Pharmacopoeias. In *Jpn* and *US*.
USP 31 (Guanabenz Acetate). A white or almost white powder with not more than a slight odour. Sparingly soluble in water and in 0.1N hydrochloric acid; soluble in alcohol and in propylene glycol. A 0.7% solution in water has a pH of 5.5 to 7.0. Store in airtight containers. Protect from light.

Adverse Effects and Precautions
As for Clonidine Hydrochloride, p.1247.

Overdosage. Overdosage with guanabenz has been reported.[1] The main symptoms were lethargy, drowsiness, bradycardia, and hypotension. A 45-year-old woman who had taken 200 to 240 mg of guanabenz with alcohol recovered after gastric lavage and intravenous fluids; a 3-year-old child who had taken 12 mg of guanabenz responded to atropine and dopamine. Naloxone had little effect in either patient.

1. Hall AH, *et al*. Guanabenz overdose. *Ann Intern Med* 1985; **102:** 787–8.

Interactions
As for Clonidine Hydrochloride, p.1248.

Pharmacokinetics
About 75% of an oral dose of guanabenz is absorbed and undergoes extensive first-pass metabolism. Peak plasma concentrations occur about 2 to 5 hours after a dose. It is about 90% bound to plasma proteins. Guanabenz is mainly excreted in urine, almost entirely as metabolites, with less than 1% as unchanged drug; about 10 to 30% is excreted in faeces. The average elimination half-life is reported to range from 4 to 14 hours.

Uses and Administration
Guanabenz is an 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), either alone or with other antihypertensives, particularly thiazide diuretics.

Guanabenz is given orally as the acetate, but doses are usually expressed in terms of the base. Guanabenz acetate 5 mg is equivalent to about 4 mg of guanabenz.

In hypertension, the usual dose is 4 mg twice daily initially; the daily dose may be increased by amounts of 4 to 8 mg every 1 to 2 weeks according to response. Doses of up to 32 mg twice daily have been used.

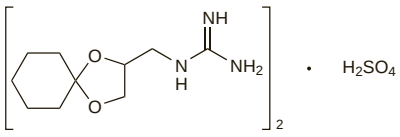
Preparations
USP 31: Guanabenz Acetate Tablets.

Proprietary Preparations (details are given in Part 3)
Braz.: Lisapres; ***USA:*** Wytensin.

Guanadrel Sulfate *(USAN, rINNM)*

CL-1388R; Guanadrel, Sulfate de; Guanadrel Sulphate; Guanadreli Sulfas; Sulfato de guanadrel; U-28288D. 1-(Cyclohexane-spiro-2′-[1′,3′]dioxolan-4′-ylmethyl)guanidine sulfate; 1-(1,4-Dioxaspiro[4.5]dec-2-ylmethyl)guanidine sulfate.

Гуанадрела Сульфат
$(C_{10}H_{19}N_3O_2)_2,H_2SO_4$ = 524.6.
CAS — 40580-59-4 (guanadrel); 22195-34-2 (guanadrel sulfate).



Pharmacopoeias. In *US*.
USP 31 (Guanadrel Sulfate). A white to off-white crystalline powder. Soluble in water; slightly soluble in alcohol and in acetone; sparingly soluble in methyl alcohol.

Adverse Effects, Treatment, and Precautions
As for Guanethidine Monosulfate, below. Guanadrel has been reported to cause less diarrhoea, and less orthostatic hypotension on rising in the morning, than guanethidine, but orthostatic symptoms seem to occur with a similar frequency to guanethidine during the day.

Interactions
As for Guanethidine Monosulfate, below.

Pharmacokinetics
Guanadrel is rapidly and almost completely absorbed from the gastrointestinal tract, with a bioavailability of about 85%. It is widely distributed throughout the body and about 20% is bound to plasma proteins. It is reported not to cross the blood-brain barrier. Plasma concentrations decline in a biphasic manner: the half-life varies widely between individuals, in the initial phase from 1 to 4 hours, and in the terminal phase from 5 to 45 hours, with a mean of about 10 hours. Guanadrel is metabolised in the liver and about 85% is excreted in the urine over 24 hours as the unchanged drug and its metabolites. About 40 to 50% of the drug is excreted unchanged.

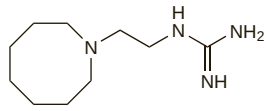
Uses and Administration
Guanadrel is an antihypertensive with actions and uses similar to those of guanethidine (below). After oral administration, guanadrel acts within 2 hours with the maximum effect after 4 to 6 hours. The hypotensive effect is reported to last for 4 to 14 hours following a single dose. It has been given orally as the sulfate in the management of hypertension, although it has largely been superseded by other drugs less likely to cause orthostatic hypotension.

Preparations
USP 31: Guanadrel Sulfate Tablets.

Guanethidine Monosulfate *(USAN, rINNM)*

Guanéthidine, monosulfate de; Guanethidine Monosulphate *(BANM)*; Guanethidini Monosufas; Guanethidini monosulfas; Guanethidini Sulfas; Guanethidin-monosulfát; Guanetidiinimonosulfaatti; Guanetidinmonosulfat; Guanetidin-monoszulfát; Guanetidino monosulfatas; Monosulfato de guanetidina; NSC-29863 (guanethidine hemisulfate); Su-5864 (guanethidine hemisulfate). 1-[2-(Perhydroazocin-1-yl)ethyl]guanidine monosulfate.

Гуанетидина Моносульфат
$C_{10}H_{22}N_4,H_2SO_4$ = 296.4.
CAS — 55-65-2 (guanethidine); 60-02-6 (guanethidine hemisulfate); 645-43-2 (guanethidine monosulfate).
ATC — C02CC02; S01EX01.
ATC Vet — QC02CC02; QS01EX01.



(guanethidine)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.
Chin. includes the hemisulfate.
Ph. Eur. 6.2 (Guanethidine Monosulphate). A colourless crystalline powder. Freely soluble in water; practically insoluble in alcohol. A 2% solution in water has a pH of 4.7 to 5.5. Protect from light.
USP 31 (Guanethidine Monosulfate). A white to off-white crystalline powder. Very soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform. A 2% solution in water has a pH of 4.7 to 5.7.

Adverse Effects
The commonest adverse effects of guanethidine are severe postural and exertional hypotension and diarrhoea which may be particularly troublesome during the initial stages of therapy and during dose adjustment. Dizziness, syncope, muscle weakness, and lassitude are liable to occur, especially on rising from sitting or lying. Orthostatic hypotension may be severe enough to provoke angina, renal impairment, and transient cerebral ischaemia. Other frequent adverse effects are bradycardia, failure of ejaculation, fatigue, headache, and salt and water retention and oedema, which may be accompanied by breathlessness and may occasionally precipitate overt heart failure.

Nausea, vomiting, dry mouth, nasal congestion, parotid tenderness, blurring of vision, depression, myalgia, muscle tremor, paraesthesias, hair loss, dermatitis, disturbed micturition, priapism, aggravation or precipitation of asthma, and exacerbation of peptic ulcer disease have also been reported. Guanethidine may possibly cause anaemia, leucopenia, and thrombocytopenia.

When guanethidine is used as eye drops, common adverse effects are conjunctival hyperaemia and miosis. Burning sensations and ptosis have also occurred. Superficial punctate keratitis has been reported particularly after prolonged use of high doses.

Treatment of Adverse Effects
Withdrawal of guanethidine or dose reduction reverses many adverse effects. Diarrhoea may also be controlled by giving codeine phosphate or antimuscarinics. If overdosage occurs the benefit of gastric decontamination is uncertain, but activated charcoal may be given if the patient presents within 1 hour. Hypotension may respond to placing the patient in the supine position with the feet raised. If hypotension is severe it may be necessary to give intravenous fluid replacement and small doses of vasopressors may be given cautiously. The patient must be monitored for several days.

Precautions
Guanethidine should not be given to patients with phaeochromocytoma, as it may cause a hypertensive crisis, or to patients with heart failure not caused by hypertension.

It should be used with caution in patients with renal impairment, cerebrovascular disorders, or ischaemic heart disease, or with a history of peptic ulcer disease or asthma. Exercise and heat may increase the hypotensive effect of guanethidine, and dosage requirements may be reduced in patients who develop fever.

There may be an increased risk of cardiovascular collapse or cardiac arrest in patients undergoing surgery while taking guanethidine, but authorities have differed as to whether the drug should be stopped before elective surgery. Former US licensed product information recommended stopping up to 2 or 3 weeks beforehand. In patients undergoing emergency procedures or where treatment has not been interrupted large doses of atropine should be given before induction of anaesthesia.

Patients undergoing treatment with eye drops containing guanethidine should be examined regularly for signs of conjunctival damage.

Interactions
Patients taking guanethidine may show increased sensitivity to the action of adrenaline, amfetamine, and other sympathomimetics, resulting in exaggerated pressor effects. The hypotensive effects may also be antagonised by tricyclic antidepressants, MAOIs, and phenothiazine derivatives and related antipsychotics (although phenothiazines may also exacerbate orthostatic hypotension, which may be more relevant clinically). In the UK licensed product information suggests that MAOIs should be stopped at least 14 days before beginning guanethidine, although in the USA a minimum of a week has been recommended as adequate. It has been reported that oral contraceptives may reduce the hypotensive action of guanethidine. Use of digoxin or other digitalis derivatives with guanethidine may cause excessive bradycardia.

The hypotensive effects of guanethidine may be enhanced by thiazide diuretics, other antihypertensives, and levodopa. Alcohol may cause orthostatic hypotension in patients taking guanethidine.

Pharmacokinetics
Guanethidine is variably and incompletely absorbed from the gastrointestinal tract with less than 50% of the dose reaching the systemic circulation. It is actively taken up into adrenergic neurones by the mechanism responsible for noradrenaline reuptake. A plasma concentration of 8 nanograms/mL is reported to be necessary for adrenergic blockade, but the dose required to achieve this varies between individuals due to differences in absorption and metabolism. Guanethidine is partially metabolised in the liver, and is excreted in the urine as metabolites and unchanged guanethidine. It has a terminal half-life of about 5 days. Guanethidine does not penetrate the blood-brain barrier significantly.

Uses and Administration
Guanethidine is an antihypertensive that acts by selectively inhibiting transmission in postganglionic adrenergic nerves. It is believed to act mainly by preventing the release of noradrenaline at nerve endings. Guanethidine causes the depletion of noradrenaline stores in peripheral sympathetic nerve terminals but does not prevent the secretion of catecholamines by the adrenal medulla.

When given orally its maximal effects may take 1 to 3 weeks to appear on continued dosing and persist for 1 to 3 weeks after treatment has been stopped. It causes an initial reduction in cardiac output but its main hypotensive effect is to cause peripheral vasodilatation; it reduces the vasoconstriction which normally results from standing up and which is the result of reflex sympathetic nervous activity. In the majority of patients it reduces standing blood pressure but has a lesser effect on supine blood pressure. When applied topically to the eye guanethidine reduces the production of aqueous humour.

Guanethidine is used in the management of hypertension (p.1171). Eye drops of guanethidine have been used for open-angle glaucoma (p.1873) and for lid retraction associated with hyperthyroidism. Guanethidine has also been used in the management of neuropathic pain syndromes (see below).

Guanethidine is used in the treatment of hypertension when other drugs have proved inadequate, but it has largely been superseded by other drugs less likely to cause orthostatic hypotension. Tolerance to guanethidine has occurred in some patients; this may be countered by concomitant diuretic therapy.

In **hypertension**, the usual initial oral dose of guanethidine monosulfate has been 10 mg daily. This is increased by increments of 10 to 12.5 mg, not more often than every 5 to 7 days, according to response. The usual maintenance dose has been 25 to 50 mg once daily.

Children have been given 200 micrograms/kg daily with increments of 200 micrograms/kg every 7 to 10 days until a satisfactory response is achieved.

Guanethidine monosulfate has been given intramuscularly in the treatment of hypertensive crises, including severe pre-eclampsia, but more suitable drugs are available. An intramuscular dose of 10 to 20 mg is reported to produce a fall in blood pressure within 30 minutes.

Eye drops containing guanethidine monosulfate have been used in the treatment of open-angle **glaucoma** (usually combined with adrenaline), and for the lid retraction that may accompany hyperthyroidism.

Pain syndromes. Sympathetic nerve blocks may be used in the management of acute or chronic pain associated with a well-defined anatomical site. Guanethidine is one of a number of drugs that have been used for intravenous regional sympathetic block in the management of neuropathic pain (see Complex Regional Pain Syndrome, p.6), to reduce pain and to maintain blood flow.

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†.

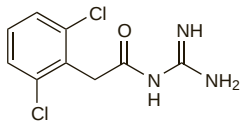
Multi-ingredient: ***Arg.:*** Normatensil†; ***Austria:*** Thilodigon†; ***Ger.:*** Esimil†; Thilodigon; ***Irl.:*** Ganda; ***USA:*** Esimil.

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)