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:

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 alpha2-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. I-(Cyclohexanespiro-2'-[1',3']dioxolan-4'-ylmethyl)guanidine sulfate; I-(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).

$$\begin{bmatrix} \\ \\ \\ \\ \\ \\ \\ \end{bmatrix}_{2}^{NH} NH_{2} \end{bmatrix}_{2} \cdot H_{2}SO_{4}$$

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 hypoten-

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). I-[2-(Perhydroazocin-I-yl)ethyl]guanidine monosulfate.

Гуанетидина Моносульфат

 $\begin{array}{l} C_{10}H_{22}N_4H_2SO_4=296.4.\\ \text{CAS} \qquad 55\text{-}65\text{-}2 \ (\text{guanethidine}); \ 60\text{-}02\text{-}6 \ (\text{guanethidine})\\ \text{hemisulfate}); \ 645\text{-}43\text{-}2 \ (\text{guanethidine} \ \text{monosulfate}). \end{array}$ ATC — CO2CCO2: SOIEXOI.

ATC Vet — QC02CC02; QS01EX01.

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

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 guanethi-

dine, 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 guanethi-

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 me-

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 openangle 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.