However, reviews and studies[1,2] in patients with reflex sympathetic dystrophy failed to find any benefit from guanethidine.

1. Jadad AR, *et al.* Intravenous regional sympathetic blockade for pain relief in reflex sympathetic dystrophy: a systematic review and a randomized, double-blind crossover study. *J Pain Symptom Manage* 1995; **10:** 13–20.
2. Livingstone JA, Atkins RM. Intravenous regional guanethidine blockade in the treatment of post-traumatic complex regional pain syndrome type 1 (algodystrophy) of the hand. *J Bone Joint Surg Br* 2002; **84:** 380–6.

Preparations

BP 2008: Guanethidine Tablets;
USP 31: Guanethidine Monosulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Ismelin; ***Gr.:*** Ismelin; ***UK:*** Ismelin; ***USA:*** Ismelin†.

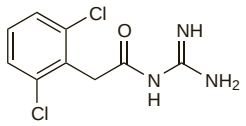
Multi-ingredient: ***Arg.:*** Normatensil†; ***Austria:*** Thilodigon†; ***Ger.:*** Esimil†; Thilodigon; ***Irl.:*** Ganda; ***USA:*** Esimil.

Guanfacine Hydrochloride *(BANM, USAN, rINNM)*

BS-100-141; Guanfacine, Chlorhydrate de; Guanfacini Hydrochloridum; Hidrocloruro de guanfacina; LON-798. *N*-Amidino-2-(2,6-dichlorophenyl)acetamide hydrochloride.

Гуанфацина Гидрохлорид

$C_9H_9Cl_2N_3O,HCl$ = 282.6.
CAS — 29110-47-2 (guanfacine); 29110-48-3 (guanfacine hydrochloride).
ATC — C02AC02.
ATC Vet — QC02AC02.



(guanfacine)

Pharmacopoeias. In *US.*
USP 31 (Guanfacine Hydrochloride). Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Clonidine Hydrochloride, p.1247. Rebound hypertension may occur but is delayed due to the longer half-life.

◊ Reviews.

1. Jerie P. Clinical experience with guanfacine in long-term treatment of hypertension, part II: adverse reactions to guanfacine. *Br J Clin Pharmacol* 1980; **10** (suppl 1): 157S–164S.
2. Board AW, *et al.* A postmarketing evaluation of guanfacine hydrochloride in mild to moderate hypertension. *Clin Ther* 1988; **10:** 761–75.

Withdrawal. Rapid reduction of the guanfacine dosage resulted in rebound hypertension leading to generalised seizures and coma in a 47-year-old patient with renal failure who was receiving haemodialysis.[1] Use with phenobarbital may have enhanced the metabolism of guanfacine and contributed to the development of the withdrawal effect.

1. Kiechel JR, *et al.* Pharmacokinetic aspects of guanfacine withdrawal syndrome in a hypertensive patient with chronic renal failure. *Eur J Clin Pharmacol* 1983; **25:** 463–6.

Interactions

As for Clonidine Hydrochloride, p.1248.

Pharmacokinetics

Guanfacine is rapidly absorbed after oral doses and peak plasma concentrations occur 1 to 4 hours after ingestion. The oral bioavailability is reported to be about 80%. It is about 70% bound to plasma proteins. It is excreted in urine as unchanged drug and metabolites; about 50% of a dose is reported to be eliminated unchanged. The normal elimination half-life ranges from 10 to 30 hours, tending towards the upper range in older patients.

Renal impairment. A study[1] in patients with normal or impaired renal function found that guanfacine clearance and serum concentrations were not significantly different in the 2 groups, suggesting that non-renal elimination plays an important role in patients with renal impairment.

1. Kirch W, *et al.* Elimination of guanfacine in patients with normal and impaired renal function. *Br J Clin Pharmacol* 1980; **10** (suppl 1): 33S–35S.

Uses and Administration

Guanfacine is a centrally acting alpha$_2$-adrenoceptor agonist with actions and uses similar to those of clonidine (p.1248). It is used in the management of hypertension (p.1171), although other drugs are usually preferred. It may be used alone or with other antihypertensives, particularly thiazide diuretics. It has also been tried in the management of opioid withdrawal and in hyperactivity disorders.

Guanfacine is given orally as the hydrochloride, but doses are usually expressed in terms of the base. Guanfacine hydrochloride 1.15 mg is equivalent to about 1 mg of guanfacine. In hypertension the usual initial dose is 1 mg daily increasing after 3 to 4 weeks to 2 mg daily if necessary.

◊ Reviews.

1. Cornish LA. Guanfacine hydrochloride: a centrally acting antihypertensive agent. *Clin Pharm* 1988; **7:** 187–97.

Tourette's syndrome. Guanfacine may be used as an alternative to clonidine in the management of patients with mild to moderate symptoms of Tourette's syndrome (see Tics, p.954). First-line use of these drugs is increasingly favoured in such patients because of a relative lack of serious adverse effects when compared with the commonly used antipsychotics.

Preparations

USP 31: Guanfacine Tablets.

Proprietary Preparations (details are given in Part 3)
Belg.: Estulic; ***Cz.:*** Estulic†; ***Fr.:*** Estulic; ***Hung.:*** Estulic; ***Jpn:*** Estulic†; ***Neth.:*** Estulic†; ***Rus.:*** Estulic (Эстулик); ***USA:*** Tenex.

Heparin *(BAN)*

Heparíini; Heparina; Heparinum; Heparyna.
CAS — 9005-49-6.
ATC — B01AB01; C05BA03; S01XA14.
ATC Vet — QB01AB01; QC05BA03; QS01XA14.

Description. Heparin is an anionic polysaccharide of mammalian origin with irregular sequence. It consists principally of alternating iduronate and glucosamine residues, most of which are sulfated. It may be described as a sulfated glucosaminoglycan. Heparin has the characteristic property of delaying the clotting of freshly shed blood. It may be prepared from the lungs of oxen or the intestinal mucosa of oxen, pigs, or sheep.
Heparin is often described in the literature as standard heparin or unfractionated heparin to distinguish it from low-molecular-weight heparins.

Heparin Calcium *(BANM)*

Calcium Heparin; Heparíinikalsium; Heparin Kalsiyum; Heparin Sodyum; Heparin vápenatá sůl; Heparina cálcica; Héparine calcique; Heparinkalcium; Heparino kalcio druska; Heparinum calcicum; Heparyna wapniowa.
CAS — 37270-89-6.
ATC — B01AB01; C05BA03; S01XA14.
ATC Vet — QB01AB01; QC05BA03; QS01XA14.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Heparin Calcium). The potency of heparin calcium intended for parenteral use is not less than 150 international units per mg and the potency of heparin calcium not intended for parenteral use is not less than 120 international units per mg, both calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers.
USP 31 (Heparin Calcium). The calcium salt of heparin with a potency, calculated on the dried basis, of not less than 140 USP units in each mg. USP heparin units are not equivalent to international units. The source of the material is usually the intestinal mucosa or other suitable tissues of domestic mammals used for food by man and should be stated on the label. A 1% solution in water has a pH of 5.0 to 7.5. Store in airtight containers at temperatures below 40°, preferably between 15 and 30°.

Incompatibility. See Heparin Sodium, below.

Heparin Sodium *(BANM, rINN)*

Hepariininatrium; Heparin sodná sůl; Heparina sódica; Héparine sodique; Heparinnatrium; Heparino natrio druska; Heparinum natricum; Heparyna sodowa; Sodium Heparin; Soluble Heparin.

Гепарин Натрий
CAS — 9041-08-1.
ATC — B01AB01; C05BA03; S01XA14.
ATC Vet — QB01AB01; QC05BA03; QS01XA14.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Heparin Sodium). The potency of heparin sodium intended for parenteral use is not less than 150 international units per mg and the potency of heparin sodium not intended for parenteral use is not less than 120 international units per mg, both calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers.
USP 31 (Heparin Sodium). The sodium salt of heparin with a potency, calculated on the dried basis, of not less than 140 USP units in each mg. USP heparin units are not equivalent to international units. The source of the material is usually the intestinal mucosa or other suitable tissues of domestic mammals used for food by man and should be stated on the label. A white or pale-coloured amorphous, odourless or almost odourless, hygroscopic powder. Soluble 1 in 20 of water. A 1% solution in water has a pH of 5.0 to 7.5. Store in airtight containers at temperatures below 40°, preferably between 15 and 30°.

Incompatibility. Incompatibility has been reported between heparin calcium or sodium and alteplase, amikacin sulfate, amiodarone hydrochloride, ampicillin sodium, aprotinin, benzylpenicillin potassium or sodium, cefalotin sodium, ciprofloxacin lactate, cytarabine, dacarbazine, daunorubicin hydrochloride, diazepam, dobutamine hydrochloride, doxorubicin hydrochloride, droperidol, erythromycin lactobionate, gentamicin sulfate, haloperidol lactate, hyaluronidase, hydrocortisone sodium succinate, kanamycin sulfate, meticillin sodium, netilmicin sulfate, some opioid analgesics, oxytetracycline hydrochloride, some phenothiazines, polymyxin B sulfate, streptomycin sulfate, tetracycline hydrochloride, tobramycin sulfate, vancomycin hydrochloride, and vinblastine sulfate. Heparin sodium has also been reported to be incompatible with cisatracurium besilate,[1] labetalol hydrochloride,[2] levofloxacin,[3] nicardipine hydrochloride,[4] reteplase,[5] and vinorelbine tartrate.[6] Although visually compatible,[7] cefmetazole sodium is reported to inactivate heparin sodium.

Glucose can have variable effects,[8,9] but glucose-containing solutions are generally considered suitable diluents for heparin. Incompatibility has also been reported between heparin and fat emulsion.

1. Trissel LA, *et al.* Compatibility of cisatracurium besylate with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1735–41.
2. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1048–51.
3. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; **56:** 1458–9.
4. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
5. Committee on Safety of Medicines/Medicines Control Agency. Reteplase (Rapilysin): incompatibility with heparin. *Current Problems* 2000; **26:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)
6. Balthasar JP. Concentration-dependent incompatibility of vinorelbine tartrate and heparin sodium. *Am J Health-Syst Pharm* 1999; **56:** 1891.
7. Hutching SR, *et al.* Compatibility of cefmetazole sodium with commonly used drugs during Y-site delivery. *Am J Health-Syst Pharm* 1996; **53:** 2185–8.
8. Anderson W, Harthill JE. The anticoagulant activity of heparins in dextrose solutions. *J Pharm Pharmacol* 1982; **34:** 90–6.
9. Wright A, Hecker J. Long term stability of heparin in dextrose-saline intravenous fluids. *Int J Pharm Pract* 1995; **3:** 253–5.

Units

The fifth International Standard for unfractionated heparin was established in 1998. The USP 31 states that USP and international units are not equivalent, although doses expressed in either appear to be essentially the same.

Adverse Effects

Heparin can give rise to haemorrhage as a consequence of its action. It can also cause thrombocytopenia, either through a direct effect or through an immune effect producing a platelet-aggregating antibody. Consequent platelet aggregation and thrombosis may therefore exacerbate the condition being treated. The incidence of thrombocytopenia is reported to be greater with bovine than porcine heparin.

Hypersensitivity reactions may occur, as may local irritant effects, and skin necrosis. Alopecia and osteoporosis resulting in spontaneous fractures have occurred after prolonged use of heparin.

Effects on the adrenal glands. Heparin inhibits the secretion of aldosterone and so may cause hyperkalaemia.[1] Although all patients treated with heparin may develop reduced aldosterone concentrations, most are able to compensate through the renin-angiotensin system. Patients on prolonged heparin therapy or those unable to compensate, such as patients with diabetes mellitus or renal impairment or those also receiving potassium-sparing drugs such as ACE inhibitors, may present with symptoms of hyperkalaemia. The UK CSM suggests[2] that plasma-potassium concentration should be monitored in all patients with risk factors, particularly those receiving heparin for more than 7 days. The hyperkalaemia is usually transient or resolves when heparin is stopped and treatment is not generally required; fludrocortisone was successfully used to treat resistant hyperkalaemia in a patient in whom continued heparin therapy was necessary.[3]

Adrenal insufficiency secondary to adrenal haemorrhage has also been associated with heparin; heparin-induced thrombocytopenia may be implicated.[4]

1. Oster JR, *et al.* Heparin-induced aldosterone suppression and hyperkalemia. *Am J Med* 1995; **98:** 575–86.
2. 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)

3. Sherman DS, *et al.* Fludrocortisone for the treatment of heparin-induced hyperkalemia. *Ann Pharmacother* 2000; **34:** 606–10.
4. Dahlberg PJ, *et al.* Adrenal insufficiency secondary to adrenal hemorrhage: two case reports and a review of cases confirmed by computed tomography. *Arch Intern Med* 1990; **150:** 905–9.

Effects on the blood. *Haemorrhage* is a recognised risk with heparin.[1] The risk of major bleeding may be lower with continuous intravenous infusion than with intermittent intravenous injection; risk may increase with heparin dose and patient age.[2]

Heparin has been associated with the development of *thrombocytopenia*. The reported incidence has varied greatly; up to 6% appears to be a reasonable estimate[3,4] although up to 10% has also been quoted.[5] Thrombocytopenia induced by heparin may be of two types. The first is an acute, but usually mild, fall in platelet count occurring within 1 to 4 days of starting therapy and which often resolves without stopping treatment. A direct effect of heparin on platelet aggregation appears to be responsible. The second type of thrombocytopenia, which has an immunological basis, is more serious. It usually occurs after 5 to 11 days although its onset may be more rapid in patients previously exposed to heparin;[6] delayed presentation up to 40 days after stopping heparin has also been reported.[7-9] It is often associated with thromboembolic complications due to platelet-rich thrombi (the 'white clot syndrome') or, more rarely, bleeding. Of 34 cases of heparin-associated thrombocytopenia reported to the UK CSM from 1964 to 1989, bleeding or thromboembolic complications occurred in 11 patients, 7 of whom died.[3] This type of thrombocytopenia appears to occur more often with bovine heparin than with heparin from other species,[10] and least frequently with low-molecular-weight-heparins;[11] the mechanism appears to be development of antibodies to a complex formed between heparin and platelet factor-4 (found on platelets and endothelial cells), which then cause platelet activation and thrombin generation.[12] Patients with lupus anticoagulant may also be more susceptible.[13] The reaction is independent of dose or route of administration; there have been reports of thrombocytopenia after use of heparin flushes[14] or heparin-coated catheters.[15]

Monitoring of platelet counts is therefore advised in patients given heparin. A baseline platelet count should be obtained in all patients. This should be repeated at least every 2 to 3 days in those given therapeutic doses of unfractionated heparin;[11] monitoring on alternate days from days 4 to 14 is recommended when unfractionated heparin is used for prophylaxis.[11,16] For low-molecular-weight heparins the risk may be lower but monitoring is recommended in most patients; platelet counts should be checked every 2 to 4 days from days 4 to 14.[16] Patients exposed to heparin within the previous 100 days may be sensitised to it and after re-exposure should have a platelet count within 24 hours.[11,16]

The **management** of heparin-induced thrombocytopenia has been reviewed.[11,12,16-19] Heparin should be stopped immediately in those who develop thrombocytopenia. It should be noted, however, that thrombosis has occurred in patients whose reduction in platelet count was relatively mild and who may not be considered to be thrombocytopenic.[20-23] On withdrawal of heparin, a heparinoid such as danaparoid[16,24,25] may be tried, provided that an *in-vitro* platelet aggregation test shows that there is no cross-reactivity with heparin. Alternatively, the direct thrombin inhibitors lepirudin[16,25,26] or argatroban[25,27] may be used; bivalirudin[11,12,19] or fondaparinux[11,28] are further options. Similar recommendations have been made for children.[29] Low-molecular-weight heparins have been used; they are associated with a lower incidence of induced thrombocytopenia than unfractionated heparin[30] but the rate of cross-reactivity is high and they are not generally recommended.[16,25,27] Oral anticoagulants have also been used, but an increased risk of venous limb gangrene has been reported[31] with warfarin and it should not be given until the platelet count has recovered.[11,16] Dermatan sulfate[32] has also been used. Thrombocytopenia has been managed with aspirin and dipyridamole or with normal immunoglobulin.[33] A fibrinolytic such as urokinase has been used in a few cases of occlusive thrombosis.[34,35]

There may be a relationship between heparin-induced thrombocytopenia and skin necrosis (see below).

There have been reports[36] of spinal haematomas developing spontaneously after the use of low-molecular-weight heparins.

1. Walker AM, Jick H. Predictors of bleeding during heparin therapy. *JAMA* 1980; **244:** 1209–12.
2. 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.
3. CSM. Heparin-induced thrombocytopenia. *Current Problems 28* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024446&RevisionSelectionMethod=LatestReleased (accessed 22/05/08)
4. Derlon A, *et al.* Thrombopénies induites par l'héparine: symptomatologie, détection, fréquence. *Therapie* 1988; **43:** 199–203.
5. Aster RH. Heparin-induced thrombocytopenia and thrombosis. *N Engl J Med* 1995; **332:** 1374–6.
6. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med* 2001; **344:** 1286–92.
7. Warkentin TE, Kelton JG. Delayed-onset heparin-induced thrombocytopenia and thrombosis. *Ann Intern Med* 2001; **135:** 502–6.
8. Rice L, *et al.* Delayed-onset heparin-induced thrombocytopenia. *Ann Intern Med* 2002; **136:** 210–15.
9. Warkentin TE, Bernstein RA. Delayed-onset heparin-induced thrombocytopenia and cerebral thrombosis after a single administration of unfractionated heparin. *N Engl J Med* 2003; **348:** 1067–9.
10. Bell WR, Royall RM. Heparin-associated thrombocytopenia: a comparison of three heparin preparations. *N Engl J Med* 1980; **303:** 902–7.
11. Warkentin T, *et al.* Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 340S–380S.
12. Menajovsky LB. Heparin-induced thrombocytopenia: clinical manifestations and management strategies. *Am J Med* 2005; **118** (suppl 8A): 21S–30S.
13. Auger WR, *et al.* Lupus anticoagulant, heparin use, and thrombocytopenia in patients with chronic thromboembolic pulmonary hypertension: a preliminary report. *Am J Med* 1995; **99:** 392–6.
14. Heeger PS, Backstrom JT. Heparin flushes and thrombocytopenia. *Ann Intern Med* 1986; **105:** 143.
15. Laster JL, *et al.* Thrombocytopenia associated with heparin-coated catheters in patients with heparin-associated antiplatelet antibodies. *Arch Intern Med* 1989; **149:** 2285–7.
16. Keeling D, *et al.* on behalf of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. The management of heparin induced thrombocytopenia. *Br J Haematol* 2006; **133:** 259–69. Also available at: http://www.bcshguidelines.com/pdf/bjh_020606.pdf (accessed 07/06/06)
17. Dager WE, White RH. Treatment of heparin-induced thrombocytopenia. *Ann Pharmacother* 2002; **36:** 489–503.
18. Messmore HL, *et al.* Benefit-risk assessment of treatments for heparin-induced thrombocytopenia. *Drug Safety* 2003; **26:** 625–41.
19. Arepally GM, Ortel TL. Heparin-induced thrombocytopenia. *N Engl J Med* 2006; **355:** 809–17.
20. Phelan BK. Heparin-associated thrombosis without thrombocytopenia. *Ann Intern Med* 1983; **99:** 637–8.
21. Trono DP, *et al.* Thrombocytopenia and heparin-associated thrombosis. *Ann Intern Med* 1984; **100:** 464–5.
22. Ramirez-Lassepas M, Cipolle RJ. Heparin and thrombocytopenia. *Ann Intern Med* 1984; **100:** 613.
23. Hach-Wunderle V, *et al.* Heparin-associated thrombosis despite normal platelet counts. *Lancet* 1994; **344:** 469–70.
24. Wilde MI, Markham A. Danaparoid: a review of its pharmacology and clinical use in the management of heparin-induced thrombocytopenia. *Drugs* 1997; **54:** 903–24.
25. Januzzi JL, Jang I-K. Heparin induced thrombocytopenia: diagnosis and contemporary antithrombin management. *J Thromb Thrombolysis* 1999; **7:** 259–64.
26. Greinacher A, *et al.* Recombinant hirudin (lepirudin) provides safe and effective anticoagulation in patients with heparin-induced thrombocytopenia: a prospective study. *Circulation* 1999; **99:** 73–80.
27. Warkentin TE. Heparin-induced thrombocytopenia: pathogenesis, frequency, avoidance and management. *Drug Safety* 1997; **17:** 325–41.
28. Parody R, *et al.* Fondaparinux (ARIXTRA) as an alternative anti-thrombotic prophylaxis when there is hypersensitivity to low molecular weight and unfractionated heparins. *Haematologica* 2003; **88:** ECR32. Also available at: http://www.haematologica.org/cgi/reprint/88/11/ECR32.pdf (accessed 19/08/08)
29. Risch L, *et al.* Heparin-induced thrombocytopenia in paediatrics: clinical characteristics, therapy and outcomes. *Intensive Care Med* 2004; **30:** 1615–24.
30. 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.
31. Warkentin TE, *et al.* The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. *Ann Intern Med* 1997; **127:** 804–12.
32. Taliani MR, *et al.* Dermatan sulphate in patients with heparin-induced thrombocytopenia. *Br J Haematol* 1999; **104:** 87–9.
33. Frame JN, *et al.* Correction of severe heparin-associated thrombocytopenia with intravenous immunoglobulin. *Ann Intern Med* 1989; **111:** 946–7.
34. Krueger SK, *et al.* Thrombolysis in heparin-induced thrombocytopenia with thrombosis. *Ann Intern Med* 1985; **103:** 159.
35. Clifton GD, Smith MD. Thrombolytic therapy in heparin-associated thrombocytopenia with thrombosis. *Clin Pharm* 1986; **5:** 597–601.
36. Heppner PA, *et al.* Spontaneous spinal hematomas and low-molecular-weight heparin: report of four cases and review of the literature. *J Neurosurg Spine* 2004; **1:** 232–6.

Effects on the bones. Osteoporosis is a rare complication of long-term heparin therapy. Treatment and prophylaxis of thromboembolism in pregnancy is one of the few indications for long term use of heparin, so most reports and studies of heparin-induced osteoporosis have been in pregnant women.[1] The incidence of symptomatic osteoporosis in patients given heparin long term has been estimated to be about 2%.[1,2] Subclinical reduction in bone density occurs in up to one-third of patients,[2] but it is not possible to predict which of these patients will develop osteoporotic fractures. Pregnancy normally causes reversible bone demineralisation, so the combination of pregnancy and heparin therapy may therefore result in symptomatic osteoporosis in susceptible individuals.[1,3] Bone changes may be reversible.[1] Although some evidence suggests that bone demineralisation is dose- and duration-dependent, this has not been conclusively established.[1,3] Use of low-molecular-weight heparins is associated with a lower risk of heparin-induced osteoporosis.[2]

1. Nelson-Piercy C. Heparin-induced osteoporosis. *Scand J Rheumatol* 1998; **27** (suppl 107): 68–71.
2. Bates SM, *et al.* Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 844S–886S.
3. Farquharson RG. Heparin, osteoporosis and pregnancy. *Br J Hosp Med* 1997; **58:** 205–7.

Effects on electrolyte balance. See Effects on the Adrenal Glands, above.

Effects on lipid metabolism. Use of heparin leads to the release of lipoprotein lipase into the plasma. Postprandial lipidaemia is reduced due to increased hydrolysis of triglycerides into free fatty acids and glycerol. Raised concentrations of free fatty acids have been reported after heparin use but the magnitude of this effect may have been overestimated.[1] Rebound hyperlipidaemia may occur when heparin is withdrawn. With long-term use reserves of lipoprotein lipase may be depleted; severe hypertriglyceridaemia reported in a pregnant woman was attributed to long-term heparin prophylaxis that was thought to have resulted in lipoprotein lipase deficiency.[2]

1. Riemersma RA, *et al.* Heparin-induced lipolysis, an exaggerated risk. *Lancet* 1981; **ii:** 471.
2. Watts GF, *et al.* Lipoprotein lipase deficiency due to long-term heparinization presenting as severe hypertriglyceridaemia in pregnancy. *Postgrad Med J* 1991; **67:** 1062–4.

Effects on the liver. Increases in transaminase values, usually reversible on discontinuing therapy, have been reported in patients given therapeutic[1-3] or prophylactic[3] doses of heparin. A prospective study[4] found increased transaminases that were assessed as probably due to heparin in 8 of 54 patients; the reaction seemed to occur more frequently with therapeutic doses. Increased transaminases have also been reported[5] in 2 patients receiving low-molecular-weight-heparins.

1. Sonnenblick M, *et al.* Hyper-transaminasemia with heparin therapy. *BMJ* 1975; **3:** 77.
2. Dukes GE, *et al.* Transaminase elevations in patients receiving bovine or porcine heparin. *Ann Intern Med* 1984; **100:** 646–50.
3. Monreal M, *et al.* Adverse effects of three different forms of heparin therapy: thrombocytopenia, increased transaminases, and hyperkalaemia. *Eur J Clin Pharmacol* 1989; **37:** 415–18.
4. Guevara A, *et al.* Heparin-induced transaminase elevations: a prospective study. *Int J Clin Pharmacol Ther Toxicol* 1993; **31:** 137–41.
5. Hui C-K, *et al.* Low molecular weight heparin-induced liver toxicity. *J Clin Pharmacol* 2001; **41:** 691–4.

Effects on sexual function. There have been several reports of priapism associated with the use of heparin. The prognosis is poor, impotence following more often than in priapism of other aetiologies. The mechanism of heparin-induced priapism is unclear.[1]

1. Baños JE, *et al.* Drug-induced priapism: its aetiology, incidence and treatment. *Med Toxicol* 1989; **4:** 46–58.

Effects on the skin. Skin necrosis is a rare complication of heparin use.[1,2] It may be a localised reaction at the site of subcutaneous injection or possibly be related to heparin-induced thrombocytopenia (see Effects on the Blood, above). An immune mechanism may be responsible.

Eczematous plaque reactions have developed several days after starting subcutaneous heparin. A type IV hypersensitivity reaction has been implicated.[3] Low-molecular-weight heparins may be an alternative but cross-reactivity can occur.[4]

Recurrent fixed eczematous lesions have been attributed to heparin used intravenously during haemodialysis.[5]

1. Ulrick PJ, Manoharan A. Heparin-induced skin reaction. *Med J Aust* 1984; **140:** 287–9.
2. Fowlie J, *et al.* Heparin-associated skin necrosis. *Postgrad Med J* 1990; **66:** 573–5.
3. Bircher AJ, *et al.* Eczematous infiltrated plaques to subcutaneous heparin: a type IV allergic reaction. *Br J Dermatol* 1990; **123:** 507–14.
4. O'Donnell BF, Tan CY. Delayed hypersensitivity reactions to heparin. *Br J Dermatol* 1993; **129:** 634–6.
5. Mohammed KN. Symmetric fixed eruption to heparin. *Dermatology* 1995; **190:** 91.

Hypersensitivity. An increased incidence of severe hypersensitivity reactions, including fatalities, was reported with some heparin preparations in early 2008;[1] it was suggested that the presence of an over-sulfated chondroitin sulfate contaminant may have been responsible.[1,2]

See Effects on the Blood and Effects on the Skin, above, for further hypersensitivity reactions associated with heparin.

1. FDA. Update to healthcare facilities and healthcare professionals about heparin and heparin-containing medical products. Available at: http://www.fda.gov/cdrh/safety/heparin-healthcare-update.pdf (accessed 22/05/08)
2. Kishimoto TK, *et al.* Contaminated heparin associated with adverse clinical events and activation of the contact system. *N Engl J Med* 2008; **358:** 2457–67.

Treatment of Adverse Effects

Slight haemorrhage due to overdosage can usually be treated by stopping heparin. Severe bleeding may be reduced by the slow intravenous injection of protamine sulfate (p.1461). The dose is dependent on the amount of heparin to be neutralised and ideally should be titrated against assessments of the coagulability of the patient's blood. As heparin is being continuously excreted, the dose of protamine should be reduced if it is more than 15 minutes since the last dose of heparin; for example, if protamine sulfate is given 30 minutes after heparin the dose may be reduced to about one-half. Not more than 50 mg of protamine sulfate should be inject-

ed for any one dose; patients should be carefully monitored as further doses may be required. The Ph. Eur. 6.2 specifies that 1 mg of protamine sulfate precipitates not less than 100 international units of heparin, but adds that this potency is based on a specific reference batch of heparin sodium. UK licensed product information has stated that each mg of protamine sulfate will usually neutralise the anticoagulant effect of at least 80 international units of heparin (lung) or at least 100 international units of heparin (mucous), and US information that each mg of protamine sulfate neutralises approximately 90 USP units of heparin (lung) or about 115 USP units of heparin (mucous).

Thrombocytopenia. For reference to the treatment of heparin-induced thrombocytopenia and associated thromboembolic complications, see Effects on the Blood under Adverse Effects, above.

Precautions

Heparin should not be given to patients who are haemorrhaging. In general it should not be given to patients at serious risk of haemorrhage, although it has been used with very careful control; patients at risk include those with haemorrhagic blood disorders, thrombocytopenia, peptic ulcer disease, cerebrovascular disorders, bacterial endocarditis, severe hypertension, oesophageal varices, or patients who have recently undergone surgery at sites where haemorrhage would be an especial risk. Caution is required in hepatic and renal impairment; severe hepatic or renal impairment may be a contra-indication. Heparin should not be given by intramuscular injection. Since heparin has caused thrombocytopenia with severe thromboembolic complications, platelet counts should be monitored in all patients (see Effects on the Blood, under Adverse Effects, above). Heparin should be stopped if thrombocytopenia develops. A test dose has been recommended for patients with a history of allergy.

Dosage of heparin may need to be reduced in the elderly; elderly women appear to be especially susceptible to haemorrhage after use of heparin.

Catheters and cannulas. Serum concentrations of sodium and potassium could be falsely elevated in samples obtained through heparin-bonded umbilical catheters due to release of benzalkonium chloride used in the manufacturing process of some catheters.[1] It was unknown if the amount released would be toxic to small premature neonates.

1. Gaylord MS, *et al.* Release of benzalkonium chloride from a heparin-bonded umbilical catheter with resultant factitious hypernatremia and hyperkalemia. *Pediatrics* 1991; **87:** 631–5.

Hyperkalaemia. For recommendations concerning the monitoring of patients susceptible to developing hyperkalaemia, such as those with diabetes mellitus or renal impairment, see Effects on the Adrenal Glands under Adverse Effects, above.

Pregnancy. Heparin does not cross the placenta, and therefore adverse effects on the fetus would not be expected.[1,2] A review[1] of the literature, however, indicated 2 spontaneous abortions and 17 still-births in 135 pregnancies exposed to heparin; 29 infants were premature, 10 of whom died. Another literature review[2] found adverse outcomes in 21.7% of heparin-treated patients, but this dropped to 10.4% when pregnancies with co-morbid conditions were excluded. A further drop to 3.6% was observed when cases of prematurity with normal outcome were also excluded. The death rate of 2.5% and prematurity rate of 6.8% in heparin-treated patients was similar to that found in the normal population. It was concluded that heparin appears safer for the fetus than warfarin when used during pregnancy. Similar results have also been reported with low-molecular-weight heparins; a systematic review[3] found an adverse outcome in 9.3% of 486 pregnancies in which low-molecular-weight heparin was used, but this dropped to 3.1% in women without comorbid conditions.

For further details on the use of heparin and low-molecular-weight heparins in pregnancy, see under Uses and Administration, below.

1. Hall JG, *et al.* Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 1980; **68:** 122–40.
2. Ginsberg JS, Hirsh J. Optimum use of anticoagulants in pregnancy. *Drugs* 1988; **36:** 505–12.
3. Sanson B-J, *et al.* Safety of low-molecular-weight heparin in pregnancy: a systematic review. *Thromb Haemost* 1999; **81:** 668–72.

Preservative. The preservatives used in heparin preparations have been implicated in unwanted effects. Benzyl alcohol in heparinised flushing solutions has been suspected of causing toxicity in neonates (see p.1631). Chlorobutanol present in another heparin preparation caused a sharp fall in blood pressure (see Effects on the Cardiovascular System under Chlorobutanol, p.1639).

Spinal anaesthesia. Spinal and epidural haematomas, sometimes leading to paralysis, have occurred after spinal or epidural anaesthesia or analgesia in patients given heparin or low-molecular-weight heparins. The risk of haematoma appears to be higher in patients with indwelling epidural catheters or in those also given other drugs that affect haemostasis.[1] It is generally recommended that central nerve block should be avoided in patients on full-dose anticoagulation.[2] However, the use of prophylactic doses of anticoagulants with central nervous blockade is less clear.[2,3] The reported risk of haematoma with low-molecular-weight heparins has been higher in the USA where higher doses have been used for prophylaxis.[3] Recommendations to reduce the risk of spinal haematoma include waiting until after blockade has been completed to give prophylactic heparin or low-molecular-weight heparin. Where anticoagulant prophylaxis has already been given, blockade should be delayed if possible until 4 to 6 hours after heparin, and the catheter should not be removed until 4 hours after heparin.[2] It is recommended that low-molecular-weight heparin should not be given within 8 to 10 hours before or after central nerve block or catheter removal.[2,3]

There have also been cases of spontaneous spinal haematomas (unrelated to trauma, surgery, or lumbar puncture) occurring after use of low-molecular-weight heparins (see Effects on the Blood, above).

1. Wysowski DK, *et al.* Spinal and epidural hematoma and low-molecular-weight heparin. *N Engl J Med* 1998; **338:** 1774.
2. Armstrong RF, *et al.* Epidural and spinal anaesthesia and the use of anticoagulants. *Hosp Med* 1999; **60:** 491–6.
3. Dolenska S. Neuroaxial blocks and LMWH thromboprophylaxis. *Hosp Med* 1998; **59:** 940–3.

Interactions

Heparin should be used with care with oral anticoagulants or drugs, such as aspirin and dipyridamole, that affect platelet function. NSAIDs may also increase the risk of haemorrhage. Other drugs that affect the coagulation process and which may therefore increase the risk of haemorrhage include dextrans, thrombolytic enzymes such as streptokinase, high doses of penicillins and some cephalosporins, some contrast media, asparaginase, and epoprostenol; for use of heparin with drotrecogin alfa (activated) see p.1078. Estimations of oral anticoagulant control may be modified by heparin's action on prothrombin.

ACE inhibitors. For reference to hyperkalaemia in patients on heparin and ACE inhibitors, see Effects on the Adrenal Glands under Adverse Effects, above.

Alcohol. Heavy drinkers were found to be at greater risk of major heparin-associated bleeding than moderate drinkers or non-drinkers.[1]

1. Walker AM, Jick H. Predictors of bleeding during heparin therapy. *JAMA* 1980; **244:** 1209–12.

Aprotinin. For comment on the use of heparin with aprotinin, see Effects on Coagulation Tests under Aprotinin, p.1055.

Glyceryl trinitrate. Glyceryl trinitrate has been reported to reduce the activity of heparin when both drugs are given simultaneously by the intravenous route.[1] This effect has been seen even with low doses of glyceryl trinitrate.[2] Propylene glycol present in the glyceryl trinitrate formulation may[3] or may not[1] contribute to the effect. No interaction was reported when glyceryl trinitrate was given immediately after heparin.[4]

1. Habbab MA, Haft JI. Heparin resistance induced by intravenous nitroglycerin. *Arch Intern Med* 1987; **147:** 857–60.
2. Brack MJ, *et al.* The effect of low dose nitroglycerine on plasma heparin concentrations and activated partial thromboplastin times. *Blood Coag Fibrinol* 1993; **4:** 183–6.
3. Col J, *et al.* Propylene glycol-induced heparin resistance during nitroglycerin infusion. *Am Heart J* 1985; **110:** 171–3.
4. Bode V, *et al.* Absence of drug interaction between heparin and nitroglycerin. *Arch Intern Med* 1990; **150:** 2117–19.

Tobacco. Reduced half-life and increased elimination of heparin have been reported in smokers compared with non-smokers.[1]

1. Cipolle RJ, *et al.* Heparin kinetics: variables related to disposition and dosage. *Clin Pharmacol Ther* 1981; **29:** 387–93.

Pharmacokinetics

Heparin is not absorbed from the gastrointestinal tract. After intravenous or subcutaneous injection heparin is extensively bound to plasma proteins. It does not cross the placenta and it is not distributed into breast milk. The half-life of heparin depends on its dose and route as well as the method of calculation and is subject to wide inter- and intra-individual variation; a range of 1 to 6 hours with an average of 1.5 hours has been cited. It may be slightly prolonged in renal impairment, decreased in patients with pulmonary embolism, and either increased or decreased in patients with liver disorders. Heparin is taken up by the reticuloendothelial system. It is excreted in the urine, mainly as metabolites, although after large doses up to 50% may be excreted unchanged.

◊ References.

1. Estes JW. Clinical pharmacokinetics of heparin. *Clin Pharmacokinet* 1980; **5:** 204–20.
2. Kandrotas RJ. Heparin pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 1992; **22:** 359–74.

Uses and Administration

Heparin is an anticoagulant used principally in the treatment and prophylaxis of thromboembolic disorders (p.1187). It is often described as standard heparin or unfractionated heparin to distinguish it from low-molecular-weight heparins (p.1329).

Heparin inhibits clotting of blood *in vitro* and *in vivo* by enhancing the action of antithrombin III. Antithrombin III, which is present in plasma, inhibits the activity of activated clotting factors including thrombin (factor IIa) and activated factor X (factor Xa). Heparin increases the rate of this inhibition, but in a manner that is dependent on its dose. With normal therapeutic doses heparin has an inhibitory effect on both thrombin and factor Xa. The inhibition of thrombin blocks the conversion of fibrinogen to fibrin, and the inhibition of factor Xa blocks the conversion of prothrombin to thrombin. The low doses that are given subcutaneously for the prophylaxis of thromboembolism have a selective effect on inhibition of factor Xa. Very high doses are reported to reduce the activity of antithrombin III. Heparin also has some effect on platelet function, inhibits the formation of a stable fibrin clot, and has an antilipidaemic effect. For an explanation of the coagulation cascade, see Haemostasis and Fibrinolysis, p.1045.

Heparin is used in the treatment and prophylaxis of venous thromboembolism (deep-vein thrombosis and pulmonary embolism, p.1189), especially prophylaxis in surgical patients and in those pregnant women at particular risk. It is also used in the management of arterial thromboembolism including that associated with unstable angina pectoris (p.1157), myocardial infarction (p.1175), acute peripheral arterial occlusion (p.1178), and stroke (p.1185). It is often used as a precursor to oral anticoagulation and is withdrawn once the oral anticoagulant is exerting its full effect.

Heparin has been tried in the treatment of disseminated intravascular coagulation. It is also used to prevent coagulation during haemodialysis and other extracorporeal circulatory procedures such as cardiopulmonary bypass. Other uses include the anticoagulation of blood for transfusion or blood samples and the flushing of catheters and cannulas to maintain patency.

Heparin and its salts are constituents of many topical preparations for the treatment of various inflammatory disorders.

Administration and dosage. Heparin is given intravenously, preferably by continuous infusion, or by subcutaneous injection. It may be given as the calcium or sodium salt and it is generally accepted that there is little difference in their effects. Oral formulations of heparin are under investigation.

Doses of heparin for treatment (sometimes termed 'full-dose' heparin), and in some cases prophylaxis, of thromboembolism should be monitored and determined as discussed below under Control of Heparin Therapy. The subcutaneous doses of heparin commonly used for prophylaxis (often termed 'low-dose') do not require routine monitoring. A test dose has been recommended for patients with a history of allergy. Although international and USP units are not strictly equivalent, doses expressed in either appear to be essentially the same.

For **treatment of venous thromboembolism**, an intravenous loading dose of 5000 units (10 000 units may be required in severe pulmonary embolism) is followed by continuous intravenous infusion of 1000 to 2000 units/hour or subcutaneous injection of

15 000 units every 12 hours. Alternatively, intermittent intravenous injection of 5000 to 10 000 units every 4 to 6 hours is suggested in some product literature. Children and small adults are given a lower intravenous loading dose followed by maintenance with continuous intravenous infusion of 15 to 25 units/kg per hour or subcutaneous injection of 250 units/kg every 12 hours.

For **prophylaxis** of **postoperative venous thromboembolism**, subcutaneous doses used are 5000 units 2 hours before surgery then every 8 to 12 hours for 7 days or until the patient is ambulant. Similar doses are used to prevent thromboembolism during pregnancy in women with a history of deep-vein thrombosis or pulmonary embolism; the dosage may need to be increased to 10 000 units every 12 hours during the third trimester.

In the management of **unstable angina** or acute **peripheral arterial embolism,** heparin may be given by continuous intravenous infusion in the same doses as those recommended for the treatment of venous thromboembolism. Doses that have been recommended for the prevention of re-occlusion of the coronary arteries following thrombolytic therapy in **myocardial infarction** include 5000 units intravenously followed by 1000 units/hour intravenously with alteplase; a dose of 12 500 units subcutaneously every 12 hours for at least 10 days may be used to prevent mural thrombosis.

Control of heparin therapy. Treatment with full-dose heparin must be monitored to ensure that the dose is providing the required effect on antithrombin III. The most commonly used test to monitor the action of heparin is the activated partial thromboplastin time (APTT). The APTT of patients on full-dose heparin should generally be maintained at 1.5 to 2.5 times the control value although the optimum therapeutic range varies between individual laboratories depending on the APTT reagent in use. Regular monitoring is essential, preferably on a daily basis. Prophylaxis with low-dose subcutaneous heparin is not routinely monitored; the APTT is not significantly prolonged in these patients. A dose-adjusted regimen to maintain minimal prolongation of the APTT may be required in patients with malignancy or undergoing orthopaedic surgery to ensure adequate protection against thromboembolism. Other tests used include the activated clotting time (ACT). The value of measurements of heparin concentration in the blood remains to be established.

◊ General references to anticoagulation with heparin.

1. Hirsh J. Heparin. *N Engl J Med* 1991; **324:** 1565–74.
2. Freedman MD. Pharmacodynamics, clinical indications, and adverse effects of heparin. *J Clin Pharmacol* 1992; **32:** 584–96.
3. Hyers TM. Heparin therapy: regimens and treatment considerations. *Drugs* 1992; **44:** 738–49.
4. Hirsh J, Fuster V. Guide to anticoagulant therapy part 1: heparin. *Circulation* 1994; **89:** 1449–68.
5. Baglin T, *et al.* for the British Committee for Standards in Haematology. Guidelines on the use and monitoring of heparin. *Br J Haematol* 2006; **133:** 19–34.
   Also available at: http://www.bcshguidelines.com/pdf/heparin_220506.pdf (accessed 01/06/06)
6. Hirsh J, *et al.* Parenteral anticoagulants: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 141S–159S.

Action. Heparin is well established as an anticoagulant and antithrombotic and acts primarily by binding to, and enhancing the activity of, antithrombin III. However, the physiological role of endogenous heparin has not been clearly defined, despite its presence in mast cells, its ability to interact with numerous proteins, and its close structural similarity to heparan sulfate (suleparoid), the ubiquitous cell-surface glycosaminoglycan.[1,2] Endogenous heparin activity may have a role in protecting against atherosclerosis.[3] Non-anticoagulant properties of heparin or low-molecular-weight heparins have been reported to include anti-inflammatory activity, with a possible application in, for example, asthma[4-6] or inflammatory bowel disease; however, studies in patients with active ulcerative colitis have not found any benefit.[7] For mention of the use of aerosolised heparin with acetylcysteine to treat inhalation injury, see Burns, under Acetylcysteine, p.1549. The risk of bleeding is a major obstacle to the use of heparin for non-anticoagulant purposes.

1. Lane DA, Adams L. Non-anticoagulant uses of heparin. *N Engl J Med* 1993; **329:** 129–30.
2. Page CP. Proteoglycans: the "Teflon" of the airways? *Thorax* 1997; **52:** 924–5.
3. Engelberg H. Actions of heparin in the atherosclerotic process. *Pharmacol Rev* 1996; **48:** 327–52.
4. Martineau P, Vaughan LM. Heparin inhalation for asthma. *Ann Pharmacother* 1995; **29:** 71–2.
5. Ahmed T, *et al.* Prevention of exercise-induced bronchoconstriction by inhaled low-molecular-weight heparin. *Am J Respir Crit Care Med* 1999; **160:** 576–81.
6. Stelmach I, *et al.* The effect of inhaled heparin on airway responsiveness to histamine and leukotriene D4. *Allergy Asthma Proc* 2003; **24:** 59–65.
7. Chande N, *et al.* Unfractionated or low-molecular weight heparin for induction of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 15/05/08).

Administration. The activated partial thromboplastin time (APTT) is the test most commonly used to monitor intravenous full-dose heparin therapy. Heparin dosing algorithms have been developed[1,2] so that the time taken to achieve a therapeutic APTT and maintain it in the therapeutic range (usually 1.5 to 2.5 times the control value) is shortened and thus the risk of recurrent thrombosis and major bleeding complications is reduced. An automated method of monitoring and regulation has been tried.[3] Although use of ideal body-weight for dosage calculation in obese patients has been suggested, actual body-weight may be more appropriate,[4,5] but maximum bolus doses and infusion rates should be set, to avoid overdosage in morbidly obese patients.

However, the therapeutic ranges used in such algorithms are not applicable to all APTT reagents because the latter vary in their sensitivity to heparin.[6] The optimum therapeutic range therefore varies between individual laboratories depending on the APTT reagent used. Dosing algorithms may be adapted by calibrating the therapeutic APTT with plasma-heparin concentrations.[6,7]

A weight-based algorithm for treatment doses of subcutaneous heparin in deep-vein thrombosis has also been proposed.[8]

1. Cruickshank MK, *et al.* A standard heparin nomogram for the management of heparin therapy. *Arch Intern Med* 1991; **151:** 333–7.
2. Raschke RA, *et al.* The weight-based heparin dosing nomogram compared with a "standard care" nomogram: a randomized controlled trial. *Ann Intern Med* 1993; **119:** 874–81.
3. Newby LK, *et al.* An automated strategy for bedside aPTT determination and unfractionated heparin infusion adjustment in acute coronary syndromes: insights from PARAGON A. *J Thromb Thrombolysis* 2002; **14:** 33–42.
4. Yee WP, Norton LL. Optimal weight base for a weight-based heparin dosing protocol. *Am J Health-Syst Pharm* 1998; **55:** 159–62.
5. Yee WP, Norton LL. Clarification of weight-based heparin protocol. *Am J Health-Syst Pharm* 2002; **59:** 1788.
6. Brill-Edwards P, *et al.* Establishing a therapeutic range for heparin therapy. *Ann Intern Med* 1993; **119:** 104–9.
7. Volles DF, *et al.* Establishing an institution-specific therapeutic range for heparin. *Am J Health-Syst Pharm* 1998; **55:** 2002–6.
8. Prandoni P, *et al.* Use of an algorithm for administering subcutaneous heparin in the treatment of deep venous thrombosis. *Ann Intern Med* 1998; **129:** 299–302.

Catheters and cannulas. Solutions of heparin sodium 10 or 100 units/mL in sodium chloride 0.9% are used for the flushing of intravenous catheters, cannulas, and other indwelling intravenous infusion devices used for intermittent dosing (heparin locks). A meta-analysis[1] of controlled studies was, however, unable to show any major advantage of either strength of heparin sodium solution over sodium chloride 0.9% alone in maintaining peripheral cannula patency or reducing the incidence of thrombophlebitis, and sodium chloride 0.9% is therefore recommended for cannulas intended to be in place for 48 hours or less. Less use of heparin flush solutions could minimise the risk of adverse effects such as thrombocytopenia and reduce the risk of incompatibilities with intravenous drugs.

Use of heparin-bonded catheters or the addition of heparin to intravenous fluids such as total parenteral nutrition solutions has also been tried in an attempt to maintain indwelling intravenous infusion devices (but see Catheters and Cannulas under Precautions, above). Continuous infusion of heparin-containing fluids may prolong the patency of peripheral arterial catheters.[1] To maintain the patency of umbilical artery catheters in neonates, US guidelines[2] suggest continuous infusion of heparin at a concentration of 0.25 to 1 unit/mL.

Central venous catheters are also subject to thrombus formation and their use may be complicated by vascular thrombosis and systemic infection. A meta-analysis[3] of prophylactic heparin used with central venous and pulmonary artery catheters suggested that heparin reduces catheter-related vascular thrombosis and may reduce catheter-related infection. This analysis included a range of heparin doses and methods of administration, as well as heparin-bonded catheters, and the authors suggested that further study was needed. More specific systematic reviews have found that continuous infusion of heparin reduces the incidence of catheter occlusion in neonates with peripherally-placed central venous catheters,[4] and that heparin-bonded catheters may reduce the risk of catheter occlusion in children with central venous catheters.[5] Further evidence that heparin infusion reduces the risk of catheter-related infection has also been reported.[6] Very low doses of warfarin (1 mg daily) may protect against thrombosis in patients with central venous catheters.[7]

1. Randolph AG, *et al.* Benefit of heparin in meta-analysis of randomised controlled trials. *BMJ* 1998; **316:** 969–75.
2. Monagle P, *et al.* Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 887S–968S.
3. Randolph AG, *et al.* Benefit of heparin in central venous and pulmonary artery catheters: a meta-analysis of randomized controlled trials. *Chest* 1998; **113:** 165–71.
4. Shah PS, Shah VS. Continuous heparin infusion to prevent thrombosis and catheter occlusion in neonates with peripherally placed percutaneous central venous catheters. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 15/05/08).
5. Shah PS, Shah N. Heparin-bonded catheters for prolonging the patency of central venous catheters in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 15/05/08).
6. Abdelkefi A, *et al.* Randomized trial of prevention of catheter-related bloodstream infection by continuous infusion of low-dose unfractionated heparin in patients with hematologic and oncologic disease. *J Clin Oncol* 2005; **23:** 7864–70.
7. Bern MM, *et al.* Very low doses of warfarin can prevent thrombosis in central venous catheters: a randomized prospective trial. *Ann Intern Med* 1990; **112:** 423–8.

Disseminated intravascular coagulation. Heparin has been used with some success in disseminated intravascular coagulation (p.1048) associated with a variety of conditions. However, this use is considered by some to be controversial and should be reserved for specific situations where the risk of bleeding is relatively minor in comparison with the possible beneficial effect on formation of microthromboses. A suggested intravenous dose is 500 units/hour, adjusted if necessary according to clinical response.[1] The maximum dose given intravenously is usually 1000 units/hour because of the risk of bleeding.

1. Baglin T, *et al.* for the British Committee for Standards in Haematology. Guidelines on the use and monitoring of heparin. *Br J Haematol* 2006; **133:** 19–34.
   Also available at: http://www.bcshguidelines.com/pdf/heparin_220506.pdf (accessed 01/06/06)

Extracorporeal circulation. Anticoagulation with heparin is necessary during procedures such as cardiopulmonary bypass and haemodialysis and haemofiltration. In the case of bypass, heparin is added to the crystalloid solution and any stored blood used for priming the bypass machine and is given intravenously before cannulation of the heart and major blood vessels. Activated clotting time (ACT) is monitored throughout. After bypass is stopped, anticoagulation can be reversed with protamine but caution is advised because of potential toxicity on the cardiopulmonary circulation.

At the start of haemodialysis sessions patients generally get a loading dose of heparin followed by continuous infusion into the exit line of the extracorporeal circuit until about one hour before the end of dialysis. The dose of heparin varies widely depending on body-weight, volume of the extracorporeal circulation, dialysis membrane biocompatibility, and pump speed.

Idiopathic thrombocytopenic purpura. Subcutaneous injection of a low dose of heparin improved platelet counts in a small number of patients with idiopathic thrombocytopenic purpura (p.1505) that was resistant to standard corticosteroid therapy.[1] However, heparin may itself cause thrombocytopenia, even at very low doses (see Effects on the Blood under Adverse Effects, above).

1. Shen ZX, *et al.* Thrombocytopoietic effect of heparin given in chronic immune thrombocytopenic purpura. *Lancet* 1995; **346:** 220–1.

Malignant neoplasms. Cancer is a risk factor for thromboembolism and anticoagulants are often used in patients with malignant neoplasms. There is some evidence that outcomes are improved in patients treated with heparin, and both unfractionated and low-molecular-weight heparins have therefore been studied in patients with malignant neoplasms but no other indication for anticoagulation. Systematic reviews[1,2] have found that there is a clinically significant improvement in survival, although the risk of bleeding is also increased.

1. Akl EA, *et al.* Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 23/05/08).
2. Lazo-Langner A, *et al.* The effect of low-molecular-weight heparin on cancer survival. A systematic review and meta-analysis of randomized trials. *J Thromb Haemost* 2007; **5:** 729–37.

Pregnancy. Heparin or low-molecular-weight heparins are the anticoagulants of choice for use in pregnancy although they are not without risk for the fetus (see Pregnancy, under Precautions, above), and for the mother.

Guidelines on thrombosis associated with pregnancy have been published.[1-3] Pregnant women may require anticoagulation for the treatment or prophylaxis of venous thromboembolism (p.1189), or for the prevention of systemic thromboembolism associated with prosthetic heart valves (p.1187). Patients with a history of thromboembolism or a thrombophilic abnormality such as inherited deficiencies of antithrombin III, protein C, or protein S or acquired antiphospholipid antibodies may be at particular risk. Women with antiphospholipid antibodies may also be at increased risk of fetal loss (see Systemic Lupus Erythematosus, p.1513) and treatment with low-dose aspirin is usually recommended.[2] Addition of heparin has been reported to further reduce the risk,[4,5] and treatment with heparin or low-molecular-

weight heparin, in addition to aspirin, has therefore also been recommended.[3]

1. Royal College of Obstetricians and Gynaecologists. Thromboembolic disease in pregnancy and the puerperium: acute management (February 2007). Available at: http://www.rcog.org.uk/resources/Public/pdf/green_top_28_thromboembolic_minorrevision.pdf (accessed 05/02/08)
2. Royal College of Obstetricians and Gynaecologists. Thromboprophylaxis during pregnancy, labour and after vaginal delivery (January 2004). Available at: http://www.rcog.org.uk/index.asp?PageID=535 (accessed 23/05/05)
3. Bates SM, *et al.* Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 844S–886S.
4. Rai R, *et al.* Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ* 1997; **314:** 253–7.
5. Empson M, *et al.* Recurrent pregnancy loss with antiphospholipid antibody: a systematic review of therapeutic trials. *Obstet Gynecol* 2002; **99:** 135–44.

Reperfusion and revascularisation procedures. Heparin has an established role as an adjunct to percutaneous vascular interventions and bypass surgery, to prevent perioperative thrombosis of the target artery, and is usually given with aspirin or other antiplatelet drugs (see Reperfusion and Revascularisation Procedures, p.1181). High doses are used, particularly in patients undergoing bypass surgery with extracorporeal circulation, and bleeding is a common problem. Although heparin may have an antiproliferative effect, treatment with systemic heparin (unfractionated or low-molecular-weight) appears to have no effect on restenosis;[1] however, a study using local application of enoxaparin suggested that restenosis was reduced.[2] Heparin-coated intracoronary stents have also been used; they improve outcomes compared with balloon angioplasty,[3] but have not been shown to be superior to bare-metal stents[4] or to have any additional effect on restenosis.[5,6] Heparin-coated stents have also been used successfully in cerebrovascular interventions.[7]

1. Grassman ED, *et al.* A randomized trial of the low-molecular-weight heparin certoparin to prevent restenosis following coronary angioplasty. *J Invasive Cardiol* 2001; **13:** 723–8.
2. Kiesz RS, *et al.* Local delivery of enoxaparin to decrease restenosis after stenting: results of initial multicenter trial: Polish-American Local Lovenox NIR Assessment study (The POLONIA study). *Circulation* 2001; **103:** 26–31.
3. Serruys PW, *et al.* Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* 1998; **352:** 673–81. Correction. *ibid.*; 1478.
4. Mehran R, *et al.* An Internet-based registry examining the efficacy of heparin coating in patients undergoing coronary stent implantation. *Am Heart J* 2005; **150:** 1171–6.
5. Wöhrle J, *et al.* Comparison of the heparin coated vs the uncoated Jostent —no influence on restenosis or clinical outcome. *Eur Heart J* 2001; **22:** 1808–16.
6. Semiz E, *et al.* Comparison of initial efficacy and long-term follow-up of heparin-coated Jostent with conventional NIR stent. *Jpn Heart J* 2003; **44:** 889–98.
7. Parkinson RJ, *et al.* Use of heparin-coated stents in neurovascular interventional procedures: preliminary experience with 10 patients. *Neurosurgery* 2006; **59:** 812–21.

Preparations

BP 2008: Heparin Injection;
USP 31: Anticoagulant Heparin Solution; Heparin Calcium Injection; Heparin Lock Flush Solution; Heparin Sodium Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Calciparine; Cervep; Croneparina; Parinix†; Riveparin; Serianon; Sobrius; Sodiparin; ***Austral.:*** Calcihep†; Calciparine†; Uniparin†; ***Austria:*** Lipohep; Liquemin; Thrombophob; Thrombophob-S; Venoruton Heparin; Viatromb; ***Belg.:*** Calparine; Liquemine†; ***Braz.:*** Actparin; Alimax; Disotron; Heptar; Liquemine; Parinorth†; Trombofob; ***Canad.:*** Hepalean; Hepalean-Lok; ***Cz.:*** Hepa-Gel†; Hepa-Salbe†; Lioton; Lipohep†; Trombex†; Viatromb; ***Fin.:*** Hepaflex; ***Fr.:*** Calciparine; ***Ger.:*** Calciparin; Essaven 60 000; Exhirud Heparin; Hepa-Gel; Hepa-Salbe; Hepaplus†; Hepathromb; Hepathrombin; Liquemin N; Perivar Venensalbe†; Sportino; Thrombareduct; Thrombophob; Traumalitan†; Venalitan; Venoruton Emulgel; Vetren; ***Gr.:*** Calciparine; Croneparina†; Hep Lok†; Hepsal; Monoparin; Multiparin; Pump-Hep†; ***Hong Kong:*** Lioton; ***Hung.:*** Heparibene; Lioton; ***India:*** Beparine; Thrombophob; ***Indon.:*** Inviclot; Thrombophob; ***Irl.:*** Calciparine†; Hep-Rinse†; Heplok†; Hepsal; Minihep†; Monoparin; Multiparin; Unihep†; ***Israel:*** Calciparin; ***Ital.:*** Ateroclar; Bioclarit†; Calciparina; Clarisco; Croneparina; Disebrin; Ecabil; Ecafast; Ecasolv; Emoklar; Epacalcica; Eparical†; Eparinlider; Eparinovis; Eparven; Epsoclar; Epsodil†; Epsodilave; Eudipar†; Flusolv; Hemofluss†; Isoclar; Lioton; Liquemin†; Mica; Normoparin; Pharepa; Reoflus; Sosefluss; Trombolisin; Zepac; ***Mex.:*** Hep-Tec; Inhepar†; Proparin; ***NZ:*** Monoparin†; Multiparin; ***Pol.:*** Coaparin; Heparizen; Lioton; Lipohep; ***Port.:*** Calciparina†; ***Rus.:*** Lioton (Лиотон); Trombless (Тромблесс); ***S.Afr.:*** Calciparine; Thrombophob; ***Spain:*** Calciparina†; Menaven; ***Switz.:*** Calciparine; Demovarin; Gelparine; HepaGel; Hepasol Lipogel; HepaSpray†; Lioton; Liquemine; ***Turk.:*** Calciparine; Liquemine; Nevparin; ***UK:*** Calciparine†; Canusal; Hepsal; Monoparin; Multiparin; ***USA:*** Hep-Lock; Hepflush; ***Venez.:*** Hirox; Liquemine†; Riveparin.

Multi-ingredient: ***Arg.:*** Contractubex; Venostasin; ***Austria:*** Ambenat; Contractubex; Derivon; Dolo-Menthoneurin; Dolobene; Etrat; Heparin Comp; Ichthalgan forte; Lipactin; Pasta Cool; Pertrombon; Sensicutan; Thrombophob; Venobene; Venostasin compositum; Vetren; ***Belg.:*** Lipactin; ***Braz.:*** Contractubex; Dolobene; Trombofob; Venalot H; Venostasin†; ***Canad.:*** Lipactin; ***Cz.:*** Contractubex; Dolo-Rubriment†; Dolobene; Heparin-Gel†; Sensicutan; ***Fin.:*** Lipactin; Trombosol; ***Fr.:*** Cirkan a la Prednacinolone; Esberiven; ***Ger.:*** Contractubex; Dolo-Menthoneurin†; Dolobene; Enelbin-Salbe N†; Essaven Tri-Complex†; Essaven†; Etrat Sportgel†; Heparin Comp†; Heparin Kombi-Gel†; Heparin Plus†; Ichthalgan†; Kelofibrase†; Lipactin; Ostochont†; Sensicutan; Trauma-Puren†; Venengel†; Venoplant AHS†; ***Hong Kong:*** Contractubex; Dolobene; ***Hung.:*** Contractubex; Dolobene; ***India:*** Beparine; Contractubex; Proctosedyl; Thrombophob; ***Indon.:*** Thrombophob; ***Ital.:*** Edeven; Essaven; Flebs; Idracemi Eparina; Luxazone Eparina; Proctosoll; Reparil; Venotrauma†; Via Mal Traumagel; Vit Eparin; Xantervit Eparina; ***Philipp.:*** Contractubex; ***Pol.:*** Alcepalan; Biherpan; Cepan; Contractubex; Dolobene; Savarix; Tointex; ***Port.:*** DM Gel; ***Rus.:*** Contractubex (Контрактубекс); Dolobene (Долобене); Heparin Ointment (Гепариновая Мазь); Hepatrombin (Гепатромбин); Hepatrombin H (Гепатромбин Г); Nigepan (Нигепан); Venolife (Веналайф); ***S.Afr.:*** Essaven†; ***Spain:*** Essavenon; Venacol; ***Switz.:*** Assan; Assan thermo; Butaparin; Contractubex; Dolo-Arthrosenex; Dolobene; Gorgonium; Hepabuzone; Heparinol; Hepathrombine†; Keli-med; Keppur; Lipactin; Lyman; Phlebostasin compositum†; Ralur†; Sportium; Sportusal; Venoplant comp; Venoplant-N†; Venucreme; Venugel.

Heparinoids

Heparinoides.

Profile

The term heparinoid includes heparin derivatives and has also been used more loosely to include naturally occurring and synthetic highly-sulfated polysaccharides of similar structure. Such compounds have been described in many ways; some of the terms used include sulfated glucosaminoglycans; glycosaminoglycan polysulfate compounds; or sulfated mucopolysaccharides.

The following anticoagulants may be described as heparinoids:

- Danaparoid Sodium, p.1255
- Dermatan Sulfate, p.1256
- Pentosan Polysulfate Sodium, p.1367
- Sodium Apolate, p.1397
- Suleparoid, p.1406
- Sulodexide, p.1406

Heparinoid preparations are available with uses ranging from anticoagulation to the alleviation of inflammation (applied topically); some are claimed to have hypolipidaemic properties.

The proprietary names listed in this monograph refer to preparations containing undefined or less readily defined heparinoids that are used in a range of conditions including musculoskeletal and joint disorders, haemorrhoids, lipid disorders, and thromboembolic disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Fleboderma; Hemeran†; Hirudoid; ***Austral.:*** Hirudoid; Lasonil; ***Austria:*** Hemeran; Hirudoid; Lasonil; ***Belg.:*** Hemeran; Hirudoid; Lasonil; ***Braz.:*** Hirudoid; Topcoid; ***Chile:*** Hirudoid; ***Cz.:*** Heparoid; Hirudoid; ***Denm.:*** Hirudoid; ***Fin.:*** Hirudoid; ***Ger.:*** Etrat Sportsalbe MPS†; Hirudoid; Lasonil N†; Sanaven MPS; ***Gr.:*** Hemeran; Lasonil N; ***Hong Kong:*** Bruise Cream†; Hepacare; Hirudoid; ***Hung.:*** Hirudoid; ***India:*** Hirudoid; ***Indon.:*** Hirudoid; ***Ital.:*** Angioflux; Ateran†; Ateroid; Ateroxide; Condral; Erevan†; Glicamin†; Hirudoid; Lasonil†; Lasoven†; Matrix; ***Neth.:*** Hirudoid; Lasonil; ***Norw.:*** Hirudoid; ***NZ:*** Hirudoid; Lasonil; ***Philipp.:*** Hirudoid; ***Pol.:*** Hirudoid; ***Port.:*** Hemeran; Hirudoid; Lasonil; ***Rus.:*** Heparoid (Гепароид); ***Singapore:*** Hirudoid; ***Spain:*** Dinoven; Hirudoid; ***Swed.:*** Hirudoid; ***Switz.:*** Hemeran; Hirudoid; ***Thai.:*** Hirudoid; Varidoid; ***Turk.:*** Hirudoid; Lasonil; ***UK:*** Bruiseze; Hirudoid; Lasonil†; ***Venez.:*** Hirudoid.

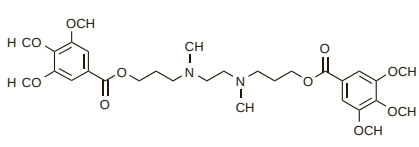
Multi-ingredient: ***Arg.:*** Mantus; ***Austral.:*** Movelat†; ***Austria:*** Lemuval; Mobilat; Mobilisin; Mobilisin plus; Moviflex; ***Belg.:*** Mobilat; Mobilisin; ***Braz.:*** Etrat†; Mobilat; Mobilisin Composto; ***Chile:*** Mobilat; Reparíven; ***Cz.:*** Ibu-Hepa; Ketazon Compositum†; Mobilat; ***Fin.:*** Mobilat; Moviflex†; ***Ger.:*** Dolo Mobilat†; Mobilat Aktiv; Mobilat†; Sanaven†; ***Gr.:*** Bayolin; ***Hong Kong:*** Mobilat†; Prelloran†; ***Hung.:*** Bayolin†; Mobilat N; Mobilisin†; ***Ital.:*** Flebs; Mobilat; Mobilisin; Momendol; Traumal†; ***Mex.:*** Mobilat; ***Neth.:*** Mobilat; ***NZ:*** Movelat†; ***Philipp.:*** Mobilat; ***Pol.:*** Helason; Ibalgin Sport; Lumbolin; Mobilat; ***Port.:*** Anacal; Mobilat; Mobilisin; Rimanal; ***Singapore:*** Mobilat†; ***Spain:*** Lasonil†; Movilat; Movilisin; ***Switz.:*** Dolo-Veniten†; Mobilat N; Mobilisin; Prelloran†; ***Thai.:*** Mobilat; Movelat†; ***UK:*** Anacal; Movelat; ***Venez.:*** Bargonil; Permucal.

Hexobendine *(BAN, USAN, rINN)*

Hexobendina; Hexobendinum.

Гексобендин

$C_{30}H_{44}N_2O_{10}$ = 592.7.
CAS — 54-03-5.
ATC — C01DX06.
ATC Vet — QC01DX06.



Hexobendine Hydrochloride *(BANM, rINNM)*

Hexobendine, Chlorhydrate d'; Hexobendini Hydrochloridum; Hidrocloruro de hexobendina; ST-7090. *NN*′-Ethylenebis(3-methylaminopropyl 3,4,5-trimethoxybenzoate) dihydrochloride.

Гексобендина Гидрохлорид

$C_{30}H_{44}N_2O_{10}$,2HCl = 665.6.
CAS — 50-62-4.
ATC — C01DX06.
ATC Vet — QC01DX06.

Profile

Hexobendine hydrochloride is a vasodilator that has been used in ischaemic heart disease. It is also included in multi-ingredient preparations used in cerebrovascular disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Ustimon.

Multi-ingredient: ***Austria:*** Instenon; ***Hong Kong:*** Instenon; ***Rus.:*** Instenon (Инстенон); ***Thai.:*** Instenon†.

Hirudin

Hirudina; Hirudine.

Profile

Hirudin is a 65-amino-acid protein that is a direct inhibitor of thrombin (see Lepirudin, p.1323). It has been extracted from leeches (p.1323) and this form is used in various topical preparations for peripheral vascular disorders. Recombinant hirudins, such as desirudin (p.1257) and lepirudin (p.1323) and analogues of hirudin, such as bivalirudin (p.1234), are used as anticoagulants.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Exhirud; ***Fr.:*** Hirucreme; ***Ger.:*** Exhirud†.

Multi-ingredient: ***Ger.:*** Haemo-Exhirud†; ***Ital.:*** Hirudex†.

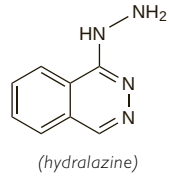
Hydralazine Hydrochloride

(BANM, rINNM)

Apressinum; Hidralazin-hidroklorid; Hidralazino hidrochloridas; Hidrocloruro de hidralazina; Hydralatsiinihydrokloridi; Hydralazin hydrochlorid; Hydralazin Hydrochloridum; Hydralazine, chlorhydrate d'; Hydralazinhydroklorid; Hydralazini hydrochloridum; Hydrallazine Hydrochloride; Idralazina. 1-Hydrazinophthalazine hydrochloride.

Гидралазина Гидрохлорид

$C_8H_8N_4$,HCl = 196.6.
CAS — 86-54-4 (hydralazine); 304-20-1 (hydralazine hydrochloride).
ATC — C02DB02.
ATC Vet — QC02DB02.



(hydralazine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Hydralazine Hydrochloride). A white or almost white, crystalline powder. Soluble in water; slightly soluble in alcohol; very slightly soluble in dichloromethane. A 2% solution in water has a pH of 3.5 to 4.2. Protect from light.
USP 31 (Hydralazine Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble 1 in 25 of water and 1 in 500 of alcohol; very slightly soluble in ether. A 2% solution in water has a pH of 3.5 to 4.2. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Stability. Discoloration of hydralazine injection was observed on several occasions after storage in a syringe for up to 12 hours.[1] Hydralazine reacts with metals and therefore the injection should be prepared using a nonmetallic filter and should be used as quickly as possible after being drawn through a needle into a syringe.

A study of the rate of degradation of hydralazine hydrochloride, 1 mg/mL in sweetened, aqueous oral liquids showed that glucose, fructose, lactose, and maltose reduced the stability of the drug.[2] In solutions containing mannitol or sorbitol, there was less than 10% degradation of hydralazine after 3 weeks. UK licensed product information states that contact with glucose causes hydralazine to be rapidly broken down and that hydralazine injection is therefore not compatible with glucose solutions.

1. Enderlin G. Discoloration of hydralazine injection. *Am J Hosp Pharm* 1984; **41:** 634.
2. Das Gupta V, *et al.* Stability of hydralazine hydrochloride in aqueous vehicles. *J Clin Hosp Pharm* 1986; **11:** 215–23.

Adverse Effects

Adverse effects are common with hydralazine, particularly tachycardia, palpitations, angina pectoris, severe headache, and gastrointestinal disturbances such as anorexia, nausea, vomiting, and diarrhoea. These adverse effects, and flushing, dizziness, and nasal congestion, which occur less often, may be seen at the start of treatment, especially if the dose is increased quickly. They generally subside with continued treatment. Other less common adverse effects include orthostatic hypoten-