statin; an initial dose of 10 mg daily is recommended in patients taking *ciclosporin* or *danazol*, and the daily dose should not exceed 20 mg in patients taking *ciclosporin*, *danazol*, *fibric acid derivatives*, or *nicotinic acid*, or 40 mg in those taking *amiodarone* or *verapamil*.

For the use of lovastatin in children, see below.

◊ General reviews.

1. Curran MP, Goa KL. Lovastatin extended release: a review of its use in the management of hypercholesterolaemia. *Drugs* 2003; **63:** 685–99.

Administration in children. Lovastatin reduces plasma-cholesterol concentrations in children and adolescents with heterozygous familial hypercholesterolaemia[1-3] and has been given safely for up to 48 weeks in boys,[2] and up to 24 weeks in girls.[3] In the USA it is licensed in children aged 10 to 17 years and is given orally in an initial dose of 10 to 20 mg once daily, increased at intervals of 4 weeks or more, if necessary, to a maximum dose of 40 mg once daily.

1. Lambert M, *et al.* Canadian Lovastatin in Children Study Group. Treatment of familial hypercholesterolemia in children and adolescents: effect of lovastatin. *Pediatrics* 1996; **97:** 619–28.
2. Stein EA, *et al.* Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA* 1999; **281:** 137–44.
3. Clauss SB, *et al.* Efficacy and safety of lovastatin therapy in adolescent girls with heterozygous familial hypercholesterolemia. *Pediatrics* 2005; **116:** 682–8.

Administration in renal impairment. Patients with renal impairment may be at increased risk of myopathy and US licensed product information states that doses of lovastatin above 20 mg daily should be used cautiously in patients with a creatinine clearance below 30 mL/minute.

Adrenoleucodystrophy. A preliminary study[1] has shown that lovastatin may be useful in the treatment of adrenoleucodystrophy (see under Lorenzo's Oil, p.2334). Lovastatin reduced the plasma levels of very-long-chain fatty acids which are known to be elevated in patients with this rare metabolic disorder.

1. Pai GS, *et al.* Lovastatin therapy for X-linked adrenoleukodystrophy: clinical and biochemical observations on 12 patients. *Mol Genet Metab* 2000; **69:** 312–22.

Preparations

USP 31: Lovastatin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Hipovastin; Loriter†; Mevlor; Sivlor†; ***Austria:*** Mevacor; ***Braz.:*** Lipoclin; Lovast†; Lovaton†; Lovax†; Mevacor; Mevalip; Minor†; Neolipid†; Reducol; ***Canad.:*** Mevacor; ***Chile:*** Colevix†; Hiposterol; Lispor; Lovacol; Mevacor†; Nij-Terol†; Sanelor; ***Cz.:*** Holetar; Lovacard†; Medostatin; Mevacor; Rancor; ***Denm.:*** Lovacodan; Mevacor; ***Fin.:*** Lovacol; Mevacor; ***Ger.:*** Lova†; Lovabeta; Lovadura; Lovagamma; Lovahexal; Mevinacor; ***Gr.:*** Aurostatin; B-Lovatin†; Cecural; Ilopar; Liferzit; Lipidless; Lostin; Lovadrug; Lovapen; Lovasten; Lovatex; Lovatop; Lowlipid; Medovascin; Mevacor; Mevastin; Mevinol†; Misodomin; Nabicortin; Terveson; Velkalov; Viking; ***Hong Kong:*** Ellanco; Lofacol†; Lomar; Medostatin; Mevacor; ***Hung.:*** Mevacor; Stoplip; ***India:*** Lovacard; Pro-HDL; Rovacor; ***Indon.:*** Cholvastin; Lipovas; Lofacol; Lotyn; Lovatrol; ***Israel:*** Lovalip†; ***Ital.:*** Lovinacor; Rextat; Tavacor; ***Malaysia:*** Lestric; Lostatin; Lovarem; Lovastin; Medostatin; Mevacor†; ***Mex.:*** Casbame; Dilucid; Liperol; Mevacor; ***Norw.:*** Mevacor; ***Pol.:*** Anlostin; Apo-Lova; Liprox; Lovasterol; Lovastin; ***Port.:*** Flozul; Lipdaune; Lipus; Mevinacor; Mevlor; Tecnolip; ***Rus.:*** Cardiostatin (Кардиостатин); Holetar (Холетар); Lovasterol (Ловастерол); Medostatin (Медостатин); Rovacor (Ровакор); ***S.Afr.:*** Lovachol; ***Singapore:*** Elstatin; Lostatin; Lovastin; Medostatin; Rovacor; ***Spain:*** Aterkey; Colesvir; Lipofren†; Liposcler; Mevacor; Mevasterol; Nergadan; Taucor; ***USA:*** Altoprev; Mevacor; ***Venez.:*** Dislipin†; Levistan; Lostatin†; Lovanil; Lovas†; Mevacor.

Multi-ingredient: ***USA:*** Advicor.

Low-molecular-weight Heparins

Depolymerised Heparins; Heparina massae molecularis minoris; Heparinas de bajo peso molecular; Hepariner, lågmolekylära; Héparines de basse masse moléculaire; Hepariny nízkomolekulární; LMW Heparins; Low-molecular-mass Heparins; Mažos molekulinės masės heparinai; Pienimolekyyliset hepariinit.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Heparins, Low-molecular Mass; Low-molecular-weight Heparins BP 2008). Salts of sulfated glucosaminoglycans having a mass-average molecular mass less than 8000. They are obtained by fractionation or depolymerisation of heparin of natural origin and display different chemical structures at the reducing or the non-reducing end of the polysaccharide chains.
The potency is not less than 70 units of anti-factor Xa activity per mg with reference to the dried substance and the ratio of anti-factor Xa activity to anti-factor IIa (antithrombin) activity is not less than 1.5.
A white or almost white hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers.

Units

The second International Standard for low-molecular-weight heparin was agreed in 2003 and is used to calibrate products for both anti-factor Xa and anti-factor IIa activities. Potency is expressed in terms of units of anti-factor Xa activity per mg and the ratio of anti-factor Xa to anti-factor IIa activity. This ratio differs for individual low-molecular-weight heparins and neither they nor unfractionated heparin can be used interchangeably unit for unit.

Adverse Effects

As for Heparin, p.1301.

◊ Reviews.

1. Gouin-Thibault I, *et al.* Safety profile of different low-molecular weight heparins used at therapeutic dose. *Drug Safety* 2005; **28:** 333–49.

Effects on the adrenal glands. Hyperkalaemia related to hypoaldosteronism has been reported in patients treated with low-molecular-weight heparins.[1-3] The UK CSM suggests[4] that plasma-potassium concentrations should be monitored in all patients with risk factors for hyperkalaemia, particularly those receiving low-molecular-weight heparins for more than 7 days (see Heparin, p.1301).

1. Levesque H, *et al.* Low molecular weight heparins and hypoaldosteronism. *BMJ* 1990; **300:** 1437–8.
2. Canova CR, *et al.* Effect of low-molecular-weight heparin on serum potassium. *Lancet* 1997; **349:** 1447–8.
3. Wiggam MI, Beringer TRO. Effect of low-molecular-weight heparin on serum concentrations of potassium. *Lancet* 1997; **350:** 292–3.
4. Committee on Safety of Medicines/Medicines Control Agency. Suppression of aldosterone secretion by heparin. *Current Problems* 1999; **25:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)

Effects on the blood. It was hoped that, because of their higher ratio of anti-factor Xa to anti-thrombin activity compared with heparin, low-molecular-weight heparins might cause less bleeding while maintaining their antithrombotic activity. Some large studies[1,2] have suggested less bleeding with low-molecular-weight heparins than with unfractionated heparin. However, meta-analyses and reviews[3,4] have been unable to confirm a significant reduction in major haemorrhage in patients treated with low-molecular-weight heparins, compared with heparin, for venous thromboembolism, although they confirmed that low-molecular-weight heparins are not associated with an increase in risk. There may be an increased risk of bleeding in patients with renal impairment,[5,6] (see Precautions, below) although the criterion of creatinine clearance 30 mL/minute or less as a guide to selecting patients at increased risk has been questioned;[7] pharmacokinetic response may vary according to the low-molecular-weight heparin used.

Thrombocytopenia has also been reported with low-molecular-weight heparins[8-10] although in one study the incidence was less than with unfractionated heparin.[11]

Thrombocytosis has also been reported.[12,13]

1. Levine MN, *et al.* Prevention of deep vein thrombosis after elective hip surgery: a randomized trial comparing low molecular weight heparin with standard unfractionated heparin. *Ann Intern Med* 1991; **114:** 545–51.
2. Hull RD, *et al.* Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med* 1992; **326:** 975–82. Correction. *ibid.* **327:** 140.
3. Gould MK, *et al.* Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 1999; **130:** 800–809.
4. Schulman S, *et al.* Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 257S–298S.
5. Cestac P, *et al.* Utilisation and safety of low molecular weight heparins: prospective observational study in medical inpatients. *Drug Safety* 2003; **26:** 197–207.
6. Lim W, *et al.* Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med* 2006; **144:** 673–84.
7. Nagge J, *et al.* Is impaired renal function a contraindication to the use of low-molecular-weight heparin? *Arch Intern Med* 2002; **162:** 2605–9.
8. Eichinger S, *et al.* Thrombocytopenia associated with low-molecular-weight heparin. *Lancet* 1991; **337:** 1425–6.
9. Lecompte T, *et al.* Thrombocytopenia associated with low-molecular-weight heparin. *Lancet* 1991; **338:** 1217.
10. Tardy B, *et al.* Thrombocytopenia associated with low-molecular-weight heparin. *Lancet* 1991; **338:** 1217.
11. Warkentin TE, *et al.* Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995; **332:** 1330–5.
12. Rizzieri DA, *et al.* Thrombocytosis associated with low-molecular-weight heparin. *Ann Intern Med* 1996; **125:** 157.
13. Liautard C, *et al.* Low-molecular-weight heparins and thrombocytosis. *Ann Pharmacother* 2002; **36**: 1351–4.

Effects on the skin. Adverse effects of low-molecular-weight heparins on the skin have been reviewed[1] and are estimated to be rare. Most low-molecular-weight heparins have been implicated. Urticarial rash or immediate hypersensitivity has been reported (see below). Delayed hypersensitivity skin reactions have occurred mainly in women. These women were generally postmenopausal, pregnant, or in the postpartum period, suggesting a hormonal influence on pathogenesis. About half of these patients also had a history of allergy to unfractionated heparin.

Skin necrosis reactions are usually localised to the subcutaneous injection site, although distant lesions have also been reported. There has been a report[2] of diffuse skin necrosis leading to fatality in a patient given enoxaparin.

1. Wütschert R, *et al.* Adverse skin reactions to low molecular weight heparins: frequency, management and prevention. *Drug Safety* 1999; **20:** 515–25.
2. Nadir Y, *et al.* A fatal case of enoxaparin induced skin necrosis and thrombophilia. *Eur J Haematol* 2006; **77:** 166–8.

Hypersensitivity. Reports of hypersensitivity reactions associated with low-molecular-weight heparins are rare. However, a patient being treated with enoxaparin 20 mg subcutaneously daily developed a widespread pruritic urticaria and swelling of lips and tongue after 3 days of treatment.[1] Antihistamines and prednisone given with enoxaparin failed to control the reaction and enoxaparin was stopped after a further 3 days. Urticaria and angioedema rapidly resolved on withdrawal.

Delayed hypersensitivity skin reactions have also been reported (see above).

1. Odeh M, Oliven A. Urticaria and angioedema induced by low-molecular-weight heparin. *Lancet* 1992; **340:** 972–3.

Treatment of Adverse Effects

Severe bleeding with low-molecular-weight heparins, usually caused by accidental overdosage, may be reduced by the slow intravenous injection of protamine sulfate (p.1461). The recommended doses of protamine sulfate are given in the individual monographs and should completely neutralise the anti-thrombin effect of the low-molecular-weight heparin but will only partially neutralise the anti-factor-Xa effect. Not more than 50 mg of protamine sulfate should be injected for any one dose.

Precautions

As for Heparin, p.1303.

Low-molecular-weight heparins should not be given to patients who have developed thrombocytopenia with heparin and who have a positive *in-vitro* platelet aggregation test (that is, cross-reactivity) with the particular low-molecular-weight heparin to be used.

Monitoring of plasma-anti-factor-Xa activity may be considered in patients with an increased risk of bleeding, for example the elderly or those with renal impairment or extremes of body-weight, and in patients with active bleeding.

Licensed product information for some low-molecular-weight heparins contra-indicates their use in patients with prosthetic heart valves as they may not provide adequate prophylaxis against thromboembolism even at high doses (but see under Valvular Heart Disease, p.1187, for references to their use).

Spinal anaesthesia. Spinal and epidural haematomas, sometimes leading to paralysis, have occurred in patients receiving low-molecular-weight heparins with spinal or epidural anaesthesia or analgesia (see p.1303).

Interactions

As for Heparin, p.1303.

Pharmacokinetics

Although the precise pharmacokinetic parameters of different low-molecular-weight heparins vary (see individual monographs), they generally have a greater bioavailability after subcutaneous injection and a longer half-life than heparin.

◊ References.

1. Kandrotas RJ. Heparin pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 1992; **22:** 359–74.
2. Samama MM, Gerotziafas GT. Comparative pharmacokinetics of LMWHs. *Semin Thromb Hemost* 2000; **26** (suppl 1): 31–8.

Uses and Administration

Low-molecular-weight heparins are salts of fragments of heparin produced by chemical or enzymatic depolymerisation of the heparin molecule. Commercially available low-molecular-weight heparins differ in their method of production, molecular-weight range, and degree of sulfation. Those included in *Martindale* are:

- Ardeparin, p.1216
- Bemiparin, p.1223
- Certoparin, p.1242

- Dalteparin, p.1255
- Enoxaparin, p.1277
- Nadroparin, p.1346
- Parnaparin, p.1366
- Reviparin, p.1388
- Tinzaparin, p.1413

Like heparin (p.1303), these compounds enhance the action of antithrombin III but they are characterised by a higher ratio of anti-factor Xa to anti-factor IIa (antithrombin) activity than heparin. Low-molecular-weight heparins have less effect on platelet aggregation than heparin. They have no significant effect on blood coagulation tests such as activated partial thromboplastin time (APTT). Therapy may be monitored by measurement of plasma-anti-factor-Xa activity but monitoring is less frequently required than with heparin since low-molecular-weight heparins have a more predictable effect.

Low-molecular-weight heparins are used in the management of venous thromboembolism (deep-vein thrombosis and pulmonary embolism, p.1189). They are used for prophylaxis, particularly during surgery, and for treatment of established thromboembolism. They are given by subcutaneous injection once or twice daily. They are also used intravenously to prevent coagulation during haemodialysis and other extracorporeal circulatory procedures. They may be given subcutaneously in the management of unstable angina (p.1157) and both intravenously and subcutaneously in acute myocardial infarction (p.1175).

Doses are expressed either in terms of the weight of low-molecular-weight heparin or in terms of units of anti-factor Xa activity. Since low-molecular-weight heparins differ in their relative inhibition of factor Xa and thrombin, doses, even when expressed in terms of anti-factor-Xa activity, cannot be equated. Different preparations of the same low-molecular-weight heparin may appear to have different doses depending on the reference preparation used.

◊ References.

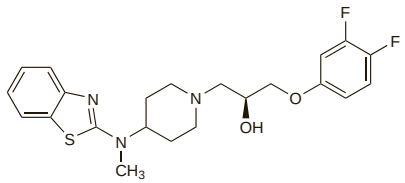
1. Green D, *et al.* Low molecular weight heparin: a critical analysis of clinical trials. *Pharmacol Rev* 1994; **46:** 89–109.
2. Nurmohamed MT, *et al.* Low molecular weight heparin(oid)s: clinical investigations and practical recommendations. *Drugs* 1997; **53:** 736–51.
3. Weitz JI. Low-molecular-weight heparins. *N Engl J Med* 1997; **337:** 688–98. Correction. *ibid.*: 1567.
4. Deitelzweig SB, *et al.* Venous thromboembolism prevention with LMWHs in medical and orthopedic surgery patients. *Ann Pharmacother* 2003; **37:** 402–11.
5. Hirsh J, *et al.* Parenteral anticoagulants: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 141S–159S.

Lubeluzole *(BAN, USAN, rINN)*

Lubeluzol; Lubéluzole; Lubeluzolum; R-87926. (*S*)-1-{4-[1,3-Benzothiazol-2-yl(methyl)amino]piperidino}-3-(3,4-difluorophenoxy)propan-2-ol.

Лубелузол

$C_{22}H_{25}F_2N_3O_2S$ = 433.5.
CAS — 144665-07-6.



Profile

Lubeluzole is a neuroprotectant that has been investigated for ischaemic stroke, but results have been disappointing.

◊ References.

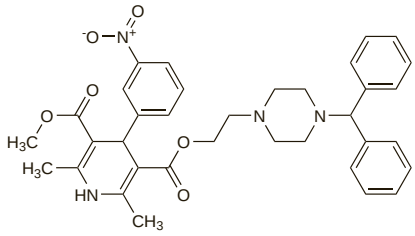
1. Gandolfo C, *et al.* Lubeluzole for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 24/06/05).

Manidipine Hydrochloride *(rINNM)*

CV-4093; Franidipine Hydrochloride; Hidrocloruro de manidipino; Manidipine, Chlorhydrate de; Manidipini Hydrochloridum. 2-[4-(Diphenylmethyl)-1-piperazinyl]ethyl methyl (±)-1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate dihydrochloride.

Манидипина Гидрохлорид

$C_{35}H_{38}N_4O_6,2HCl$ = 683.6.
CAS — 120092-68-4 (manidipine); 89226-75-5 (manidipine hydrochloride); 126229-12-7 (manidipine hydrochloride).
ATC — C08CA11.
ATC Vet — QC08CA11.



(manidipine)

Profile

Manidipine is a dihydropyridine calcium-channel blocker (see Nifedipine, p.1350). It is given by mouth as the hydrochloride in the management of hypertension (p.1171) in a usual dose of 10 to 20 mg once daily.

◊ Reviews.

1. McKeage K, Scott LJ. Manidipine: a review of its use in the management of hypertension. *Drugs* 2004; **64:** 1923–40.
2. Roca-Cusachs A, Triposkiadis F. Antihypertensive effect of manidipine. *Drugs* 2005; **65** (suppl 2): 11–19.
3. Otero ML. Manidipine-delapril combination in the management of hypertension. *Vasc Health Risk Manag* 2007; **3:** 255–63.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Iperten; ***Braz.:*** Manivasc; ***Fr.:*** Iperten; ***Ger.:*** Manyper; ***Gr.:*** Manyper; ***Ital.:*** Iperten; Vascoman; ***Jpn:*** Calslot; ***Philipp.:*** Caldine; ***Spain:*** Artedil; ***Thai.:*** Madiplot.

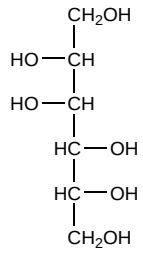
Multi-ingredient: ***Braz.:*** Hipertil; ***Gr.:*** Vivace.

Mannitol ⊗

Cordycepic Acid; E421; Manita; Manitol; Manitolis; Manna Sugar; Mannit; Mannite; Mannitoli; Mannitolum. D-Mannitol.

Маннит; Маннитол

$C_6H_{14}O_6$ = 182.2.
CAS — 69-65-8.
ATC — A06AD16; B05BC01; B05CX04.
ATC Vet — QA06AD16; QB05BC01; QB05CX04.



Description. Mannitol is a hexahydric alcohol related to mannose ($C_6H_{12}O_6$ = 180.2). It is isomeric with sorbitol (p.1965).

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

Ph. Eur. 6.2 (Mannitol). A white or almost white crystalline powder or free-flowing granules. It exhibits polymorphism. Freely soluble in water; very slightly soluble in alcohol.

USP 31 (Mannitol). A white odourless crystalline powder or free-flowing granules with a sweet taste. Soluble 1 in 5.5 of water; very slightly soluble in alcohol; practically insoluble in ether; slightly soluble in pyridine; soluble in alkaline solutions.

Incompatibility. Mannitol should never be added to whole blood for transfusion or given through the same set by which blood is being infused. For details of the adverse effects of mannitol on red blood cells, see Effects on the Blood under Adverse Effects, below.

Supersaturated solutions. Supersaturated aqueous solutions are prepared with the aid of heat. Any crystals that form during storage of the injection should be dissolved by warming before use; this may be a particular problem with the 20 and 25% injections which are supersaturated. A 5.07% solution in water is isosmotic with serum.

Adverse Effects

The most common adverse effect associated with mannitol therapy is fluid and electrolyte imbalance including circulatory overload and acidosis at high doses. The expansion of extracellular volume can precipitate pulmonary oedema and patients with diminished cardiac reserve are at special risk. The shift of fluid from the intracellular to extracellular compartment can cause tissue dehydration; dehydration of the brain, particularly in patients with renal failure, may give rise to CNS symptoms.

When given orally, mannitol causes diarrhoea. Intravenous infusion of mannitol has been associated with nausea, vomiting, thirst, headache, dizziness, chills, fever, tachycardia, chest pain, hyponatraemia, dehydration, blurred vision, urticaria, and hypotension or hypertension. Large doses have been associated rarely with acute renal failure. Hypersensitivity reactions have occurred.

Extravasation of the solution may cause oedema and skin necrosis; thrombophlebitis may occur.

Effects on the blood. Agglutination and irreversible crenation of erythrocytes occurred when blood was mixed with varying proportions of a 10% mannitol solution.[1] It was suggested that intravenous infusions should be carefully controlled and given at a slow rate. This observation could have particular relevance to patients with sickle-cell disease.[2,3] Although agglutination and crenation had been observed *in vitro*, dilutional effects would make *in-vivo* interaction with blood cells less likely.[4]

1. Roberts BE, Smith PH. Hazards of mannitol infusions. *Lancet* 1966; **ii:** 421–2.
2. Konotey-Ahulu FID. Hazards of mannitol infusions. *Lancet* 1966; **ii:** 591.
3. Roberts BE, Smith PH. Hazards of mannitol infusions. *Lancet* 1966; **ii:** 591.
4. Samson JH. Hazards of mannitol infusions. *Lancet* 1966; **ii:** 1191.

Effects on the gastrointestinal tract. Potentially explosive intracolonic concentrations of hydrogen gas have been measured in patients given mannitol before colonoscopy,[1,2] and cases of colonic explosion, including fatalities, have been reported in patients undergoing colonoscopic electrocautery, who had received mannitol bowel preparation. However, the risk of explosion was considered to be small when air or carbon dioxide insufflation and suction were used during the colonoscopy procedure.[2,3]

Colonic perforation and subsequent death has been attributed to the use of mannitol for the treatment of constipation.[4]

1. La Brooy SJ, *et al.* Potentially explosive colonic concentrations of hydrogen after bowel preparation with mannitol. *Lancet* 1981; **i:** 634–6.
2. Avgerinos A, *et al.* Bowel preparation and the risk of explosion during colonoscopic polypectomy. *Gut* 1984; **25:** 361–4.
3. Trotman I, Walt R. Mannitol and explosions. *Lancet* 1981; **i:** 848.
4. Moses FM. Colonic perforation due to oral mannitol. *JAMA* 1988; **260:** 640.

Effects on the kidneys. Focal osmotic nephrosis occurred in a patient given mannitol 20% intravenously.[1]

Acute oliguric renal failure has been associated with the use of large doses of mannitol in patients with previously normal renal function,[2-4] and acute renal failure developed[5] in a patient with diabetes mellitus complicated by nephropathy after he was given 420 g of mannitol intravenously over 4 days.

1. Goodwin WE, Latta H. Focal osmotic nephrosis due to the therapeutic use of mannitol: a case of perirenal hematoma after renal biopsy. *J Urol (Baltimore)* 1970; **103:** 11–14.
2. Whelan TV, *et al.* Acute renal failure associated with mannitol intoxication. *Arch Intern Med* 1984; **144:** 2053–5.
3. Goldwasser P, Fotino S. Acute renal failure following massive mannitol infusion: appropriate response of tubuloglomerular feedback? *Arch Intern Med* 1984; **144:** 2214–16.
4. Rabetoy GM, *et al.* Where the kidney is concerned, how much mannitol is too much? *Ann Pharmacother* 1993; **27:** 25–8.
5. Matsumura M. Mannitol-induced toxicity in a diabetic patient receiving losartan. *Am J Med* 2001; **110:** 331.

Overdosage. Severe mannitol intoxication was reported in 8 patients with renal failure given large, and sometimes enormous, amounts of mannitol intravenously over 1 to 3 days.[1] These patients had CNS involvement out of proportion to uraemia, severe hyponatraemia, a large osmolality gap, and fluid overload. Six patients were treated with haemodialysis and this was considered to be more effective than peritoneal dialysis, which was used in 1 patient.

1. Borges HF, *et al.* Mannitol intoxication in patients with renal failure. *Arch Intern Med* 1982; **142:** 63–6.