels and prostate cancer risk. *J Natl Cancer Inst* 2004; 96: 696–703.
7. Lippman SM, *et al.* Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2009; 301: 39–51.
8. Gann PH. Randomized trials of antioxidant supplementation for cancer prevention: first bias, now chance—next, cause. *JAMA* 2009; 301: 102–3.
9. Tabassum A, *et al.* Ingestion of selenium and other antioxidants during prostate cancer radiotherapy: a good thing? *Cancer Treat Rev* 2010; 36: 230–4.
10. Brinkman M, *et al.* Use of selenium in chemoprevention of bladder cancer. *Lancet Oncol* 2006; 7: 766–74.

Adverse Effects

Overdosage of selenium has been associated with loss of hair, nail changes, diarrhoea, dermatitis, metallic taste, garlic odour of breath, irritability, fatigue, and peripheral neuropathy.

Effects on glucose metabolism. A study into the effects of selenium on non-melanoma skin cancer found a higher rate of diabetes mellitus in those who received nearly 8 years of selenium supplements compared with placebo.[1] This prompted some to suggest that, until further studies show otherwise, people whose diets provide the recommended daily allowance of selenium should avoid supplements.[2]

1. Stranges S, *et al.* Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. *Ann Intern Med* 2007; 147: 217–23.
2. Bleys J, *et al.* Selenium and diabetes: more bad news for supplements. *Ann Intern Med* 2007; 147: 271–2.

Effects on mortality. A systematic review[1] of the effect of antoxidant supplements on mortality in randomised primary and secondary prevention studies considered that selenium had no significant effect on mortality, either beneficial or harmful; however, it was recommended that future studies should be monitored closely for evidence of harm.

1. Bjelakovic G, *et al.* Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).

Toxicity. *Chronic* exposure to high amounts of selenium has been reported to cause toxic effects on endocrine function, hepatotoxicity, gastrointestinal disturbances, and dermatological effects such as nail and hair loss and dermatitis. There has been some suggestion also of neurotoxicity, and a possible increased risk of amyotrophic lateral sclerosis. Studies have had conflicting results, and different inorganic and organic forms may vary greatly in biological activity, toxicity, and nutritional importance.[1]

Acute toxicity has also been reported; characteristic symptoms of selenium toxicity are garlicky or sour breath odour, vomiting and gastrointestinal disturbances, restlessness, hypersalivation, muscle spasms, haemolysis, liver necrosis, cerebral and pulmonary oedema, coma, and death.[1-3] A man who had taken vitamin tablets containing between 500 and 1000 times the amount of selenium labelled on the bottle developed generalised alopecia, changes in nail colour, diarrhoea, worsening fatigue, and paraesthesias. Two weeks after stopping the vitamins, early regrowth of hair and yellowish-white and red transverse lines on his nails were noted.[2] In another case, an elderly man who was concerned that he might have prostate cancer ingested 10 g of sodium selenite. He developed significant abdominal pain, vomiting and diarrhoea, hypotension, and ventricular tachycardia. Blood tests showed acidosis, hypokalaemia and an excessive selenium concentration. Despite symptomatic therapy, he suffered a cardiac arrest and died.[3] The FDA[4] found hazardous amounts of selenium in certain dietary supplements after receiving 43 reports of serious adverse effects in people using the products. Adverse effects usually started after 5 to 10 days of daily ingestion and included significant hair loss, muscle cramps, diarrhoea, joint pain, fatigue, deformation or loss of finger nails, and blistering skin. The daily dose taken by one patient was found to be about 24 mg, more than 400 times the US recommended daily allowance of 55 micrograms.[5]

1. Vinceti M, *et al.* Adverse health effects of selenium in humans. *Rev Environ Health* 2001; 16: 233–51.
2. Clark RF, *et al.* Selenium poisoning from a nutritional supplement. *JAMA* 1996; 275: 1087–8.
3. See KA, *et al.* Accidental death from acute selenium poisoning. *Med J Aust* 2006; 185: 388–9.
4. FDA. FDA finds hazardous levels of selenium in samples of "Total Body Formula" and "Total Body Mega Formula": dietary supplement products linked to adverse reactions (issued 9th April 2008). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116878.htm (accessed 22/07/10)
5. Sutter ME, *et al.* Selenium toxicity: a case of selenosis caused by a nutritional supplement. *Ann Intern Med* 2008; 148: 970–1.

Pharmacokinetics

Selenium compounds are generally readily absorbed from the gastrointestinal tract. Selenium is stored in red blood cells, the liver, spleen, heart, and nails. It is converted in tissues to its metabolically active forms. Selenium is excreted in the urine, and to a lesser extent in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Sele200; Selebound; *Austral.*: Selemite-B†; Seleno Forte; *Austria*: Selen; Selenase; *Canad.*: Formula 2†; Micro Se; Selepen†; *Cz.*: Selenase; *Ger.*: Cefasel; Seleject†; Selen-loges; Selenase; Seltrans; Uniselen†; *Gr.*: Selenase T; *Hong Kong*: Selepen; *Hung.*: Selen Plus; Selenor; Selesyn; *Irl.*: Selesyn; *Neth.*: Selenase; *Port.*: Selenase; *Switz.*: Selenase; *Turk.*: Selenase; *UK*: Selenase; *Ukr.*: Cefasel (Цефасель); Selenaza (Селеназа); *USA*: Sele-Pak†; Selepen†.

Multi-ingredient Preparations. *Arg.*: Antioxidante Plus; Centella Asiatica Compuesta; Fem Plus 50; Herbaccion Antioxidante; Hipersel; Ipri V Plus; Ipri V Total; Krebs Plus; Magnesio 102 Plus; Marathon Antioxidante; Parselenium E; Radite Plus; Selder; Senexon Plus; Super Antioxidante; Tonovital Antioxidante; *Austral.*: Advanced Prostate Care; Bio ACE Excell; Femme-F; For Eyes; Homme-F; Lutein-Vision Advanced; Lutein-Vision; Prosta Balance; Prostate Care; Prostate Health Formula; Radiance; ResveratoX; *Braz.*: Lymium; Ocuvite Lutein; *Canad.*: DMTX; Ester Aces; Formula AO†; Formula PC†; Geri-Plus†; Prostaplex; Protect†; Super AO Factors; Super AO Formula†; Synergistic Selenium; Watkins Vision†; *Chile*: Biofax†; Larotabe; Natursel-C; Reparex; Seresis; Vitagenol; *Fr.*: Anti-oxydant 200; Anti-oxydant P4; Arbum; Bio-Selenium†; Cledist; Derm; Donalis; GliSODine Solaire; Gynalpha Plus†; Nat'Os; Naturophta Macula; Oxelio; Phytosolaire†; Proselem; Prostabiol; ProstaSecurA; Selenium + Zinc†; Selomega; Sun Vue; Superoxylase; Ultraselem; *Hong Kong*: Ocuvite; *Hung.*: Cellactive; Humet-R; *India*: Actima; Adrovit; Advit-A; Alcored; Alphamix; Aminos; Aminut; Androvit; Antoxid; Aritom-L; Avitaz Plus; Aza Cap; B7 Plus; Beta-Sclerobion; Bio-10; Cad-11; Cadred; Cally Plus; Carbion; Carbona; Carfol-Z; Carofit-D; Carron; Cobadex-CZS; Cobal Plus; Cobalvit Plus; Cobanerve Plus; Cobanerve; Coq Forte; D-Gard; Delage; Deoxidant; Derantox; Dianuron; EC; Ecobal; Efcoba Forte; Eldervit-ZC; Elgrape; Elmecob Plus; Elnutra; Elonyl-Z; Elrox-AO; Enhance; Evica; Exerge-HC; Exerge; Exox; Fabulae; Fef-OD; Fejet-OD; Ferisis; Feronyl; Ferox; Ferox; Ferritop-Z; Festene; Fexid-Z; Fezec; Fiolar; Flintoff; Prednil; Preecad; Frezep; FRS; Furtipil-L; Gardian; Gatdor; Gencart; Glace; Glortho Forte; Hi-Q Plus; Hi-Q Plus; Hi-Q; Hi-Q; Homoxid; Horac; Hyrase; I-Lute; Inerve; Irocafe; Irossgold; Jivak; Joyce; Jstat; Kefive Plus; L-Bex; Lancitone-CS; Layo; Lizace; Luvion; Lyco-First; Lycobig; Lycodric; Lycolife; Lycomato; Lycomint; Lycostar-CM; Lycoswift; Lyto; Lytox; Macuchek; Maxoza; Me Plus; Me-Plus; Mecoday Plus; Medifer; Medifer; Megagin; Mexivit; Mufe; NBOxid; Nerwin-MD; Neuractin Forte; Nitizest; Nocad; Nofro; Nuromin; Ocufree; Omegachek; Optivision; Osfer; Ostebon-M; Ovista; Oxi-Red; Oxibet; Oxidon; Oxipre; Oxitra; Oxy-V; Oxyban; Oxydex; Oxyeye; Oxyla-AL; Oxytret; Oxyvit; Winofit; *Indon.*: Antox; Artovit; Artro Plus; Azvit; Bevizil; Cerebrovit Active; Cerebrovit X-Cel; Colaskin; Danzet; Echinox; Eftian; Ekinase; Entrap; Erphacea; Ever E†; Eyebright; Eyevit; GCM; Hemaviton Brain Nutrient†; Hemaviton Skin Nutrient; Hepachol; Heparviton NF; Imulan; Imumax; Imunogard; Imunos; Imunos; Imunvit Plus; Joint Care Plus; Joint Care; Lanavision Plus; Lubire; Lutevision Extra; Lycoten; Lysmin Plus; Matoflam; Matovit AX; Maxivit; My Caps; Naturema; Neoboost Kids; Neoboost; Noros; Nufit; nutrivision; Nuvision; OA Forte; OA Plus; OA; Ocu-V; Oculex; Osteokom Forte; Osteokom; Osteor Plus; Osteor; Osvion Plus; Oxcal; Proliva; Qutan-10; Radiblock; Radivit; Reticopen; Retivit Plus; Retivit; Retop; Rheumatin Forte; Rheumatin; Risteon; Scaven; Selefit Plus; Seloxy AA; Seloxy; Stacare; Univoxy; Vantiz; Viceten-Z; Viopor-M Forte; Viopor-M; Viopor; Viostin Com; Vioxy-fm; Vioxy; Vitanox; *Irl.*: Antox; Ocuvite†; *Israel*: Coltect†; *Ital.*: Betaeffe Plus; Bioesse Plus; Blunorm; Caresel; Euretin Duo; Fosfarsile Forte; Influ-Zinc; Konorderm; Longevital; Neomyrt Plus; Nolder†; Omegadin Plus; Ri-Donna; Salovit; Selene; Selenium-ACE†; Semel; Tannidin Plus; Tripondil; Valcap; Visu-len; *Malaysia*: Bio-Cal; Eurobio Bio-Vizmax; Lycovid; Pharmaton with Selenium; Shine Bio ACE with Selenium; *Mex.*: Alfavit-Eox†; *Mon.*: Evestrel Jour Nuit†; *Philipp.*: ALAnerv; Carofit; Nutrof†; Omnimune; Vigor-ACE; Zeman; *Pol.*: Ekovit†; Rutinoscorbin Plus; *Port.*: Ever-Fit Dermo; Fortal Vision; Rilastil Anti-Oxidante; Rilastil Dermo Solar; *Rus.*: Complivit Oftalmo (Компливит Офтальмо); Tri-V Plus (Три-Ви Плюс)†; Triovit (Триовит); *Singapore*: Glutamine Plus; Multitrace-5; Nutrivision†; Shine Bio-Cal; Vigor-Ace; *Thai.*: Bio-Selenium Zinc; Ocuvite; *Turk.*: ACE plus Selenyum; Prostamen; *UK*: Antox; Aria; Betaimune; Estroven; GlucoSelene; NutriScience; Selene-Activ; Selenium Bonus; Silica-OK; Visio-Max; *Ukr.*: Linex Immuno (Линекс Иммуно); Livonorm (Ливонорм); Ocuvite Lutein Forte (Окювайт Лютеин форте); Pravenor (Правенор); Triovit (Триовит); Vimifor Multivitamin with Beta-Carotene (Вімібор Мультивітамін з Бета-каротином)†; Vitrum Cardio (Вітрум Кардио); Vitrum Foreyes Forte (Вітрум Форайз Форте); Vizivit (Визивит); Yohimbex-Garmonia (Йохимбекс-Гармония); *USA*: Aces; Antioxidant Formula; AquADEKS; Immunicare; REQ49+; Udamin SP; Udamin; Vitaline Selenium; *Venez.*: Kalsis; Uvagen.

Homoeopathic Preparations. *Austral.*: Hangover Relief; *Austria*: Crimax; Dalektro; Globuli gegen Hautausschlage; Selenium Med Complex; *Canad.*: Acne; Adrisin†; Alfalfa Tonic with Ginseng†; Alfalfa Tonic; Amphosca†; Cutisitum†; Fatigue; Formula FA 224†; Homeo-Form P†; Selenium Homaccord†; Ubicoenzyme; *Chile*: Bioactiv I; *Fr.*: Acidum Phosphoricum Compose†; Amphosca Orchitine; Amphosca Ovarine; Selenium Complexe No 99; *Ger.*: Heweselen†; Infi-China; Schworocor A; Sedaselect; Selen-Wied; Selenarell; Selenokehl; Tondinel H; Tondinel; *Neth.*: Dermalite; *Switz.*: Omida comprimes homeopathiques pour la gorge; *USA*: Preferred Remedies Fatigue.

Pharmacopoeial Preparations

USP 36: Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Tablets; Selenious Acid Injection; Trace Elements Injection; Water-soluble Vitamins with Minerals Capsules.

Serine *(BAN, USAN, rINN)*

β-Hydroxyalanine; S; Ser; Seriini; Serin; Serina; Serinas; L-Serine; Sérine; Serinum; Seryna; Szerin; Серин.

L-2-Amino-3-hydroxypropionic acid.

$C_3H_7NO_3$=105.1

CAS — 56-45-1 (serine); 302-84-1 (DL-serine).

UNII — 452VLY9402.

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

Ph. Eur. 8: (Serine). Fermentation product, extract or hydrolysate of protein. White or almost white crystalline powder or colourless crystals. Freely soluble in water; practically insoluble in alcohol. Protect from light.

USP 36: (Serine). White, odourless crystals. Soluble in water; practically insoluble in dehydrated alcohol and in ether.

Profile

Serine is a non-essential amino acid. It is used as a dietary supplement.

The racemic form (DL-serine) has been included in iron supplements to increase iron absorption.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Methyl Transfer.

Used as an adjunct in:. *Austria*: Aktiferrin Compositum; Aktiferrin; *Cz.*: Aktiferrin Compositum; Aktiferrin; *Hung.*: Aktiferrin; *Israel*: Aktiferrin-F; Foliferrin; *Malaysia*: Aktiferrin-F†; *Rus.*: Aktiferrin (Актиферрин); Aktiferrin Compositum (Актиферрин Композитум); *Singapore*: Aktiferrin-F†; *Switz.*: Aktiferrin-F†; Aktiferrin; *Ukr.*: Aktiferrin (Актиферрин); Aktiferrin (Актиферрин).

Silicon

Křemík; Kiezel; Kisel; Krzem; Pii; Rāni; Silicijs; Silicì; Silicio; Silício; Silicis; Siliciu; Silicium; Silisium; Silisyum; Szilicium; Кремний; Силиций.

Si=28.085

CAS — 7440-21-3 (silicon); 2445-53-6 (monomethylsilanetriol).

UNII — Z4152N8IUI.

Silicic Acid

Acido Silícico; Hydrosilicic Acid; Kieselsäure; Kiezelzuur; Kiselsyre; Kyselina Křemičitá; Pilhappo; Polysilicic Acid; Silicio Rūgštis; Silicon Hydroxide; Кремниевая Кислота.

CAS — 1343-98-2.

UNII — Y6O7T4G8P9.

Pharmacopoeias. *Jpn.* includes Light Anhydrous Silicic Acid.

Orthosilicic Acid

Monosilicic Acid; Silicon Tetrahydroxide; Tetrahydroxysilane.

$Si(OH)_4$=96.11

CAS — 10193-36-9.

UNII — 623B93YABH.

Profile

Silicon is a metalloid element that occurs widely in nature, mainly in the form of its compounds. It is an essential trace element and has been used in nutritional supplements, usually complexed with amino acids (silicon amino acid chelate; silicon hydrolysed vegetable protein chelate) to improve its bioavailability, or as its more soluble compounds, such as orthosilicic acid. Extracts of plants rich in silicon, such as equisetum (p. 2500.1) have been used similarly. Silicon also has industrial uses, particularly in electronics.

Silicic acids are compounds of silicon, oxygen, and hydrogen; when heated, they lose water to form silica gel (see Silicon Dioxide, p. 2208.3). Orthosilicic acid has been used as a source of silicon in nutritional supplements since it is the most bioavailable form of silicon (above). It is often given as choline-stabilised orthosilicic acid, a mixture with choline chloride (p. 2055.2).

Silicon compounds such as silicas (p. 2208.3) and silicones (p. 2209.2) also have pharmaceutical uses.

So called 'organic silicon' (monomethylsilanetriol) has been used in nutritional supplements. Organic silicon compounds have also been used topically for hair and skin disorders, including monomethylsilanetriol potassium citrate, methylsilanol mannuronate, a complex with hydroxyproline (methylsilanol hydroxyproline aspartate), and siloxanetriol alginate.

References.

1. Barel A, *et al.* Effect of oral intake of choline-stabilized orthosilicic acid on skin, nails and hair in women with photodamaged skin. *Arch Dermatol Res* 2005; 297: 147–53.
2. Martin KR. The chemistry of silica and its potential health benefits. *J Nutr Health Aging* 2007; 11: 94–7.
3. Wickett RR, *et al.* Effect of oral intake of choline-stabilized orthosilicic acid on hair tensile strength and morphology in women with fine hair. *Arch Dermatol Res* 2007; 299: 499–505.
4. Spector TD, *et al.* Choline-stabilized orthosilicic acid supplementation as an adjunct to calcium/vitamin D3 stimulates markers of bone formation in osteopenic females: a randomized, placebo-controlled trial. *BMC Musculoskelet Disord* 2008; 9: 85.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Florasil; *Fr.*: Dexsil Silicium.

Multi-ingredient Preparations. *Arg.*: Bagovit Avant; Celu-Ikx; *Austral.*: Advanced Bladder Care; *Canad.*: Active Calcium; *Fr.*: Cicactive; Dexsil Articulations; Dexsil Jambes Legeres; Dexsil Peau; Dexsil Sport; *Hong Kong*: Active Calcium†; Procosa II†; *India*: Orbone; *Mex.*: Maxilene; *Singapore*: Active Calcium†; Procosa II†; *Switz.*: Venadoron; Wala Baume nasal doux; Wala Baume nasal.

Sodium Feredetate *(BAN, rINN)*

Ferédétate de Sodium; Feredetato sódico; Natrii Feredetas; Sodium Ironedetate; Натрия Фередетат.

The monohydrated iron chelate of the monosodium salt of ethylenediamine-*NNN'N'*-tetra-acetic acid; Iron (III) sodium ethylenediaminetetra-acetate monohydrate.

$C_{10}H_{12}FeN_2NaO_8H_2O$=385.1

CAS — 15708-41-5 (anhydrous sodium feredetate).

ATC — B03AB03.

ATC Vet — QB03AB03.

UNII — 403J23EMFA.

Pharmacopoeias. In *Br.*

BP 2014: (Sodium Feredetate). A yellow or yellowish brown, hygroscopic, crystalline powder. A 1% solution in water has a pH of 4.0 to 6.5. Store in airtight containers.

Profile

Sodium feredetate is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given orally in doses of up to 1.42 g daily (equivalent to up to about 205 mg of iron daily).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Ferrostrane; *India*: Alfer; Barohem; Fearo-FD; Fedrer; Feranid; Perfoz Plus; Ferofast; Icrate; Irex; Irored; Kiron-UP; *Indon.*: FeRRIZ; *Philipp.*: Ferrosmate; *UK*: Sytron.

Multi-ingredient Preparations. *India*: Alnaferon; Barohem; Calcinol; Carfer; Fearo-FD; Penora-SF; Fepot; Feranid; Ferazin; Ferazin; Perfoz Plus; Ferich; Ferimax; Ferimax; Ferimax; Ferisan; Feristar; Feriz-SF; Ferofast; Ferywel; Fesoft; Glozy; Haem-XT; Haemgrow; Irex; Irofact-SF; Kiron-UP; Melan; Melan; Mighty-SF; Oxi-Red.

Pharmacopoeial Preparations
BP 2014: Sodium Feredetate Oral Solution.

Sodium Ferric Gluconate Complex *(USAN)*

Ferric Sodium Gluconate; D-Gluconic acid, iron (3+) sodium salt; Hierro gluconato sódico, complejo de; Iron Gluconate; Natrii ferrigluconas; Sodium Ferric Gluconate; Sodium ferrigluconate; Sodium-Iron(III) Gluconate Complex.

$[NaFe_2O_3(C_6H_{11}O_7)(C_{12}H_{22}O_{11})_3]_n$

CAS — 34089-81-1.
ATC Vet — QB03AC07.
UNII — CC9149U2QX.

NOTE. Distinguish from Ferrous Gluconate.

Uses and Administration

Sodium ferric gluconate complex is used as a source of iron (p. 2073.1) for iron-deficiency anaemia (p. 2073.2). It is given as a solution containing the equivalent of 12.5 mg/mL of elemental iron. The recommended dose for haemodialysis patients who are receiving epoetin therapy is 125 mg iron (10 mL) diluted in 100 mL sodium chloride 0.9%, and given as an intravenous infusion over 1 hour; it may also be given undiluted as a slow intravenous injection (at a rate of up to 12.5 mg/minute) during dialysis. This dose is usually repeated over 8 dialysis sessions to achieve a favourable response.

For doses in children, see Administration in Children below.

Administration in children. Sodium ferric gluconate complex can be given to children to treat iron-deficiency anaemia (p. 2073.2). It is given as a solution containing the equivalent of 12.5 mg/mL of elemental iron. Children 6 years of age and older on haemodialysis and who are receiving epoetin therapy may be given 1.5 mg/kg of elemental iron (0.12 mL/kg), diluted in 25 mL sodium chloride 0.9% and infused over 1 hour, up to a maximum of 125 mg per dose. This dose is usually repeated over 8 dialysis sessions to achieve a favourable response.

Anaemia of chronic renal failure. References.

1. Yorgin PD, *et al.* Sodium ferric gluconate therapy in renal transplant and renal failure patients. *Pediatr Nephrol* 2000; 15: 171–5.
2. Fishbane S, Wagner J. Sodium ferric gluconate complex in the treatment of iron deficiency for patients on dialysis. *Am J Kidney Dis* 2001; 37: 879–83.
3. Folkert VW, *et al.* Chronic use of sodium ferric gluconate complex in hemodialysis patients: safety of higher dose (> or =250 mg) administration. *Am J Kidney Dis* 2003; 41: 651–7.
4. Michael B, *et al.* Sodium ferric gluconate complex in haemodialysis patients: a prospective evaluation of long-term safety. *Nephrol Dial Transplant* 2004; 19: 1576–80.

Adverse Effects, Treatment, and Precautions

For parenteral iron, see Iron Dextran, p. 2076.1.

Hypersensitivity. For a discussion as to whether sodium ferric gluconate complex may be a safer alternative to iron dextran, see p. 2076.2.

Pharmacokinetics

Peak concentrations vary with the dose and rate at which sodium ferric gluconate complex is given. The volume of distribution does not appear to vary according to dose or rate. Elimination half-life varies by dose, and has been reported to be 0.85 hours for a dose of 62.5 mg and 1.45 hours for a dose of 125 mg; doses were given by slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Ferrlecit; *Chile*: Pentaferr; *Cz.*: Ferrlecit; *Ger.*: Ferrlecit; *Hung.*: Ferrlecit; *India*: Efecient; *Israel*: Ferrlecit; *Ital.*: Extrafer; Ferlixit; Ferri-Emina; Ferritin Ott; Ferrosprint; Hemocromo; Rossepar; Sanifer†; *Port.*: Ferritin Ott; *USA*: Ferrlecit; Nulecit†.

Multi-ingredient Preparations. *Ital.*: Ferritin Complex.

Sodium Fluoride

Fluorid sodný; Fluoruro sódico; Natrii fluoridum; Natrio fluoridas; Natrium fluoratum; Natriumfluorid; Natriumfluorid; Natriumfluoridi; Sodium, fluorure de; Sodu fluorek; Sodyum Florür; Фторид Натрия.

NaF=41.99

CAS — 7681-49-4.
ATC — A01AA01; A12CD01.
ATC Vet — QA01AA01; QA12CD01.
UNII — 8ZYQ1474W7.

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

Ph. Eur. 8: (Sodium Fluoride). A white or almost white powder or colourless crystals. Soluble in water; practically insoluble in alcohol.

USP 36: (Sodium Fluoride). A white, odourless powder. Soluble 1 in 25 of water; insoluble in alcohol.

Uses and Administration

Sodium fluoride is used to prevent dental caries and may be used to increase bone density in osteoporosis (see p. 2090.1). Sodium fluoride is used as a source of fluoride in total parenteral nutrition.

The content of sodium fluoride is usually expressed in terms of the fluoride: 2.2 mg of sodium fluoride is equivalent to about 1 mg of fluoride. Fluoride content may also be expressed as ppm: fluoride 1 mg/litre equals 1 ppm. Each g of sodium fluoride provides about 23.8 mmol of sodium and fluoride.

For **dental caries prophylaxis**, sodium fluoride is used as an adjunct to diet and oral hygiene. It may render the enamel of teeth more resistant to acid, promote remineralisation, or reduce microbial acid production. Fluoride can be given by *fluoridation* of the public water supply (p. 2090.1) to achieve a usual fluoride concentration of 1 ppm in temperate regions. The concentration may vary from 0.6 to 1.2 ppm depending on the climatic temperature with the lower concentrations being used in hotter regions where more water is likely to be consumed. Fluoridation of salt at a minimum concentration of 200 mg of fluoride per kg of salt is an alternative. Fluoridation of milk has been tried in some countries.

Dental benefits from the use of *oral* fluoride supplements by adults are unsubstantiated. *Local application* of fluoride is effective; daily mouth-rinses of sodium fluoride 0.05% (about 227 ppm fluoride) or weekly mouth-rinses of sodium fluoride 0.2% (about 909 ppm) may be used. Sodium fluoride 2% (about 9090 ppm) solution is available for topical use, under professional supervision. Fluoridated toothpastes are now widely available and are a convenient source of fluoride. In the UK, the maximum permitted fluoride level in conventional toothpastes is sodium fluoride 0.33% (1500 ppm fluoride); higher concentrations of sodium fluoride 0.62 or 1.1% (2800 or 5000 ppm fluoride) are available under professional supervision. Sodium fluoride has also been applied topically as a varnish under professional supervision. Alternatively, sodium fluoride solutions or gels acidified with phosphoric acid (commonly known as acidulated phosphate fluoride preparations) may be used. These preparations are considered to increase the fluoride uptake by the enamel and protect the enamel from demineralisation. For maximum benefit, eating, drinking, or rinsing should be avoided for at least 15 to 30 minutes after topical fluoride application.

For uses and doses of sodium fluoride in children, see Administration in Children, below.

Other fluoride compounds used in oral hygiene products and toothpastes include aluminium fluoride, ammonium fluoride, calcium fluoride (p. 2053.1), dectaflur (p. 2059.1), magnesium fluoride (p. 2080.2) nicomethanol hydrofluoride, olaflur (p. 2085.1), potassium fluoride, sodium monofluorophosphate (p. 2091.3), and stannous fluoride (p. 2094.3). Other fluorides used in the fluoridation of water supplies include sodium silicofluoride (p. 2091.3).

Sodium fluoride has also been used, like some other fluoride compounds, in **rodenticides** and **insecticides**.

Administration in children. Sodium fluoride may be given as an *oral supplement* to children considered to be at high risk of caries. The daily dosage should be adjusted for the fluoride content of the drinking water, for fluorides ingested from other sources such as the diet, and for the age of the child. Guidelines in the USA and the UK both suggest that, where the drinking water contains less than 0.3 ppm of fluoride, children may be given the following doses according to age:

- under 6 months: not recommended
- 6 months to 3 years: sodium fluoride 550 micrograms (equivalent to 250 micrograms of fluoride) daily
- 3 to 6 years: 1.1 mg (equivalent to 500 micrograms of fluoride) daily
- 6 years and over: 2.2 mg (equivalent to 1 mg of fluoride) daily.

When drinking water contains 0.3 to 0.7 ppm (0.3 to 0.6 ppm in the USA) of fluoride lower doses should be considered. Specifically, it is recommended that no additional fluoride should be given to children less than 3 years of age and for older children the above doses should be halved. If the water contains more than 0.7 ppm (0.6 ppm in the USA) of fluoride, supplementation is not recommended. Tablets should be sucked or chewed before swallowing since the topical action of fluoride on enamel and plaque is considered to be more important than the systemic effect. The value of giving fluoride during pregnancy, to benefit the child, is not established.

Sodium fluoride may also be applied *locally* in children. As for adults, daily mouth-rinses of sodium fluoride 0.05% (about 227 ppm fluoride) or weekly mouth-rinses of sodium fluoride 0.2% (about 909 ppm) may be used, but are not recommended for children aged under 6 years because they are unable to effectively spit the rinse out after use. Fluoridated toothpastes may also be used by children, but the amount applied by children aged under 6 years should be supervised to avoid excessive use or ingestion. For children aged up to 3 years, a smear of toothpaste containing at least 0.22% sodium fluoride (1000 ppm fluoride) has been suggested, and for children aged from 3 to 6 years, a pea-sized amount of toothpaste containing about 0.3% sodium fluoride (1350 to 1500 ppm fluoride). If the water supply is fluoridated or if oral fluoride supplements are being given to children under the age of 7, then a toothpaste containing less than about 0.13% sodium fluoride (600 ppm fluoride) may be advisable. Toothpastes with higher concentrations may be prescribed for older children; 0.62% sodium fluoride (2800 ppm fluoride) in children over 10 years and 1.1% sodium fluoride (5000 ppm fluoride) in children over 16 years. Sodium fluoride may also be applied topically as a varnish or a gel, see Uses and Administration, above.

Dental caries prophylaxis. There is strong and consistent evidence in favour of the efficacy of fluoride in preventing or reducing the incidence of dental caries. However, there is no strong evidence that one form of topical fluoride is more effective than another.

References.

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2. Anonymous. Fluoride supplement dosage: a statement by the British Dental Association, the British Society of Paediatric Dentistry and the British Association for the Study of Community Dentistry. *Br Dent J* 1997; 182: 6–7.
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11. Marinho VCC, *et al.* Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental caries in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 08/11/05).
12. Petersson LG, *et al.* Professional fluoride varnish treatment for caries control: a systematic review of clinical trials. *Acta Odontol Scand* 2004; 62: 170–6.
13. Twetman S, *et al.* Caries-preventive effect of sodium fluoride mouthrinses: a systematic review of controlled clinical trials. *Acta Odontol Scand* 2004; 62: 223–30.
14. Jones S, *et al.* The effective use of fluorides in public health. *Bull WHO* 2005; 83: 670–6.

15. WHO/FDI World Dental Federation/International Association for Dental Research. Beijing declaration: call to action to promote oral health by using fluoride in China and Southeast Asia (issued September 2007). Available at: http://www.fdiworldental.org/sites/default/files/media/Beijing_Declaration_English.pdf (accessed 22/07/10)
16. Azarpazhooh A, Main PA. Fluoride varnish in the prevention of dental caries in children and adolescents: a systematic review. *J Can Dent Assoc* 2008; 74: 73–9.
17. Robinson C. Fluoride and the caries lesion: interactions and mechanism of action. *Eur Arch Paediatr Dent* 2009; 10: 136–40.
18. Poulsen S. Fluoride-containing gels, mouth rinses and varnishes: an update of evidence of efficacy. *Eur Arch Paediatr Dent* 2009; 10: 157–61.
19. Marinho VC. Cochrane reviews of randomized trials of fluoride therapies for preventing dental caries. *Eur Arch Paediatr Dent* 2009; 10: 183–91.
20. Walsh T, *et al.* Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2010 (accessed 10/06/10).
21. Hiiri A, *et al.* Fit and fissure sealants versus fluoride varnishes for preventing dental decay in children and adolescents. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2010 (accessed 10/06/10).

Fluoridation of water. Some countries add fluoride to water supplies to prevent dental caries. This has been the subject of much controversy.

References.

1. MRC. MRC working group report: water fluoridation and health (issued September 2002). Available at: http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002482 (accessed 10/03/08)
2. The British Fluoridation Society/The UK Public Health Association/The British Dental Association/The Faculty of Public Health. One in a million: the facts about water fluoridation. 2nd edition. Available at: http://www.bfsweb.org/onemillion/onemillion.htm (accessed 10/03/08)
3. Cheng KK, *et al.* Adding fluoride to water supplies. *BMJ* 2007; 335: 699–702.
4. Yeung CA. A systematic review of the efficacy and safety of fluoridation. *Evid Based Dent* 2008; 9: 39–43.
5. CDC. Populations receiving optimally fluoridated public drinking water—United States, 1992-2006. *MMWR* 2008; 57: 737–41.

Human requirements. In the USA dietary reference intakes have been set for fluoride. These propose an adequate intake (see p. 2046.1) for dental caries prevention to be 4 mg daily in adult men and 3 mg in women;[1] lower values are suggested in children and adolescents, depending on age. The tolerable upper intake level is 10 mg daily in adults.[1]

1. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride.* Washington, DC: National Academy Press, 1999. Also available at: http://www.nap.edu/openbook.php?isbn=0309063507 (accessed 21/07/08)

Osteoporosis. Fluoride has been given (usually as sodium fluoride or sodium monofluorophosphate) in the treatment of osteoporosis (p. 1168.1) to improve bone strength by inducing subclinical fluorosis. The main effect of fluoride on the skeleton is to stimulate osteoblasts and increase trabecular bone mass. Because antiresorptive drugs cannot restore lost bone mass, this is potentially valuable in the treatment of osteoporosis. However, too much fluoride can increase bone fragility, and the overall effect on the incidence of fracture has not been established. A systematic review[1] of 11 studies found that fluoride can increase bone mineral density (BMD) at the lumbar spine after 2 and 4 years of treatment, but did not reduce vertebral fractures. As the dose of fluoride increased, the risk of non-vertebral fractures and gastrointestinal adverse effects increased, without any effect on the vertebral fracture rate. Similar findings were reported in another review,[2] but an increased BMD in the hip was also reported, and although no effect was seen on the overall risk of fractures, a subgroup analysis found low daily doses of fluoride (20 mg or less) were associated with a reduction in vertebral and non-vertebral fracture risk. No difference was noted in the fracture risk reduction for either sodium fluoride or sodium monofluorophosphate. However, most studies in both reviews[1,2] also used calcium, making it difficult to assess the effect of fluoride alone on BMD or fracture risk. Fluoride is not considered first-line therapy for postmenopausal osteoporosis.[1]

1. Haguenauer D, *et al.* Fluoride for treating postmenopausal osteoporosis. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2000 (accessed 07/04/10).
2. Vestergaard P, *et al.* Effects of treatment with fluoride on bone mineral density and fracture risk—a meta-analysis. *Osteoporos Int* 2008; 19: 257–68.

Adverse Effects and Treatment

In the controlled amounts recommended for fluoridation of drinking water and at the recommended doses used in dentistry for caries prophylaxis, sodium fluoride has not been shown to have significant adverse effects.

In **acute poisoning**, sodium fluoride taken orally is corrosive, forming hydrofluoric acid in the stomach. Adverse effects include a salty or soapy taste, increased salivation, gastrointestinal disturbances, abdominal pain, weakness, drowsiness, faintness, and shallow breathing; more serious effects include hypocalcaemia, hypomagnesaemia, hyperkalaemia, tremors, hyperreflexia, tetany, convulsions, cardiac arrhythmias, shock, respiratory arrest, and cardiac failure. Death may occur within 2 to 4 hours.

Although there is much interindividual variation, a single oral dose of 5 to 10 g of sodium fluoride would be considered lethal in an untreated adult by most authorities. However, severe poisoning has been reported after oral doses of less than 1 g, and the minimum dose that can cause possibly fatal toxicity in children has been suggested to be 5 mg/kg of fluoride ion.

Treatment of acute poisoning involves gastric lavage with lime water or a weak solution of another calcium salt to precipitate fluoride, maintenance of high urine output, slow intravenous injections of calcium gluconate 10% for hypocalcaemia and tetany, and symptomatic and supportive measures. Magnesium sulfate may be given to correct hypomagnesaemia, and aluminium hydroxide may also reduce fluoride absorption. Haemodialysis may be considered.

Chronic fluoride poisoning may result in skeletal fluorosis, manifestations of which include increased density and coarsened trabeculation of bone and calcification in ligaments, tendons, and muscle insertions. Clinical signs are bone pain, stiffness, limited movement, and in severe cases, crippling deformities. Prolonged excessive intake by children during the period of tooth development before eruption can result in dental fluorosis characterised by mottled enamel. At fluoride concentrations in drinking water of 1 to 2 ppm (1 to 2 mg/litre) dental fluorosis is mild with white opaque flecks on the teeth. At higher concentrations, enamel defects become more severe with brown to black staining and the teeth have a pitted corroded appearance.

The **fluoridation** of water (above) has been a subject of considerable controversy. Suggestions that it increases the incidence of thyroid disorders, chromosome aberrations, and cancer have not been substantiated.

Reviews of the toxic effects of fluoride salts.

1. WHO. Fluorine and Fluorides. *Environmental Health Criteria 36.* Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc36.htm (accessed 08/11/05)
2. Whitford GM. The physiological and toxicological characteristics of fluoride. *J Dent Res* 1990; 69 (Spec Iss): 539–49.
3. Whitford GM. The metabolism and toxicity of fluoride. *Monogr Oral Sci* 1996; 16: 1–153.
4. WHO. Fluorides. *Environmental Health Criteria 227.* Geneva: WHO, 2002. Available at: http://www.inchem.org/documents/ehc/ehc/ehc227.htm (accessed 08/11/05)
5. Dhar V, Bhatnagar M. Physiology and toxicity of fluoride. *Indian J Dent Res* 2009; 20: 350–5.

Carcinogenicity. Based on comparisons of cancer mortality rates for communities residing in fluoridated and non-fluoridated cities, it was alleged that artificial fluoridation of water might be associated with an increased risk of cancer.[1] Re-examination of these data by others did not confirm the relationship, nor did further studies in a number of countries.[2] In Great Britain, the Working Party on Fluoridation of Water and Cancer[3] found nothing that could lead them to conclude that either fluoride occurring naturally in water, or fluoride added to water supplies, was capable of inducing cancer, or of increasing the mortality from cancer. In this respect, fluoridation of drinking water was considered safe. Further study in *animal* models by the USA National Toxicology Programme[4] found no evidence of carcinogenicity in female *rats* or in *mice* of either sex. A small number of osteosarcomas was found in male *rats* in the medium- and high-dose groups, although the association between sodium fluoride and the tumour was uncertain. A review of epidemiological evidence of possible carcinogens in drinking water stated that additional data gathered since 1990 did not support an association between the risk of osteosarcoma, or any other cancer, and the fluoride in drinking water.[5]

A cohort study of workers exposed to high levels of fluoride dust reported excess incidences of primary lung cancer and bladder tumours.[6]

1. Yiamouyiannis J, Burk D. Fluoridation and cancer: age-dependence of cancer mortality related to artificial fluoridation. *Fluoride* 1977; 10: 102–25S.
2. Clemmesen J. The alleged association between artificial fluoridation of water supplies and cancer: a review. *Bull WHO* 1983; 61: 871–83.
3. DHSS. *Fluoridation of water and cancer: a review of the epidemiological evidence: report of the working party.* London: HMSO, 1985.
4. Public Health Service report on fluoride benefits and risks. *JAMA* 1991; 266: 1061–2, 1066–7.
5. Cantor KP. Drinking water and cancer. *Cancer Causes Control* 1997; 8: 292–308.
6. Grandjean P, Olsen JH. Extended follow-up of cancer incidence in fluoride-exposed workers. *J Natl Cancer Inst* 2004; 96: 802–3.

Effects on bones and joints. Exacerbation of **rheumatoid arthritis** in a 68-year-old woman was attributed to sodium fluoride given for osteoporosis.[1]

An increased risk of **hip fracture** in the elderly has been suggested as being associated with fluoridated water;[2] another study[3] reported that this association was confined to fluoride concentrations of more than 110 micrograms/litre. However, a large case-control study[4] found no increase in the risk of hip fracture for people ingesting fluoridated water at concentrations of about 1 mg/litre (1 ppm). Similarly, a large prospective study[5] in older white women found no increase in the risk of fractures with long-term exposure to fluoridated drinking water, and even a suggestion of a reduction in the risk of fractures of the hip and vertebrae, due to increased bone mineral density of the *femoral neck* and *lumbar spine*, in those women continuously exposed to fluoridation. An epidemiological study in a large rural Chinese population found that long-term fluoride exposure from drinking water containing 4.32 ppm or more increased the risk of overall fracture as well as *hip fracture*. Water containing 1 to 1.06 ppm decreased the risk of overall fractures relative to areas with negligible water fluoridation; a similar protective effect on the risk of hip fractures was not seen. Although the number of hip fractures were small, the authors suggested that this supported other findings that fluoride concentrations of about 1 ppm in drinking water do not increase the risk of hip fracture.[6] For comment on the influence of therapeutic doses of fluoride on the incidence of fractures, see above under Osteoporosis in Uses and Administration.

Use of fluoride, particularly in doses of 40 mg or more daily, may be associated with a **peripheral pain syndrome**, usually manifested as bone pain in the distal lower limbs, but sometimes involving the upper limbs and axial skeleton. The cause is uncertain: both stress fractures and increased bone growth at the site of pain have been proposed.[7]

Fluoride-related **bone disease** (skeletal fluorosis) manifesting as osteomalacia or osteosclerosis, has been reported after excessive consumption of tea (brewed, bottled, or iced).[8,9] Some bottled teas were found to have fluoride concentrations above the FDA's limit of 2.4 ppm for bottled beverages.[9]

1. Duell PB, Chesnut CH. Exacerbation of rheumatoid arthritis by sodium fluoride treatment of osteoporosis. *Arch Intern Med* 1991; 151: 783–4.
2. Danielson C, *et al.* Hip fractures and fluoridation in Utah's elderly population. *JAMA* 1992; 268: 746–8.
3. Jacqmin-Gadda H, *et al.* Fluorine concentration in drinking water and fractures in the elderly. *JAMA* 1995; 273: 775–6.
4. Hillier S, *et al.* Fluoride in drinking water and risk of hip fracture in the UK: a case-control study. *Lancet* 2000; 355: 265–9.
5. Phipps KR, *et al.* Community water fluoridation, bone mineral density, and fractures: prospective study of effects in older women. *BMJ* 2000; 321: 860–4.
6. Li Y, *et al.* Effect of long-term exposure to fluoride in drinking water on risks of bone fractures. *J Bone Miner Res* 2001; 16: 932–9.
7. Jones G, Sambrook PN. Drug-induced disorders of bone metabolism: incidence, management and avoidance. *Drug Safety* 1994; 10: 480–9.
8. Ballanger Johnson JE, *et al.* Fluoride-related bone disease associated with habitual tea consumption. *Mayo Clin Proc* 2007; 82: 719–24. Correction. *ibid.*: 1017. [dosage error]
9. Whyte MP. Fluoride levels in bottled teas. *Am J Med* 2006; 119: 189–90.

Effects on the kidneys. Nephrotoxicity has been associated with high plasma concentrations of fluoride during anaesthesia with fluorine-containing anaesthetics such as methoxyflurane (p. 1907.3). Elevated fluoride ion concentrations have also been noted in the plasma of patients receiving enflurane or isoflurane, although no clinical effect on renal function was found (see Effects on the Kidneys, p. 1900.1 and Metabolism, p. 1904.3).

Fluorosis. Discussions of chronic fluorosis.[1-5] In a 1994 report, WHO considered that in temperate climates, *teeth* seemed not to be affected if fluoride concentrations in drinking water were not greatly above 1 ppm; fluorosis affecting bone had not been detected at concentrations of 4 to 8 ppm in temperate regions, although it could occur at concentrations of more than 6 ppm in tropical areas.[6] However, a later systematic review[7] of the effects of water fluoridation, which included 214 studies worldwide, considered that at a concentration of 1 ppm, an estimated 12.5% of exposed people would develop sufficient fluorosis of their teeth to cause aesthetic concern. Swallowing of fluoridated toothpaste by young children has been implicated as a risk factor for fluorosis.[4,8] Higher concentrations of fluoride in toothpaste have been associated with less caries, but with higher levels of fluorosis,[9] and toothpastes with lower concentrations of fluoride have been recommended for use in children.[8,9] The use of infant formula feeds reconstituted with fluoridated water may result in ingestion of large amounts of fluoride[5] and subsequent fluorosis;[3] bottled water may also contain fluoride.[5]

Skeletal fluorosis associated with excess tea consumption has also been reported (see Effects on Bones and Joints, above).

1. Anonymous. Chronic fluorosis. *BMJ* 1981; 282: 253–4.
2. Mason JO. A message to health professionals about fluorosis. *JAMA* 1991; 265: 2939.
3. Horowitz HS. Proper use of fluoride products in fluoridated communities. *Lancet* 1999; 353: 1462.
4. Whelton HP, *et al.* A review of fluorosis in the European Union: prevalence, risk factors and aesthetic issues. *Community Dent Oral Epidemiol* 2004; 32 (suppl): 9–18.
5. Levy SM. An update on fluorides and fluorosis. *J Can Dent Assoc* 2003; 69: 286–91.
6. WHO. Fluorides and oral health: report of a WHO expert committee on oral health status and fluoride use. *WHO Tech Rep Ser 846* 1994. Available at: http://libdoc.who.int/trs/WHO_TRS_846.pdf (accessed 24/03/09)

7. McDonagh MS, *et al.* Systematic review of water fluoridation. *BMJ* 2000; 321: 855–9.
8. Rock WP, Sabieha AM. The relationship between reported toothpaste usage in infancy and fluorosis of permanent incisors. *Br Dent J* 1997; 183: 165–70.
9. Steiner M, *et al.* Effect of 1000 ppm relative to 250 ppm fluoride toothpaste: a meta-analysis. *Am J Dent* 2004; 17: 85–8.

Gum disease. In the Davangere district of India, the fluoride concentration in the drinking water ranges from 1.5 to 3 ppm; there is virtually no dental care. In a study of patients with dental fluorosis in this district, a strong association was found between the occurrence of periodontal disease and the severity of fluorosis; periodontitis was also high in subjects with poor oral hygiene. Gingivitis reduced as the degree of fluorosis increased. Fluoride may have a role in the aetiology and pathogenesis of gum disease.[1]

1. Vandana KL, Reddy MS. Assessment of periodontal status in dental fluorosis subjects using community periodontal index of treatment needs. *Indian J Dent Res* 2007; 18: 67–71.

Hypersensitivity. Dermatitis, urticaria, headaches, gastrointestinal reactions, stomatitis, and mouth ulcers have all been reported as hypersensitivity reactions after use of fluoride-containing toothpastes, tablets, drops or drinking water.[1] Topical treatment of the teeth with a sodium fluoride preparation has been reported to cause severe disseminated acute urticaria and facial angioedema, requiring hospitalisation.[2] However, 2 other cases of reaction to the same commercial preparation were considered to be due to colophony (p. 2484.2) contained in the preparation.[3] It has been suggested that, in cases of probable toothpaste allergy, lack of response to patch tests on the skin may be because fluoride crosses the oral mucous membrane more easily than the skin.[4]

Stomatitis has also been reported after use of gels containing olaflur and dectaflur.[5]

1. Mummery RV. Claimed fluoride allergy. *Br Dent J* 1984; 157: 48.
2. Camarasa JG, *et al.* Contact urticaria from sodium fluoride. *Contact Dermatitis* 1993; 28: 294.
3. Isaksson M, *et al.* Contact allergy to Duraphat. *Scand J Dent Res* 1993; 101: 49–51.
4. Brun R. Recurrent benign aphthous stomatitis and fluoride allergy. *Dermatology* 2004; 208: 181.
5. Ganter G, *et al.* Contact dermatitis and stomatitis due to amine fluoride. *Contact Dermatitis* 1997; 37: 248.

Overdosage. References.

1. McIvor ME. Acute fluoride toxicity: pathophysiology and management. *Drug Safety* 1990; 5: 79–85.
2. Gessner BD, *et al.* Acute fluoride poisoning from a public water system. *N Engl J Med* 1994; 330: 95–9.
3. Arnow PM, *et al.* An outbreak of fatal fluoride intoxication in a long-term hemodialysis unit. *Ann Intern Med* 1994; 121: 339–44.
4. Shulman JD, Wells LM. Acute fluoride toxicity from ingesting home-use dental products in children, birth to 6 years of age. *J Public Health Dent* 1997; 57: 150–8.

Precautions

When considering fluoride supplementation, allowance should be made for fluorides ingested from other sources; fluoride supplements in children are not generally recommended when the fluoride content of drinking water is over 0.7 ppm (0.6 ppm in the USA) (see also Uses and Administration, p. 2089.2). Care should be taken to prevent children swallowing excessive fluoride after topical application to teeth.

Patients with impaired renal function may be particularly susceptible to fluorosis. Regular dialysis with fluoridated water may result in additional fluoride absorption; a maximum concentration of 0.2 ppm of fluoride in the dialysate has been recommended. Dialysis patients not using deionised water are at risk from changes in the fluoride content of the water supply.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sodium fluoride as not porphyrinogenic when used for caries prevention; it may be used as a drug of first choice and no precautions are needed. Sodium fluoride is not classified when used as a mineral supplement.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Interactions

Aluminium, calcium, and magnesium salts may decrease the absorption of fluoride.

Pharmacokinetics

Sodium fluoride and other soluble fluorides are readily absorbed from the gastrointestinal tract. Inhaled fluorides (from industrial fumes and dusts) are absorbed through the lungs. Fluoride is deposited mainly in the bones and teeth. It is principally excreted in the urine but small amounts may also be excreted in faeces and sweat. It crosses the placenta and is present in saliva, nails, and hair. There is some evidence of distribution into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aquafresh Ultimate White; Elgydium Junior; Elgydium Proteccion Caries; Fluordent; Fluorogel; Fluoroplat; Naf Buches; Opalescence; *Austral.*: Flurets†; NeutraFluor; *Austria*: Duraphat; Fluodont†; Sensodyne Proschmelz; Zymafluor; *Belg.*: Fluodontyl; Fluor; Z-Fluor; *Braz.*: Fluotrat; *Canad.*: Fluocal†; Fluor-A-Day; Nafrinse†; Oro-NaP†; PDF; Perfect Solutions†; Sensodyne ProNamel; Solu-Flur†; Xerolube†; *Chile*: Caristop; Fluocaril Bi-Fluore†; Gengisyl†; Vitaflur; Vitis Orthodontic Pasta; Vitis Pasta; *Cz.*: Zymafluor; *Denm.*: Duraphat; Fluorolex; *Fin.*: Duraphat; Fludent; Fluorlette†; *Fr.*: Duraphat; Elgydium Protection Caries; Fluodontyl; Fluor†; Fluorex; Sanogyl; Zymafluor; *Ger.*: Duraphat; Fluoretten; Ossin†; Sensodyne Proschmelz; Zymafluor†; *Gr.*: Apoflux; Duraphat; Flurexil; *Hung.*: Arthrofluor†; Dentocar; Zymafluor; *India*: Denex-PF; Naf; Otoflour; *Indon.*: Fluoricare; Listermint†; Vinafluor; *Irl.*: Duraphat; *Israel*: Duraphat; Fluvium†; Teeth Tough†; Zymafluor; *Ital.*: AZ Verde†; Cleanicdent; Dentosan Extra Fluor†; Duraphat; Eburdent; Fluor-In†; Fluorinse; Listerine Difesa; Zymafluor; *Mex.*: Audifluor; *Neth.*: Dentigel; Duraphat; En-De-Kay; Zymafluor; *Norw.*: Duraphat; Fluorette; Flux; *Philipp.*: Infaflor; *Pol.*: Fluossen†; Zymafluor†; *Port.*: Duraphat; Elmex; Fluor-In; Maxfluor; Zymafluor; *S.Afr.*: Listerfluor; Zymafluor; *Spain*: Fluodontyl†; Fluor; *Swed.*: Dentan; Dentirol Fluor; Duraphat; Fludent; Fluorette; Top dent fluor; *Switz.*: Duraphat; Paro Fluor; Sensodyne Proemail Fluorid; Zymafluor; *Thai.*: Flu-Ride; Zymafluor; *Turk.*: Dentiflour; Fluoxytil; Zymafluor; *UK*: Duraphat; En-De-Kay; Fluor-A-Day; Fluorigard; Sensodyne Mint; *USA*: ACT; Denta Plus; DentaGel; Dry Mouth Relief; EtheDent; Fluor-a-day; Fluorigard; Fluorinse; Fluoritab; Flura; Karidium; Karigel-N; Karigel; Listerine Tooth Defense; Ludent; Luride; Minute-Gel; MouthKote F/R; NeutraGard Advanced; OrthoWash; Pediaflor†; Pharmaflur; Phos-Flur; Point-Two; Prevident; ReNaf; SF 5000 Plus; SF Gel; SodiPhluor; Thera-Flur.

Multi-ingredient Preparations. *Arg.*: ADC Fluor; Aquafresh Sensitive; Bucal Hyper Sensitive; Bucal Tac Whitening Gel; Buclorhex; Cal-C-Vita Fluor; Desensyl; Elgydium Dientes Sensibles; Emoform Total; Esmedent con Fluor; Esmedent; Fluordent PX; Fluordent PX; Fluorogel 2001 para Dientes Sensibles; Fluorogel 2001; Kdesin; Ostelin F; Parodontax Fluor; Pervinox Extra Mint; Pervinox Fresh Mint; Pervinox Fruit; Revelplac 2001; Sensident; Sensigel; Sensodyne Antisarro; Sensodyne Bicarbonato de Sodio; Sensodyne Blanqueador; Sensodyne Cool; Sensodyne Proteccion Total; Sensodyne Rapido Alivio; Squam; Squam; Tac Fluor; Tri-Vi-Fluor; Vitasol F; *Austral.*: Macleans Sensitive; *Austria*: Elmex; Ossiplex†; *Belg.*: Elmex; Fluocaril; Sedemol; Sulfa-Sedemol; *Braz.*: Calci-Ped; Calciferol Composto; Calcifix B12; Calcifix Irradiado; Calcifluol; Calcigenol; Calcinol Complexo; Calciofar; Calferon; Calvita B12†; Deficical B12; Femme com Fluor; Kindcalcio†; Malvatricin Branqueador†; Malvatricin Natural†; Malvatricin; Malvatrikids F; Malvatrikids Junior; Natalins com Fluor; Nativit Fluor; Noplak Max; Poly-Vi-Fluor; Sensodyne Antitartaro; Sensodyne C/Bicarbonato de Sodio; Sensodyne Cool†; Sensodyne Fresh Mint; Sensodyne Protecao Total; Tri-Vi-Fluor; *Canad.*: Cepacol with Fluoride†; Gel-Kam Dentinbloc; Listerine Antiseptic with Fluoride; Oral-B Anti-Bacterial with Fluoride; Perfect Solutions 1-Minute†; Perfect Solutions In Office Rinse†; Sensodyne-F; Sensodyne; *Chile*: Cariax; Caristop; Elgydium Dientes Sensibles; FKD; Fluorencil; Listermint Con Fluor†; Oralgene; Orthokin; Sensaid; Vitis Encias Pasta; Vitis Orthodontic Colutorio; *Cz.*: Elmex; *Denm.*: Bifluorid; *Fin.*: Elmex; Xerodent; *Fr.*: Bifluorid; Elgydium Dents Sensibiles; Elgydium Protection email; Fluocaril Bi-Fluore; Fluocaril blancheur†; Fluocaril dents sensibles†; Fluocaril Junior and Fluocaril Kids†; Fluoselgine; Fluosterol; Gum HaliControl; Listerine protection dents et gencives; Parogencyl prevention gencives†; Paroplak†; Sanogyl Fluo†; Sensigel; Zymaduo; *Ger.*: D-Fluoretten; Elmex; Fluor-Vigantoletten; Gum SensiPro†; Ledermix Fluorid; Multifluorid†; Ossiplex†; Ossofortin Plus; Zymafluor D†; *Gr.*: Fluocaril Bi-Fluore; *Hong Kong*: Listerine Teeth and Gum Defence; Sensodyne Gentle†; *Hung.*: Elmex; Klimin; *India*: AM-PM Junior; AM-PM Special; Clohex Plus; Dentasep-F; Florocid; Fluoritop-MR; Garlin; HAA; Icee Mth Wsh; Kidodent; Me-Fresh; Nitra-OR; *Indon.*: Hical; Osteocal Plus; Sensodyne Cool Gel; Solvita Baby; *Irl.*: Colgate Total; *Israel*: Elmex; Elmex; *Ital.*: Actifluor; Actisens; Aqua Emoform; AZ Protezione Gengive; AZ Tartar Control; Benodent; Broxo al Fluoro; Colgate Total; Dentosan Junior; Dentosan Ortodontico; Dentosan Sensibile; Eburdent P; Elmex; Emoform Actisens; Emoform-Tat; Fluocaril Bi-Fluore; Fluocaril; Lacalut; Oral-B Collutorio Denti Gengive; Oral-B Denti Sensibili; Osteo Complex; Otofluor; Plax; Ridiodent; *Mex.*: Amident; Fluoxytil†; *Neth.*: Elmex; Fluocaril Bi-Fluore†; *Norw.*: Xerodent; *NZ*: Listerine Teeth Defence; *Philipp.*: Listerine Teeth & Gum Defense; Natalbes; Natalins-M; Poly-Vi-Flor; Xylorinse; *Pol.*: Bifluorid; Elmex; Fluormex; Fluoro-zel; *Port.*: Bexident; Fluocaril Bi-Fluore; *Rus.*: Elgyfluor (Элгифлуор); Parodontocide (Пародонтоцид); Sensigel (Сенсигель); *S.Afr.*: Ossiplex†; *Singapore*: 2Sensitive; Elgydium Sensitive; Elgyfluor†; Listerine Teeth & Gum Defense; Sensigel; *Spain*: Vitagama Fluor†; *Swed.*: Bifluorid; Xerodent; *Switz.*: Elmex; Paro aux fluorures d'amines Gelee; *Thai.*: FBC Plus; Poly-Vi-Flor†; *Turk.*: D-Flor†; Kalsifluor; Nesgarin; Sensodyne Gel; Sensoral; Xialine; Zymaduo; *UK*: AS Saliva Orthana; CB12; Dentyl pH; Hydrotab; Listermint with Fluoride; Macleans Mouthguard; Sensodyne-P; *Ukr.*: Vitaftor (Витафтор)†; *USA*: ControlRx; Florical; Fluoridex Daily Defense Sensitivity Relief; Mulvidren-F Softab; Poly-Vi-Flor with Iron; Poly-Vi-Flor; Polytabs-F; Sensitivity Protection Crest; Sensodyne iso-active; Soluvite; Tri-A-Vite F; Tri-Vi-Flor; Tri-Vi-Floro; Trivitamin Fluoride Drops; Vi-Daylin/F; *Venez.*: Sensodyne.

Pharmacopoeial Preparations

BP 2014: Sodium Fluoride Mouthwash; Sodium Fluoride Oral Drops; Sodium Fluoride Oral Solution; Sodium Fluoride Tablets; USP 36: Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Sodium Fluoride and Acidulated Phosphate Topical Solution; Sodium Fluoride and Phosphoric Acid Gel; Sodium Fluoride Gel; Sodium Fluoride Oral Solution; Sodium Fluoride Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Sodium Monofluorophosphate

Fluorofosfato sódico; MFP; Sodium; Monofluorofosfato sódico; Natrii Monofluorophosphas; Natriummonofluorfosfat; Natriummonofluorifosfaatti; Sodium Fluorophosphate; Монофторфосфат Натрия.

Disodium phosphorofluoridate.

Na_2PO_3F=143.9

CAS — 10163-15-2.

ATC — A01AA02; A12CD02.

ATC Vet — QA01AA02; QA12CD02.

UNII — C810JCZ56Q.

Pharmacopoeias. In *US.*

USP 36: (Sodium Monofluorophosphate). A white to slightly grey, odourless powder. Freely soluble in water. pH of a 2% solution in water is between 6.5 and 8.0.

Profile

Sodium monofluorophosphate is used as a source of fluoride (see Sodium Fluoride, p. 2089.2) in toothpastes for the prevention of dental caries. It may also be given orally in the management of osteoporosis.

In the UK, the maximum permitted fluoride level in toothpastes is 1.14% of sodium monofluorophosphate (0.15% or 1500 ppm of fluoride). Formulations for children under 7 years of age typically contain sodium monofluorophosphate 0.38% (500 ppm fluoride); higher concentrations may be used, but the amount applied should be supervised to avoid excessive use or ingestion.

Other monofluorophosphate salts permitted for use in oral hygiene products and dentifrices include ammonium monofluorophosphate, calcium monofluorophosphate, and potassium monofluorophosphate. Glutamine monofluorophosphate has been used for osteoporosis.

Osteoporosis. For reference to the use of fluorides, including sodium monofluorophosphate, in the treatment of osteoporosis, see under Uses and Administration of Sodium Fluoride, p. 2090.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aquafresh Triple Protection; *Austral.*: Fluorocare; *Braz.*: Confident; Emoform AP; Malvatricin Antitartaro†; Unique Plus; *Chile*: Fluocaril Bi-Fluore†; Gengisyl†; Oralfresh Proteccion; *India*: Denex-PF; Inissiate; Kidodent; Magdent-R; *Ital.*: Isifluor; Neo Fluostomygen; Platinum; *USA*: Biotene Dry Mouth; *Venez.*: Aquafresh.

Multi-ingredient Preparations. *Arg.*: Adolcas; Desensyl; Emoform Total; Fluordent PX; Hexiben; Negaporosis; Sensodyne-F; Squam; *Austria*: Fluocalcic†; *Belg.*: Fluocaril; *Braz.*: Emoform AT; Fluomint†; Malvatricin Antiplaca†; Malvatricin Branqueador†; Malvatricin Dentes Sensiveis†; Malvatricin Natural Organic†; Malvatricin Natural Soft†; Malvatricin Natural†; Malvatricin Plus†; Odontis-Rx; Sensodyne-F†; *Chile*: Caristop Sensitive; Caristop; Fluorencil; *Cz.*: Tridin; *Fr.*: Emoform Dents Sensibles; Fluocaril Bi-Fluore; Fluocaril Junior and Fluocaril Kids†; Sanogyl Fluo†; *Ger.*: Tridin Forte†; Tridin; *Gr.*: Fluocaril Bi-Fluore; *Hong Kong*: Tridin; *Hung.*: Tridin; *India*: Denoseal-F; Denpot-KF; Hydent K; Hydent; K-Dent-F; Klinit; Magdent-KF; Nitra; Nitrodent-KF; Nitrodent-R; *Ital.*: Aqua Emoform; Biogreen; Broxo al Fluoro; Dentosan Junior; Emoform-Tat; Fluocaril Bi-Fluore; FluorD3†; Formedico; Neo Emoform; Neo-Stomygen; Periogard Plus; Stomygen; Tridin; *Mex.*: Dentsiblen†; Fluoxytil†; Periodentyl; *Neth.*: Fluocaril Bi-Fluore†; *Pol.*: Fluoro-zel; *Port.*: Fluocaril Bi-Fluore; *Singapore*: Biotene; Oral-Seven; *Switz.*: Emoform-F au fluor†; *Turk.*: Sensodyne-F; *USA*: Monocal; Optimoist; Sensodyne-F.

Sodium Silicofluoride

Fluorosilicato sódico; Fluosilicato sódico; Hexafluorosilicato sódico; Silicofluoruro sódico; Sodium Fluorosilicate; Sodium

Fluosilicate; Sodium Hexafluorosilicate; Кремнефтористый Натрий.
Na_2SiF_6=188.1.
CAS — 16893-85-9.
UNII — 806AV2E065.

Profile

Sodium silicofluoride is used as a source of fluoride (see Sodium Fluoride, p. 2089.2) for the fluoridation of drinking water. It has also been considered for inclusion in oral hygiene products.

Other silicofluoride (fluorosilicate) salts permitted for use in oral hygiene products include ammonium silicofluoride, magnesium silicofluoride, and potassium silicofluoride.

Sodium silicofluoride has also been used in insecticides.

Sorbitol

E420; D-Sorbitol; Sorbitoli; Sorbitolis; Sorbitolum; Szorbit; Сорбит; Сорбитол.
D-Glucitol.
$C_6H_{14}O_6$=182.2
CAS — 50-70-4.
ATC — A06AD18; A06AG07; B05CX02; V04CC01.
ATC Vet — QA06AD18; QA06AG07; QB05CX02; QV04CC01.
UNII — 506T60A25R.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *Viet.* Also in *USNF.*

US includes only Sorbitol Solution.

Ph. Eur. 8: (Sorbitol). A white or almost white crystalline powder. It exhibits polymorphism. Very soluble in water; practically insoluble in alcohol.

USNF 31: (Sorbitol). White, odourless, hygroscopic powder, granules, or crystalline masses having a sweet taste with a cold sensation. Soluble 1 in 0.45 of water; sparingly soluble in alcohol; practically insoluble in solvent ether. pH of a 10% w/w solution in water is between 3.5 and 7.0.

Incompatibility. For reference to the incompatibility of sorbitol with hydroxybenzoates, see p. 1757.3.

Uses and Administration

Sorbitol is a polyhydric sugar alcohol (polyol) with about half the sweetening power of sucrose. It occurs naturally in many fruits and vegetables and is prepared commercially by the reduction of glucose.

It has been given as a 30% solution as an alternative to glucose in parenteral nutrition (p. 2044.1) but its use is not recommended because of the risk of lactic acidosis.

Sorbitol may be given as an osmotic laxative in the management of constipation (p. 1804.3); daily doses of about 14 to 42 g orally, or 30 to 36 g rectally have been used.

Solutions containing about 3% of sorbitol are used as irrigating fluids in transurethral surgical procedures.

Sorbitol was formerly given intravenously as a 50% solution as an osmotic diuretic.

Sorbitol also acts as a bulk sweetening agent. It is used in limited quantities as a sweetener in energy-reduced diabetic food products. It is also used as an alternative to sucrose in many sugar-free oral liquid preparations and in sugar-free foods as it is less likely to cause dental caries.

Sorbitol also has humectant and stabilising properties and is used in various pharmaceutical and cosmetic products including toothpaste.

Adverse Effects and Precautions

As for Fructose, p. 2068.2.

Effects on electrolyte balance. Sorbitol is used as a vehicle in some proprietary preparations of activated charcoal intended to reduce drug absorption after poisoning; the sorbitol increases the palatability of the preparation and also produces an osmotic diarrhoea that facilitates elimination of the activated charcoal and adsorbed drug. Repeated doses of such preparations are often advocated but there have been reports[1-3] of severe sorbitol-induced hypernatraemia in adults and children. In all cases, charcoal in a 70% sorbitol suspension had been given. It has been recommended that fluid and electrolyte balance be monitored closely, and that preparations with lower concentrations of sorbitol be used if possible.[2,3] For debate about such multiple dose therapy see Poisoning, under Activated Charcoal, p. 1538.1.

1. Gazda-Smith B, Synhavsky A. Hypernatraemia following treatment of theophylline toxicity with activated charcoal and sorbitol. *Arch Intern Med* 1990; **150**: 689 and 692.
2. Allerton JP, Strom JA. Hypernatremia due to repeated doses of charcoal-sorbitol. *Am J Kidney Dis* 1991; **17**: 581–4.
3. Farley TA. Severe hypernatremic dehydration after use of an activated charcoal-sorbitol suspension. *J Pediatr* 1986; **109**: 719–22.

Effects on the gastrointestinal tract. Sorbitol is often used as a sweetener in sugar-free preparations and the risk of sorbitol-induced diarrhoea associated with such products has been highlighted.[1-4] Chronic sorbitol-induced diarrhoea with associated pneumatosis intestinalis has been reported in a child given 21.7 g sorbitol daily in liquid medications.[5] Colonic and upper gastrointestinal necrosis, including some fatalities, have been reported after use of sodium polystyrene sulfonate in sorbitol, and may have been associated with the sorbitol component, see p. 1575.3.

It has also been suggested that sorbitol contributed to the morbidity in a patient who developed septicaemia as a complication of intestinal pseudo-obstruction, after the use of charcoal with sorbitol to treat self-poisoning with theophylline.[6] It was suggested that gaseous distension after bacterial metabolism of sorbitol had rendered the bowel wall ischaemic, facilitating passage of bacteria or of endotoxin into the systemic circulation.

1. Brown AM, Masson E. Hidden' sorbitol in proprietary medicines - a cause for concern? *Pharm J* 1990; **245**: 211.
2. Edes TE, *et al.* Diarrhea in tube-fed patients: feeding formula not necessarily the cause. *Am J Med* 1990; **88**: 91–3.
3. Johnston KR, *et al.* Gastrointestinal effects of sorbitol as an additive in liquid medications. *Am J Med* 1994; **97**: 185–91.
4. Bauditz J, *et al.* Severe weight loss caused by chewing gum. *BMJ* 2008; **336**: 96–7.
5. Duncan B, *et al.* Medication-induced pneumatosis intestinalis. *Pediatrics* 1997; **99**: 633–6.
6. Longdon P, Henderson A. Intestinal pseudo-obstruction following the use of enteral charcoal and sorbitol and mechanical ventilation with papaveretum sedation for theophylline poisoning. *Drug Safety* 1992; **7**: 74–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sorbitol 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 07/10/11)

Pharmacokinetics

Sorbitol is poorly absorbed from the gastrointestinal tract after oral or rectal use. It is metabolised mainly in the liver, to fructose (see p. 2068.3), a reaction catalysed by the enzyme sorbitol dehydrogenase. Some sorbitol may be converted directly to glucose by the enzyme aldose reductase.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Sorbilax; *Braz.*: Minilax; *Rus.*: Sorbit (Сорбит); *Swed.*: Resulax.

Multi-ingredient Preparations. *Arg.*: Humectante Bucal; Micronema; *Austral.*: Aquae; Carbosorb XS; Fleet Micro-Enema†; Microlax; *Austria*: Glandosane; Microklist; Yal; *Belg.*: Microlax; Spagulax Sorbitol†; *Braz.*: Anekron; Colachofra; Hepalin; Hepatox; *Canad.*: Charac Tol; Charcodote; Microlax; Moi-Stir; *Chile*: Secand; Solucion Irrigacion Vesical†; Tabletas Phillips; Ureadin Rx PS; *Cz.*: Yal; *Denm.*: Klyx; *Fin.*: Klyx; Microlax; *Fr.*: Actigess†; Apilaxe; Artisial; Cicatridine; Hepagrume; Hepargitol; Microlax; Nivabetol†; Parapsyllium; Schoum; Spagulax au Sorbitol†; SST†; *Ger.*: Flacar; Freka-Drainjet Purisole†; Glandosane; Microklist; Saliva natura; Xerotin; Yal; *Gr.*: Collyre Vitaphakol; Suprin; *Hong Kong*: Glandosane; Microlax†; Osmofundin†; Salivart†; *Hung.*: Balansol; Rehydrosol†; *India*: Al-Live; Alkasol-P; Aminocore 5-S Plus; Aminofusion; Anorexin Plus; Aqvet; Bioferum Forte; Bioffin; Brofentol; Celemin; Celemix Combi; Cyaptin-SF; Cyaptin; Cyp-L; Cypine-TS; Cypolin; Cypon-L; Cyprea-T/ Cyprobit; Decyp-P; Perricos; Ferritop Iron Tonic; Ferrofit; Porliv; Fortil; Gastrozyme; Gelusil Plus; Growise; Haematinga; Hb-Rich; Hepachol; Hepoline; Hermin; Livocip; Mecolin; Siloxogene; Sorbiline; Sorliv; *Indon.*: Aminofusin L; Aminovel; Amnorel; Celemin; Ferobion; Intrafusin SX-E; Laxarec; Microlax; Nutrisol-S; Pan Amin G; Pronita; Tutofusin LC; Tutofusin OpS; Valamin; *Israel*: Biolax Protect; Biolax†; Charcodote; Spray Mint; *Ital.*: Citroepatina†; Macrolax; Novilax; Sorbidis; *Jpn*: Lactec G; *Mex.*: Clyss-Go; *Neth.*: Klyx; Microlax; *Norw.*: Klyx; Microlax; *NZ*: Carbosorb XS; Microlax; *Pol.*: Purisole SM†; Rektiolax; *Port.*: Clyss-Go; Glandosane†; Purisole; *Rus.*: Aminosol (Аминосол); Hepasol A (Гепасол А); Highmix (Хайомикс); Microlax (Микролакс); Reosorbilact (Реосорбилакт); Sorbilact (Сорбилакт); *S.Afr.*: Agofell†; *Singapore*: Charcodote; Microlax; Minica S; Osmofundin; *Spain*: Sugarbil†; *Swed.*: Klyx; Microlax; Omnilax; *Switz.*: Agarol Soft†; Glandosane; Microklist; Microlax; Pursana; Yal; *Thal.*: Glandosane; *Turk.*: Charflo Sorbitol†; Kanslak; Libalaks; Sabalaks; Yal; *UK*: Glandosane; Luborant†; Relaxit; Saliva Natura; SST; Xerotin; *Ukr.*: Hepasol A (Гепасол А); Lactoprotein-C (Лактопротеин-С); Reosorbilact (Реосорбилакт); Rheosorbilact (Реосорбилакт); Sorbilact (Сорбилакт); Turusol (Турусол); *USA*: Actidose with Sorbitol; Moi-Stir; Numoisyn; Plax; Salivart.

Pharmacopoeial Preparations

Ph. Eur.: Sorbitol, Liquid (Crystallising); Sorbitol, Liquid (Non-crystallising); Sorbitol, Liquid, Partially Dehydrated;
USNF 31: Noncrystallizing Sorbitol Solution;
USP 36: Sorbitol Solution.

Soya Bean

Habas de Soja; Soja Bean; Soyabean; Soybean; Соевый Боб.
ATC Herb — HA10BX5002 (Glycine max: seed).
UNII — L7HT8F1ZOD.

Description. Soya bean is the seed of the soya plant *Glycine max* (*G. hispida*; *G. soja* (L.) Merr.). It is a source of soya oil and soya protein. *G.soja* Siebold & Zucc. is wild soybean.

Soya Oil

Aceite de soja; Soiae Oleum; Soijaöly; Sojų aliejus; Soja Bean Oil; Soja, huile de; Sojae oleum; Sojaolja; Sójový olej; Soya Yağı; Soya-bean Oil; Soyabean Oil; Soybean Oil; Szójababolaj; Соевое Масло.
CAS — 8001-22-7.
ATC Herb — HD02WB5002 (Glycine max: oil); HB05BA5003 (Glycine max: oil).
UNII — 241ATL177A (soya oil); A2M91M918C (hydrogenated soya oil).

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

Eur. (see p. vii) includes both hydrogenated and refined oils. *Ger.* also includes a partially hydrogenated oil. *USNF* includes the hydrogenated oil.

Ph. Eur. 8: (Soya-bean Oil, Refined; Soiae Oleum Raffinatum). It is the fatty oil obtained from seeds of *G. max* (*G. hispida*) by extraction and subsequent refining. It may contain a suitable antoxidant and is a clear, pale yellow liquid. Practically insoluble in alcohol; miscible with petroleum spirit. Store in well-filled containers at a temperature not exceeding 25 degrees. Protect from light.

The BP 2014 directs that when Soya Oil, Soyabean Oil, or Soya-bean Oil is demanded, Refined Soya Oil shall be supplied.

Ph. Eur. 8: (Soya-bean Oil, Hydrogenated; Soiae Oleum Hydrogenatum). It is obtained by refining, bleaching, hydrogenation, and deodorisation of soya oil. It consists mainly of triglycerides of palmitic and stearic acids and is a white or almost white mass or powder which melts to a clear, pale yellow liquid when heated. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane, in petroleum spirit after heating, and in toluene. Protect from light.

USP 36: (Soybean Oil). The refined fixed oil obtained from the seeds of the soya plant *Glycine max* (Fabaceae). It may contain suitable antoxidants. A clear, pale yellow, oily liquid having a characteristic odour. Insoluble in water; miscible with chloroform and with ether. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

USNF 31: (Hydrogenated Soybean Oil). The product obtained by refining, bleaching, hydrogenation, and deodorisation of oil obtained from seeds of the soya plant, *Glycine max* (Fabaceae). It consists mainly of triglycerides of palmitic and stearic acids. A white mass or powder that melts to a clear, pale yellow liquid when heated. M.p. between 66 degrees and 72 degrees. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane, in petroleum spirit after heating, and in toluene. Store in airtight containers. Protect from light.

Incompatibility. For mention of the stability and compatibility of solutions and emulsions for parenteral nutrition see under Enteral and Parenteral Nutrition, p. 2044.2.

Uses and Administration

Emulsions of fractionated soya oil containing 10, 20, or 30% are given by slow intravenous infusion as part of total parenteral nutrition regimens (p. 2044.1), usually with amino acid and carbohydrate solutions. The solutions and emulsions may be given at separate sites, at the same site through a Y-connector, or combined in one admixture. Fat emulsions provide a high energy intake in a relatively small volume. They may also be used to prevent or correct essential fatty acid deficiency. When used as a calorie source the dose of the emulsion is determined by the energy requirements and clinical status of the patient; the amount of total carbohydrate, generally, should not comprise more than 60% of patients' total calorie intake. For the prevention and correction of fatty acid deficiency about 5 to 10% of total calorific intake should be as an intravenous fat emulsion.

The composition and dosage recommendations of commercial preparations do differ slightly but they should be started slowly. Suggested initial rates for the 10% and 20% products are 1 mL/minute and 0.5 mL/minute respectively for 15 to 30 minutes. The rate may then be increased and up to about 500 mL (or 10 mL/kg) of 10% or