Dosage. When given orally, digoxin may take effect within about 2 hours and the maximum effect may be reached in about 6 hours. Initially a loading dose may be given to digitalise the patient, although this may not be necessary in, for example, mild heart failure.

Dosage should be carefully adjusted to the needs of the individual patient. Factors which may be considered include the patient's age, lean body-mass, renal status, thyroid status, electrolyte balance, degree of tissue oxygenation, and the nature of the underlying cardiac or pulmonary disease. Bearing in mind the above factors, steady-state plasma-digoxin concentrations (in a sample taken at least 6 hours after a dose) of 0.5 to 2 nanograms/mL are generally considered acceptable, although in patients with heart failure concentrations at the lower end of the range may be more appropriate. For reference to therapeutic drug monitoring, see below.

If rapid digitalisation is required then a loading dose is given to allow for the large volume of distribution. A total loading dose of 750 to 1500 micrograms of digoxin may be given by mouth during the initial 24-hour period, either as a single dose, or where there is less urgency or greater risk of toxicity, in divided doses at 6-hourly intervals. In some patients, for example those with mild heart failure, a loading dose may not be necessary, and digitalisation may be achieved more slowly with doses of 250 micrograms once or twice daily; steady-state plasma concentrations are achieved in about 7 days in patients with normal renal function. The usual maintenance dose of digoxin is 125 to 250 micrograms by mouth daily, but may range from 62.5 to 500 micrograms daily. In elderly patients therapy should generally start gradually and with smaller doses (but see under Administration in the Elderly, below).

In urgent cases, provided that the patient has not received cardiac glycosides during the previous 2 weeks, digoxin may be given intravenously initially. The intravenous dose ranges from 500 to 1000 micrograms and generally produces a definite effect on the heart rate in about 10 minutes, reaching a maximum within about 2 hours. It is given by intravenous infusion, either as a single dose given over 2 or more hours, or in divided doses each over 10 to 20 minutes. Maintenance treatment is then usually given by mouth. Digoxin has also been given intramuscularly but this route is not generally recommended since such injections may be painful and tissue damage has been reported. Digoxin should not be given subcutaneously as intense local irritation may occur.

Children's doses are complex. They are based on bodyweight and the developmental stage of the child as well as on response. Premature infants are especially sensitive to digoxin but, along with all other neonates, infants, and children up to about 10 years of age, still require doses that are higher per kg body-weight than those used for adults. Preterm infants receive lower doses than full-term infants, while children aged 2 to 10 years require lower doses than children up to 2 years of age. As an indication of the doses used, oral loading doses recommended by licensed product information in the UK range from 25 to 45 micrograms/kg over 24 hours and in the USA the range is 20 to 60 micrograms/kg; the range for intravenous loading doses given over 24 hours is 20 to 35 micrograms/kg in the UK and 15 to 50 micrograms/kg in the USA.

Doses should be reduced in patients with renal impairment (see below).

◊ General reviews on the actions and uses of digoxin and the other cardiac glycosides.

1. Opie LH. Digitalis and sympathomimetic stimulants. *Lancet* 1980; **i:** 912–18.
2. Taggart AJ, McDevitt DG. Digitalis: its place in modern therapy. *Drugs* 1980; **20:** 398–404.
3. Chamberlain DA. Digitalis: where are we now? *Br Heart J* 1985; **54:** 227–33.
4. Doherty JE. Clinical use of digitalis glycosides: an update. *Cardiology* 1985; **72:** 225–54.
5. Smith TW. Digitalis: mechanisms of action and clinical use. *N Engl J Med* 1988; **318:** 358–65.
6. Hampton JR. Digoxin. *Br J Hosp Med* 1997; **58:** 321–3.
7. Riaz K, Forker AD. Digoxin use in congestive heart failure: current status. *Drugs* 1998; **55:** 747–58.
8. Campbell TJ, MacDonald PS. Digoxin in heart failure and cardiac arrhythmias. *Med J Aust* 2003; **179:** 98–102.

Administration in the elderly. The volume of distribution of digoxin and the elimination half-life increase with age.[1] Therefore there are problems in giving digoxin to elderly patients since steady-state plasma concentrations may not be reached for up to 2 weeks. Fears of toxicity have led some practitioners to use a fixed 'geriatric' dose of 62.5 micrograms daily. However, such a dose can produce subtherapeutic concentrations.[2] The routine use of very low doses of digoxin in the elderly is inappropriate and dosage should be individualised.

1. McMurray J, McDevitt DG. Treatment of heart failure in the elderly. *Br Med Bull* 1990; **46:** 202–29.
2. Nolan L, *et al*. The need for reassessment of digoxin prescribing for the elderly. *Br J Clin Pharmacol* 1989; **27:** 367–70.

Administration in renal impairment. The pharmacokinetics of cardiac glycosides in patients with renal impairment have been reviewed.[1] The rate but not the extent of digoxin absorption is reduced in renal impairment but this is unlikely to be clinically important. Plasma-protein binding may also be reduced but since digoxin is poorly bound to these proteins and has a large apparent volume of distribution this also is unlikely to be important. The apparent volume of distribution is reduced by one-third to one-half and the loading dose of digoxin should therefore be reduced; an oral loading dose of 10 micrograms/kg is suggested (but see also under Therapeutic Drug Monitoring, below). Non-renal clearance of digoxin is unaffected or only slightly reduced but renal clearance is reduced, the extent being closely related to creatinine clearance. The elimination half-life of digoxin is prolonged and it therefore takes longer to reach steady state and longer for toxicity to resolve. Because of the reduction in renal clearance of digoxin, maintenance doses must be reduced in line with renal function. Serum-digoxin concentration should be monitored although the presence of digoxin-like immunoreactive substances may make interpretation difficult. In addition, the presence of hyperkalaemia in patients with renal impairment may reduce sensitivity to the effects of digoxin.[2]

Since digoxin has such a large distribution volume, procedures such as peritoneal dialysis and haemodialysis remove only very small amounts of drug from the body and no dosage supplement is needed.

1. Aronson JK. Clinical pharmacokinetics of cardiac glycosides in patients with renal dysfunction. *Clin Pharmacokinet* 1983; **8:** 155–78.
2. Matzke GR, Frye RF. Drug administration in patients with renal insufficiency: minimising renal and extrarenal toxicity. *Drug Safety* 1997; **16:** 205–31.

Therapeutic drug monitoring. Digoxin has a narrow therapeutic index. It is generally considered that plasma-digoxin concentrations required for a therapeutic effect are usually between 0.5 and 2.0 nanograms/mL,[1-3] although some studies[4-6] have suggested that concentrations of 0.5 to 0.9 nanograms/mL are adequate for heart failure; concentrations at the upper end of the range may be associated with worse outcomes.[5,6] The factor for converting nanograms/mL to nanomoles/litre is 1.28.

Digoxin dosage can be calculated in uncomplicated cases by considering the patient's weight, renal function, and clinical status. Therapeutic drug monitoring is *not* considered to be necessary in patients with a satisfactory clinical response to conventional doses in the absence of signs or symptoms of toxicity.[1,2] Measurement of plasma-digoxin concentrations is useful if poor compliance is suspected, if response is poor or there is a deterioration in response without apparent reason, if renal function is fluctuating, when it is unknown if a cardiac glycoside has been previously taken, during drug interactions, and to confirm clinical toxicity.[1,3,7] A plasma concentration should never be considered in isolation and should be used with other patient data as an important component in clinical decision making. This is particularly important in the diagnosis of digoxin toxicity since signs and symptoms of toxicity may be difficult to distinguish from the underlying disease and can occur within the usual therapeutic range.

A number of factors may influence the response to digoxin and thus the interpretation of digoxin assays. These include renal impairment, extremes of age, thyroid disease, patient compliance, drug interactions, and electrolyte disturbances.[1-3,7] Variations in the bioavailability of different digoxin preparations have also caused problems. Renal impairment and hypokalaemia are two of the most important factors affecting dosage of digoxin and whenever plasma-digoxin concentrations are assayed renal function and plasma potassium should also be measured. A dosing nomogram has been proposed[8] relating dose in patients with heart failure to renal function and either height or ideal body weight: for most patients with moderate or severe renal impairment (creatinine clearance below 60 mL/minute) an oral dose of 125 micrograms every other day was considered sufficient. The interpretation of digoxin assays is further confounded by the presence of digoxin-like immunoreactive substances in patients with renal or hepatic impairment, in pregnant women, and in neonates. Blood samples for digoxin assay should be taken at least 6 hours after a dose to allow for distribution.[1,3,7]

The usefulness of plasma-digoxin concentrations in the diagnosis of toxicity in children is unclear. For children older than 12 months the adult guidelines can probably be followed, and for younger children the trend for increased risk of toxicity at increased plasma-digoxin concentrations appears to hold but the threshold for toxicity may be higher, especially in children less than 3 months old.[1]

1. Aronson JK. Indications for the measurement of plasma digoxin concentrations. *Drugs* 1983; **26:** 230–42.
2. Lee TH, Smith TW. Serum digoxin concentration and diagnosis of digitalis toxicity: current concepts. *Clin Pharmacokinet* 1983; **8:** 279–85.
3. Aronson JK, Hardman M. Digoxin. *BMJ* 1992; **305:** 1149–52.
4. Adams KF, *et al*. Clinical benefits of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol* 2002; **39:** 946–53.
5. Rathore SS, *et al*. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003; **289**: 871–8.
6. Adams KF, *et al*. Relationship of serum digoxin concentration to mortality and morbidity in women in the Digitalis Investigation Group trial: a retrospective analysis. *J Am Coll Cardiol* 2005; **46:** 497–504.
7. Brodie MJ, Feely J. Practical clinical pharmacology: therapeutic drug monitoring and clinical trials. *BMJ* 1988; **296:** 1110–14.
8. Bauman JL, *et al*. A method of determining the dose of digoxin for heart failure in the modern era. *Arch Intern Med* 2006; **166:** 2539–45.

Preparations

BP 2008: Digoxin Injection; Digoxin Tablets; Paediatric Digoxin Injection; Paediatric Digoxin Oral Solution;
USP 31: Digoxin Elixir; Digoxin Injection; Digoxin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Cardiogoxin; Digocard-G; Lanicor; Lanoxin; ***Austral.:*** Lanoxin; Sigmaxin; ***Austria:*** Lanicor; ***Belg.:*** Lanoxin; ***Braz.:*** Cardcor; Cardionil; Cimecard; Digitax; Digixina†; Digobal; Digox†; Digoxan†; Digoxen; Digoxil; Lanoxin†; Valoxin; ***Canad.:*** Lanoxin; ***Fr.:*** Hemigoxine Nativelle; ***Ger.:*** Digacin; Digoregen†; Dilanacin†; Lanicor; Lenoxin; ***Hong Kong:*** Lanoxin; ***India:*** Cardioxin†; Lanoxin; ***Indon.:*** Fargoxin; Lanoxin; ***Irl.:*** Lanoxin; ***Israel:*** Lanoxin; ***Ital.:*** Eudigox; Lanoxin; ***Jpn:*** Digosin; ***Malaysia:*** Lanoxin; ***Mex.:*** Lanoxin; Mapluxin; ***Neth.:*** Lanoxin; ***Norw.:*** Lanoxin; ***NZ:*** Lanoxin; ***Philipp.:*** Lanoxin; ***Port.:*** Lanoxin; ***S.Afr.:*** Lanoxin; Purgoxin; ***Singapore:*** Lanoxin; ***Spain:*** Lanacordin; ***Swed.:*** Lanacrist; Lanoxin; ***Thai.:*** Grexin; Lanoxin; Toloxin; ***UK:*** Lanoxin; ***USA:*** Digitek; Lanoxicaps†; Lanoxin; ***Venez.:*** Lanicor.

Dihydralazine Sulfate *(rINNM)*

Dihidralazino sulfatas, hidratuotas; Dihidralazin-szulfát-hidrát; Dihydralatsiinisulfaatti, hydratoitu; Dihydralazine, Sulfate de; Dihydralazine (sulfate de) hydraté; Dihydralazine Sulphate *(BANM)*; Dihydralazini Sulfas; Dihydralazini sulfas hydricus; Dihydralazinsulfát; Dihydralazinsulfat, hydratiserat; Dihydralazinum Sulfuricum; Dihydralazyny siarczan; Dihydrallazine Sulphate; Sulfato de dihidralazina. Phthalazine-1,4-diyldihydrazine sulfate hemipentahydrate.

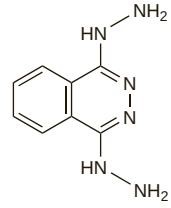
Дигидралазина Сульфат

$C_8H_{10}N_6.H_2SO_4.2/H_2O$ = 333.3.

CAS — 484-23-1 (dihydralazine); 7327-87-9 (dihydralazine sulfate).

ATC — C02DB01.

ATC Vet — QC02DB01.



(dihydralazine)

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

Ph. Eur. 6.2 (Dihydralazine Sulphate, Hydrated). A white or slightly yellow crystalline powder. Slightly soluble in water; practically insoluble in dehydrated alcohol. It dissolves in dilute mineral acids.

Profile

Dihydralazine is a vasodilator with actions and uses similar to those of hydralazine (p.1305). It is given orally as the sulfate. Dihydralazine sulfate hemipentahydrate 14.45 mg is equivalent to about 12.5 mg of anhydrous dihydralazine sulfate. In hypertension (p.1171) the usual initial dose is the equivalent of 12.5 mg of anhydrous dihydralazine sulfate twice daily and the maximum recommended dose is 50 mg twice daily. Higher doses have been used in the management of heart failure.

Other salts of dihydralazine that have been used in oral preparations include the hydrochloride and the tartrate. The mesilate is given by injection.

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

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Nepresol; ***Belg.:*** Nepresol; ***Cz.:*** Nepresol†; ***Fr.:*** Nepressol; ***Ger.:*** Depressan; Nepresol; ***Gr.:*** Nepresol; ***Hong Kong:*** Nepresol†; ***Hung.:*** De-

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

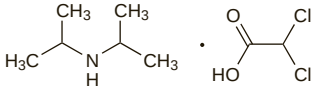
Multi-ingredient: ***Braz.:*** Adelfan-Esidrex†; ***Ger.:*** Adelphan-Esidrix†; Obsilazin N†; Tri-Torrat†; Triniton; ***Hong Kong:*** Adelphane-Esidrex; ***India:*** Adelphane; Adelphane-Esidrex; Beptazine; Beptazine-H; ***Indon.:*** Dellasidrex; ***Rus.:*** Adelphane-Esidrex (Адельфан-эзидрекс); Triresid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

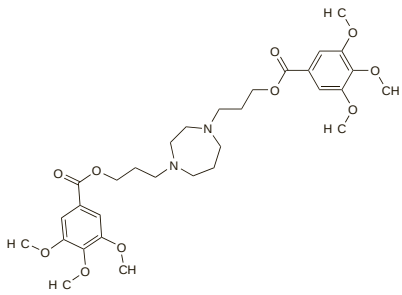
Дилазепа Гидрохлорид

$C_{31}H_{44}N_2O_{10}$,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.

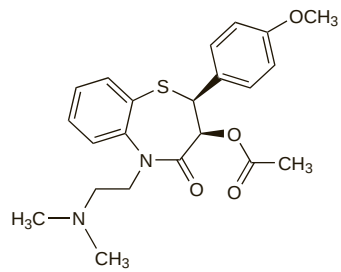
Дилтиазема Гидрохлорид

$C_{22}H_{26}N_2O_4S$,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-