Clonidine *(BAN, USAN, rINN)*

Clonidina; Clonidinum; Klonidiini; Klonidin; ST-155-BS. 2-(2,6-Dichloroanilino)-2-imidazoline; 2,6-Dichloro-*N*-(imidazolidin-2-ylidene)aniline.

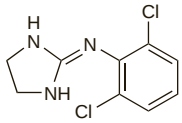
Клонидин

$C_9H_9Cl_2N_3$ = 230.1.

CAS — 4205-90-7.

ATC — C02AC01; N02CX02; S01EA04.

ATC Vet — QC02AC01; QN02CX02; QS01EA04.



Pharmacopoeias. In *US.*

USP 31 (Clonidine). A white to almost white, crystalline powder. Freely soluble in alcohol and in methyl alcohol. Store in airtight containers.

Clonidine Hydrochloride *(BANM, USAN, rINNM)*

Clonidine, chlorhydrate de; Clonidini hydrochloridum; Hidrocloruro de clonidina; Klonidiinihydrokloridi; Klonidin-hidroklorid; Klonidin-hydrochlorid; Klonidinhydroklorid; Klonidino hidrochloridas; Klonidyny chlorowodorek; ST-155.

Клонидина Гидрохлорид

$C_9H_9Cl_2N_3$,HCl = 266.6.

CAS — 4205-91-8.

ATC — C02AC01; N02CX02; S01EA04.

ATC Vet — QC02AC01; QN02CX02; QS01EA04.

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

Ph. Eur. 6.2 (Clonidine Hydrochloride). A white or almost white crystalline powder. Soluble in water and in dehydrated alcohol. A 5% solution in water has a pH of 4.0 to 5.0.

USP 31 (Clonidine Hydrochloride). pH of a 5% solution in water is between 3.5 and 5.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Treatment

Drowsiness, dry mouth, dizziness, and headache are common when starting therapy with clonidine. Constipation is also common, and other adverse effects reported include depression, anxiety, fatigue, nausea, anorexia, parotid pain, sleep disturbances, vivid dreams, impotence and loss of libido, urinary retention or incontinence, orthostatic hypotension, and dry, itching, or burning sensations in the eye. Fluid retention may occur and is usually transient, but may be responsible for a reduction in the hypotensive effect during continued treatment. Clonidine can cause rashes and pruritus, and these are more common with transdermal delivery systems. Bradycardia, including sinus bradycardia with AV block, other ECG disturbances, heart failure, hallucinations, cramp, Raynaud's syndrome, gynaecomastia, and transient abnormalities in liver function tests have been reported less often. Large doses have been associated with initial increases in blood pressure and transient hyperglycaemia, although these do not persist during continued therapy.

Symptoms of overdosage include transient hypertension or profound hypotension, bradycardia, sedation, miosis, respiratory depression, convulsions, and coma. Treatment consists of general supportive measures. An alpha blocker may be given if necessary for hypertension, and atropine may be required for bradycardia and associated hypotension. Cardiac pacing may be needed rarely.

Sudden withdrawal of clonidine may produce rebound hypertension—see Precautions, below.

Effects on the gastrointestinal tract. Constipation is a relatively common adverse effect of clonidine, US licensed product information reporting an incidence of about 10%. Ileus or pseudo-obstruction of the bowel have been reported;[1-3] withdrawal of clonidine was associated with a return of bowel function to normal. Abdominal pain mimicking acute appendicitis occurred in another patient; symptoms recurred on restarting the drug and subsided on withdrawal.[4]

1. Davidov M, *et al.* The antihypertensive effects of an imidazoline compound. *Clin Pharmacol Ther* 1967; **8:** 810–16.
2. Bear R, Steer K. Pseudo-obstruction due to clonidine. *BMJ* 1976; **1:** 197.
3. Bauer GE, Hellestrand KJ. Pseudo-obstruction due to clonidine. *BMJ* 1976; **1:** 769.
4. Mjörndal T, Mellbring G. Abdominal pain associated with clonidine. *BMJ* 1986; **292:** 174.

Effects on the heart. Clonidine has been associated with impaired atrioventricular conduction in a few patients,[1,2] although some of these may have had underlying conduction defects and had previously received digitalis, which may have contributed to their condition. Other ECG abnormalities may also occur. Sudden death has been reported in 3 children receiving clonidine and methylphenidate,[3,4] although the significance of these reports has been questioned.[5]

1. Kibler LE, Gazes PC. Effect of clonidine on atrioventricular conduction. *JAMA* 1977; **238:** 1930–2.
2. Abiuso P, Abelow G. Atrioventricular dissociation in a patient receiving clonidine. *JAMA* 1978; **240:** 108–9.
3. Maloney MJ, Schwam, JS. Clonidine and sudden death. *Pediatrics* 1995; **96:** 1176–7.
4. Fenichel RR. Combining methylphenidate and clonidine: the role of post-marketing surveillance. *J Child Adolesc Psychopharmacol* 1995; **5:** 155–6.
5. Blackman JA, *et al.* Clonidine and electrocardiograms. *Pediatrics* 1996; **98:** 1223–4.

Effects on mental function. There have been occasional reports of disturbed mental state in patients given clonidine.[1-4]

1. Lavin P, Alexander CP. Dementia associated with clonidine therapy. *BMJ* 1975; **1:** 628.
2. Enoch MD, Hammad GEM. Acute hallucinosis due to clonidine. *Curr Med Res Opin* 1977; **4:** 670–1.
3. Brown MJ, *et al.* Clonidine hallucinations. *Ann Intern Med* 1980; **93:** 456–7.
4. Delaney J, *et al.* Clonidine-induced delirium. *Int J Cardiol* 2006; **113:** 276–8.

Effects on the skin. Skin reactions have been reported in up to 50% of patients using clonidine transdermal patches.[1] Localised erythema and irritation during early treatment are usually mild, but allergic contact dermatitis may develop.[2-4] Skin reactions may become commoner during prolonged treatment; although only mild skin reactions were seen in a study of transdermal clonidine during 8 to 14 weeks of treatment in 15 patients, severe skin reactions occurred after an average of 20 weeks in 4 of 5 patients who continued treatment.[5] Despite a claim that skin reactions were due to a component in the patch and not to clonidine itself,[6] positive patch tests to clonidine have been obtained.[2,4] Subsequent reaction to oral clonidine in patients who develop skin reactions to the transdermal patch is reported to be rare.[7,8]

1. Carmichael AJ. Skin sensitivity and transdermal drug delivery: a review of the problem. *Drug Safety* 1994; **10:** 151–9.
2. Groth H, *et al.* Allergic skin reactions to transdermal clonidine. *Lancet* 1983; **ii:** 850–1.
3. McMahon FG, Weber MA. Allergic skin reactions to transdermal clonidine. *Lancet* 1983; **ii:** 851.
4. Boekhorst JC. Allergic contact dermatitis with transdermal clonidine. *Lancet* 1983; **ii:** 1031–2.
5. Dick JBC, *et al.* Skin reactions to long-term transdermal clonidine. *Lancet* 1987; **i:** 516.
6. Anonymous. Transdermal clonidine sensitiser identified? *Pharm J* 1984; **233:** 16.
7. Bigby M. Transdermal clonidine dermatitis. *JAMA* 1987; **258:** 1819.
8. Burris JF. Transdermal clonidine dermatitis. *JAMA* 1987; **258:** 1819–20.

PEMPHIGOID. Anogenital cicatricial pemphigoid has been reported[1] in a patient receiving long-term clonidine therapy.

1. van Joost T, *et al.* Drug-induced anogenital cicatricial pemphigoid. *Br J Dermatol* 1980; **102:** 715–18.

Hypersensitivity. See Effects on the Skin, above.

Overdosage. Analysis by the UK National Poisons Information Service[1] of poisoning by clonidine in 133 children and 37 adults between 1976 and 1977 revealed that there were no deaths but clinical features were often severe. Supportive measures were usually adequate but atropine was often needed for severe and persistent bradycardia. Forced diuresis was not advised because hypotension could be enhanced and there was no evidence that excretion of clonidine was increased. More recently, death has been reported[2] in a 23-month old child.

Direct medical evaluation has been recommended[3] for children who have ingested the following amounts: 100 micrograms or more in those aged 4 years and under; more than 200 micrograms in those aged 5 to 8 years; and 400 micrograms or more in older children; 4 hours may be long enough to detect full onset of symptoms. However, others[4] believe that medical evaluation is indicated in any child who has unintentionally ingested more than a weight-appropriate therapeutic dose.

Although naloxone has been suggested as an antidote for clonidine overdose, no reversal of the hypotensive effects of clonidine 300 micrograms was noted in 6 hypertensive subjects given naloxone by intravenous infusion.[5] In a retrospective analysis of 47 children with clonidine poisoning, only 3 of 19 given naloxone showed definite improvement;[6] it was concluded that naloxone is at best an inconsistent antidote for clonidine poisoning.

Severe symptoms of overdosage have also been reported after the ingestion of clonidine transdermal patches,[7] and following probable subcutaneous injection during filling of an epidural pump reservoir.[8]

1. Stein B, Volans GN. Dixarit overdose: the problem of attractive tablets. *BMJ* 1978; **2:** 667–8.
2. Klein-Schwartz W. Trends and toxic effects from pediatric clonidine exposures. *Arch Pediatr Adolesc Med* 2002; **156:** 392–6.
3. Spiller HA, *et al.* Toxic clonidine ingestion in children. *J Pediatr* 2005; **146:** 263–6.
4. Langhan M, Chan GM. Clonidine exposures, not toxicity. *J Pediatr* 2006; **148:** 565.
5. Rogers JF, Cubeddu LX. Naloxone does not antagonise the antihypertensive effect of clonidine in essential hypertension. *Clin Pharmacol Ther* 1983; **34:** 68–73.
6. Wiley JF, *et al.* Clonidine poisoning in young children. *J Pediatr* 1990; **116:** 654–8.
7. Raber JH, *et al.* Clonidine patch ingestion in an adult. *Ann Pharmacother* 1993; **27:** 719–22. Correction. *ibid.*; 1143.
8. Frye CB, Vance MA. Hypertensive crisis and myocardial infarction following massive clonidine overdose. *Ann Pharmacother* 2000; **34:** 611–15.

Precautions

Clonidine should be used with caution in patients with cerebrovascular disease, ischaemic heart disease including myocardial infarction, renal impairment, occlusive peripheral vascular disorders such as Raynaud's disease, or those with a history of depression.

Clonidine causes drowsiness and patients should not drive or operate machinery where loss of attention could be dangerous.

Systemic effects also occur after epidural use and patients should be closely monitored, particularly during the first few days of therapy.

Intravenous injections of clonidine should be given slowly to avoid a possible transient pressor effect especially in patients already taking other antihypertensives such as guanethidine or reserpine.

Withdrawal of clonidine therapy should be gradual as stopping suddenly may cause rebound hypertension, sometimes severe. Symptoms of increased catecholamine release such as agitation, sweating, tachycardia, headache, and nausea may also occur. Beta blockers can exacerbate the rebound hypertension and if both are being used, clonidine should not be stopped until several days after the withdrawal of the beta blocker. Patients should be warned of the risk of missing a dose or stopping the drug without consulting their doctor and should carry a reserve supply.

Although hypotension may occur during anaesthesia in clonidine-treated patients clonidine should not be withdrawn; indeed, if necessary it should be given intravenously during the operation to avoid the risk of rebound hypertension.

Abuse. Despite its central effects and ability to cause a form of physical dependence, WHO rated the likelihood of abuse as very low.[1] However, clonidine may potentiate the psychoactive effects of morphine and abuse has been reported.[2]

1. WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser 775* 1989. Available at: http://libdoc.who.int/trs/WHO_TRS_775.pdf (accessed 19/08/08)
2. Sullivan JT, *et al.* Does clonidine alter the abuse potential of morphine? *Clin Pharmacol Ther* 1995; **57:** 163.

Diabetes mellitus. The effects of clonidine on carbohydrate metabolism appear to be variable. Some studies suggest that it does not affect carbohydrate metabolism in diabetic[1] or non-diabetic hypertensive patients,[2] although there has been a report of a diabetic patient in whom clonidine was associated with elevated fasting blood-glucose values,[3] and increased insulin requirements were noted in a diabetic child treated with clonidine for tics.[4] Conversely, clonidine was associated with severe hypoglycaemia in children when used as a provocative test for growth hormone deficiency (see Growth Retardation, below). However, a study in 10 diabetic hypertensive patients found that although clonidine impaired response to an acute glucose load, it did not significantly affect diabetic control over a 10-week period.[5] Problems may arise when clonidine is given to diabetics with autonomic neuropathy: both severe orthostatic hypotension[6] and paradoxical hypertension[7] have been reported.

For discussion of the use of clonidine in diabetic diarrhoea see below.

1. Nilsson-Ehle P, *et al.* Lipoproteins and metabolic control in hypertensive type II diabetics treated with clonidine. *Acta Med Scand* 1988; **224:** 131–4.
2. Molitch ME, *et al.* Effects of antihypertensive medications on carbohydrate metabolism. *Curr Ther Res* 1986; **39:** 398–407.
3. Okada S, *et al.* Effect of clonidine on insulin secretion: a case report. *J Int Med Res* 1986; **14:** 299–302.
4. Mimouni-Bloch A, Mimouni M. Clonidine-induced hyperglycemia in a young diabetic girl. *Ann Pharmacother* 1993; **27:** 980.
5. Guthrie GP, *et al.* Clonidine in patients with diabetes and mild hypertension. *Clin Pharmacol Ther* 1983; **34:** 713–17.
6. Moffat B. Postural hypotension induced by clonidine in insulin dependent diabetes. *BMJ* 1985; **290:** 822.
7. Young E, *et al.* Paradoxical hypertension from clonidine. *Ann Intern Med* 1984; **101:** 282–3.

ECT. Maximal ECT stimuli were unsuccessful in producing seizures in 4 of 7 treatment attempts in a 66-year-old patient receiving clonidine.[1] It was suggested that clonidine may elevate the seizure threshold.

1. Elliott RL. Case report of a potential interaction between clonidine and electroconvulsive therapy. *Am J Psychiatry* 1983; **140:** 1237–8.

Porphyria. Clonidine hydrochloride has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

The hypotensive effect of clonidine may be enhanced by diuretics, other antihypertensives, and drugs that cause hypotension. However, beta blockers may exacerbate rebound hypertension following clonidine withdrawal (see Precautions, above), and tricyclic antidepressants may antagonise the hypotensive effect. The sedative effect of clonidine may be enhanced by CNS depressants.

Antidepressants. Although tricyclic antidepressants commonly cause orthostatic hypotension, they may antagonise the hypotensive effects of clonidine. Blood pressure control was lost in 4 of 5 hypertensive patients taking clonidine and a diuretic when they were given *desipramine* 75 mg daily.[1] Increase in blood pressure generally occurred in the second week of treatment, but 1 patient had a dramatic rise in blood pressure within 24 hours of starting treatment. The mechanism is thought to be due to a central interaction between clonidine and the tricyclic antidepressant, although a peripheral effect cannot be completely excluded.[2] Loss of blood pressure control also occurred in a patient receiving guanfacine, another alpha$_2$-adrenoceptor agonist, when *amitriptyline* was given.[3] The reaction recurred with *imipramine*. However, in another study clonidine was given to 11 patients taking amitriptyline or imipramine, and 10 achieved good blood pressure control, although 4 developed an acute rise in blood pressure when methyldopa or guanethidine was added.[4] *Maprotiline*[5] or *mianserin*[6] do not appear to interact with clonidine.

1. Briant RH, *et al*. Interaction between clonidine and desipramine in man. *BMJ* 1973; **1:** 522–3.
2. van Spanning HW, van Zwieten PA. The interference of tricyclic antidepressants with the central hypotensive effect of clonidine. *Eur J Pharmacol* 1973; **24:** 402–4.
3. Buckley M, Feely J. Antagonism of antihypertensive effect of guanfacine by tricyclic antidepressants. *Lancet* 1991; **337:** 1173–4.
4. Raftos J, *et al*. Clonidine in the treatment of severe hypertension. *Med J Aust* 1973; **1:** 786–93.
5. Gundert-Remy U, *et al*. Lack of interaction between the tetracyclic antidepressant maprotiline and the centrally acting antihypertensive drug clonidine. *Eur J Clin Pharmacol* 1983; **25:** 595–9.
6. Elliott HL, *et al*. Absence of an effect of mianserin on the actions of clonidine or methyldopa in hypertensive patients. *Eur J Clin Pharmacol* 1983; **24:** 15–19.

Antipsychotics. Acute, severe hypotension occurred in 2 agitated hypertensive patients after use of clonidine with either *chlorpromazine* or *haloperidol*. Both patients had mitral insufficiency.[1]

1. Fruncillo RJ, *et al*. Severe hypotension associated with concurrent clonidine and antipsychotic medication. *Am J Psychiatry* 1985; **142:** 274.

Dopaminergic antiparkinsonian drugs. For a report of the inhibition of the therapeutic effect of *levodopa* by clonidine, see Antihypertensives, p.807.

Immunosuppressants. For a report of clonidine increasing whole blood-*ciclosporin* concentrations, see p.1827.

Pharmacokinetics

Clonidine is well absorbed from the gastrointestinal tract, and peak plasma concentrations occur about 3 to 5 hours after an oral dose. It is about 20 to 40% protein bound. About 50% of a dose is metabolised in the liver. It is excreted in the urine as unchanged drug and metabolites, 40 to 60% of an oral dose being excreted in 24 hours as unchanged drug; about 20% of a dose is excreted in the faeces, probably via enterohepatic circulation. The elimination half-life has been variously reported to range between 6 and 24 hours, extended to up to 41 hours in patients with renal impairment. Clonidine crosses the placenta and is distributed into breast milk.

It is absorbed through the skin; absorption is reported to be better from the chest or arm than from the thigh. Therapeutic plasma concentrations are achieved 2 or 3 days after application of a transdermal patch and are roughly equivalent to trough concentrations achieved after oral dosage. Therapeutic plasma concentrations are maintained for about 8 hours after removal of the delivery system and then decline slowly over several days.

◊ Reviews.

1. Lowenthal DT, *et al*. Clinical pharmacokinetics of clonidine. *Clin Pharmacokinet* 1988; **14:** 287–310.

Pregnancy. A study in 5 pregnant women treated with clonidine for pre-eclampsia[1] reported an average ratio of cord- to plasma-concentrations of 0.87, indicating placental transfer of clonidine.

1. Boutroy MJ, *et al*. Clonidine placental transfer and neonatal adaption. *Early Hum Dev* 1988; **17:** 275–86.

Uses and Administration

Clonidine is an imidazoline antihypertensive that appears to act centrally to reduce sympathetic tone, resulting in a fall in diastolic and systolic blood pressure and a reduction in heart rate. The exact mechanism is unclear; clonidine stimulates alpha$_2$ adrenoceptors and central imidazoline receptors, but it is not known which receptors mediate which effects. It also acts peripherally, and this peripheral activity may be responsible for the transient increase in blood pressure seen during rapid intravenous injection as well as contributing to the hypotensive effect during chronic use. Peripheral resistance is reduced during continuous treatment. Cardiovascular reflexes remain intact so orthostatic hypotension is uncommon.

Clonidine is used in the management of hypertension (p.1171), including hypertensive crises, although other drugs with fewer adverse effects are now generally preferred. It may be given with a thiazide diuretic, but use with a beta blocker should be avoided where possible. Clonidine has also been used in the prophylactic treatment of migraine or recurrent vascular headaches (but see below) and in the treatment of menopausal flushing. It is used with opioids in the management of cancer pain and has been tried for various other forms of pain (below). Other uses of clonidine have included the symptomatic treatment of opioid withdrawal (see under Substance Dependence, below), the diagnosis of phaeochromocytoma (below), and as eye drops in the management of glaucoma (p.1873). It has also been tried in Tourette's syndrome (below) and numerous other disorders.

Clonidine is used as the hydrochloride. When given orally, its haemodynamic effects appear in about 30 to 60 minutes, reaching a maximum after 2 to 4 hours and lasting up to 8 hours. Tolerance to clonidine has been reported. Withdrawal of clonidine should be gradual because of the risk of rebound hypertension.

In **hypertension**, the usual initial oral dose of clonidine hydrochloride is 50 to 100 micrograms three times daily (or in the USA, 100 micrograms twice daily), increased every second or third day according to response; the usual maintenance dose is 300 to 1200 micrograms daily but doses of 1800 micrograms or more daily may sometimes be required. Modified-release preparations have been used. Clonidine may also be given by transdermal delivery systems that are applied once a week and deliver 100 to 300 micrograms of clonidine base daily at a constant rate.

Clonidine hydrochloride may be given by slow intravenous injection over 10 to 15 minutes in hypertensive crises, usually in doses of 150 to 300 micrograms. The effect usually appears within 10 minutes, but transient hypertension may precede hypotension if the injection is given too rapidly. The hypotensive effect reaches a maximum about 30 to 60 minutes after injection and the duration is about 3 to 7 hours; up to 750 micrograms may be given intravenously over 24 hours. Although oral dosage does not produce a sufficiently rapid hypotensive effect for use in an emergency situation, a dose of 100 to 200 micrograms initially followed by 50 to 100 micrograms every hour until control of blood pressure is achieved or a maximum of 500 to 800 micrograms is reached, has been recommended for the control of severe hypertension.

In the prophylaxis of **migraine** or recurrent vascular headaches and in the treatment of **menopausal flushing**, an oral dose of 50 micrograms twice daily has been used, increased, if there is no remission after 2 weeks, to 75 micrograms twice daily.

In the management of severe **cancer pain**, clonidine hydrochloride may be given by continuous epidural infusion with an opioid, in an initial dose of 30 micrograms/hour, adjusted according to response.

Anxiety disorders. Clonidine has been tried in various anxiety disorders but evidence of efficacy is limited. A review[1] of its use in panic disorder (p.952) considered that it might be useful as a last-line anxiolytic in patients unresponsive to standard treatment as occasional success had been obtained in a few patients. There have also been isolated reports of small numbers of patients with post-traumatic stress disorder (p.953) who have benefited from clonidine.[2]

For mention of clonidine as an adjuvant to sedative drugs in the intensive care unit see p.957.

1. Puzantian T, Hart LL. Clonidine in panic disorder. *Ann Pharmacother* 1993; **27:** 1351–3.
2. Harmon RJ, Riggs PD. Clonidine for posttraumatic stress disorder in preschool children. *J Am Acad Child Adolesc Psychiatry* 1996; **35:** 1247–9.

Cardiac arrhythmias. Atrial fibrillation (p.1160) is managed by treatment to slow the increased ventricular responses or by cardioversion. Control of ventricular rate is usually achieved with digoxin, beta blockers, or calcium-channel blockers but clonidine, which reduces sympathetic tone and thus reduces heart rate, has also been tried.[1-3]

1. Roth A, *et al*. Clonidine for patients with rapid atrial fibrillation. *Ann Intern Med* 1992; **116:** 388–90.
2. Scardi S, *et al*. Oral clonidine for heart rate control in chronic atrial fibrillation. *Lancet* 1993; **341:** 1211–12.
3. Simpson CS, *et al*. Clinical assessment of clonidine in the treatment of new-onset rapid atrial fibrillation; a prospective, randomized clinical trial. *Am Heart J* 2001; **142:** e3.

Diarrhoea. Some studies have shown that clonidine possesses antidiarrhoeal properties. Clonidine may stimulate alpha$_2$ adrenoceptors on enterocytes thus promoting fluid and electrolyte absorption and inhibiting anion secretion. It may also modify intestinal motility or rectal sphincter tone.

Most experience with clonidine is in diabetic diarrhoea (see Diabetic Complications, p.433). Clonidine 100 to 600 micrograms by mouth every 12 hours reduced diabetic diarrhoea in 3 patients with type 1 diabetes[1] and good results have also been reported in such patients when transdermal clonidine was used.[2,3] Benefit has also been reported in patients with symptoms of diabetic gastroparesis in addition to diarrhoea.[3,4] However, oral (but perhaps not transdermal) clonidine may worsen orthostatic hypotension in patients with diabetic diarrhoea and this may limit its usefulness.[5] Clonidine has also been tried in patients with high intestinal output after small bowel transplantation[6] or jejunostomy,[7] and in diarrhoea-predominant irritable bowel syndrome[8] or for the gastrointestinal effects of opioid withdrawal.[9]

1. Fedorak RN, *et al*. Treatment of diabetic diarrhea with clonidine. *Ann Intern Med* 1985; **102:** 197–9.
2. Sacerdote A. Topical clonidine for diabetic diarrhea. *Ann Intern Med* 1986; **105:** 139.
3. Sacerdote AS. Topical clonidine and diabetic gastroparesis. *Ann Intern Med* 1990; **112:** 796.
4. Migliore A, *et al*. Diabetic diarrhea and clonidine. *Ann Intern Med* 1988; **109:** 170–1.
5. Ogbonnaya KI, Arem R. Diabetic diarrhea: pathophysiology, diagnosis, and management. *Arch Intern Med* 1990; **150:** 262–7.
6. Rovera G, *et al*. The use of clonidine for the treatment of high intestinal output following small bowel transplantation. *Transplant Proc* 1997; **29:** 1853–4.
7. Buchman AL, *et al*. Clonidine reduces diarrhea and sodium loss in patients with proximal jejunostomy: a controlled study. *J Parenter Enteral Nutr* 2006; **30:** 487–91.
8. Camilleri M, *et al*. A randomized, controlled exploratory study of clonidine in diarrhea-predominant irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2003; **1:** 111–21.
9. Ma H, *et al*. The effect of clonidine on gastrointestinal side effects associated with ultra-rapid opioid detoxification. *Anesth Analg* 2003; **96:** 1409–12.

Extrapyramidal disorders. There is limited evidence[1] from small studies that clonidine might reduce symptoms of antipsychotic-induced akathisia and tardive dyskinesia (p.971). However, adverse effects such as sedation and hypotension may limit use.

1. Ahmed I, Takeshita J. Clonidine: a critical review of its role in the treatment of psychiatric disorders. *CNS Drugs* 1996; **6:** 53–70.

Growth retardation. Clonidine has been reported to be a stimulant of growth hormone release, presumably as a result of central alpha-adrenergic stimulation, and has been tried in the diagnosis and management of growth retardation (p.1798). It may be given orally as a provocative test for growth hormone deficiency,[1,2] particularly in children,[3] although some consider measurement of circulating somatomedins (insulin-like growth factors; IGFs) to be more useful than provocative tests. A combination of both may be required to confirm diagnosis;[4] guidelines have been suggested.[5] Caution is required when performing the test in children since severe hypoglycaemia has been

reported.[6] Clonidine has also been tried in the treatment of growth retardation, both in children with growth hormone deficiency and in short children without proven deficiency, but results have been contradictory and largely unsatisfactory.[7-9]

1. Gil-Ad I, *et al.* Oral clonidine as a growth hormone stimulation test. *Lancet* 1979; **ii:** 278–80.
2. Hoffman WH, *et al.* Relationship of plasma clonidine to growth hormone concentrations in children and adolescents. *J Clin Pharmacol* 1989; **29:** 538–42.
3. Hindmarsh PC, Swift PGF. An assessment of growth hormone provocation tests. *Arch Dis Child* 1995; **72:** 362–8.
4. Cianfarani S, *et al.* Height velocity and IGF-I assessment in the diagnosis of childhood onset GH insufficiency: do we still need a second GH stimulation test? *Clin Endocrinol (Oxf)* 2002; **57:** 161–7.
5. Evans C, Gregory JW. The investigation of short stature: a survey of practice in Wales and suggested practical guidelines. *J Clin Pathol* 2004; **57:** 126–30.
6. Huang C, *et al.* Hypoglycemia associated with clonidine testing for growth hormone deficiency. *J Pediatr* 2001; **139:** 323–4.
7. Pintor C, *et al.* Clonidine treatment for short stature. *Lancet*; 1987; **i:** 1226–30.
8. Pescovitz OH, Tan E. Lack of benefit of clonidine treatment for short stature in a double-blind, placebo-controlled trial. *Lancet* 1988; **ii:** 874–7.
9. Allen DB. Effects of nightly clonidine administration on growth velocity in short children without growth hormone deficiency: a double-blind, placebo-controlled study. *J Pediatr* 1993; **122:** 32–6.

Hyperactivity. Drug treatment of attention deficit hyperactivity disorder (ADHD, p.2148) is usually begun with a central stimulant; clonidine has been tried mainly as an adjunct to stimulant therapy. A meta-analysis[1] of clonidine used to treat this disorder occurring alone or with other conditions, including tic disorders (see Tourette's Syndrome, below), concluded that clonidine may be a useful second-line treatment but is less effective than stimulants and is associated with many adverse effects. There have been reports[2] of sudden death when clonidine has been used with stimulants, but the role of the drugs in these events is unclear. A study[3] in children with both ADHD and Tourette's syndrome found that clonidine used with methylphenidate was more effective than either drug alone, and only 1 child had evidence of adverse cardiac effects. Others have since reported on the efficacy[4] and safety[5] of clonidine in ADHD, alone or with methylphenidate.

Clonidine has also been tried in the management of children with disturbed behaviour (p.954).

1. Connor DF, *et al.* A meta-analysis of clonidine for symptoms of attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 1999; **38:** 1551–9.
2. Fenichel RR. Combining methylphenidate and clonidine: the role of post-marketing surveillance. *J Child Adolesc Psychopharmacol* 1995; **5:** 155–6.
3. The Tourette's Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial. *Neurology* 2002; **58:** 527–36.
4. Palumbo DR, *et al.* Clonidine for attention-deficit/hyperactivity disorder: I. Efficacy and tolerability outcomes. *J Am Acad Child Adolesc Psychiatry* 2008; **47:** 180–8.
5. Daviss WB, *et al.* Clonidine for attention-deficit/hyperactivity disorder: II. ECG changes and adverse events analysis. *J Am Acad Child Adolesc Psychiatry* 2008; **47:** 189–98.

Menopausal disorders. Although HRT is the mainstay of treatment for menopausal disorders (p.2077) clonidine has been of some use in countering vasomotor symptoms in patients who cannot use HRT;[1,2] however, some studies have failed to show a reduction in hot flushes. The adverse effects reported in normotensive women, including orthostatic hypotension, may mean that it is best reserved for women who are also hypertensive.

Clonidine has also been tried[3] for hot flushes in women receiving tamoxifen.

1. Young RL, *et al.* Management of menopause when estrogen cannot be used. *Drugs* 1990; **40:** 220–30.
2. Lucero MA, McCloskey WW. Alternatives to estrogen for the treatment of hot flashes. *Ann Pharmacother* 1997; **31:** 915–17.
3. Pandya KJ, *et al.* Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. *Ann Intern Med* 2000; **132:** 788–93.

Migraine. Propranolol is probably the most well established drug for prophylaxis of migraine (p.616). Many other drugs have been used, including clonidine, but a review of clinical studies[1] indicated that it was a poor first choice and seemed unlikely to work even as a last resort. It has been used in patients whose attacks may be precipitated by tyramine-containing foods.

1. Anonymous. Clonidine in migraine prophylaxis—now obsolete. *Drug Ther Bull* 1990; **28:** 79–80.

Orthostatic hypotension. Paradoxically, clonidine has produced beneficial effects in a few patients with orthostatic hypotension (p.1530), including that due to autonomic neuropathy[1] and that possibly due to brimonidine and betaxolol eye drops in a hypertensive woman with glaucoma;[2] clonidine improved both the orthostatic hypotension and the supine hypertension.

1. Acott PD, *et al.* Effectiveness of clonidine in congenital orthostatic hypotension. *J Pediatr* 1990; **116:** 666–7.
2. Brahmbhatt R, *et al.* Normalization of blood pressure in a patient with severe orthostatic hypotension and supine hypertension using clonidine. *Hypertension* 2001; **37:** e24.

Pain. Giving opioids and local anaesthetics by the epidural or intrathecal routes can produce effective analgesia but adverse effects are common. Many other drugs, including clonidine, have been tried by these routes, alone or as adjuncts. Clonidine is thought to produce analgesia by a direct action on alpha$_2$ adrenoceptors in the spinal cord. It has been used in various types of pain, such as postoperative pain (p.4), labour pain (p.7), and the pain associated with cancer (p.5), particularly neuropathic pain (p.8). It has been used alone but is more usually given with local anaesthetics and/or opioids; it has been given by various routes including epidural, intrathecal, intravenous, intramuscular, oral, and transdermal use. An early meta-analysis[1] of postoperative epidural use of clonidine was unable to reach a conclusion owing to the large number of variables. Two subsequent systematic reviews considered that addition of clonidine to intermediate-acting local anaesthetics improved their activity in certain peripheral nerve blocks,[2] and that adding clonidine to intrathecal local anaesthetics reduced intra-operative pain, although it increased the risk of hypotension.[3] However, the role and appropriate dosage of clonidine in local anaesthesia remained unclear.[2,3] For further discussion of pain and its management, see p.2. See also Premedication, below.

1. Armand S, *et al.* Meta-analysis of the efficacy of extradural clonidine to relieve postoperative pain: an impossible task. *Br J Anaesth* 1998; **81:** 126–34.
2. McCartney CJL, *et al.* Should we add clonidine to local anesthetic for peripheral nerve blockade? A qualitative systematic review of the literature. *Reg Anesth Pain Med* 2007; **32:** 330–8.
3. Elia N, *et al.* Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials. *Reg Anesth Pain Med* 2008; **33:** 159–67.

Phaeochromocytoma. Clonidine acts centrally to suppress catecholamine release and may be used[1] in the diagnosis of phaeochromocytoma (p.1179). Experience gained with the clonidine suppression test and a review of published studies indicated that it is of value in selected patients with moderately elevated plasma and/or urinary catecholamine concentrations.[2]

1. Bravo EL, *et al.* Clonidine-suppression test: a useful aid in the diagnosis of pheochromocytoma. *N Engl J Med* 1981; **305:** 623–6.
2. Lenz T, *et al.* Clonidine suppression test revisited. *Blood Pressure* 1998; **7:** 153–9.

Premedication. Clonidine has been given pre-operatively for its sedative, anxiolytic, and analgesic effects (see also Pain, above), and to provide haemodynamic stability and reduce anaesthetic requirements; it is often given orally, although other routes such as intranasal and intravenous have also been tried. It has often been tried in children,[1] in whom pre-operative use has also been reported to reduce postoperative vomiting[2] (similar results have been reported in adult women[3]). Clonidine may attenuate the perioperative stress response and has been shown to reduce perioperative oxygen consumption, which is a marker of sympathetic activation.[4] It may also reduce the risk of perioperative myocardial ischaemia.[5]

1. Bergendahl H, *et al.* Clonidine in paediatric anaesthesia: review of the literature and comparison with benzodiazepines for premedication. *Acta Anaesthesiol Scand* 2006; **50:** 135–43.
2. Mikawa K, *et al.* Oral clonidine premedication reduces vomiting in children after strabismus surgery. *Can J Anaesth* 1995; **42:** 977–81.
3. Oddby-Muhrbeck E, *et al.* Effects of clonidine on postoperative nausea and vomiting in breast cancer surgery. *Anesthesiology* 2002; **96:** 1109–14.
4. Taittonen MT, *et al.* Effect of clonidine and dexmedetomidine premedication on perioperative oxygen consumption and haemodynamic state. *Br J Anaesth* 1997; **78:** 400–406.
5. Nishina K, *et al.* Efficacy of clonidine for prevention of perioperative myocardial ischemia: a critical appraisal and meta-analysis of the literature. *Anesthesiology* 2002; **96:** 323–9.

Restless legs syndrome. Numerous drugs have been tried for the treatment of restless legs syndrome (see Sleep-associated Movement Disorders, p.958). Symptomatic improvement has been reported with clonidine in a number of case studies[1,2] and small controlled trials,[3] but adverse effects may limit its use.

1. Handwerker JV, Palmer RF. Clonidine in the treatment of "restless leg" syndrome. *N Engl J Med* 1985; **313:** 1228–9.
2. Zoe A, *et al.* High-dose clonidine in a case of restless legs syndrome. *Ann Pharmacother* 1994; **28:** 878–81.
3. Wagner ML, *et al.* Randomized, double-blind, placebo-controlled study of clonidine in restless legs syndrome. *Sleep* 1996; **19:** 52–8.

Shivering. Numerous drugs, including clonidine, have been tried for the treatment of postoperative shivering (p.1779). Clonidine's central and peripheral effects could both account for its antishivering activity, but some have suggested that it acts by resetting the central threshold temperature for shivering. Several studies[1-3] have suggested that clonidine is effective for the treatment of postoperative shivering. Typical doses of 75 to 150 micrograms intravenously have been used. Clonidine given intra-operatively,[4-7] including to neurosurgical patients after mild hypothermia,[8] has also been reported to reduce the incidence of postoperative shivering. However, one study[9] has found nefopam to be superior to clonidine for prevention of postoperative shivering.

1. Joris J, *et al.* Clonidine and ketanserin both are effective treatment for postanesthetic shivering. *Anesthesiology* 1993; **79:** 532–9.
2. Capogna G, Celleno D. IV clonidine for post-extradural shivering in parturients: a preliminary study. *Br J Anaesth* 1993; **71:** 294–5.
3. Schwarzkopf KRG, *et al.* A comparison between meperidine, clonidine and urapidil in the treatment of postanesthetic shivering. *Anesth Analg* 2001; **92:** 257–60.
4. Steinfath M, *et al.* Clonidine administered intraoperatively prevents postoperative shivering. *Br J Clin Pharmacol* 1995; **39:** 580P–581P.
5. Vanderstappen I, *et al.* The effect of prophylactic clonidine on postoperative shivering: a large prospective double-blind study. *Anaesthesia* 1996; **51:** 351–5.
6. Sia S. I.v. clonidine prevents post-extradural shivering. *Br J Anaesth* 1998; **81:** 145–6.
7. Piper SN, *et al.* A comparison of urapidil, clonidine, meperidine and placebo in preventing postanesthetic shivering. *Anesth Analg* 2000; **90:** 954–7.
8. Stapelfeldt C, *et al.* Intraoperative clonidine administration to neurosurgical patients. *Anesth Analg* 2005; **100:** 226–32.
9. Piper SN, *et al.* A comparison of nefopam and clonidine for the prevention of postanaesthetic shivering: a comparative, double-blind and placebo-controlled dose-ranging study. *Anaesthesia* 2004; **59:** 559–64.

Spasticity. Clonidine, given alone or as an adjunct to baclofen, has been tried in patients with various forms of spasticity (p.1887) including those refractory to baclofen.[1-5]

1. Nance PW, *et al.* Clonidine in spinal cord injury. *Can Med Assoc J* 1985; **133:** 41–2.
2. Donovan WH, *et al.* Clonidine effect on spasticity: a clinical trial. *Arch Phys Med Rehabil* 1988; **69:** 193–4.
3. Sandford PR, *et al.* Clonidine in the treatment of brainstem spasticity: case report. *Am J Phys Med Rehabil* 1992; **71:** 301–3.
4. Middleton JW, *et al.* Intrathecal clonidine and baclofen in the management of spasticity and neuropathic pain following spinal cord injury: a case study. *Arch Phys Med Rehabil* 1996; **77:** 824–6.
5. Lubsch L, *et al.* Oral baclofen and clonidine for treatment of spasticity in children. *J Child Neurol* 2006; **21:** 1090–2.

Substance dependence. ***ALCOHOL.*** Although drug treatment of alcohol withdrawal (p.1626) is usually with a benzodiazepine, clonidine has shown benefit[1] in mild to moderate withdrawal, although it has no effect on convulsions or delirium tremens and should not be used as sole therapy. It may be considered with a benzodiazepine when opioid withdrawal is also taking place.

1. Mayo-Smith MF, *et al.* Pharmacological management of alcohol withdrawal: a meta-analysis and evidence-based practice guideline. *JAMA* 1997; **278:** 144–51.

OPIOID ANALGESICS. Clonidine has been reported to be useful in controlling withdrawal symptoms after abrupt withdrawal of opioids (p.101). However, a systematic review[1] of the use of alpha$_2$-adrenoceptor agonists, including clonidine, concluded that, for gradual withdrawal, they were no more effective than reducing doses of methadone over a period of around 10 days, and patients experienced more adverse effects and stopped treatment sooner with clonidine. Clonidine is usually given orally in three or four divided doses to a maximum of 1 mg daily.

Clonidine has also been used with naltrexone to shorten the withdrawal syndrome, allowing withdrawal to be achieved within 6 days.[2] Subsequent modification to the regimen allowed 38 of 40 patients addicted to methadone to withdraw completely in 4 to 5 days.[3] Patients required a mean of 2.3 mg of clonidine on the first day which reduced, but did not abolish, symptoms. A further modification was reported allowing opioid withdrawal with minimal drop-out over 2 to 3 days.[4]

Clonidine has also been used in the management of neonatal abstinence syndrome (p.102) in infants born to opioid-addicted mothers maintained on methadone.[5,6] Benefit occurred in 6 of 7 such infants given an initial clonidine dose of 0.5 to 1 microgram/kg orally, increased over 1 to 2 days to 3 to 5 micrograms/kg daily in divided doses. Total length of treatment ranged from 6 to 17 days. The infant who failed to respond was born to a mother also given haloperidol, desipramine, and theophylline.[6] However, a systematic review[7] found insufficient evidence to support the use of clonidine in the management of neonatal abstinence syndrome.

1. Gowing L, *et al.* Alpha2 adrenergic agonists for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 26/09/05).
2. Charney DS, *et al.* Clonidine and naltrexone: a safe, effective, and rapid treatment of abrupt withdrawal from methadone therapy. *Arch Gen Psychiatry* 1982; **39:** 1327–32.
3. Charney DS, *et al.* The combined use of clonidine and naltrexone as a rapid, safe, and effective treatment of abrupt withdrawal from methadone. *Am J Psychiatry* 1986; **143:** 831–7.
4. Brewer C, *et al.* Opioid withdrawal and naltrexone induction in 48-72 hours with minimal drop-out, using a modification of the naltrexone-clonidine technique. *Br J Psychiatry* 1988; **153:** 340–3.
5. Hoder EL, *et al.* Clonidine in neonatal narcotic-abstinence syndrome. *N Engl J Med* 1981; **305:** 1284.
6. Hoder EL, *et al.* Clonidine treatment of neonatal narcotic abstinence syndrome. *Psychiatry Res* 1984; **13:** 243–51.
7. Osborn DA, *et al.* Sedatives for opiate withdrawal in newborn infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 03/03/06).

SMOKING. Nicotine dependence may be managed using behavioural or psychological counselling. In addition, nicotine replacement therapy (see Smoking Cessation, p.2354) can help alleviate withdrawal symptoms. A number of other drugs, including clonidine, have also been tried. A systematic review[1] found clonidine given in doses of 200 to 400 micrograms daily orally or the equivalent transdermally to be effective; however adverse effects limit its usefulness and clonidine

should be reserved for second-line treatment under close medical supervision in those who experience severe agitation and anxiety when stopping smoking.

Some individual studies have found clonidine to be more effective in women although the authors of the systematic review[1] recommended that these results be interpreted cautiously since some studies also found that women were less successful in giving up smoking unaided than men; treatment with clonidine, however, resulted in similar success rates in both men and women.

1. Gourlay SG, *et al.* Clonidine for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 26/09/05).

Tourette's syndrome. Clonidine is one of many drugs that have been tried in the management of Tourette's syndrome (see Tics, p.954).

Disturbance of monoamine metabolism (including dopamine, noradrenaline, and serotonin) has been implicated in Tourette's syndrome. Clonidine is thought to reduce central noradrenergic activity and may also affect other neurochemical systems, and these properties may account for its beneficial effects in this disorder. Studies of clonidine in Tourette's syndrome have produced mixed results,[1-5] although this may reflect the difficulty in study design for a disease that can vary considerably in severity and presence of comorbid conditions and whose symptoms wax and wane. A retrospective study[6] in juvenile patients given clonidine suggested that those showing improvement in the attention deficit hyperactivity disorder associated with Tourette's syndrome had previously had a longer duration of vocal tics; older children had a better overall response than younger children, who tended to suffer more from clonidine-induced drowsiness. However, no predictors of response could be identified. Nevertheless, clonidine is increasingly favoured for first-line treatment in patients with mild to moderate symptoms, because of a relative lack of serious adverse effects when compared to the commonly used antipsychotics pimozide and haloperidol, although exacerbation of tics and a marked sensation of heat have been reported[7] in one patient. Clonidine has also been reported to successfully control symptoms in some children with Tourette's syndrome unresponsive to haloperidol.[1]

Clonidine has also been used with stimulants in children with Tourette's syndrome and attention deficit hyperactivity disorder, although there have been concerns about the toxicity of such combinations (see Hyperactivity, above).

1. Cohen DJ, *et al.* Clonidine in Tourette's syndrome. *Lancet* 1979; **ii:** 551–3.
2. Shapiro AK, *et al.* Treatment of Gilles de la Tourette's syndrome with clonidine and neuroleptics. *Arch Gen Psychiatry* 1983; **40:** 1235–40.
3. Leckman JF, *et al.* Short- and long-term treatment of Tourette's syndrome with clonidine: a clinical perspective. *Neurology* 1985; **35:** 343–51.
4. Goetz CG, *et al.* Clonidine and Gilles de la Tourette's syndrome: double-blind study using objective rating methods. *Ann Neurol* 1987; **21:** 307–10.
5. Leckman JF, *et al.* Clonidine treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 1991; **48:** 324–8.
6. Lichter DG, Jackson LA. Predictors of clonidine response in Tourette syndrome: implications and inferences. *J Child Neurol* 1996; **11:** 93–7.
7. Kessler AR. Clonidine treatment increases tics in patients with Tourette syndrome: case report. *J Child Neurol* 2001; **16:** 380–1.

Preparations

BP 2008: Clonidine Injection; Clonidine Tablets;
USP 31: Clonidine Hydrochloride and Chlorthalidone Tablets; Clonidine Hydrochloride Tablets; Clonidine Transdermal System.

Proprietary Preparations (details are given in Part 3)
Arg.: Clonidural; ***Austral.:*** Catapres; ***Austria:*** Catapresan; Isoglaucon; ***Belg.:*** Catapressan; Dixarit; ***Braz.:*** Atensina; Clonesina†; Neo Clodil†; ***Canad.:*** Catapres; Dixarit; ***Chile:*** Catapresan; ***Cz.:*** Aruclonin; Catapresan; ***Denm.:*** Catapresan; ***Fin.:*** Catapresan; ***Fr.:*** Catapressan; ***Ger.:*** Aruclonin†; Catapresan; Clonid-Ophtal; Clonistada; Dispaclonidin; Dixarit†; Haemiton†; Isoglaucon; Mirfat†; Paracefan; ***Gr.:*** Catapresan; ***Hong Kong:*** Catapres†; Dixarit; ***Hung.:*** Aruclonin; ***India:*** Arkamin; Catapres; ***Indon.:*** Catapres; ***Irl.:*** Catapres; Dixarit; ***Israel:*** Clonnirit; Normopresan; ***Ital.:*** Adesipress-TTS†; Catapresan; Isoglaucon; ***Jpn:*** Catapres; ***Malaysia:*** Dixarit†; ***Mex.:*** Catapresan; Epiclodina; ***Neth.:*** Catapresan; Dixarit; ***Norw.:*** Catapresan; ***NZ:*** Catapres; Dixarit; ***Philipp.:*** Catapres; ***Pol.:*** Iporel; ***Port.:*** Catapresan; Edolglau; ***Rus.:*** Haemiton (Гемитон); ***S.Afr.:*** Dixarit; Menograine; ***Singapore:*** Dixarit†; ***Spain:*** Catapresan; Isoglaucon; ***Swed.:*** Catapresan; ***Switz.:*** Catapresan; ***Thai.:*** Catapres; Hypodine; ***UK:*** Catapres; Dixarit; ***USA:*** Catapres; Duraclon; ***Venez.:*** Catapresan; Clonipres†; Lowpres; Naclodin; Velaril.

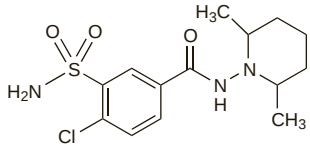
Multi-ingredient: ***Arg.:*** Bemplas; Pertenso; ***Ger.:*** Combipresan†; Haemiton compositum†; ***India:*** Arkamin-H; Catapres Diu; ***USA:*** Clorpres; Combipres†.

Clopamide *(BAN, USAN, rINN)* ⊗

Clopamida; Clopamidum; DT-327; Klopamid; Klopamidi. 4-Chloro-*N*-(2,6-dimethylpiperidino)-3-sulphamoylbenzamide; *cis*-3-(Aminosulphonyl)-4-chloro-*N*-(2,6-dimethyl-1-piperidinyl)benzamide.

Клопамид

$C_{14}H_{20}ClN_3O_3S$ = 345.8.
CAS — 636-54-4.
ATC — C03BA03.
ATC Vet — QC03BA03.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Clopamide). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Slightly soluble in water and in anhydrous alcohol; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Profile

Clopamide is a diuretic with properties similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1307) even though it does not contain a thiazide ring system. It is used for oedema, including that associated with heart failure (p.1165), and for hypertension (p.1171).

Diuresis starts in 1 to 2 hours after an oral dose, reaches a maximum in about 3 to 6 hours, and lasts for up to 24 hours.

In the treatment of oedema the usual oral dose is 10 to 20 mg daily or on alternate days. For hypertension doses of 5 to 10 mg daily, either alone, or with other antihypertensives have been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Denm.: Adurix; ***Ger.:*** Brinaldix†; ***Hung.:*** Brinaldix; ***India:*** Brinaldix.

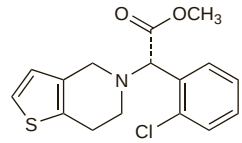
Multi-ingredient: ***Austria:*** Brinerdin; ***Belg.:*** Viskaldix; ***Braz.:*** Viskaldix; ***Chile:*** Viskaldix; ***Cz.:*** Crystepin; ***Fr.:*** Viskaldix; ***Ger.:*** Briserin N; Viskaldix; ***Gr.:*** Viskaldix; ***Hung.:*** Viskaldix; ***Irl.:*** Viskaldix; ***Ital.:*** Brinerdina; ***Malaysia:*** Viskaldix; ***Neth.:*** Viskaldix; ***Philipp.:*** Viskaldix; ***Pol.:*** Normatens; ***Port.:*** Brinerdine†; ***Rus.:*** Crystepin (Кристепин); Viskaldix (Вискалдикс); ***S.Afr.:*** Brinerdin; ***Spain:*** Brinerdina†; ***Switz.:*** Brinerdine; Viskaldix; ***Thai.:*** Bedin; Brinerdin; Hyperdine†; Viskaldix†; ***UK:*** Viskaldix; ***Venez.:*** Viskaldix†.

Clopidogrel Bisulfate *(USAN, rINNM)*

Bisulfato de clopidogrel; Clopidogrel, Bisulfate de; Clopidogrel Bisulphate *(BANM)*; Clopidogrel Hydrogen Sulphate; Clopidogreli Bisulfas; PCR-4099 (clopidogrel); SR-25990C. Methyl (*S*)-2-chlorophenyl(4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-5-yl)acetate bisulphate; Methyl (+)-(*S*)-α-(*o*-chlorophenyl)-6,7-dihydrothieno-[3,2-*c*]pyridine-5(4*H*)-acetate sulphate.

Клопидогрела Бисульфат

$C_{16}H_{16}ClNO_2S,H_2SO_4$ = 419.9.
CAS — 113665-84-2 (clopidogrel); 94188-84-8 (clopidogrel); 120202-66-6 (clopidogrel bisulfate).
ATC — B01AC04.
ATC Vet — QB01AC04.



(clopidogrel)

Pharmacopoeias. In *US.*
USP 31 (Clopidogrel Bisulfate). A white to off-white powder. Freely soluble in water and in methyl alcohol; practically insoluble in ether.

Adverse Effects and Precautions

As for Ticlopidine, p.1411.

The incidence of adverse effects, particularly blood dyscrasias, is lower with clopidogrel, although fatalities have been reported (see Effects on the Blood, p.1411). Routine blood counts are not necessary, although they should be performed promptly when clinical signs suggest blood dyscrasias. Other adverse effects, reported rarely, include serum sickness, interstitial pneumonitis, erythema multiforme, Stevens-Johnson syndrome, lichen planus, and myalgia.

Consideration should be given to stopping clopidogrel 5 to 7 days before elective surgery.

Effects on the blood. For reports of blood dyscrasias associated with clopidogrel therapy see under Adverse Effects of Ticlopidine, p.1411.

Effects on taste. Loss of taste occurred in 2 patients 6 to 8 weeks after starting treatment with clopidogrel, but recovered fully when clopidogrel was withdrawn.[1] Rechallenge in 1 of the patients led to recurrence of the taste loss, which persisted when treatment was stopped.

1. Golka K, *et al.* Reversible ageusia as an effect of clopidogrel treatment. *Lancet* 2000; **355:** 465–6.

Hypersensitivity. Clopidogrel has been associated with hypersensitivity reactions including angioedema.[1] There have also been reports[2-5] of a hypersensitivity syndrome comprising fever, rash, and varying additional symptoms.

1. Fischer TC, *et al.* Clopidogrel-associated angioedema. *Am J Med* 2003; **114:** 77–8.
2. Sarrot-Reynauld F, *et al.* Severe hypersensitivity associated with clopidogrel. *Ann Intern Med* 2001; **135:** 305–6.
3. Phillips EJ, *et al.* Serum sickness-like reaction associated with clopidogrel. *Br J Clin Pharmacol* 2003; **56:** 583.
4. Wolf I, *et al.* Clopidogrel-induced systemic inflammatory response syndrome. *Mayo Clin Proc* 2003; **78:** 618–20.
5. Doogue MP, *et al.* Clopidogrel hypersensitivity syndrome with rash, fever, and neutropenia. *Mayo Clin Proc* 2005; **80:** 1368–70.

Resistance. Results from platelet aggregation studies suggest that there is considerable variation in response to clopidogrel, although the clinical relevance of a low response (clopidogrel resistance) is unclear.[1,2] There is some evidence that the risk of cardiovascular events is higher in patients with clopidogrel resistance,[3] but this is not established. Factors that may contribute to clopidogrel resistance include drug interactions and genetic variation in platelet sensitivity or clopidogrel metabolism.[1,2] Patients with diabetes mellitus also appear to have a lower response.[4]

1. Nguyen TA, *et al.* Resistance to clopidogrel: a review of the evidence. *J Am Coll Cardiol* 2005; **45:** 1157–64.
2. Angiolillo DJ, *et al.* Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *J Am Coll Cardiol* 2007; **49:** 1505–16.
3. Geisler T, *et al.* Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation. *Eur Heart J* 2006; **27:** 2420–5.
4. Geisler T, *et al.* Platelet response to clopidogrel is attenuated in diabetic patients undergoing coronary stent implantation. *Diabetes Care* 2007; **30:** 372–4.

Interactions

Clopidogrel should be used with caution in patients receiving other drugs that increase the risk of bleeding, including anticoagulants, other antiplatelets, and NSAIDs. Clopidogrel may inhibit the cytochrome P450 isoenzyme CYP2C9 and interactions with drugs metabolised by this isoenzyme are theoretically possible; it may also inhibit CYP2B6 (see Bupropion, below).

Antifungals. A study[1] in healthy subjects found that *ketoconazole* decreased the plasma concentration of the active metabolite of clopidogrel; platelet inhibitory action was also reduced.

1. Farid NA, *et al.* Cytochrome P450 3A inhibition by ketoconazole affects prasugrel and clopidogrel pharmacokinetics and pharmacodynamics differently. *Clin Pharmacol Ther* 2007; **81:** 735–41.

Bupropion. A study[1] in healthy subjects found that clopidogrel reduced the conversion of bupropion to its active metabolite, suggesting that clopidogrel inhibits the cytochrome P450 isoenzyme CYP2B6.

1. Turpeinen M, *et al.* Effect of clopidogrel and ticlopidine on cytochrome P450 2B6 activity as measured by bupropion hydroxylation. *Clin Pharmacol Ther* 2005; **77:** 553–9.

Ciclosporin. For reports of rhabdomyolysis developing in patients when given clopidogrel in addition to ciclosporin and a statin, see Statins, below.

Statins. There have been reports of rhabdomyolysis developing in patients when given clopidogrel in addition to ciclosporin and a statin (atorvastatin[1,2], lovastatin[3], or simvastatin[3]). Rhabdomyolysis is a recognised adverse effect when ciclosporin and statins are used together (see Immunosuppressants under Interactions of Simvastatin, p.1393), but the patients in these reports had previously received the combination without incident and developed rhabdomyolysis 1 to 3 weeks after clopidogrel was started. It has been suggested[2] that the mechanism is a three way interaction involving competition for binding sites on the cytochrome P450 isoenzyme CYP3A4 between statins and clopidogrel, exacerbated by ciclosporin-mediated enzyme inhibition.

Although it has been suggested that statins may decrease the antiplatelet effect of clopidogrel, evidence for such an interaction is conflicting and the clinical relevance has not been established.[4]

1. Anon. Clopidogrel (Plavix): suspected drug interaction with atorvastatin (Lipitor) and cyclosporine resulting in rhabdomyolysis. *Can Adverse React News* 2005; **15** (Apr): 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n2_e.pdf (accessed 01/09/05)
2. Burton JR, *et al.* Clopidogrel-precipitated rhabdomyolysis in a stable heart transplant patient. *Ann Pharmacother* 2007; **41:** 133–7.
3. Uber PA, *et al.* Clopidogrel and rhabdomyolysis after heart transplantation. *J Heart Lung Transplant* 2003; **22:** 107–8.
4. Tafreshi MJ, *et al.* Combination of clopidogrel and statins: a hypothetical interaction or therapeutic dilemma? *Pharmacotherapy* 2006; **26:** 388–94.