pressan; ***India:*** Nepresol; ***Malaysia:*** Nepresol†; ***S.Afr.:*** Nepresol†; ***Swed.:*** Nepresol†; ***Switz.:*** Nepresol†; ***Thai.:*** Nepresol.

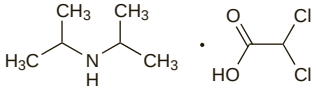
Multi-ingredient: ***Braz.:*** Adelfan-Esidrex†; ***Ger.:*** Adelphan-Esidrix†; Obsilazin N†; Tri-Torrat†; Triniton; ***Hong Kong:*** Adelphane-Esidrex; ***India:*** Adelphane; Adelphane-Esidrex; Beptazine; Beptazine-H; ***Indon.:*** Dellasidrex; ***Rus.:*** Adelphane-Esidrex (Адельфан-эзидрекс); Triresid K (Трирезид К); ***Spain:*** Adelfan-Esidrex†; ***Switz.:*** Adelphan-Esidrex; ***Turk.:*** Adelphan; Adelphan-Esidrex.

Di-isopropylammonium Dichloroacetate

Diisopropilamina, dicloroacetato de; Di-isopropylamine Dichloroacetate; Di-isopropylamine Dichloroethanoate; DIPA-DCA.

$C_8H_{17}Cl_2NO_2$ = 230.1.

CAS — 660-27-5.



Profile

Di-isopropylammonium dichloroacetate is a vasodilator that has been given in peripheral and cerebral vascular disorders. Preparations containing it have sometimes been described as 'pangamic acid' (p.2362).

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Disotat†; Oxypangam†; ***Mex.:*** Ditrei.
Multi-ingredient: ***Hong Kong:*** Liverall†; ***Spain:*** Vitaber A E.

Dilazep Hydrochloride *(rINNM)*

Asta C-4898; Dilazep, Chlorhydrate de; Dilazepi Hydrochloridum; Hidrocloruro de dilazep. Perhydro-1,4-diazepin-1,4-diylbis(trimethylene 3,4,5-trimethoxybenzoate) dihydrochloride.

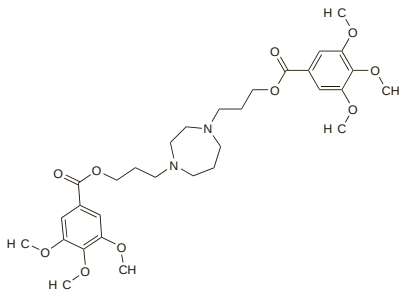
Дилазепа Гидрохлорид

$C_{31}H_{44}N_2O_{10}$,2HCl = 677.6.

CAS — 35898-87-4 (dilazep); 20153-98-4 (dilazep hydrochloride).

ATC — C01DX10.

ATC Vet — QC01DX10.



(dilazep)

Pharmacopoeias. *Jpn* includes the monohydrate.

Profile

Dilazep hydrochloride is a vasodilator that is used in ischaemic heart disease.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Cormelian; ***Jpn:*** Comelian.

Diltiazem Hydrochloride

(BANM, USAN, rINNM)

CRD-401; Diltiatseemihydrokloridi; Diltiazem, chlorhydrate de; Diltiazem Hidroklorür; Diltiazem hydrochlorid; Diltiazem-hidroklorid; Diltiazemhydroklorid; Diltiazemi hydrochloridum; Diltiazemo hidrochloridas; Diltiazemu chlorowodorek; Hidrocloruro de diltiazem; Latiazem Hydrochloride; MK-793 (diltiazem malate). (+)-*cis*-3-Acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one hydrochloride; (2*S*,3*S*)-5-(2-Dimethylaminoethyl)-2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepin-3-yl acetate hydrochloride.

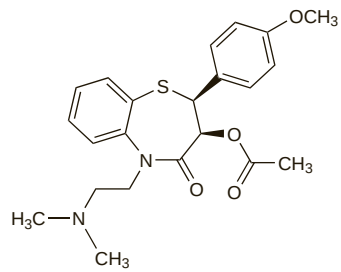
Дилтиазема Гидрохлорид

$C_{22}H_{26}N_2O_4S$,HCl = 451.0.

CAS — 42399-41-7 (diltiazem); 33286-22-5 (diltiazem hydrochloride); 144604-00-2 (diltiazem malate).

ATC — C08DB01.

ATC Vet — QC08DB01.



(diltiazem)

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

Ph. Eur. 6.2 (Diltiazem Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water, in dichloromethane, and in methyl alcohol; slightly soluble in dehydrated alcohol. The pH of a 1% solution in water is 4.3 to 5.3. Store in airtight containers. Protect from light.

USP 31 (Diltiazem Hydrochloride). A white, odourless, crystalline powder, or small crystals. Freely soluble in water, in chloroform, in formic acid, and in methyl alcohol; sparingly soluble in dehydrated alcohol; insoluble in ether. Store in airtight containers. Protect from light.

Adverse Effects

Treatment with diltiazem is generally well tolerated. Headache, ankle oedema, hypotension, dizziness, flushing, fatigue, and nausea and other gastrointestinal disturbances (including anorexia, vomiting, constipation or diarrhoea, taste disturbances, and weight gain) may occur. Gingival hyperplasia has been reported. Rashes, possibly due to hypersensitivity, are normally mild and transient, but in a few cases erythema multiforme or exfoliative dermatitis has developed; photosensitivity reactions may also occur. Transient elevations in liver enzyme values, and occasionally hepatitis, have been reported.

Diltiazem may depress cardiac conduction and has occasionally led to AV block, bradycardia, and rarely asystole or sinus arrest.

Overdosage with diltiazem may be associated with bradycardia, with or without AV conduction defects, and hypotension.

Diltiazem has been shown to cause teratogenicity in *animal* studies.

Effects on mortality. For discussion of the possibility that calcium-channel blockers might be associated with increased cardiovascular mortality, see under Adverse Effects of Nifedipine, p.1350.

Angioedema. Periorbital angioedema, accompanied by pruritus or burning and erythema developed in 2 patients given diltiazem.[1]

1. Sadick NS, *et al.* Angioedema from calcium channel blockers. *J Am Acad Dermatol* 1989; **21:** 132–3.

Effects on the blood. Thrombocytopenia has been reported in association with diltiazem.[1,2]

1. Lahav M, Arav R. Diltiazem and thrombocytopenia. *Ann Intern Med* 1989; **110:** 327.
2. Michalets EL, Jackson DV. Diltiazem-associated thrombocytopenia. *Pharmacotherapy* 1997; **17:** 1345–8.

Effects on carbohydrate metabolism. Although raised blood-glucose concentrations and insulin requirements have been reported[1] in a patient with type 1 diabetes mellitus during diltiazem therapy, particularly at high doses, a study[2] in 11 obese black women, who were nondiabetic but had a family history of type 2 diabetes, failed to find any effect of diltiazem 240 mg daily on plasma-glucose and C-peptide concentrations, nor any clinical signs of glucose intolerance.

1. Pershadsingh HA, *et al.* Association of diltiazem therapy with increased insulin resistance in a patient with type I diabetes mellitus. *JAMA* 1987; **257:** 930–1.
2. Jones BJ, *et al.* Effects of diltiazem hydrochloride on glucose tolerance in persons at risk for diabetes mellitus. *Clin Pharm* 1988; **7:** 235–8.

Effects on the ears. There have been isolated reports[1] of tinnitus associated with several calcium-channel blockers including nifedipine, nicardipine, nitrendipine, diltiazem, verapamil, and cinnarizine.

1. Narváez M, *et al.* Tinnitus with calcium-channel blockers. *Lancet* 1994; **343:** 1229–30.

Effects on the gastrointestinal tract. Gastrointestinal disturbances including nausea, vomiting, and constipation, may occur with calcium-channel blockers. A case[1] of intestinal pseudo-obstruction was reported in a 74-year-old neutropenic man receiving chemotherapy for leukaemia after diltiazem was added to treat new-onset atrial fibrillation. A diagnosis of neutropenic enterocolitis was ruled out and symptoms resolved when diltiazem was stopped; it was concluded that diltiazem was the probable cause.

A similar case attributed to verapamil[2] has been reported.

1. Young RP, Wu H. Intestinal pseudo-obstruction caused by diltiazem in a neutropenic patient. *Ann Pharmacother* 2005; **39:** 1749–51.
2. Schultz HS, Vernon B. Intestinal pseudo-obstruction related to using verapamil. *West J Med* 1989; **151:** 556–8.

Effects on the heart. ***AV BLOCK.*** AV block appears to be uncommon in patients receiving diltiazem, but is potentially serious when it occurs. Prescription-event monitoring[1] of a cohort of 10 119 patients for 1 year revealed 22 reports of AV block during diltiazem treatment. At least 8 patients had third-degree heart block, and 12 required a pacemaker; 3 died within 72 hours of the onset of heart block. A high proportion of these patients were also receiving beta blockers, which is in line with other reports.[2,3] (See also Beta Blockers under Interactions, below.) There is some evidence that the incidence of this effect may depend on the serum concentration of diltiazem. In a study[4] in patients receiving diltiazem after myocardial infarction, patients with serum-diltiazem concentrations greater than 150 nanograms/mL were more likely to experience AV block than patients with concentrations of diltiazem below this value.

1. Waller PC, Inman WHW. Diltiazem and heart block. *Lancet* 1989; **i:** 617.
2. Hossack KF. Conduction abnormalities due to diltiazem. *N Engl J Med* 1982; **307:** 953–4.
3. Ishikawa T, *et al.* Atrioventricular dissociation and sinus arrest induced by oral diltiazem. *N Engl J Med* 1983; **309:** 1124–5.
4. Nattel S, *et al.* Determinants and significance of diltiazem plasma concentrations after acute myocardial infarction. *Am J Cardiol* 1990; **66:** 1422–8.

MYOCARDIAL INFARCTION. Results from at least one large multicentre study (the Multicenter Diltiazem Postinfarction Trial) suggest that diltiazem, although apparently of benefit after myocardial infarction in patients with normal left ventricular function (as indicated by absence of pulmonary congestion), was associated with an increased risk of cardiac death or non-fatal re-infarction in patients with impaired left ventricular function.[1] Long-term follow-up[2] indicated that diltiazem also increased the risk of late-onset heart failure in postinfarction patients with left ventricular dysfunction.

1. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988; **319:** 385–92.
2. Goldstein RE, *et al.* Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. *Circulation* 1991; **83:** 52–60.

WITHDRAWAL. Life-threatening coronary vasospasm, which was fatal in one patient, occurred in 4 patients after coronary revascularisation for unstable angina.[1] Treatment with a calcium-channel blocker (diltiazem or nifedipine) had been discontinued between 8 and 18 hours before the procedure and this abrupt withdrawal was thought to be responsible for the rebound vasospasm. The coronary vasospasm was managed with glyceryl trinitrate and nifedipine.

Withdrawal of diltiazem over a 4-day period from a patient with stable angina pectoris was followed by recurrence of anginal attacks.[2] Ambulatory ECG monitoring confirmed worsening myocardial ischaemia that responded to re-introduction of diltiazem. Two further patients had a similar withdrawal effect.

1. Engelman RM, *et al.* Rebound vasospasm after coronary revascularization in association with calcium antagonist withdrawal. *Ann Thorac Surg* 1984; **37:** 469–72.
2. Subramanian VB, *et al.* Calcium antagonist withdrawal syndrome: objective demonstration with frequency-modulated ambulatory ST-segment monitoring. *BMJ* 1983; **286:** 520–1.

Effects on the kidneys. Diltiazem may be of benefit in various kidney disorders (see under Uses, below). However, there are a few reports of acute renal failure associated with diltiazem use.[1,2] Acute interstitial nephritis has been proposed as a mechanism.[2,3]

1. ter Wee PM, *et al.* Acute renal failure due to diltiazem. *Lancet* 1984; **ii:** 1337–8.
2. Abadín JA, *et al.* Probable diltiazem-induced acute interstitial nephritis. *Ann Pharmacother* 1998; **32:** 656–8.
3. Achenbach V, *et al.* Acute renal failure due to diltiazem. *Lancet* 1985; **i:** 176.

Effects on mental function. By September 1989, the WHO collaborative programme for international drug monitoring had gathered 8 cases of mental depression (severe in 2) associated with diltiazem therapy.[1] Time of onset of symptoms varied from a few hours to a few months after starting treatment with diltiazem. There was some evidence that the problem might be dose-related as 5 of the 8 cases were receiving doses of 180 mg daily or more.

Psychoses have been reported rarely in association with diltiazem. A patient[2] who developed hallucinations (both auditory and visual) and paranoid delusions after 2 days of diltiazem therapy was subsequently treated with nifedipine without abnormal effects. Another patient[3] with bipolar affective disorder that had been well-controlled by lithium carbonate for some years developed acute psychosis with extrapyramidal symptoms of cog-

wheel rigidity and ataxia, which was thought to represent an interaction between diltiazem and lithium.

1. Biriell C, *et al.* Depression associated with diltiazem. *BMJ* 1989; **299:** 796.
2. Bushe CJ. Organic psychosis caused by diltiazem. *J R Soc Med* 1988; **81:** 296–7.
3. Binder EF. Diltiazem-induced psychosis and a possible diltiazem-lithium interaction. *Arch Intern Med* 1991; **151:** 373–4.

Effects on the mouth. A study involving 115 patients given nifedipine, diltiazem, or verapamil for at least 3 months indicated that gingival hyperplasia is an important side-effect that may occur with calcium-channel blockers.[1]

1. Steele RM, *et al.* Calcium antagonist-induced gingival hyperplasia. *Ann Intern Med* 1994; **120:** 663–4.

Effects on the nervous system. Akathisia has been reported in a patient the day after starting treatment with diltiazem. Symptoms disappeared when diltiazem was withdrawn and recurred on rechallenge after the third dose.[1] Similar symptoms in association with mania have also been reported in another patient given diltiazem.[2]

1. Jacobs MB. Diltiazem and akathisia. *Ann Intern Med* 1983; **99:** 794–5.
2. Brink DD. Diltiazem and hyperactivity. *Ann Intern Med* 1984; **100:** 459–60.

PARKINSONISM. Parkinsonism developed in an elderly patient with heart disease and hypertension when diltiazem was added to existing drug therapy.[1] Symptoms worsened over 3 months but improved significantly when diltiazem was slowly withdrawn. On rechallenge severe tremor, impaired gait, and cogwheel rigidity recurred, but resolved when the drug was stopped again except for slight residual cogwheel rigidity.

An acute parkinsonian syndrome also developed[2] in a patient taking lithium and tiotixene when diltiazem was added, and was thought to represent an interaction between lithium and diltiazem. See also Effects on Mental Function, above.

1. Dick RS, Barold SS. Diltiazem-induced parkinsonism. *Am J Med* 1989; **87:** 95–6.
2. Valdiserri EV. A possible interaction between lithium and diltiazem: case report. *J Clin Psychiatry* 1985; **46:** 540–1.

Effects on the skin. A variety of skin disorders have been associated with diltiazem therapy, including acute pustular dermatitis,[1-3] cutaneous vasculitis,[4,5] erythema multiforme,[6,7] pruritic macular rashes,[3,8] severe toxic erythema,[9] subacute lupus erythematosus-like eruptions,[10] and photosensitivity reactions.[11] Analysis of cutaneous adverse reactions to diltiazem indicated that acne, rash, and urticaria were among the commonest.[12] There have also been a few reports of exfoliative dermatitis, erythema multiforme, Stevens Johnson syndrome, and toxic epidermal necrolysis.[3,12]

For a report of periorbital skin rash associated with diltiazem, see Angioedema, above.

Cross-sensitivity, manifest as a pruritic maculopapular rash, has been reported between diltiazem and amlodipine.[13]

1. Lambert DG, *et al.* Acute generalized exanthematous pustular dermatitis induced by diltiazem. *Br J Dermatol* 1988; **118:** 308–9.
2. Vicente-Calleja JM, *et al.* Acute generalized exanthematous pustulosis due to diltiazem: confirmation by patch testing. *Br J Dermatol* 1997; **137:** 837–9.
3. Knowles S, *et al.* The spectrum of cutaneous reactions associated with diltiazem: three cases and a review of the literature. *J Am Acad Dermatol* 1998; **38:** 201–6.
4. Carmichael AJ, Paul CJ. Vasculitic leg ulcers associated with diltiazem. *BMJ* 1988; **297:** 562.
5. Sheehan-Dare RA, Goodfield MJ. Severe cutaneous vasculitis induced by diltiazem. *Br J Dermatol* 1988; **119:** 134.
6. Berbis P, *et al.* Diltiazem associated erythema multiforme. *Dermatologica* 1989; **179:** 90.
7. Sanders CJG, Neumann HAM. Erythema multiforme, Stevens-Johnson syndrome, and diltiazem. *Lancet* 1993; **341:** 967.
8. Wirebaugh SR, Geraets DR. Reports of erythematous macular skin eruptions associated with diltiazem therapy. *DICP Ann Pharmacother* 1990; **24:** 1046–9.
9. Wakeel RA, *et al.* Severe toxic erythema caused by diltiazem. *BMJ* 1988; **296:** 1071.
10. Crowson AN, Magro CM. Diltiazem and subacute cutaneous lupus erythematosus-like lesions. *N Engl J Med* 1995; **333:** 1429.
11. Saladi RN, *et al.* Diltiazem induces severe photodistributed hyperpigmentation: case series, histoimmunopathology, management, and review of the literature. *Arch Dermatol* 2006; **142:** 206–10.
12. Stern R, Khalsa JH. Cutaneous adverse reactions associated with calcium channel blockers. *Arch Intern Med* 1989; **149:** 829–32.
13. Baker BA, Cacchione JG. Dermatologic cross-sensitivity between diltiazem and amlodipine. *Ann Pharmacother* 1994; **28:** 118–19.

Overdosage. See under Treatment of Adverse Effects, below.

Treatment of Adverse Effects

As for Nifedipine, p.1352, but see also below.

Diltiazem and its metabolites are poorly dialysable.

Overdosage. The consequences and treatment of diltiazem overdosage are similar to nifedipine (p.1352), although death and life-threatening complications might be more common with diltiazem.[1] Up to 1994, 6 cases of fatal overdose with diltiazem had been reported in the literature.[2] Measurement of diltiazem concentrations to assist in diagnosis and management of overdosage has been suggested,[2] but others[3] have disputed its value.

The following are individual reports of overdosage with diltiazem:

- A patient who took about 10.8 g of diltiazem developed hypotension and complete heart block. Dopamine, isoprenaline, and calcium chloride were required to maintain the blood pressure. The ECG reverted to sinus rhythm after 31 hours. The plasma-diltiazem concentration was 1670 nanograms/mL 43 hours after ingestion and fell to 12.1 nanograms/mL over a further 55.5 hours with an elimination half-life of 7.9 hours.[4]
- In a further case a patient took 5.88 g of diltiazem with alcohol, and developed severe junctional bradycardia, hypotension, and reduced cardiac function that did not respond to intravenous calcium gluconate. The maximum plasma-diltiazem concentration of 6090 nanograms/mL occurred 7 hours after presentation. About half of the dose was vomited after treatment with activated charcoal. The patient was treated with cardiac pacing and a dopamine infusion; he reverted to sinus rhythm within 24 hours, and a subsequent episode of atrial fibrillation was treated successfully with digoxin.[5]
- Charcoal haemoperfusion had a limited effect in improving the clearance of diltiazem in a patient who had taken 14.94 g of diltiazem.[6] The patient developed severe hypotension, complete heart block, and acute renal failure. Supportive care included cardiac pacing and numerous vasopressors including intravenous glucagon and infusions of dopamine, adrenaline, and noradrenaline.

1. Buckley NA, *et al.* Overdose with calcium channel blockers. *BMJ* 1994; **308:** 1639.
2. Roper TA. Overdose of diltiazem. *BMJ* 1994; **308:** 1571.
3. Lip GYH, Ferner RE. Overdose of diltiazem. *BMJ* 1994; **309:** 193.
4. Malcolm N, *et al.* Massive diltiazem overdosage: clinical and pharmacokinetic observations. *Drug Intell Clin Pharm* 1986; **20:** 888.
5. Ferner RE, *et al.* Pharmacokinetics and toxic effects of diltiazem in massive overdose. *Hum Toxicol* 1989; **8:** 497–9.
6. Williamson KM, Dunham GD. Plasma concentrations of diltiazem and desacetyldiltiazem in an overdose situation. *Ann Pharmacother* 1996; **30:** 608–11.

Precautions

Diltiazem is contra-indicated in patients with the sick sinus syndrome, pre-existing second- or third-degree AV block, or marked bradycardia, and should be used with care in patients with lesser degrees of AV block or bradycardia. Diltiazem has been associated with the development of heart failure and great care is required in patients with impaired left ventricular function. Sudden withdrawal of diltiazem might be associated with an exacerbation of angina.

Treatment with diltiazem should begin with reduced doses in elderly patients and in patients with hepatic or renal impairment.

Abuse. Abuse of diltiazem by body builders and rugby players has been alleged. Such abuse is possibly because of evidence that diltiazem increases maximum oxygen consumption after training. A body builder who admitted to taking diltiazem in high doses suffered severe abdominal cramps.[1]

1. Richards H, *et al.* Use of diltiazem in sport. *BMJ* 1993; **307:** 940.

Breast feeding. Diltiazem is distributed into breast milk; in a woman receiving oral diltiazem 60 mg four times daily, concentrations in breast milk were similar to those in serum.[1] The manufacturers therefore recommend that diltiazem should generally be avoided during breast feeding. However, in another report,[2] a mother breast fed twins for at least 6 months while receiving diltiazem and no adverse effects were reported in the infants. Since there have been no reports of adverse effects, the American Academy of Pediatrics considers[3] that diltiazem is usually compatible with breast feeding.

1. Okada M, *et al.* Excretion of diltiazem in human milk. *N Engl J Med* 1985; **312:** 992–3.
2. Lubbe WF. Use of diltiazem during pregnancy. *N Z Med J* 1987; **100:** 121.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Porphyria. Diltiazem is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Renal impairment. A patient with end-stage renal failure requiring haemodialysis developed hypotension, bradycardia, metabolic acidosis, hyperkalaemia, and acute congestive heart failure about 60 hours after his last haemodialysis.[1] The patient had been taking diltiazem 60 mg three times daily. The symptoms were attributed to diltiazem toxicity due to accumulation of diltiazem and its metabolites which are poorly dialysed and normally excreted partially in the urine.

1. Patel R, *et al.* Toxic effects of diltiazem in a patient with chronic renal failure. *J Clin Pharmacol* 1994; **34:** 273–4.

Interactions

Increased depression of cardiac conduction with risk of bradycardia and AV block may occur when diltiazem is given with drugs such as amiodarone, beta blockers, digoxin, and mefloquine. Enhanced antihypertensive effect may occur if used with other antihypertensive drugs or drugs that cause hypotension such as aldesleukin and antipsychotics. Diltiazem is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 and may also inhibit the metabolism of drugs sharing the same pathway. Interactions may also be expected with enzyme inducers, such as carbamazepine, phenobarbital, phenytoin, and rifampicin, and with enzyme inhibitors, such as cimetidine and HIV-protease inhibitors.

Antidepressants. For a report of diltiazem increasing the bioavailability of *imipramine* and *nortriptyline*, see Calcium-channel Blockers under the Interactions of Amitriptyline, p.380.

Antiepileptics. For reports of diltiazem use precipitating *carbamazepine* and *phenytoin* toxicity, see p.475 and p.499, respectively.

Anxiolytics. For the effect of diltiazem on plasma-*buspirone* concentrations, see p.966.

Benzodiazepines. For the effects of diltiazem on plasma concentrations of *midazolam* or *triazolam*, see Calcium-channel Blockers under Interactions of Diazepam, p.990.

Beta blockers. Profound bradycardia has been reported in a number of patients when diltiazem was used with a beta blocker.[1,2] Diltiazem decreases the clearance of a single dose of *propranolol* or *metoprolol*, though not *atenolol*, and elevated concentrations of beta blocker may be responsible for the bradycardic effects.[3] This is unlikely to be the full story, however, since atenolol, which was unaffected in this study, has been implicated in producing bradycardia when diltiazem was added in a patient with myocardial ischaemia.[2]

1. Hassell AB, Creamer JE. Profound bradycardia after the addition of diltiazem to a β blocker. *BMJ* 1989; **298:** 675.
2. Nagle RE, *et al.* Diltiazem and heart block. *Lancet* 1989; **i:** 907.
3. Tateishi T, *et al.* Effect of diltiazem on the pharmacokinetics of propranolol, metoprolol and atenolol. *Eur J Clin Pharmacol* 1989; **36:** 67–70.

Calcium-channel blockers. For the effect of diltiazem and *nifedipine* on each other's plasma concentrations, see p.1353.

Ciclosporin. For reports of a potentially beneficial interaction between diltiazem and ciclosporin, see Transplantation under Uses and Administration, below.

Corticosteroids. Diltiazem has been reported to reduce the clearance of *methylprednisolone* (see Calcium-channel Blockers, p.1495).

Digoxin. For a discussion of interactions between digoxin and calcium-channel blockers including diltiazem, see p.1262.

General anaesthetics. Two patients on diltiazem therapy developed impaired myocardial conduction during anaesthesia with *enflurane*;[1] one of the patients had severe sinus bradycardia that progressed to asystole. Additive cardiodepressant effects of diltiazem and enflurane were considered responsible.

1. Hantler CB, *et al.* Impaired myocardial conduction in patients receiving diltiazem therapy during enflurane anesthesia. *Anesthesiology* 1987; **67:** 94–6.

Histamine H_2-antagonists. *Cimetidine* caused increases in plasma-diltiazem concentrations and in plasma-deacetyldiltiazem concentrations in 6 subjects given a single oral dose of diltiazem 60 mg. *Ranitidine* produced a similar, though less marked effect.[1]

1. Winship LC, *et al.* The effect of ranitidine and cimetidine on single-dose diltiazem pharmacokinetics. *Pharmacotherapy* 1985; **5:** 16–19.

Lithium. Neurotoxicity has been reported in patients receiving lithium and diltiazem, see Effects on Mental Function and Parkinsonism under Effects on the Nervous System, above.

Theophylline. For the effect of diltiazem on plasma-theophylline concentrations, see p.1144.

Pharmacokinetics

Diltiazem is almost completely absorbed from the gastrointestinal tract after oral doses, but undergoes extensive first-pass hepatic metabolism. Peak plasma concentrations occur about 3 to 4 hours after an oral dose. The bioavailability has been reported to be about 40%, although there is considerable interindividual variation in plasma concentrations. Diltiazem is about 80% bound to plasma proteins. It is distributed into breast milk. It is extensively metabolised in the liver, primarily by the cytochrome P450 isoenzyme CYP3A4; one of the metabolites, desacetyldiltiazem, has been reported to have 25 to 50% of the activity of the parent com-

pound. The half-life of diltiazem is reported to be about 3 to 5 hours. About 2 to 4% of a dose is excreted in urine as unchanged diltiazem with the remainder excreted as metabolites in bile and urine. Diltiazem and its metabolites are poorly dialysable.

◊ General reviews.

1. Kelly JG, O'Malley K. Clinical pharmacokinetics of calcium antagonists: an update. *Clin Pharmacokinet* 1992; **22:** 416–33.

Bioavailability. Studies of the pharmacokinetics of diltiazem in healthy subjects after single and multiple doses,[1-3] indicated that bioavailability was increased after multiple doses, probably because of decreased presystemic elimination.[3]

1. Höglund P, Nilsson L-G. Pharmacokinetics of diltiazem and its metabolites after repeated multiple-dose treatments in healthy volunteers. *Ther Drug Monit* 1989; **11:** 543–50.
2. Höglund P, Nilsson L-G. Pharmacokinetics of diltiazem and its metabolites after repeated single dosing in healthy volunteers. *Ther Drug Monit* 1989; **11:** 551–7.
3. Höglund P, Nilsson L-G. Pharmacokinetics of diltiazem and its metabolites after single and multiple dosing in healthy volunteers. *Ther Drug Monit* 1989; **11:** 558–66.

Renal impairment. The pharmacokinetics of diltiazem and its major metabolite desacetyldiltiazem in patients with severe renal impairment were similar to those in patients with normal renal function.[1] Nevertheless, reduced doses may be necessary in patients with renal impairment (see under Uses and Administration below). See also under Precautions, above.

1. Pozet N, *et al*. Pharmacokinetics of diltiazem in severe renal failure. *Eur J Clin Pharmacol* 1983; **24:** 635–8.

Uses and Administration

Diltiazem is a benzothiazepine calcium-channel blocker (p.1154) and class IV antiarrhythmic (p.1153). It is a peripheral and coronary vasodilator with limited negative inotropic activity but its vasodilator properties are less marked than those of the dihydropyridine calcium-channel blocker nifedipine (p.1350). Unlike nifedipine, diltiazem inhibits cardiac conduction, particularly at the sino-atrial and atrioventricular nodes.

Diltiazem hydrochloride is given orally in the management of angina pectoris (p.1157) and hypertension (p.1171) and is available in a number of formulations for dosage once, twice, or three times daily. In some countries it is available for intravenous use in the treatment of various cardiac arrhythmias (atrial fibrillation or flutter and paroxysmal supraventricular tachycardia) (p.1160). It has also been used topically in the management of anal fissure (see below).

The variety of formulations means that dosage is dependent on the preparation used. Reduced doses may be required in the elderly or those with renal or hepatic impairment (see below).

In **angina pectoris** an initial dose is 60 mg orally three times daily (or 30 mg four times daily in the USA), increased if necessary to 360 mg daily; up to 480 mg daily has sometimes been given. Formulations suitable for once- or twice-daily use may be given in doses of 120 to 480 mg daily; up to 540 mg daily has been given.

In **hypertension** diltiazem hydrochloride may be given as modified-release capsules or tablets. Depending on the formulation, an initial dose is 60 to 120 mg twice daily, increased as required to a maximum of 360 mg daily. Formulations suitable for once-daily dosage may be given in similar daily doses, although up to 540 mg daily has been given.

In **cardiac arrhythmias** an initial dose of 250 micrograms/kg by bolus intravenous injection over 2 minutes has been suggested; a further dose of 350 micrograms/kg may be given after 15 minutes if the response is inadequate. Subsequent doses should be individualised for each patient. For those with atrial fibrillation or flutter, a continued reduction in heart rate may be achieved with an intravenous infusion of diltiazem hydrochloride after the bolus injection. An initial infusion rate of 5 to 10 mg/hour, may be increased as necessary in increments of 5 mg/hour up to a rate of 15 mg/hour. The infusion may be continued for up to 24 hours.

◊ General reviews.

1. Buckley MM-T, *et al*. Diltiazem: a reappraisal of its pharmacological properties and therapeutic use. *Drugs* 1990; **39:** 757–806.
2. Fisher M, Grotta J. New uses for calcium channel blockers: therapeutic implications. *Drugs* 1993; **46:** 961–75.
3. Weir MR. Diltiazem: ten years of clinical experience in the treatment of hypertension. *J Clin Pharmacol* 1995; **35:** 220–32.

Action. The haemodynamic and electrophysiological effects of diltiazem appear to resemble those of verapamil more than those of nifedipine.[1] It inhibits sino-atrial and atrioventricular nodal function in doses used clinically. The effects on sino-atrial function are more pronounced than those observed after verapamil. Diltiazem causes a decrease in the rate-pressure product indicating that decreased oxygen demand is a likely mechanism of action in relieving angina pectoris. Like verapamil, but unlike nifedipine, diltiazem does not appear to cause significant increases in coronary blood flow. The negative inotropic effect of diltiazem is presumably counteracted by afterload reduction.

1. Soward AL, *et al*. The haemodynamic effects of nifedipine, verapamil and diltiazem in patients with coronary artery disease: a review. *Drugs* 1986; **32:** 66–101.

Administration in hepatic or renal impairment. The dose of diltiazem hydrochloride may need to be reduced in patients with hepatic or renal impairment, and in the elderly. In the UK an initial dose of 120 mg daily is usually suggested, as a single dose or in 2 divided doses by mouth depending on the formulation. The dose may be increased cautiously, but only if the heart rate remains above 50 beats/minute.

Anorectal disorders. Beneficial responses to diltiazem reported[1,2] in 2 patients with *proctalgia fugax* may have been due to smooth muscle relaxation. The resting pressure of the internal anal sphincter was decreased by a mean of 20.6% in all but 1 of 13 subjects given a single 60-mg oral dose of diltiazem.[2] A small study[3] has compared oral with topical diltiazem in the management of *anal fissure* (p.1891). Despite a higher response rate with the topical drug, no significant difference in benefit was seen between the 2 routes. A subsequent study[4] suggested topical diltiazem (2%) might be of benefit in patients with anal fissure unresponsive to topical nitrates. Sustained benefit after a 6-week treatment course has also been reported in some patients.[5]

1. Boquet J, *et al*. Diltiazem for proctalgia fugax. *Lancet* 1986; **i:** 1493.
2. Jonard P, Essamri B. Diltiazem and internal anal sphincter. *Lancet* 1987; **i:** 754.
3. Jonas M, *et al*. A randomized trial of oral vs topical diltiazem for chronic anal fissures. *Dis Colon Rectum* 2001; **44:** 1074–8.
4. Jonas M, *et al*. Diltiazem heals glyceryl trinitrate-resistant chronic anal fissures: a prospective study. *Dis Colon Rectum* 2002; **45:** 1091–5.
5. Nash GF, *et al*. The long-term results of diltiazem treatment for anal fissure. *Int J Clin Pract* 2006; **60:** 1411–13.

Cardiomyopathies. Although calcium-channel blockers should be used with caution in patients with heart failure, symptomatic improvement has been reported in patients with dilated cardiomyopathy (p.1163) given diltiazem.[1]

1. Figulla HR, *et al*. Diltiazem improves cardiac function and exercise capacity in patients with idiopathic dilated cardiomyopathy: results of the Diltiazem in Dilated Cardiomyopathy Trial. *Circulation* 1996; **94:** 346–52.

Connective tissue and muscular disorders. Subcutaneous deposition of calcium (calcinosis) can occur in a number of inflammatory conditions, particularly in juvenile dermatomyositis (see Polymyositis and Dermatomyositis, p.1510). Treatment of calcinosis is difficult, but there have been a number of reports of the successful use of diltiazem in children[1,2] and adults[3] with dermatomyositis, as well as in adults with CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias) syndrome,[4] scleroderma,[5] and lupus panniculitis.[6] Another study,[7] however, found only a limited response in patients with systemic sclerosis.

1. Oliveri MB, *et al*. Regression of calcinosis during diltiazem treatment in juvenile dermatomyositis. *J Rheumatol* 1996; **23:** 2152–5.
2. Ichiki Y, *et al*. An extremely severe case of cutaneous calcinosis with juvenile dermatomyositis, and successful treatment with diltiazem. *Br J Dermatol* 2001; **144:** 894–7.
3. Vinen CS, *et al*. Regression of calcinosis associated with adult dermatomyositis following diltiazem therapy. *Rheumatology (Oxford)* 2000; **39:** 333–4.
4. Palmieri GMA, *et al*. Treatment of calcinosis with diltiazem. *Arthritis Rheum* 1995; **38:** 1646–54.
5. Dolan AL, *et al*. Diltiazem induces remission of calcinosis in scleroderma. *Br J Rheumatol* 1995; **34:** 576–8.
6. Morgan KW, *et al*. Calcifying lupus panniculitis in a patient with subacute cutaneous lupus erythematosus: response to diltiazem and chloroquine. *J Rheumatol* 2001; **28:** 2129–32.
7. Vayssairat M, *et al*. Clinical significance of subcutaneous calcinosis in patients with systemic sclerosis: does diltiazem induce its regression? *Ann Rheum Dis* 1998; **57:** 252–4.

Kidney disorders. Calcium-channel blockers may be of benefit in various forms of kidney disorder (see Nifedipine, p.1355). Diltiazem has been reported to reduce urinary protein excretion without exacerbating pre-existing renal dysfunction in diabetic patients.[1,2] A small study[3] in 15 hypertensive patients with type 2 diabetes mellitus, albuminuria, and renal impairment found that diltiazem only reduced urinary albumin excretion when patients received a restricted dietary sodium intake of 50 mmol daily.

Diltiazem may also reduce the nephrotoxicity associated with certain drugs. Reduced nephrotoxicity has been reported when diltiazem is given to healthy subjects receiving netilmicin,[4] but diltiazem does not appear to modify the acute renal failure associated with tubular damage which may be caused by methotrexate.[5] Diltiazem may reduce ciclosporin-induced nephrotoxicity (see Transplantation, below).

1. Bakris GL. Effects of diltiazem or lisinopril on massive proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; **112:** 707–8.
2. Demarie BK, Bakris GL. Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; **113:** 987–8.
3. Bakris GL, Smith A. Effects of sodium intake on albumin excretion in patients with diabetic nephropathy treated with long-acting calcium antagonists. *Ann Intern Med* 1996; **125:** 201–4.
4. Lortholary O, *et al*. Calcium antagonists and aminoglycoside nephrotoxicity. *Am J Med* 1990; **88:** 445.
5. Deray G, *et al*. The effects of diltiazem on methotrexate-induced nephrotoxicity. *Eur J Clin Pharmacol* 1989; **37:** 337–40.

Migraine. For reference to the use of calcium-channel blockers, including diltiazem, in the management of migraine, see under Nifedipine, p.1355.

Myocardial infarction. For reference to the use of diltiazem in the acute and long-term management of myocardial infarction, see under Uses of Verapamil, p.1424.

Transplantation. Diltiazem increases blood-ciclosporin concentrations when given by mouth in doses of 60 to 180 mg daily to transplant patients receiving ciclosporin therapy.[1-3] In consequence, ciclosporin doses can be reduced by about one-third, at a considerable saving in cost.[2,3] However, the effect may not occur in all patients,[4] and may vary with differing formulations,[5] and it has been suggested that blood-ciclosporin concentrations should be closely monitored if diltiazem is used for this purpose. In addition to this effect, which is apparently due to non-competitive inhibition of ciclosporin metabolism by diltiazem,[6] there is evidence of improved renal graft-function in patients given the combined therapy, suggesting that diltiazem may reduce ciclosporin-induced nephrotoxicity.[1,2] However, a 4-year follow-up study in patients treated with ciclosporin and diltiazem found that diltiazem had no effect on the progression to chronic allograft nephropathy.[7] Improved survival has been reported[8] in a retrospective study of patients given diltiazem for its ciclosporin-sparing effect, but it was unclear if this was a direct effect of diltiazem or was related to other factors associated with its use.

1. Wagner K, Neumayer H-H. Prevention of delayed graft function in cadaver kidney transplants by diltiazem. *Lancet* 1985; **ii:** 1355–6.
2. Neumayer H-H, Wagner K. Diltiazem and economic use of cyclosporin. *Lancet* 1986; **ii:** 523.
3. Bourge RC, *et al*. Diltiazem-cyclosporine interaction in cardiac transplant recipients: impact on cyclosporine dose and medication costs. *Am J Med* 1991; **90:** 402–4.
4. Jones TE, Morris RG. Diltiazem does not always increase blood cyclosporin concentration. *Br J Clin Pharmacol* 1996; **42:** 642–4.
5. Jones TE, *et al*. Formulation of diltiazem affects cyclosporin-sparing activity. *Eur J Clin Pharmacol* 1997; **52:** 55–8.
6. Brockmöller J, *et al*. Pharmacokinetic interaction between cyclosporin and diltiazem. *Eur J Clin Pharmacol* 1990; **38:** 237–42.
7. Ingsathit A, *et al*. Co-administration of diltiazem and cyclosporine for kidney transplant recipients: a four year follow-up study. *J Med Assoc Thai* 2006; **89** (suppl 2): S235–S241.
8. McDonald SP, Russ GR. Associations between use of cyclosporine-sparing agents and outcome in kidney transplant recipients. *Kidney Int* 2002; **61:** 2259–65.

Preparations

USP 31: Diltiazem Hydrochloride Extended-release Capsules; Diltiazem Hydrochloride Oral Solution; Diltiazem Hydrochloride Oral Suspension; Diltiazem Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Acalix; Corodrox; Dilahim; Diltenk; Diltiacor†; Dilzen-G; Hart; Incoril; Kaltiazem; Ritmocit†; Tilazem; ***Austral.:*** Auscard†; Cardizem; Coras; Diltahexal; Dilzem; Vasocardol; ***Austria:*** Corazem†; Diltahexal; Diltiastad; Dilzem; ***Belg.:*** Progor; Tildiem; ***Braz.:*** Angiolong; Balcor; Calzem; Cardizem; Cordil; Diltiacor; Diltipress; Diltizem; Diltor; Incoril; ***Canad.:*** Apo-Diltiaz; Cardizem; Novo-Diltazem; Nu-Diltiaz; Tiazac; ***Chile:*** Acasmul; Grifodilzem; Incoril; Tilazem; Tildiem; ***Cz.:*** Aldizem†; Altiazem†; Blocalcin; Diacordin; Dilzem†; Etizem†; Tiakem†; ***Denm.:*** Cardil; Cardizem; Dilcor; Myonil; Tilker; Viazem†; ***Fin.:*** Cardizem; Dilmin; Dilpral; Dilzem; ***Fr.:*** Bi-Tildiem; Deltazen; Diacor; Dilrene; Mono-Tildiem; Tildiem; ***Ger.:*** Corazet†; Dil-Sanorania; Dilsal; Dilta; Diltabeta; Diltahexal; Diltapham†; Diltaretard; Dilti; Diltiagamma; Diltiuc†; Dilzanton; Dilzem; Dilzicardin†; ***Gr.:*** Alfener; Cardil; Diltelan; Diltem†; Dilzanol†; Dipen; Elvesil; Ergoclavin; Mavitalon; Mycarzem†; Rubiten; Saubasin; Ternel; Tildiem; Zem†; Zilden; ***Hong Kong:*** Altiazem; Apo-Diltiaz; Cardium; Diltan†; Herbesser; Retalzem†; Wontizem; ***Hung.:*** Blocalcin; Dilrene; Diltan†; Dilzem; ***India:*** Dilcardia†; Dilcontin; Dilgard; Dilzem; DTM; Iski; Kaizem; ***Indon.:*** Cordizem; Dilmen; Dilso; Farmabes; Herbesser; Lanodil; ***Irl.:*** Adizem; Diltam; Dilzem; Entrydil; Tildiem; ***Israel:*** Adizem; Dilatam; Levodex; ***Ital.:*** Altiazem; Angidil†; Angipress†; Angizem; Citizem†; Diacardin; Diladel; Dilem; Diliter; Dilzene; Etyzem; Longazem; Tildiem; ***Jpn:*** Herbesser; ***Malaysia:*** Cardil; Cascor; Dilcard†; Dilem†; Herbesser; Mono-Tildiem; ***Mex.:*** Angiotrofin; Anremed; Presoken†; Presoquim†; Sertidel; Tilazem; ***Neth.:*** Diloc; Surazem; Tiadil; Tildiem; ***Norw.:*** Cardizem; Tilker†; ***NZ:*** Cardizem; Dilcard†; Diltahexal; Dilzem; ***Philipp.:*** Angiozem; Cordazem; Dilatam; Dilcardia; Diltelan; Diltime; Dilzem; Dyalac; Filazem; Mono-Tildiem; Tildiem; Vasmulax; Zandil; Zemtrial; ***Pol.:*** Blocalcin; Diacordin; Dilocard; Dilzem; Oxycardil; ***Port.:*** Alandiem; Balcor†; Cal-Antagon; Carzem†; Diacardyne†; Dilfar; Dilongo†; Diltiangina; Diltiem; Duplide†; Etizem; Herbesser; Lacerol†; Tiadil†; Tilker; ***Rus.:*** Altiazem (Алтиазем); Blocalcin (Блокальцин); Cardil (Кардил); Diazem (Диазем); Dilcardia (Дилкардия); ***S.Afr.:*** Dilatam; Tilazem; Zildem; ***Singapore:*** Beatizem; Cardil; Cardium; Dilatam†; Herbesser; Mono-Tildiem; ***Spain:*** Angiodrox; Cardiser; Carreldon; Clobendian; Corolater; Cronodine; Dilaclan; Diltiwas; Dinisor; Doclis; Lacerol; Masdil; Tilker; Trumsal; Uni Masdil; ***Swed.:*** Cardizem; Coramil; Viazem†; ***Switz.:*** Coridil; Dilzem; Escozem†; Tildiem; ***Thai.:*** Altiazem†; Angizem†; Cardil; Carzem; Cascor; Denazox; Dilem; Dilizem; Diltec; Dilzem†; Ditizem; Herbesser; Medozem†; Progor; ***Turk.:*** Altizem; Dilticard; Diltizem; Kardil; Tildiem; ***UK:*** Adizem; An-

giozem†; Angitil; Calcicard; Dilcardia; Dilzem; Disogram; Optil; Slozem; Tildiem; Viazem; Zemtard; ***USA:*** Cardizem; Cartia; Dilacor; Dilt-CD; Dilt-XR; Diltia; Taztia; Tiazac; ***Venez.:*** Acalix; Corazem; Cordisil; Daltazen; Presoquin; Tilazem.

Multi-ingredient: ***Arg.:*** Lotrix†; ***USA:*** Teczem.

Dimetofrine Hydrochloride *(rINNM)* ⊗

Dimétofrine, Chlorhydrate de; Dimetofrini Hydrochloridum; Dimetophrine Hydrochloride; Hidrocloruro de dimetofrina. 4-Hydroxy-3,5-dimethoxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride.

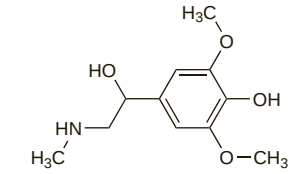
Диметофрина Гидрохлорид

$C_{11}H_{17}NO_4,HCl$ = 263.7.

CAS — 22950-29-4 (dimetofrine); 22775-12-8 (dimetofrine hydrochloride).

ATC — C01CA12.

ATC Vet — QC01CA12.



(dimetofrine)

Profile

Dimetofrine hydrochloride is a sympathomimetic (p.1407) that has been used for its vasopressor effects in the treatment of hypotensive states. It has also been used in preparations for cold and influenza symptoms.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Pressamina†.

Multi-ingredient: ***Ital.:*** Raffreddoremed.

Dipyridamole *(BAN, USAN, rINN)*

Dipiridamol; Dipiridamolis; Dipirydamol; Dipyridamol; Dipyridamoli; Dipyridamolum; NSC-515776; RA-8. 2,2′,2″,2‴-[(4,8-Dipiperidinopyrimido[5,4-*d*]pyrimidine-2,6-diyl)dinitrilo]tetraethanol.

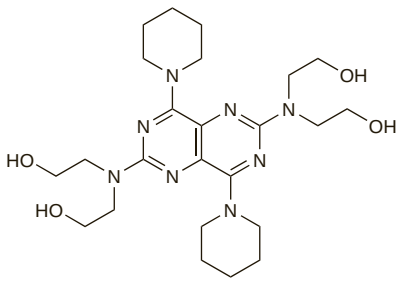
Дипиридамол

$C_{24}H_{40}N_8O_4$ = 504.6.

CAS — 58-32-2.

ATC — B01AC07.

ATC Vet — QB01AC07.



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

Ph. Eur. 6.2 (Dipyridamole). A bright yellow crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol; freely soluble in acetone. It dissolves in dilute solutions of mineral acids. Protect from light.

USP 31 (Dipyridamole). An intensely yellow, crystalline powder or needles. Slightly soluble in water; very soluble in chloroform, in alcohol, and in methyl alcohol; very slightly soluble in acetone and in ethyl acetate. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

Gastrointestinal disturbances, including nausea, vomiting, and diarrhoea, headache, dizziness, faintness, hypotension, facial flushing, and skin rash and other hypersensitivity reactions may occur after use of dipyridamole. Dipyridamole can also induce chest pain or lead to a worsening of the symptoms of angina. Cardiac arrhythmias have been reported in patients given dipyridamole during thallium-201 imaging. Aminophylline may reverse some of the adverse effects.

Dipyridamole should be used with caution in patients with hypotension, unstable angina, aortic stenosis, recent myocardial infarction, heart failure, or coagulation disorders. Intravenous dipyridamole should not be given to patients with these conditions or to those with arrhythmias, conduction disorders, asthma, or a history of bronchospasm (but see Myocardial Imaging, below). Oral dipyridamole should be stopped 24 hours before intravenous use for stress testing.

Effects on the biliary tract. Gallstones containing unconjugated dipyridamole were removed from 2 patients who had been taking dipyridamole for 15 and 10 years, respectively.[1] A gallstone containing unconjugated dipyridamole recurred in a patient who continued to take the drug after endoscopic removal of a similar stone 18 months earlier.[2]

1. Moesch C, *et al.* Biliary drug lithiasis: dipyridamole gallstones. *Lancet* 1992; **340:** 1352–3.
2. Sautereau D, *et al.* Recurrence of biliary drug lithiasis due to dipyridamole. *Endoscopy* 1997; **29:** 421–3.

Effects on the heart. Transient myocardial ischaemia occurred in 4 patients with unstable angina and multivessel coronary artery disease during oral treatment with dipyridamole.[1] See Myocardial Imaging, below, for additional reports.

1. Keltz TN, *et al.* Dipyridamole-induced myocardial ischemia. *JAMA* 1987; **257:** 1515–16.

Effects on the muscles. Symptoms resembling acute pseudopolymyalgia rheumatica developed in a patient taking dipyridamole.[1]

1. Chassagne P, *et al.* Pseudopolymyalgia rheumatica with dipyridamole. *BMJ* 1990; **301:** 875.

Effects on taste. A disagreeable taste associated with other gastrointestinal symptoms occurred in a patient taking dipyridamole.[1] Two similar cases had been reported to the UK CSM.

1. Willoughby JMT. Drug-induced abnormalities of taste sensation. *Adverse Drug React Bull* 1983; **100:** 368–71.

Myocardial imaging. Dipyridamole may be used in association with thallium-201 in myocardial stress imaging. Safety data from over 3900 patients has been summarised.[1] Adverse effects which occurred within 24 hours of dipyridamole intravenously (mean dose 560 micrograms/kg) were recorded. Ten patients had major adverse effects and 1820 patients experienced minor adverse effects. Myocardial infarction occurred in 4 patients, 3 of whom had unstable angina before scanning. Six patients developed acute bronchospasm, 4 of whom had a history of asthma or had wheezing before using dipyridamole. Adverse effects considered to be minor included chest pain in 19.7% of patients, ST-T-segment depression in 7.5%, ventricular extrasystoles in 5.2%, headache in 12.2%, dizziness in 11.8%, nausea in 4.6%, and hypotension in 4.6%. Aminophylline was effective in relieving symptoms of adverse effects in 97% of 454 patients.

Hypersensitivity reactions including anaphylaxis and angioedema have been reported.[2,3]

UK licensed product information contra-indicates intravenous dipyridamole in patients with hypotension, unstable angina, aortic stenosis, recent myocardial infarction, heart failure, coagulation disorders, arrhythmias, conduction disorders, asthma, or a history of bronchospasm. However, a review[4] of pharmacological stress testing suggested that with appropriate patient selection and adequate monitoring, the incidence of life-threatening adverse reactions is negligible. It was also considered that dipyridamole-thallium-201 imaging could be safely performed in the early post-myocardial infarction period.

1. Ranhosky A, *et al.* The safety of intravenous dipyridamole thallium myocardial perfusion imaging. *Circulation* 1990; **81:** 1205–9.
2. Weinmann P, *et al.* Anaphylaxis-like reaction induced by dipyridamole during myocardial scintigraphy. *Am J Med* 1994; **97:** 488.
3. Angelides S, *et al.* Acute reaction to dipyridamole during myocardial scintigraphy. *N Engl J Med* 1999; **340:** 394.
4. Beller GA. Pharmacologic stress imaging. *JAMA* 1991; **265:** 633–8.

Interactions

Dipyridamole may enhance the actions of oral anticoagulants due to its antiplatelet effect. It inhibits the reuptake of adenosine and may enhance its effects; the dose of adenosine must be reduced if both drugs are given. Dipyridamole may also inhibit the uptake of fludarabine and may reduce its efficacy.

The absorption of dipyridamole may be reduced by drugs such as antacids that increase gastric pH.

Anticoagulants. Dipyridamole may induce bleeding in patients receiving oral anticoagulants without altering prothrombin times (see Antiplatelets, under Warfarin, Interactions, p.1429).

Xanthines. Xanthines may antagonise some of the effects of dipyridamole due to their action as adenosine antagonists. *Aminophylline* may be used to reverse some of the adverse effects of dipyridamole. Intravenous *caffeine* has been reported[1] to attenuate the haemodynamic response to dipyridamole and it has been suggested that caffeine should be avoided for at least 24 hours before the test in patients receiving dipyridamole for myocardial imaging.

1. Smits P, *et al.* Dose-dependent inhibition of the hemodynamic response to dipyridamole by caffeine. *Clin Pharmacol Ther* 1991; **50:** 529–37.

Pharmacokinetics

Dipyridamole is incompletely absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 75 minutes after an oral dose. Dipyridamole is more than 90% bound to plasma proteins. A terminal half-life of 10 to 12 hours has been reported. Dipyridamole is metabolised in the liver and is mainly excreted as glucuronides in the bile. Excretion may be delayed by enterohepatic recirculation. A small amount is excreted in the urine. Dipyridamole is distributed into breast milk.

◊ References.

1. Mahony C, *et al.* Dipyridamole kinetics. *Clin Pharmacol Ther* 1982; **31:** 330–8.
2. Mahony C, *et al.* Plasma dipyridamole concentrations after two different dosage regimens in patients. *J Clin Pharmacol* 1983; **23:** 123–6.

Uses and Administration

Dipyridamole is an adenosine reuptake inhibitor and phosphodiesterase inhibitor with antiplatelet and vasodilating activity and is used in thromboembolic disorders (p.1187). Oral dipyridamole is used for the prophylaxis of thromboembolism after cardiac valve replacement (p.1187) and in the management of stroke (below); it has also been used in the management of myocardial infarction (p.1175). Dipyridamole given intravenously results in marked coronary vasodilatation and is used in stress testing in patients with ischaemic heart disease (see Myocardial Imaging, below).

For the prophylaxis of **thromboembolism** after cardiac valve replacement, dipyridamole is given with an oral anticoagulant. The usual adult dose is 300 to 600 mg daily by mouth in divided doses before meals. Children have been given 5 mg/kg by mouth daily in divided doses.

For the secondary prevention of **stroke** or transient ischaemic attack dipyridamole is given as a modified-release preparation, alone or with aspirin, in a dose of 200 mg twice daily.

◊ General references.

1. FitzGerald GA. Dipyridamole. *N Engl J Med* 1987; **316:** 1247–57.
2. Gibbs CR, Lip GYH. Do we still need dipyridamole? *Br J Clin Pharmacol* 1998; **45:** 323–8.

Myocardial imaging. Perfusion abnormalities due to coronary artery disease are usually absent at rest but are present during stress, and stress imaging may therefore be used in the assessment of myocardial function. The stress is usually supplied by exercise, but when exercise is inappropriate pharmacological methods such as dipyridamole may be used.

Dipyridamole has been used with thallium-201 scintigraphy in adults and children and is usually given intravenously in a dose of 567 micrograms/kg over 4 minutes. Thallium-201 is given within 3 to 5 minutes after completion of the infusion of dipyridamole. Initial images are obtained after 5 minutes and delayed images are obtained 2.5 to 4 hours later. Dipyridamole (300 to 400 mg) has also been given as an oral suspension; thallium-201 is given about 45 minutes later to coincide with peak dipyridamole-serum concentrations.

Dipyridamole has also been used in echocardiography.[1,2] The intravenous dipyridamole dose used to obtain maximum sensitivity is often higher (750 to 840 micrograms/kg) than the dose used in scintigraphy.[1]

1. Beller GA. Pharmacologic stress imaging. *JAMA* 1991; **265:** 633–8.
2. Buchalter MB, *et al.* Dipyridamole echocardiography: the bedside stress test for coronary artery disease. *Postgrad Med J* 1990; **66:** 531–5.

Stroke. The value of long-term antiplatelet therapy with aspirin in patients who have suffered an ischaemic stroke (p.1185) or transient ischaemic attack is well-established, with a reduction in the risk of both stroke and other vascular events.[1] The use of dipyridamole has been more controversial. Early studies with dipyridamole, used alone or with aspirin, failed to show any benefit over aspirin alone. The European Stroke Prevention Study-2 (ESPS-2),[2] which compared aspirin and dipyridamole, alone or together, with placebo, found that both drugs reduced the risk of stroke and that the effects appeared to be additive. The study