Nifedipine *(BAN, USAN, rINN)*

Bay-a-1040; Nifedipiini; Nifedipin; Nifedipina; Nifedipinas; Nifédipine; Nifedipino; Nifedipinum. Dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate.

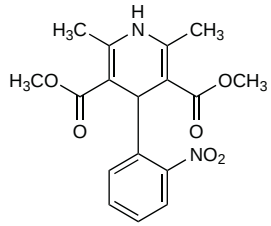
Нифедипин

$C_{17}H_{18}N_2O_6$ = 346.3.

CAS — 21829-25-4.

ATC — C08CA05.

ATC Vet — QC08CA05.



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

Ph. Eur. 6.2 (Nifedipine). A yellow crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone. When exposed to daylight or to certain wavelengths of artificial light it is converted to a nitrosophenylpyridine derivative, while exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Solutions should be prepared in the dark or under light of wavelength greater than 420 nm, immediately before use. Protect from light.

USP 31 (Nifedipine). A yellow powder. Practically insoluble in water; soluble 1 in 10 of acetone. When exposed to daylight or to certain wavelengths of artificial light it is converted to a nitrosophenylpyridine derivative, while exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Store in airtight containers. Protect from light.

Stability. Yellow food colourings such as curcumin have been used[1] to slow photodegradation of nifedipine solutions. An extemporaneously prepared solution of nifedipine in a peppermint-flavoured vehicle was reported[2] to be stable for at least 35 days when stored in amber glass bottles.

1. Thoma K, Klimek R. Photostabilization of drugs in dosage forms without protection from packaging materials. *Int J Pharmaceutics* 1991; **67:** 169–75.
2. Dentinger PJ, *et al.* Stability of nifedipine in an extemporaneously compounded oral solution. *Am J Health-Syst Pharm* 2003; **60:** 1019–22.

Adverse Effects

The most common adverse effects of nifedipine are associated with its vasodilator action and often diminish on continued therapy. They include dizziness, flushing, headache, hypotension, peripheral oedema, tachycardia, and palpitations. Nausea and other gastrointestinal disturbances, increased micturition frequency, lethargy, eye pain, visual disturbances, and mental depression have also occurred. A paradoxical increase in ischaemic chest pain may occur at the start of treatment and in a few patients excessive fall in blood pressure has led to cerebral or myocardial ischaemia or transient blindness.

There have been reports of rashes (including erythema multiforme), fever, and abnormalities in liver function, including cholestasis, due to hypersensitivity reactions. Gingival hyperplasia, myalgia, tremor, and impotence have been reported.

Some tablets formulated for once-daily use are covered in a membrane which is not digested and may cause gastrointestinal obstruction; bezoars may rarely occur.

Overdosage may be associated with bradycardia and hypotension; hyperglycaemia, metabolic acidosis, and coma may also occur.

Nifedipine has been reported to be teratogenic in *animals*.

Effects on mortality. Since 1995 there have been reports and reviews that have implicated calcium-channel blockers (particularly short-acting nifedipine and high doses) in increasing cardiovascular[1] and overall mortality.[2] Possible links with cancer, haemorrhage, and depression and suicide are discussed separately (see Cancer Occurrence, Effects on the Blood, and Effects on Mental Function, below, respectively).

In response, the US National Heart, Lung, and Blood Institute issued a statement warning that short-acting nifedipine should be used with great caution (if at all), especially at higher doses, in the treatment of hypertension, angina, and myocardial infarction,[3] and in some countries short-acting nifedipine preparations have been withdrawn. However, there has been much debate and controversy over the reports that questioned the safety of calcium-channel blockers.[4-6]

A review by the WHO/ISH pointed out that much of the evidence for adverse effects comes from observational studies or small randomised studies and concluded that, as there was insufficient evidence to confirm either benefit or harm, recommendations on the management of angina, hypertension, and myocardial infarction should remain unchanged.[7] In addition, many of the studies that led to the negative reports used the older short-acting calcium-channel blockers. The calcium-channel blockers used now are largely modified-release formulations of short half-life blockers or are calcium-channel blockers with long half-lives.

Studies completed after the WHO/ISH review have generally failed to show any increase in mortality with calcium-channel blockers, although their effects on cardiovascular outcomes remain less clear. A placebo-controlled study (SYST-EUR) reported[8] a reduction in incidence of stroke and cardiovascular events in 4695 elderly patients treated with nitrendipine (and enalapril and hydrochlorothiazide in addition if necessary) for isolated systolic hypertension, while a retrospective cohort study[9] in post-myocardial infarction patients failed to show any increase in mortality after one year in those receiving calcium-channel blockers. Another cohort study[10] in patients with hypertension also found no overall increase in mortality with calcium-channel blockers, although there was a trend towards a higher rate with short-acting formulations. A meta-analysis[11] of randomised studies comparing calcium-channel blockers with other antihypertensives in patients with hypertension suggested that calcium-channel blockers were associated with an increased risk of major cardiovascular events (except stroke) although all-cause mortality was not increased. However, large, long-term studies have found no difference in cardiovascular outcomes or overall mortality in patients randomised to amlodipine or chlortalidone,[12] while a lower incidence of cardiovascular events was reported for amlodipine compared with atenolol.[13] A long-term study[14] of nifedipine added to standard therapy in patients with stable angina also found no increased mortality, and there was a reduced need for coronary interventions.

1. Psaty BM, *et al.* The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 1995; **274:** 620–5.
2. Furberg CD, *et al.* Nifedipine: dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995; **92:** 1326–31.
3. McCarthy M. US NIH issues warning on nifedipine. *Lancet* 1995; **346:** 689–90.
4. Opie LH, Messerli FH. Nifedipine and mortality: grave defects in the dossier. *Circulation* 1995; **92:** 1068–72.
5. Grossman E, Messerli FH. Calcium antagonists in cardiovascular disease: a necessary controversy but an unnecessary panic. *Am J Med* 1997; **102:** 147–9.
6. Stanton AV. Calcium channel blockers. *BMJ* 1998; **316:** 1471–3.
7. Ad Hoc Subcommittee of the Liaison Committee of the World Health Organisation and the International Society of Hypertension. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. *J Hypertens* 1997; **15:** 105–15.
8. Staessen JA, *et al.* Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997; **350:** 757–64. Correction. *ibid.*; 1636.
9. Jollis JG, *et al.* Calcium channel blockers and mortality in elderly patients with myocardial infarction. *Arch Intern Med* 1999; **159:** 2341–8.
10. Abascal VM, *et al.* Calcium antagonists and mortality risk in men and women with hypertension in the Framingham Heart Study. *Arch Intern Med* 1998; **158:** 1882–6.
11. Pahor M, *et al.* Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials. *Lancet* 2000; **356:** 1949–54.
12. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid.*; **289:** 178.
13. Dahlöf B, *et al.* Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; **366:** 895–906.
14. Poole-Wilson PA, *et al* on behalf of the ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system) investigators. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet* 2004; **364:** 849–57.

Carcinogenicity. An observational study carried out between 1988 and 1992 suggested that calcium-channel blockers were associated with an increased risk of cancer.[1] Subsequent studies have failed to support this finding.[2-7] A review by the WHO/ISH concluded that there is no good evidence that calcium-channel blockers increase cancer risk,[8] and the biological basis for an effect of calcium-channel blockers on cancer risk has also been questioned.[9] The large, long-term, randomised Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT)[10] found no increase in the incidence of cancer in patients receiving a calcium-channel blocker (amlodipine) compared with those receiving a diuretic (chlortalidone).

1. Pahor M, *et al.* Calcium-channel blockade and incidence of cancer in aged populations. *Lancet* 1996; **348:** 493–7.
2. Jick H, *et al.* Calcium-channel blockers and risk of cancer. *Lancet* 1997; **349:** 525–8.
3. Rosenberg L, *et al.* Calcium channel blockers and the risk of cancer. *JAMA* 1998; **279:** 1000–4.
4. Braun S, *et al.* Calcium channel blocking agents and risk of cancer in patients with coronary heart disease. *J Am Coll Cardiol* 1998; **31:** 804–8.
5. Sajadieh A, *et al.* Verapamil and risk of cancer in patients with coronary artery disease. *Am J Cardiol* 1999; **83:** 1419–22.
6. Meier CR, *et al.* Angiotensin-converting enzyme inhibitors, calcium channel blockers, and breast cancer. *Arch Intern Med* 2000; **160:** 349–53.
7. Cohen HJ, *et al.* Calcium channel blockers and cancer. *Am J Med* 2000; **108:** 210–15.
8. Ad Hoc Subcommittee of the Liaison Committee of the World Health Organisation and the International Society of Hypertension. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. *J Hypertens* 1997; **15:** 105–15.
9. Mason RP. Calcium channel blockers, apoptosis and cancer: is there a biologic relationship? *J Am Coll Cardiol* 1999; **34:** 1857–66.
10. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid.*; **289:** 178.

Effects on the blood. Treatment with nifedipine significantly reduces platelet aggregation *in vitro*[1] and results indicating inhibition of platelet function in healthy subjects receiving oral (but not intravenous) nifedipine have been reported.[2,3] Thus, concern has been expressed[4] that calcium-channel blockers may have the potential to produce haemorrhagic complications in surgical patients (specifically, those undergoing coronary bypass surgery). Major surgical bleeding was associated with nimodipine in patients undergoing cardiac valve replacement,[5] although it has been used in other situations apparently without an increased risk of bleeding.[6]

Conflicting results have been reported with regard to the risk of gastrointestinal bleeding. A prospective cohort study in 1636 elderly hypertensive patients,[7] and a subsequent case-control study,[8] reported that calcium-channel blockers were associated with an increased risk of gastrointestinal haemorrhage compared with beta blockers. However, it was suggested[9] that this may have been due to a protective effect of beta blockers rather than an adverse effect of calcium-channel blockers, and another study[10] also suggested that the risk of gastrointestinal bleeding was not materially increased by calcium-channel blockers.

Calcium-channel blockers have also been associated with a number of blood dyscrasias; there have been case reports of aplastic anaemia with nifedipine,[11] and of thrombocytopenia with amlodipine[12] and with diltiazem.[13,14]

1. Ośmiałwska Z, *et al.* Effect of nifedipine monotherapy on platelet aggregation in patients with untreated essential hypertension. *Eur J Clin Pharmacol* 1990; **39:** 403–4.
2. Winther K, *et al.* Dose-dependent effects of verapamil and nifedipine on in vivo platelet function in normal volunteers. *Eur J Clin Pharmacol* 1990; **39:** 291–3.
3. Walley TJ, *et al.* The effects of intravenous and oral nifedipine on ex vivo platelet function. *Eur J Clin Pharmacol* 1989; **37:** 449–52.
4. Becker RC, Alpert JS. The impact of medical therapy on hemorrhagic complications following coronary artery bypass grafting. *Arch Intern Med* 1990; **150:** 2016–21.
5. Wagenknecht LE, *et al.* Surgical bleeding: unexpected effect of a calcium antagonist. *BMJ* 1995; **310:** 776–7.
6. Öhman J and others. Surgical bleeding and calcium antagonists. *BMJ* 1995; **311:** 388–9. [Several letters.]
7. Pahor M, *et al.* Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old. *Lancet* 1996; **347:** 1061–5.
8. Kaplan RC, *et al.* Use of calcium channel blockers and risk of hospitalized gastrointestinal tract bleeding. *Arch Intern Med* 2000; **160:** 1849–55.
9. Suissa S, *et al.* Antihypertensive drugs and the risk of gastrointestinal bleeding. *Am J Med* 1998; **105:** 230–5.
10. Kelly JP, *et al.* Major upper gastrointestinal bleeding and the use of calcium channel blockers. *Lancet* 1999; **353:** 559.
11. Laporte J-R, *et al.* Fatal aplastic anaemia associated with nifedipine. *Lancet* 1998; **352:** 619–20.
12. Usalan C, *et al.* Severe thrombocytopenia associated with amlodipine treatment. *Ann Pharmacother* 1999; **33:** 1126–7.
13. Lahav M, Arav R. Diltiazem and thrombocytopenia. *Ann Intern Med* 1989; **110:** 327.
14. Michalets EL, Jackson DV. Diltiazem-associated thrombocytopenia. *Pharmacotherapy* 1997; **17:** 1345–8.

Effects on the brain. Cerebral ischaemia[1,2] has been reported in small numbers of patients given nifedipine.

1. Nobile-Orazio E, Sterzi R. Cerebral ischaemia after nifedipine treatment. *BMJ* 1981; **283:** 948.
2. Schwartz M, *et al.* Oral nifedipine in the treatment of hypertensive urgency: cerebrovascular accident following a single dose. *Arch Intern Med* 1990; **150:** 686–7.

Effects on carbohydrate metabolism. There are reports of deterioration of diabetes,[1] reduction in glucose tolerance,[2] and development of diabetes[1,3] in patients given nifedipine. Nifedipine has also been reported to increase plasma-glucose concentrations.[3,4] However, other reports and studies have found no

change in glucose tolerance in either diabetic or non-diabetic patients taking nifedipine.[5-10]

See also Diabetes Mellitus under Precautions, below.

1. Bhatnagar SK, *et al.* Diabetogenic effects of nifedipine. *BMJ* 1984; **289:** 19.
2. Giugliano D, *et al.* Impairment of insulin secretion in man by nifedipine. *Eur J Clin Pharmacol* 1980; **18:** 395–8.
3. Zezulka AV, *et al.* Diabetogenic effects of nifedipine. *BMJ* 1984; **289:** 437–8.
4. Charles S, *et al.* Hyperglycaemic effect of nifedipine. *BMJ* 1981; **283:** 19–20.
5. Harrower ADB, Donnelly T. Hyperglycaemic effect of nifedipine. *BMJ* 1981; **283:** 796.
6. Greenwood RH. Hyperglycaemic effect of nifedipine. *BMJ* 1982; **284:** 50.
7. Abadie E, Passa P. Diabetogenic effects of nifedipine. *BMJ* 1984; **289:** 438.
8. Dante A. Nifedipine and fasting glycemia. *Ann Intern Med* 1986; **104:** 125–6.
9. Whitcroft I, *et al.* Calcium antagonists do not impair long-term glucose control in hypertensive non-insulin dependent diabetics (NIDDS). *Br J Clin Pharmacol* 1986; **22:** 208P.
10. Tentorio A, *et al.* Insulin secretion and glucose tolerance in non-insulin dependent diabetic patients after chronic nifedipine treatment. *Eur J Clin Pharmacol* 1989; **36:** 311–13.

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 eyes. Individual reports have implicated nifedipine in the development of transient retinal ischaemia and blindness,[1] and of periorbital oedema.[2] In a postmarketing survey painful or stinging eyes were more common in patients receiving nifedipine (178 of 757 evaluable) than in those given captopril (45 of 289), although the cause was uncertain.[3] Nifedipine has also been suggested as a risk factor in the development of cataract,[4,5] but the numbers involved in this analysis are small[6] and it is possible that the risk, if it exists,[7] relates to hypertension rather than nifedipine treatment.[6]

1. Pitlik S, *et al.* Transient retinal ischaemia induced by nifedipine. *BMJ* 1983; **287:** 1845–6.
2. Silverstone PH. Periorbital oedema caused by nifedipine. *BMJ* 1984; **288:** 1654.
3. Coulter DM. Eye pain with nifedipine and disturbance of taste with captopril: a mutually controlled study showing a method of postmarketing surveillance. *BMJ* 1988; **296:** 1086–8.
4. van Heyningen R, Harding JJ. Do aspirin-like analgesics protect against cataract? *Lancet* 1986; **i:** 1111–13.
5. Harding JJ, van Heyningen R. Drugs, including alcohol, that act as risk factors for cataract, and possible protection against cataract by aspirin-like analgesics and cyclopenthiazide. *Br J Ophthalmol* 1988; **72:** 809–14.
6. van Heyningen R, Harding JJ. Aspirin-like analgesics and cataract. *Lancet* 1986; **ii:** 283.
7. Kewitz H, *et al.* Aspirin and cataract. *Lancet* 1986; **ii:** 689.

Effects on the heart. The use of nifedipine has been associated with the development of various heart disorders in some patients. Complete heart block has been reported in an elderly patient who had previously developed heart block with verapamil,[1] and sudden circulatory collapse has been reported in 4 patients receiving nifedipine who underwent routine coronary bypass surgery.[2] One patient died despite all attempts at resuscitation.[2] However, probably the majority of reports have concerned the development or aggravation of cardiac ischaemia, up to and including frank myocardial infarction after use of short-acting nifedipine.[3-6] Such cases appear to be chiefly associated with a too-rapid fall in blood pressure after the use of sublingual nifedipine for hypertensive urgencies or emergencies,[5,6] or occur in patients with a history of ischaemic heart disease.[3,4]

For discussion of the effects of calcium-channel blockers on cardiovascular mortality, see above.

1. Chopra DA, Maxwell RT. Complete heart block with low dose nifedipine. *BMJ* 1984; **288:** 760.
2. Goiti JJ. Calcium channel blocking agents and the heart. *BMJ* 1985; **291:** 1505.
3. Sia STB, *et al.* Aggravation of myocardial ischaemia by nifedipine. *Med J Aust* 1985; **142:** 48–50.
4. Boden WE, *et al.* Nifedipine-induced hypotension and myocardial ischemia in refractory angina pectoris. *JAMA* 1985; **253:** 1131–5.
5. O'Mailia JJ, *et al.* Nifedipine-associated myocardial ischemia or infarction in the treatment of hypertensive urgencies. *Ann Intern Med* 1987; **107:** 185–6.
6. Leavitt AD, Zweifler AJ. Nifedipine, hypotension, and myocardial injury. *Ann Intern Med* 1988; **108:** 305–6.

WITHDRAWAL. Exacerbation of coronary ischaemia and thrombosis of arteriovenous graft could have resulted from withdrawal of nifedipine in a patient.[1] Abrupt withdrawal of nisoldipine from 15 patients with stable angina pectoris after 6 weeks of therapy resulted in severe unstable angina in 2 patients and acute myocardial infarction in another.[2] It was postulated that the withdrawal effect could be due to an increase in sensitivity of vascular α_2 adrenoceptors to circulating adrenaline.

1. Mysliwiec M, *et al.* Calcium antagonist withdrawal syndrome. *BMJ* 1983; **286:** 1898.
2. Mehta J, Lopez LM. Calcium-blocker withdrawal phenomenon: increase in affinity of alpha adrenoceptors for agonist as a potential mechanism. *Am J Cardiol* 1986; **58:** 242–6.

Effects on the kidneys. Calcium-channel blockers may be of benefit in various forms of kidney disorder (see under Uses and Administration, below). However, reversible deterioration in renal function without any appreciable accompanying decline in systemic arterial blood pressure has been reported[1] in 4 patients with underlying renal insufficiency receiving nifedipine,[1] and in another report[2] nifedipine increased urinary protein excretion and exacerbated renal impairment in 14 type 2 diabetic patients.

Excessive diuresis occurred in a patient given nifedipine for angina pectoris,[3] and nocturia in 9 patients referred for prostatic surgery was also attributed to nifedipine.[4]

1. Diamond JR, *et al.* Nifedipine-induced renal dysfunction: alterations in renal hemodynamics. *Am J Med* 1984; **77:** 905–9.
2. Demarie BK, Bakris GL. Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; **113:** 987–8.
3. Antonelli D, *et al.* Excessive nifedipine diuretic effect. *BMJ* 1984; **288:** 760.
4. Williams G, Donaldson RM. Nifedipine and nocturia. *Lancet* 1986; **i:** 738.

Effects on the liver. A number of cases of hepatitis, apparently due to a hypersensitivity reaction, and frequently accompanied by fever, sweating, chills, rigor, and arthritic symptoms, have been reported in patients receiving nifedipine.[1-4]

1. Rotmensch HH, *et al.* Lymphocyte sensitisation in nifedipine-induced hepatitis. *BMJ* 1980; **281:** 976–7.
2. Davidson AR. Lymphocyte sensitisation in nifedipine-induced hepatitis. *BMJ* 1980; **281:** 1354.
3. Abramson M, Littlejohn GO. Hepatic reactions to nifedipine. *Med J Aust* 1985; **142:** 47–8.
4. Shaw DR, *et al.* Nifedipine hepatitis. *Aust N Z J Med* 1987; **17:** 447–8.

Effects on the menstrual cycle. Menorrhagia in 2 women[1] and menstrual irregularity with heavy bleeding in another[2] have been reported in association with nifedipine treatment.

1. Rodger JC, Torrance TC. Can nifedipine provoke menorrhagia? *Lancet* 1983; **ii:** 460.
2. Singh G, *et al.* Can nifedipine provoke menorrhagia? *Lancet* 1983; **ii:** 1022.

Effects on mental function. Insomnia, hyperexcitability, pacing, agitation, and depression were reported[1] in a patient in association with nifedipine therapy. The symptoms disappeared within 2 days of withdrawal of nifedipine. Four further cases of major depression, which developed within a week of starting nifedipine and resolved within a week of stopping the drug, have been reported.[2]

Although 2 epidemiological studies suggested that calcium-channel blockers may promote suicide,[3] a subsequent study[4] found no evidence of an association between depression and the use of calcium-channel blockers, and the number of suicides was low. Further studies[5,6] have also failed to find an increased risk of suicide with calcium-channel blockers compared with other antihypertensive drugs.

1. Ahmad S. Nifedipine-induced acute psychosis. *J Am Geriatr Soc* 1984; **32:** 408.
2. Hullett FJ, *et al.* Depression associated with nifedipine-induced calcium channel blockade. *Am J Psychiatry* 1988; **145:** 1277–9.
3. Lindberg G, *et al.* Use of calcium channel blockers and risk of suicide: ecological findings confirmed in population based cohort study. *BMJ* 1998; **316:** 741–5.
4. Dunn NR, *et al.* Cohort study on calcium channel blockers, other cardiovascular agents, and the prevalence of depression. *Br J Clin Pharmacol* 1999; **48:** 230–3.
5. Gasse C, *et al.* Risk of suicide among users of calcium channel blockers: population based, nested case-control study. *BMJ* 2000; **320:** 1251.
6. Sørensen HT, *et al.* Risk of suicide in users of beta-adrenoceptor blockers, calcium channel blockers and angiotensin converting enzyme inhibitors. *Br J Clin Pharmacol* 2001; **52:** 313–8.

Effects on the mouth. ***GINGIVAL HYPERPLASIA.*** A number of reports have implicated nifedipine in the development of gingival hyperplasia.[1-4] In most cases it has occurred about 1 to 6 months after starting therapy and has resolved after stopping nifedipine. A patient who had taken nifedipine for 12 years developed gingival hyperplasia shortly after the dosage of nifedipine was increased.[5] Amlodipine has also induced gingival overgrowth.[6] A study involving 115 patients given nifedipine, diltiazem, or verapamil for at least 3 months indicated that gingival hyperplasia is an important adverse effect that may occur with calcium-channel blockers in general.[7] Dihydropyridine calcium-channel blockers were among the most common drugs associated with reports of gingival hyperplasia in the Australian Adverse Drug Reactions Advisory Committee database.[8]

1. Ramon Y, *et al.* Gingival hyperplasia caused by nifedipine—a preliminary report. *Int J Cardiol* 1984; **5:** 195–204.
2. van der Wall EE, *et al.* Gingival hyperplasia induced by nifedipine, an arterial vasodilating drug. *Oral Surg* 1985; **60:** 38–40.
3. Shaftic AA, *et al.* Nifedipine-induced gingival hyperplasia. *Drug Intell Clin Pharm* 1986; **20:** 602–5.
4. Jones CM. Gingival hyperplasia associated with nifedipine. *Br Dent J* 1986; **160:** 416–17.
5. Johnson RB. Nifedipine-induced gingival overgrowth. *Ann Pharmacother* 1997; **31:** 935.
6. Ellis JS, *et al.* Gingival sequestration of amlodipine and amlodipine-induced gingival overgrowth. *Lancet* 1993; **341:** 1102–3.
7. Steele RM, *et al.* Calcium antagonist-induced gingival hyperplasia. *Ann Intern Med* 1994; **120:** 663–4.
8. Adverse Drug Reactions Advisory Committee (ADRAC). Drug-induced gingival overgrowth. *Aust Adverse Drug React Bull* 1999; **18:** 6–7. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9906.pdf (accessed 25/07/08)

PAROTITIS. Acute swelling of the parotid glands occurred in a patient after sublingual administration of nifedipine.[1]

1. Bosch X, *et al.* Nifedipine-induced parotitis. *Lancet* 1986; **ii:** 467.

Effects on the neuromuscular system. Severe muscle cramps have been reported in a few patients taking nifedipine;[1,2] in one patient[2] the cramps were associated with widespread paraesthesia. Reversible myoclonic dystonia associated with nifedipine has been reported in a patient.[3] Severe rhabdomyolysis developed in a patient with a transplanted kidney who was receiving an intravenous infusion of nifedipine.[4] The patient recovered rapidly once the infusion was stopped. There has also been a report[5] of myopathy, myalgia, and arthralgia associated with amlodipine, and of arthralgia in a patient[6] receiving diltiazem.

Parkinsonism is a recognised adverse effect of flunarizine and cinnarizine, which have calcium-channel blocking properties (see Extrapyramidal Disorders under Flunarizine, p.580). It has also been reported with diltiazem (see p.1266) and with amlodipine.[7,8]

1. Keidar S, *et al.* Muscle cramps during treatment with nifedipine. *BMJ* 1982; **285:** 1241–2.
2. Macdonald JB. Muscle cramps during treatment with nifedipine. *BMJ* 1982; **285:** 1744.
3. de Medina A, *et al.* Nifedipine and myoclonic dystonia. *Ann Intern Med* 1985; **104:** 125.
4. Horn S, *et al.* Severe rhabdomyolysis in a kidney-transplant recipient receiving intravenous nifedipine. *Lancet* 1995; **346:** 848–9.
5. Phillips BB, Muller BA. Severe neuromuscular complications possibly associated with amlodipine. *Ann Pharmacother* 1998; **32:** 1165–7.
6. Smith KM. Arthralgia associated with calcium-channel blockers. *Am J Health-Syst Pharm* 2000; **57:** 55–7.
7. Sempere AP, *et al.* Parkinsonism induced by amlodipine. *Mov Disord* 1995; **10:** 115–6.
8. Teive HA, *et al.* Parkinsonian syndrome induced by amlodipine: case report. *Mov Disord* 2002; **17:** 833–5.

Effects on the oesophagus. Calcium-channel blockers decrease lower oesophageal sphincter pressure and have been used in oesophageal motility disorders (see below), but a retrospective cohort study[1] found that calcium-channel blockers may also precipitate or exacerbate gastro-oesophageal reflux disease.

1. Hughes J, *et al.* Do calcium antagonists contribute to gastro-oesophageal reflux disease and concomitant noncardiac chest pain? *Br J Clin Pharmacol* 2007; **64:** 83–9.

Effects on the peripheral circulation. An erythromelalgia-like eruption occurred in a patient 8 weeks after starting therapy with nifedipine. Symptoms included severe burning pain and swelling in the feet and lower legs, which were fiery red, tender, and warm to the touch. Symptoms resolved in 2 days when nifedipine was stopped.[1] Similar effects have been reported in other patients on nifedipine.[2-4] Erythromelalgia has also been reported with nicardipine.[5] This type of erythromelalgia may be termed secondary erythermalgia.[6]

1. Fisher JR, *et al.* Nifedipine and erythromelalgia. *Ann Intern Med* 1983; **98:** 671–2.
2. Grunwald Z. Painful edema, erythematous rash, and burning sensation due to nifedipine. *Drug Intell Clin Pharm* 1982; **16:** 492.
3. Brodmerkel GJ. Nifedipine and erythromelalgia. *Ann Intern Med* 1983; **99:** 415.
4. Sunahara JF, *et al.* Possible erythromelalgia-like syndrome associated with nifedipine in a patient with Raynaud's phenomenon. *Ann Pharmacother* 1996; **30:** 484–6.
5. Levesque H, *et al.* Erythromelalgia induced by nicardipine (inverse Raynaud's phenomenon?) *BMJ* 1989; **298:** 1252–3.
6. Drenth JPH, Michiels JJ. Three types of erythromelalgia. *BMJ* 1990; **301:** 454–5.

Effects on the respiratory system. There have been some reports of pulmonary oedema being precipitated by nifedipine therapy in patients with aortic stenosis.[1,2] Nifedipine has also been reported to exacerbate impaired tissue oxygenation in patients with cor pulmonale secondary to obstructive airways disease.[3]

For a report of exacerbation of laryngeal oedema, see under Hypersensitivity, below.

1. Gillmer DJ, Kark P. Pulmonary oedema precipitated by nifedipine. *BMJ* 1980; **280:** 1420–1.
2. Aderka D, Pinkhas J. Pulmonary oedema precipitated by nifedipine. *BMJ* 1984; **289:** 1272.
3. Kalra L, Bone MF. Nifedipine and impaired oxygenation in patients with chronic bronchitis and cor pulmonale. *Lancet* 1989; **i:** 1135–6.

Effects on the skin and nails. The commonest skin reactions to nifedipine have been rash, pruritus, urticaria, alopecia, and exfoliative dermatitis;[1] there have been a few reports of erythema multiforme and the Stevens-Johnson syndrome.[1] Erythema multiforme occurred in a patient after substitution of amlodipine for nifedipine[2] and cross-sensitivity, manifest as a pruritic maculopapular rash, has been reported between amlodipine and diltiazem.[3] Generalised pruritus has been reported with amlodipine.[4] Other skin reactions that have been reported with nifedipine include severe photosensitivity reactions,[5] nonthrom-

bocytopenic purpuric rashes,[6] and telangiectasias,[7] including photodistributed telangiectasias,[8] and pemphigoid nodularis.[9] Photodistributed telangiectasias have also been reported with amlodipine,[10,11] and in one case[10] recurred 3 years later. Amlodipine has also been associated[12] with a case of lichen planus.

For reference to erythromelalgia, see under Effects on the Peripheral Circulation, above.

Nail and periungual pigmentation developed[13] in a 75-year-old man 18 months after starting amlodipine; it was much improved 2 years after the drug was stopped.

1. Stern R, Khalsa JH. Cutaneous adverse reactions associated with calcium channel blockers. *Arch Intern Med* 1989; **149:** 829–32.
2. Bewley AP, *et al.* Erythema multiforme following substitution of amlodipine for nifedipine. *BMJ* 1993; **307:** 241.
3. Baker BA, Cacchione JG. Dermatologic cross-sensitivity between diltiazem and amlodipine. *Ann Pharmacother* 1994; **28:** 118–19.
4. Orme S, *et al.* Generalised pruritus associated with amlodipine. *BMJ* 1997; **315:** 463.
5. Thomas SE, Wood ML. Photosensitivity reactions associated with nifedipine. *BMJ* 1986; **292:** 992.
6. Oren R, *et al.* Nifedipine-induced nonthrombocytopenic purpura. *DICP Ann Pharmacother* 1989; **23:** 88.
7. Tsele E, Chu AC. Nifedipine and telangiectasias. *Lancet* 1992; **339:** 365–6.
8. Collins P, Ferguson J. Photodistributed nifedipine-induced facial telangiectasia. *Br J Dermatol* 1993; **129:** 630–3.
9. Ameen M, *et al.* Pemphigoid nodularis associated with nifedipine. *Br J Dermatol* 2000; **142:** 575–7.
10. Basarab T, *et al.* Calcium antagonist-induced photo-exposed telangiectasia. *Br J Dermatol* 1997; **136:** 974–5.
11. Grabczynska SA, Cowley N. Amlodipine induced-photosensitivity presenting as telangiectasia. *Br J Dermatol* 2000; **142:** 1255–6.
12. Swale VJ, McGregor JM. Amlodipine-associated lichen planus. *Br J Dermatol* 2001; **144:** 920–1.
13. Sladden MJ, *et al.* Longitudinal melanonychia and pseudo-Hutchinson sign associated with amlodipine. *Br J Dermatol* 2005; **153:** 219–20.

Effects on taste. Distortion of taste and smell has been reported in 2 patients taking nifedipine,[1] but a large survey involving 922 patients receiving nifedipine and 343 taking captopril did not show any association of taste disturbances with nifedipine.[2] Sudden loss of taste has also been reported[3] in a patient who had been taking amlodipine for several years; the sense of taste returned when amlodipine was stopped, but taste loss recurred on rechallenge.

1. Levenson JL, Kennedy K. Dysomia, dysgeusia, and nifedipine. *Ann Intern Med* 1985; **102:** 135–6.
2. Coulter DM. Eye pain with nifedipine and disturbance of taste with captopril: a mutually controlled study showing a method of postmarketing surveillance. *BMJ* 1988; **296:** 1086–8.
3. Sadasivam B, Jhaj R. Dysgeusia with amlodipine—a case report. *Br J Clin Pharmacol* 2007; **63:** 253.

Gynaecomastia. Unilateral gynaecomastia developed in 3 men 4, 6, and 26 weeks after starting nifedipine therapy.[1]

1. Clyne CAC. Unilateral gynaecomastia and nifedipine. *BMJ* 1986; **292:** 380.

Haemorrhage. See Effects on the Blood, above.

Hypersensitivity. Nifedipine is associated with various hypersensitivity reactions including skin rashes and effects on the liver(see above).

Nifedipine, given sublingually, exacerbated laryngeal swelling that developed in a woman after the use of isosorbide dinitrate spray.[1]

1. Silfvast T, *et al.* Laryngeal oedema after isosorbide dinitrate spray and sublingual nifedipine. *BMJ* 1995; **311:** 232.

Oedema. Oedema of the feet and ankles is a common adverse effect of nifedipine and other dihydropyridine calcium-channel blockers. It occurs typically 2 or more weeks after starting treatment and is caused by pre-capillary arteriolar dilatation rather than fluid retention.[1] Evidence from a study in 10 diabetic subjects beginning nifedipine therapy, 5 of whom developed ankle oedema, suggested that nifedipine abolished the reflex vasoconstriction produced when the feet are below the level of the heart which is believed to prevent excessive fluid filtration into the tissues.[2]

The oedema may respond to simple measures such as elevation of the feet or to a reduction in dosage but if it persists the calcium-channel blocker should be withdrawn.[1]

Generalised oedema[3] and facial and upper extremity oedema[4] have been reported in patients taking amlodipine, but in both cases symptoms resolved on withdrawal of the drug.

1. Maclean D, MacConnachie AM. Selective side-effects: peripheral oedema with dihydropyridine calcium antagonists. *Prescribers' J* 1991; **31:** 4–6.
2. Williams SA, *et al.* Dependent oedema and attenuation of postural vasoconstriction associated with nifedipine therapy for hypertension in diabetic patients. *Eur J Clin Pharmacol* 1989; **37:** 333–5.
3. Şener D, *et al.* Anasarca edema with amlodipine treatment. *Ann Pharmacother* 2005; **39:** 761–3.
4. Ganeshalingham A, Wong W. Amlodipine-induced bilateral upper extremity edema. *Ann Pharmacother* 2007; **41:** 1536–8.

Treatment of Adverse Effects

Activated charcoal may be given orally to adults or children who present within 1 hour of ingesting a potentially toxic overdose of nifedipine. Alternatively, gastric lavage may be considered in adults. Supportive and symptomatic care should be given. Hypotension may respond to placing the patient in the supine position with the feet raised; plasma expanders may be given, although cardiac overload should be avoided. If hypotension is not corrected, calcium should be given intravenously. The usual initial dose is 10 to 20 mL of 10% calcium gluconate given by slow intravenous injection or infusion; alternatively, up to 10 mL of 10% calcium chloride may be given. Glucagon may also be used. If hypotension persists, an intravenous sympathomimetic such as isoprenaline, dopamine, or noradrenaline may also be necessary. Bradycardia may be treated with atropine, isoprenaline, or cardiac pacing.

Dialysis is not useful as nifedipine is highly protein bound. Plasmapheresis may be beneficial.

Overdosage. The management of calcium-channel blocker overdosage is mainly supportive (see Treatment of Adverse Effects, above). Cardiovascular effects usually predominate and, although severe toxicity is more likely in overdosage with non-dihydropyridines such as verapamil or diltiazem, treatment of overdosage is similar for all calcium-channel blockers.[1-4] Prompt gastrointestinal decontamination, atropine to reverse bradycardia, and cardiovascular support with intravenous fluids, sympathomimetics, and possibly inotropes, are the mainstays of treatment. Intravenous calcium is also widely used, and high doses may be required; intravenous glucagon may also be given. Fampridine has been suggested[5] as a specific antagonist, and successful use of vasopressin[6] or terlipressin[7] has been reported in patients with resistant hypotension. There is also some evidence that high-dose insulin, with glucose if required to maintain normal blood-glucose concentrations, may be of benefit.[8-11]

Most reports of overdosage have been with verapamil (see p.1421). The following are some individual reports with nifedipine:

- Hypotension, tachycardia, and flushing, followed by hypokalaemia, were seen in a patient who took nifedipine 600 mg as modified-release tablets together with an overdose of paracetamol, but there was no evidence of heart block.[12] The patient was given calcium gluconate intravenously and subsequently activated charcoal and lactulose. Absorption of nifedipine was essentially complete 10 hours after ingestion. Potassium chloride was given orally to treat hypokalaemia and acetylcysteine was used to manage the paracetamol poisoning.
- Third-degree AV block, progressing to asystole, developed in a 14-month-old child who ingested about 800 mg of nifedipine.[13] During cardiopulmonary resuscitation a total of 700 mg of calcium chloride was given, together with atropine, adrenaline, and sodium bicarbonate. The stomach was subsequently emptied by gastric lavage and activated charcoal given. The patient remained tachycardic and hypotensive, with evidence of pulmonary oedema and hyperglycaemia, and was given intravenous electrolytes and dopamine infusions and assisted ventilation, together with treatment to control subsequent tonic-clonic seizures. She eventually made an apparently complete recovery apart from a moderate speech delay.

1. Salhanick SD, Shannon MW. Management of calcium channel antagonist overdose. *Drug Safety* 2003; **26:** 65–79.
2. DeWitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity. *Toxicol Rev* 2004; **23:** 223–38.
3. Olson KR, *et al.* Calcium channel blocker ingestion: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol* 2005; **43:** 797–822.
4. Shepherd G. Treatment of poisoning caused by beta-adrenergic and calcium-channel blockers. *Am J Health-Syst Pharm* 2006; **63:** 1828–35.
5. Stevens JJWM, Ghosh S. Overdose of calcium channel blockers. *BMJ* 1994; **309:** 193.
6. Kanagarajan K, *et al.* The use of vasopressin in the setting of recalcitrant hypotension due to calcium channel blocker overdose. *Clin Toxicol* 2007; **45:** 56–9.
7. Leone M, *et al.* Terlipressin: a new therapeutic for calcium-channel blockers overdose. *J Crit Care* 2005; **20:** 114–15.
8. Yuan TH, *et al.* Insulin-glucose as adjunctive therapy for severe calcium channel antagonist poisoning. *J Toxicol Clin Toxicol* 1999; **37:** 463–74.
9. Boyer EW, Shannon M. Treatment of calcium-channel-blocker intoxication with insulin infusion. *N Engl J Med* 2001; **344:** 1721–2.
10. Mégarbane B, *et al.* The role of insulin and glucose (hyperinsulinaemia/euglycaemia) therapy in acute calcium channel antagonist and beta-blocker poisoning. *Toxicol Rev* 2004; **23:** 215–22.
11. Shepherd G, Klein-Schwartz W. High-dose insulin therapy for calcium-channel blocker overdose. *Ann Pharmacother* 2005; **39:** 923–30.
12. Ferner RE, *et al.* Pharmacokinetics and toxic effects of nifedipine in massive overdose. *Hum Exp Toxicol* 1990; **9:** 309–11.
13. Wells TG, *et al.* Nifedipine poisoning in a child. *Pediatrics* 1990; **86:** 91–4.

Precautions

Nifedipine should be used with caution in patients with hypotension, in patients whose cardiac reserve is poor, and in those with heart failure since deterioration of heart failure has been noted. Nifedipine should not be used in cardiogenic shock, in patients who have suffered a myocardial infarction in the previous 2 to 4 weeks, or in acute unstable angina. Nifedipine should not be used to treat an anginal attack in chronic stable angina. In patients with severe aortic stenosis nifedipine may increase the risk of developing heart failure. Sudden withdrawal of nifedipine might be associated with an exacerbation of angina. The dose may need to be reduced in patients with hepatic impairment.

Nifedipine should be stopped in patients who experience ischaemic pain after use.

Nifedipine is reported to be teratogenic in *animals* and may inhibit labour, but it has been used in hypertension in pregnancy (see Hypertension, under Uses and Administration, below).

Breast feeding. Nifedipine is distributed into breast milk[1,2] but the amount present is probably too small to be harmful. There have been no reports of any clinical effects in breast-fed infants whose mothers were receiving nifedipine and the American Academy of Pediatrics therefore considers[3] that it is usually compatible with breast feeding.

1. Ehrenkranz RA, *et al.* Nifedipine transfer into human milk. *J Pediatr* 1989; **114:** 478–80.
2. Penny WJ, Lewis MJ. Nifedipine is excreted in human milk. *Eur J Clin Pharmacol* 1989; **36:** 427–8.
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)

Diabetes mellitus. Nifedipine may modify insulin and glucose responses (see Effects on Carbohydrate Metabolism under Adverse Effects, above) calling for adjustments in antidiabetic therapy. Also some studies have suggested that nifedipine may worsen proteinuria and renal dysfunction in diabetic patients with some degree of renal insufficiency,[1,2] but other studies, (see Kidney Disorders under Uses and Administration, below), have suggested that nifedipine may have a beneficial effect on proteinuria.

Some studies have suggested that patients with diabetes mellitus[3,4] or impaired glucose metabolism[5] may be more susceptible to adverse cardiovascular effects of calcium-channel blockers. The calcium-channel blockers used in these studies were nisoldipine, amlodipine, and isradipine (long-acting or intermediate-acting calcium-channel blockers). However, two of the studies[3,4] compared the calcium-channel blocker with an ACE inhibitor and it has been suggested that ACE inhibitors may have a protective effect in patients with diabetes that is additional to their antihypertensive action. Thus, ACE inhibitors may be particularly beneficial in these patients rather than calcium-channel blockers being particularly harmful.[6]

1. Mimran A, *et al.* Contrasting effects of captopril and nifedipine in normotensive patients with incipient diabetic nephropathy. *J Hypertens* 1988; **6:** 919–23.
2. Demarie BK, Bakris GL. Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; **113:** 987–8.
3. Estacio RO, *et al.* The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998; **338:** 645–52. Correction. *ibid.*; **339:** 1339.
4. Tatti P, *et al.* Outcome results of the fosinopril versus amlodipine cardiovascular events randomized trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998; **21:** 597–603.
5. Byington RP, *et al.* Isradipine, raised glycosylated haemoglobin, and risk of cardiovascular events. *Lancet* 1997; **350:** 1075–6.
6. Poulter NR. Calcium channel blockers and cardiovascular risk in diabetes. *Lancet* 1998; **351:** 1809–10.

Interference with laboratory estimations. Nifedipine may give falsely elevated spectrophotometric values of urinary vanillylmandelic acid; HPLC estimations are unaffected.

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

Withdrawal. Sudden withdrawal of nifedipine might be associated with an exacerbation of angina.

For a report of life-threatening coronary vasospasm occurring after withdrawal of nifedipine before a revascularisation procedure, see under Effects on the Heart, in Diltiazem, p.1265.

Interactions

Nifedipine may enhance the antihypertensive effects of other antihypertensive drugs such as beta blockers although the combination is generally well tolerated. Enhanced antihypertensive effects may also be seen if used with drugs such as aldesleukin and antipsychotics that cause hypotension. Nifedipine may modify insulin and glucose responses (see Effects on Carbohydrate Metabolism, above) and therefore diabetic patients may need to adjust their antidiabetic treatment when receiving nifedipine. Nifedipine is extensively metab-

olised in the liver by the cytochrome P450 isoenzyme CYP3A4, and interactions may occur with other drugs, such as quinidine, sharing the same metabolic pathway, and with enzyme inducers, such as carbamazepine, phenytoin, and rifampicin, and enzyme inhibitors, such as cimetidine, erythromycin, and HIV-protease inhibitors.

Alcohol. A study involving 10 healthy subjects showed that the area under the concentration-time profile for nifedipine 20 mg was increased by 54% when taken orally with alcohol, and maximum pulse rate was achieved more rapidly, which was in line with *animal* and *in-vitro* studies suggesting that the metabolism of nifedipine is inhibited by alcohol.[1]

1. Qureshi S, *et al.* Nifedipine-alcohol interaction. *JAMA* 1990; **264:** 1660–1.

Antiarrhythmics. Nifedipine and *quinidine* probably have a common metabolic pathway in the liver and might be expected to interact if given concurrently. In one study,[1] quinidine appeared to inhibit nifedipine metabolism resulting in increased serum concentrations of nifedipine; quinidine concentrations were unchanged. However, conflicting effects on serum-quinidine concentrations have been reported, see p.1384.

1. Bowles SK, *et al.* Evaluation of the pharmacokinetic and pharmacodynamic interaction between quinidine and nifedipine. *J Clin Pharmacol* 1993; **33:** 727–31.

Antibacterials. The macrolide antibacterials are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may inhibit the metabolism of calcium-channel blockers. Two days after *clarithromycin* was started,[1] vasodilatory shock and heart block occurred in a 77-year-old man whose antihypertensive medication included nifedipine. Clarithromycin was continued and when his condition improved nifedipine was reintroduced at half the previous dose; his blood pressure was stable on discharge.

1. Gerónimo-Pardo M, *et al.* Clarithromycin–nifedipine interaction as possible cause of vasodilatory shock. *Ann Pharmacother* 2005; **39:** 538–42.

Antidiabetics. See Diabetes Mellitus under Precautions and Effects on Carbohydrate Metabolism under Adverse Effects, above.

Antiepileptics. The effects of dihydropyridine calcium-channel blockers may be reduced by enzyme-inducing antiepileptics such as *carbamazepine*, *phenobarbital*, and *phenytoin*.[1-4] In contrast, *sodium valproate* has been reported to increase plasma-nimodipine concentrations.[3]

For reports of an interaction between dihydropyridines and *phenytoin* resulting in raised serum-phenytoin concentration, see p.499.

1. Capewell S, *et al.* Reduced felodipine bioavailability in patients taking anticonvulsants. *Lancet* 1988: **ii:** 480–2.
2. Schellens JHM, *et al.* Influence of enzyme induction and inhibition on the oxidation of nifedipine, sparteine, mephenytoin and antipyrine in humans as assessed by a "cocktail" study design. *J Pharmacol Exp Ther* 1989; **249:** 638–45.
3. Tartara A, *et al.* Differential effects of valproic acid and enzyme-inducing anticonvulsants on nimodipine pharmacokinetics in epileptic patients. *Br J Clin Pharmacol* 1991; **32:** 335–40.
4. Yasui-Furukori N, Tateishi T. Carbamazepine decreases antihypertensive effect of nilvadipine. *J Clin Pharmacol* 2002; **42:** 100–103.

Antifungals. Azole antifungals inhibit the cytochrome P450 enzyme system and may therefore interfere with metabolism of calcium-channel blockers. Two women who had been taking felodipine for about a year developed peripheral oedema a few days after starting treatment with *itraconazole*.[1] Plasma-felodipine concentrations were measured in one of the women before and during a subsequent course of itraconazole and increased considerably when the two drugs were used together. A similar interaction occurred when itraconazole therapy was started in a patient already taking nifedipine.[2] Potentiation of the effects of nifedipine by *fluconazole* has also been reported.[3]

1. Neuvonen PJ, Suhonen R. Itraconazole interacts with felodipine. *J Am Acad Dermatol* 1995; **33:** 134–5.
2. Tailor SAN, *et al.* Peripheral edema due to nifedipine-itraconazole interaction: a case report. *Arch Dermatol* 1996; **132:** 350–2.
3. Kremens B, *et al.* Loss of blood pressure control on withdrawal of fluconazole during nifedipine therapy. *Br J Clin Pharmacol* 1999; **47:** 707–8.

Antihistamines. Severe angina developed in a patient stabilised on nifedipine who took *terfenadine* 60 mg for seasonal allergy. The pain resolved within an hour or two.[1]

1. Falkenberg HM. Possible interaction report. *Can Pharm J* 1988; **121:** 294.

Antineoplastics. For reports of increased *vincristine* toxicity in children also receiving itraconazole and nifedipine concomitantly, see Antifungals under Interactions of Vincristine, p.787.

Antivirals. The HIV-protease inhibitors are known to inhibit the cytochrome P450 isoenzyme CYP3A4 and may therefore interfere with the metabolism of calcium-channel blockers. A woman stable on felodipine developed oedema[1] in both legs when she was given *nelfinavir* after a needle-stick injury. The oedema resolved on withdrawal of felodipine, and was attributed to inhibition of felodipine metabolism. A study[2] in healthy subjects found that *indinavir plus ritonavir* increased exposure to both amlodipine and diltiazem.

1. Izzedine H, *et al.* Nelfinavir and felodipine: a cytochrome P450 3A4-mediated drug interaction. *Clin Pharmacol Ther* 2004; **75:** 362–3.
2. Glesby MJ, *et al.* Pharmacokinetic interactions between indinavir plus ritonavir and calcium channel blockers. *Clin Pharmacol Ther* 2005; **78:** 143–53.

Beta blockers. Although nifedipine is often used with beta blockers without untoward effects, heart failure has been reported in a few patients with angina who were given nifedipine and a beta blocker.[1,2] Severe hypotension has been reported in 1 of 15 angina patients given nifedipine and *atenolol*;[3] withdrawal of the beta blocker precipitated severe unstable angina in this patient. Severe hypotension in a patient was attributed to the use of nifedipine with *propranolol*, and was thought to have contributed to fatal myocardial infarction.[4]

1. Anastassiades CJ. Nifedipine and beta-blocker drugs. *BMJ* 1980; **281:** 1251–2.
2. Robson RH, Vishwanath MC. Nifedipine and beta-blockade as a cause of cardiac failure. *BMJ* 1982; **284:** 104.
3. Opie LH, White DA. Adverse interaction between nifedipine and β-blockade. *BMJ* 1980; **281:** 1462.
4. Staffurth JS, Emery P. Adverse interaction between nifedipine and beta-blockade. *BMJ* 1981; **282:** 225.

Calcium-channel blockers. Plasma concentrations of nifedipine were increased in a study in 6 healthy subjects when pretreated with *diltiazem*; the elimination half-life of nifedipine was prolonged from 2.54 hours to 3.40 hours after pretreatment with diltiazem 30 mg daily and to 3.47 hours after 90 mg daily. The effect was probably due to reduced hepatic metabolism of nifedipine.[1] Nifedipine and diltiazem are reported to be metabolised by the same hepatic enzyme and, conversely, pretreatment with nifedipine has resulted in increased concentrations of diltiazem.[2]

1. Tateishi T, *et al.* Dose dependent effect of diltiazem on the pharmacokinetics of nifedipine. *J Clin Pharmacol* 1989; **29:** 994–7.
2. Tateishi T, *et al.* The effect of nifedipine on the pharmacokinetics and dynamics of diltiazem: the preliminary study in normal volunteers. *J Clin Pharmacol* 1993; **33:** 738–40.

Digoxin. For the effect of nifedipine and other dihydropyridine calcium-channel blockers on digoxin, see p.1262.

Grapefruit juice. Grapefruit juice inhibits the cytochrome P450 isoenzyme CYP3A4, particularly in the intestinal wall, and has been shown to increase markedly the bioavailability of oral calcium-channel blockers;[1-3] calcium-channel blockers given intravenously appear to be unaffected.[4] The interaction may be less significant with calcium-channel blockers such as amlodipine that have a higher bioavailability,[5] but most calcium-channel blockers should not be taken orally at the same time as grapefruit juice.[6] A stereoselective effect has also been reported.[7]

1. Bailey DG, *et al.* Interaction of citrus juices with felodipine and nifedipine. *Lancet* 1991; **337:** 268–9.
2. Bailey DG, *et al.* Effect of grapefruit juice and naringin on nisoldipine pharmacokinetics. *Clin Pharmacol Ther* 1993; **54:** 589–94.
3. Lundahl J, *et al.* Relationship between time of intake of grapefruit juice and its effect on pharmacokinetics and pharmacodynamics of felodipine in healthy subjects. *Eur J Clin Pharmacol* 1995; **49:** 61–7.
4. Rashid TJ, *et al.* Factors affecting the absolute bioavailability of nifedipine. *Br J Clin Pharmacol* 1995; **40:** 51–8.
5. Vincent J, *et al.* Lack of effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of amlodipine. *Br J Clin Pharmacol* 2000; **50:** 455–63.
6. Committee on Safety of Medicines/Medicines Control Agency. Drug interactions with grapefruit juice. *Current Problems* 1997; **23:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015623&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)
7. Uno T, *et al.* Effect of grapefruit juice on the disposition of manidipine enantiomers in healthy subjects. *Br J Clin Pharmacol* 2006; **61:** 533–7.

Histamine H_2-antagonists. Pharmacokinetic studies have indicated that use of nifedipine with *cimetidine* can increase the bioavailability of nifedipine.[1-4] An increase in the area under the plasma concentration-time curve of between 77 and 92% has been reported.[2,3] Potentiation of the hypotensive effect of nifedipine by cimetidine was also shown in 7 hypertensive patients.[1] The mechanism of the interaction was thought to be due to inhibition of the cytochrome P450 system by cimetidine and thus inhibition of the metabolism of nifedipine.

Ranitidine was found to have little effect on the pharmacokinetics of nifedipine, although there was an increase in the bioavailability of nifedipine during use of ranitidine.[5] *Famotidine* has been reported not to interact with nifedipine.[6]

1. Kirch W, *et al.* Einfluß von cimetidin und ranitidin auf pharmakokinetik und antihypertensiven effekt von nifedipin. *Dtsch Med Wochenschr* 1983; **108:** 1757–61.
2. Renwick AG, *et al.* Factors affecting the pharmacokinetics of nifedipine. *Eur J Clin Pharmacol* 1987; **32:** 351–5.
3. Smith SR, *et al.* Ranitidine and cimetidine: drug interactions with single dose and steady-state nifedipine administration. *Br J Clin Pharmacol* 1987; **23:** 311–15.
4. Schwartz JB, *et al.* Effect of cimetidine or ranitidine administration on nifedipine pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 1988; **43:** 673–80.
5. Kirch W, *et al.* Ranitidine increases bioavailability of nifedipine. *Clin Pharmacol Ther* 1985; **37:** 204.
6. Kirch W, *et al.* Negative effects of famotidine on cardiac performance assessed by noninvasive hemodynamic measurements. *Gastroenterology* 1989; **96:** 1388–92.

Immunosuppressants. Flushing, paraesthesias, and rashes were reported in 2 patients given nifedipine 40 mg daily while taking *ciclosporin* for psoriasis.[1] A study in 8 psoriatic patients indicated that giving nifedipine with ciclosporin resulted in reduced recovery of the principal metabolite of nifedipine, presumably because ciclosporin reduced nifedipine metabolism through competition for the cytochrome P450 metabolising enzymes.

For reference to the effects of calcium-channel blockers on ciclosporin concentrations in blood, see p.1827. For the possible protective effect of nifedipine against ciclosporin-induced nephrotoxicity, see Transplantation under Uses and Administration, below.

For the effect of nifedipine on *tacrolimus*, see p.1845.

1. McFadden JP, *et al.* Cyclosporin decreases nifedipine metabolism. *BMJ* 1989; **299:** 1224.

Magnesium salts. Profound hypotension has been reported in 2 women in whom a single oral dose of nifedipine 10 mg was added to treatment with magnesium sulfate infusion for pre-eclampsia; both women were also receiving methyldopa.[1] Neuromuscular blockade has been reported in 2 women after use of nifedipine with intravenous magnesium sulfate. In one woman receiving nifedipine as a tocolytic, symptoms of neuromuscular blockade occurred immediately on injection of magnesium sulfate and resolved within 25 minutes of stopping the injection.[2] In another woman who was receiving a magnesium sulfate infusion for pre-eclampsia, symptoms developed 30 minutes after the second of 2 doses of nifedipine had been given and improved after receiving calcium gluconate injection.[3]

1. Waisman GD, *et al.* Magnesium plus nifedipine: potentiation of hypotensive effect in pre-eclampsia? *Am J Obstet Gynecol* 1988; **159:** 308–9.
2. Snyder SW, Cardwell MS. Neuromuscular blockade with magnesium sulfate and nifedipine. *Am J Obstet Gynecol* 1989; **161:** 35–6.
3. Ben-Ami M, *et al.* The combination of magnesium sulphate and nifedipine: a cause of neuromuscular blockade. *Br J Obstet Gynaecol* 1994; **101:** 262–3.

Melatonin. Melatonin may cause a reduction in blood pressure and might be expected to have additive effects if given with antihypertensives. However, in a study[1] in hypertensive patients taking nifedipine, giving melatonin led to an increase in both blood pressure and heart rate.

1. Lusardi P, *et al.* Cardiovascular effects of melatonin in hypertensive patients well controlled by nifedipine: a 24-hour study. *Br J Clin Pharmacol* 2000; **49:** 423–7.

Tobacco. In a study of the effects of cigarette smoking and the treatment of angina with nifedipine, propranolol, or atenolol, smoking was shown to have direct and adverse effects on the heart and to interfere with the efficacy of all 3 anti-anginal drugs, with nifedipine being the most affected.[1]

1. Deanfield J, *et al.* Cigarette smoking and the treatment of angina with propranolol, atenolol, and nifedipine. *N Engl J Med* 1984; **310:** 951–4.

Xanthines. For the effect of nifedipine on *theophylline*, see p.1144.

Pharmacokinetics

Nifedipine is rapidly and almost completely absorbed from the gastrointestinal tract, but undergoes extensive hepatic first-pass metabolism. Bioavailability of oral liquid-filled capsules is between 45 and 75%, but is lower for longer-acting formulations. Peak blood concentrations are reported to occur 30 minutes after oral doses of liquid-filled capsules.

Nifedipine is about 92 to 98% bound to plasma proteins. It is distributed into breast milk. It is extensively metabolised in the liver and 70 to 80% of a dose is excreted in the urine almost entirely as inactive metabolites. The half-life is about 2 hours after intravenous doses or oral liquid-filled capsules.

◊ General reviews.

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

◊ The pharmacokinetics of nifedipine have been reviewed.[1] Studies have been complicated by the difficulty in preparing a stable intravenous formulation and the problems in developing a sufficiently sensitive and specific method of analysis. Nearly 100% of an oral dose of nifedipine is absorbed in the small intestine although the bioavailability from capsules is 45 to 68%. The rate of absorption from both oral and sublingual capsules varies widely among individuals: there has been a report that high plasma-nifedipine concentrations are achieved more rapidly if the capsule is bitten and swallowed than from standard oral and sublingual administration (but this is no longer recommended—see Hypertension, below). The absorption of nifedipine from tablets is slower than from capsules, with maximum plasma concentrations occurring at 1.6 to 4.2 hours compared with 0.5 to 2.17 hours, and absorption may still be occurring at 24 to 32 hours after a dose.

Nifedipine undergoes almost complete hepatic oxidation to 3 pharmacologically inactive metabolites which are excreted in the urine. It has been reported that after oral doses 30 to 40% of the

amount absorbed is metabolised during the first pass through the liver. The elimination half-life of nifedipine is apparently dependent upon the dosage form in which it is given, with half-lives of 6 to 11 hours, 2 to 3.4 hours, and 1.3 to 1.8 hours measured after oral tablet, oral capsule, and intravenous doses respectively. The total systemic clearance of nifedipine from plasma ranges from 27 to about 66 litres/hour. Renal impairment does not substantially alter nifedipine pharmacokinetics.

1. Sorkin EM, *et al.* Nifedipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy, in ischaemic heart disease, hypertension and related cardiovascular disorders. *Drugs* 1985; **30:** 182–274.

Absorption. Although studies have indicated that the absorption of nifedipine may be affected by food the results appear to vary depending upon the preparation used. A reduction in peak plasma-nifedipine concentrations, and a delay in achieving them, was reported[1] when nifedipine *capsules* were given after a meal compared with 30 minutes before. In contrast, the bioavailability and maximum serum concentrations of nifedipine were markedly increased when a *modified-release tablet* (*Adalat L*) was given after a meal rather than fasting,[2] although another modified-release tablet (*Slofedipine*) showed delayed absorption when given after food.[3] A further tablet formulation (*Adalat OROS*) was unaffected by food,[3] while a *modified-release capsule* containing uncoated and enteric-coated granules (*Sepamit R*) was reported to have essentially the same bioavailability when taken before or after a meal.[4]

1. Hirasawa K, *et al.* Effect of food ingestion on nifedipine absorption and haemodynamic response. *Eur J Clin Pharmacol* 1985; **28:** 105–7.
2. Ueno K, *et al.* Effect of food on nifedipine sustained-release preparation. *DICP Ann Pharmacother* 1989; **23:** 662–5.
3. Schug BS, *et al.* The effect of food on the pharmacokinetics of nifedipine in two slow release formulations: pronounced lagtime after a high fat breakfast. *Br J Clin Pharmacol* 2002; **53:** 582–8.
4. Ueno K, *et al.* Effect of a light breakfast on the bioavailability of sustained-release nifedipine. *DICP Ann Pharmacother* 1991; **25:** 317–19.

Hepatic impairment. The pharmacokinetics of nifedipine were found to be considerably altered in 7 patients with liver cirrhosis.[1] Systemic plasma clearance was substantially reduced and the elimination half-life was considerably longer than in healthy subjects. In addition, systemic availability of oral nifedipine was much higher in patients with cirrhosis and was complete in 3 patients with surgical portacaval shunt. Patients with liver cirrhosis seemed to be more sensitive to the effects of nifedipine on diastolic blood pressure and heart rate, and this could be explained by the higher free drug concentrations observed. It was concluded that lower doses of nifedipine may be required in patients with liver cirrhosis, and the patient's response should be closely monitored.

1. Kleinbloesem CH, *et al*. Nifedipine: kinetics and hemodynamic effects in patients with liver cirrhosis after intravenous and oral administration. *Clin Pharmacol Ther* 1986; **40:** 21–8.

Interindividual variation. A study in 53 Dutch subjects found a bimodal distribution of plasma concentrations of nifedipine after a single oral dose; it was proposed that the higher plasma concentrations in 17% of subjects represented a slow metaboliser phenotype, with the majority of the population being fast metabolisers.[1] Although further studies[2,3] in European populations have not confirmed these results, a study in 12 Mexican subjects supported the concept of polymorphic metabolism, with 5 fast and 7 slow metabolisers, a much higher proportion of slow metabolisers than in the European studies.[4] Studies have also reported a markedly increased area under the concentration-time curve in South Asian,[5,6] Mexican,[7] and Nigerian[8] subjects compared with Caucasians. The difference did not appear to be due to diet.[5,6] The initial dose of nifedipine might need to be lower in these ethnic groups. Another population study[9] found that clearance was slower in blacks compared with whites, and in men compared with women; alcohol ingestion and smoking both also reduced nifedipine clearance.

1. Kleinbloesem CH, *et al.* Variability in nifedipine pharmacokinetics and dynamics: a new oxidation polymorphism in man. *Biochem Pharmacol* 1984; **33:** 3721–4.
2. Renwick AG, *et al.* The pharmacokinetics of oral nifedipine—a population study. *Br J Clin Pharmacol* 1988; **25:** 701–8.
3. Lobo J, *et al.* The intra- and inter-subject variability of nifedipine pharmacokinetics in young volunteers. *Eur J Clin Pharmacol* 1986; **30:** 57–60.
4. Hoyo-Vadillo C, *et al.* Pharmacokinetics of nifedipine slow release tablet in Mexican subjects: further evidence for an oxidation polymorphism. *J Clin Pharmacol* 1989; **29:** 816–20.
5. Ahsan CH, *et al.* Ethnic differences in the pharmacokinetics of oral nifedipine. *Br J Clin Pharmacol* 1991; **31:** 399–403.
6. Ahsan CH, *et al.* The influences of dose and ethnic origins on the pharmacokinetics of nifedipine. *Clin Pharmacol Ther* 1993; **54:** 329–38.
7. Castañeda-Hernández G, *et al.* Interethnic variability in nifedipine disposition: reduced systemic plasma clearance in Mexican subjects. *Br J Clin Pharmacol* 1996; **41:** 433–4.
8. Sowunmi A, *et al.* Ethnic differences in nifedipine kinetics: comparisons between Nigerians, Caucasians and South Asians. *Br J Clin Pharmacol* 1995; **40:** 489–93.
9. Krecic-Shepard ME, *et al.* Race and sex influence clearance of nifedipine: results of a population study. *Clin Pharmacol Ther* 2000; **68:** 130–42.

Uses and Administration

Nifedipine is a dihydropyridine calcium-channel blocker (p.1154). It is a peripheral and coronary vasodilator, but, unlike the rate-limiting calcium-channel blockers verapamil or diltiazem, has little or no effect on cardiac conduction and negative inotropic activity is rarely seen at therapeutic doses. Use of nifedipine results primarily in vasodilatation, with reduced peripheral resistance, blood pressure, and afterload, increased coronary blood flow, and a reflex increase in heart rate. This in turn results in an increase in myocardial oxygen supply and cardiac output. Nifedipine has no antiarrhythmic activity. Nicardipine and newer dihydropyridines such as amlodipine, felodipine, isradipine, and lacidipine may be even more selective than nifedipine for vascular smooth muscle. Nimodipine acts particularly on cerebral blood vessels. Most of the dihydropyridine calcium-channel blockers (nifedipine and lacidipine are exceptions) are chiral compounds used as racemic mixtures.

Nifedipine is used in the management of hypertension; in the management of angina pectoris (p.1157), particularly when a vasospastic element is present, as in Prinzmetal's angina, but is not suitable for relief of an acute attack; and in the treatment of Raynaud's syndrome. Nifedipine has also been tried in numerous non-vascular disorders.

Nifedipine is usually given orally. It is available in several formulations. Liquid-filled capsules with a relatively rapid onset but short duration of action are given three times daily. This short-acting preparation is not recommended for the management of hypertension (see below). There are also tablets and capsules with a slower onset and longer duration of action, enabling twice-daily dosage; although these are often referred to by nomenclature implying extended or sustained release they should be distinguished from the true extended-release preparations available in some countries that allow dosage once daily.

Doses of nifedipine are dependent upon the formulation used; they may need to be reduced in the elderly or those with impaired liver function.

For **hypertension** a long-acting preparation of nifedipine may be given in doses of 10 to 40 mg twice daily, or 20 to 90 mg once daily, depending on the preparation used.

For **angina pectoris**, nifedipine may be given as a long-acting preparation in a dose of 10 to 40 mg twice daily or 30 to 90 mg once daily, depending on the preparation. Alternatively, the liquid-filled capsules have been given in a dose of 5 to 20 mg three times daily, but longer-acting preparations are preferred.

Nifedipine has been given by injection via a coronary catheter for the treatment of coronary spasm during coronary angiography and balloon angioplasty. Blood pressure and heart rate should be monitored carefully.

In the management of **Raynaud's syndrome**, nifedipine may be given as liquid-filled capsules in a dose of 5 to 20 mg three times daily.

For the use of nifedipine in children, see below.

◊ General reviews.

1. Fisher M, Grotta J. New uses for calcium channel blockers: therapeutic implications. *Drugs* 1993; **46:** 961–75.
2. Croom KF, Wellington K. Modified-release nifedipine: a review of the use of modified-release formulations in the treatment of hypertension and angina pectoris. *Drugs* 2006; **66:** 497–528.

Administration in children. Nifedipine has been used in the management of various disorders in children. The *BNFC* recommends the following oral doses:

Hypertension; angina in Kawasaki disease or progeria:

- age 1 month to 12 years: 200 to 300 micrograms/kg 3 times daily, increased to a maximum daily dose of 3 mg/kg or 100 mg
- age 12 to 18 years: 5 to 20 mg 3 times daily, increased to a maximum daily dose of 100 mg

Hypertensive crises:

- age 1 month to 18 years: 250 to 500 micrograms/kg as a single dose

Raynaud's syndrome:

- age 2 to 18 years: 2.5 to 10 mg 2 to 4 times daily; treatment should start with low doses at night, increased gradually to avoid postural hypotension

Neonatal hyperinsulinaemic hypoglycaemia:

- see below.

Use of nifedipine capsules for acute hypertension is no longer recommended in adults because of the risk of severe adverse effects related to precipitous reductions in blood pressure (see Effects on Mortality under Adverse Effects, above). Although there have been reports of adverse effects in children,[1-3] they may be less susceptible than adults, and the use of nifedipine capsules may still be appropriate. A study[4] in 12 children aged 6 to 15 years with acute severe hypertension reported that sublingual nifedipine in a mean dose of 240 micrograms/kg (range 180 to 320 micrograms/kg) was safe and effective. A retrospective study[1] in 117 children found that nifedipine safely reduced blood pressure, and that precipitous declines only occurred with doses higher than 250 micrograms/kg, while another retrospective study[2] in 166 children found that nifedipine in a mean dose of 300 micrograms/kg (range 40 to 1300 micrograms/kg) was generally safe, although children with acute CNS injury were at higher risk of neurological adverse effects.

Other routes that have been used include rectal[5] and intranasal,[6] but these are less established.

1. Blaszak RT, *et al.* The use of short-acting nifedipine in pediatric patients with hypertension. *J Pediatr* 2001; **139:** 34–7.
2. Egger DW, *et al.* Evaluation of the safety of short-acting nifedipine in children with hypertension. *Pediatr Nephrol* 2002; **17:** 35–40.
3. Flynn JT. Nifedipine in the treatment of hypertension in children. *J Pediatr* 2002; **140:** 787–8.
4. Evans JHC, *et al.* Sublingual nifedipine in acute severe hypertension. *Arch Dis Child* 1988; **63:** 975–7.
5. Uchiyama M, Ogawa I. Rectal nifedipine in acute severe hypertension in young children. *Arch Dis Child* 1989; **64:** 632–3.
6. Lopez-Herce J, *et al.* Treatment of hypertensive crisis with intranasal nifedipine. *Crit Care Med* 1988; **9:** 914.

Amaurosis fugax. Amaurosis fugax is a form of monocular visual loss that is usually attributed to a transient ischaemic attack and is treated with antiplatelet drugs or anticoagulants (see Stroke, p.1185). Vasospasm may be an alternative cause and might explain the efficacy of the calcium-channel blockers nifedipine and verapamil reported[1] in a few patients unresponsive to standard therapy.

1. Winterkorn JMS, *et al.* Brief report: treatment of vasospastic amaurosis fugax with calcium-channel blockers. *N Engl J Med* 1993; **329:** 396–8.

Anal fissure. Calcium antagonists, including oral and topical nifedipine, have been tried[1-9] in the treatment of chronic anal fissure (p.1891).

1. Antropoli C, *et al.* Nifedipine for local use in conservative treatment of anal fissures: preliminary results of a multicenter study. *Dis Colon Rectum* 1999; **42:** 1011–5.
2. Cook TA, *et al.* Oral nifedipine reduces resting anal pressure and heals chronic anal fissure. *Br J Surg* 1999; **86:** 1269–73.
3. Perrotti P, *et al.* Topical nifedipine with lidocaine ointment vs. active control for treatment of chronic anal fissure: results of a prospective, randomized, double-blind study. *Dis Colon Rectum* 2002; **45:** 1468–75.
4. Ezri T, Susmallian S. Topical nifedipine vs. topical glyceryl trinitrate for treatment of chronic anal fissure. *Dis Colon Rectum* 2003; **46:** 805–8.
5. Ho KS, Ho YH. Randomized clinical trial comparing oral nifedipine with lateral anal sphincterotomy and tailored sphincterotomy in the treatment of chronic anal fissure. *Br J Surg* 2005; **92:** 403–8.
6. Katsinelos P, *et al.* Topical 0.5% nifedipine vs. lateral internal sphincterotomy for the treatment of chronic anal fissure: long-term follow-up. *Int J Colorectal Dis* 2006; **21:** 179–83.
7. Tranqui P, *et al.* Nonsurgical treatment of chronic anal fissure: nitroglycerin and dilatation versus nifedipine and botulinum toxin. *Can J Surg* 2006; **49:** 41–5.
8. Lysy J, *et al.* Long-term results of "chemical sphincterotomy" for chronic anal fissure: a prospective study. *Dis Colon Rectum* 2006; **49:** 858–64.
9. Katsinelos P, *et al.* Aggressive treatment of acute anal fissure with 0.5% nifedipine ointment prevents its evolution to chronicity. *World J Gastroenterol* 2006; **12:** 6203–6.

Atherosclerosis. The use of drugs that interfere with atherogenesis (the development of atheromas) has been suggested as a means of reducing diseases associated with atherosclerosis (p.1159). Calcium is thought to be necessary for several steps in atherogenesis and studies in *animals* have shown that calcium-channel blockers slow the development and progression of atherosclerotic lesions. However, studies in humans have been less convincing.[1] In a placebo-controlled study,[2] amlodipine had no demonstrable effect on angiographic progression of coronary atherosclerosis or the risk of major cardiovascular events although it was associated with fewer admissions to hospital for unstable angina and revascularisation. Similar results have been reported with nisoldipine.[3] In another study,[4] comparing lacidipine with a beta blocker, there was less progression of atherosclerosis in those receiving lacidipine and also a trend towards fewer cardiovascular events.

Calcium-channel blockers have also been tried in the prevention of restenosis after percutaneous coronary interventions. A meta-analysis[5] found that addition of calcium-channel blockers to

standard therapy reduced the risk of restenosis and the occurrence of clinical events.

1. Borcherding SM, *et al.* Calcium-channel antagonists for prevention of atherosclerosis. *Ann Pharmacother* 1993; **27:** 61–7.
2. Pitt B, *et al.* Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation* 2000; **102:** 1503–10.
3. Dens JA, *et al.* Long term effects of nisoldipine on the progression of coronary atherosclerosis and the occurrence of clinical events: the NICOLE study. *Heart* 2003; **89:** 887–92.
4. Zanchetti A, *et al.* Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. *Circulation* 2002; **106:** 2422–7.
5. Dens J, *et al.* An updated meta-analysis of calcium-channel blockers in the prevention of restenosis after coronary angioplasty. *Am Heart J* 2003; **145:** 404–8.

Cardiomyopathies. Calcium-channel blockers may have a role in some forms of cardiomyopathy (p.1163). In *hypertrophic cardiomyopathy* verapamil is probably the calcium-channel blocker of choice (see p.1424). Nifedipine does not appear to reduce left ventricular outflow tract obstruction, and conflicting results have been found with respect to improvement in the diastolic function abnormality with this drug.[1] The use of calcium-channel blockers is not standard therapy in *dilated cardiomyopathy* although symptomatic improvement has been reported[2] with diltiazem.

1. Richardson PJ. Calcium antagonists in cardiomyopathy. *Br J Clin Pract* 1988; **42** (suppl 60): 33–7.
2. 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.

Cough. Nifedipine has been reported to reduce the severity of cough induced by captopril,[1] possibly by inhibiting prostaglandin synthesis. For further details on cough associated with ACE inhibitors, see p.1194.

1. Fogari R, *et al.* Effects of nifedipine and indomethacin on cough induced by angiotensin-converting enzyme inhibitors: a double-blind, randomized, cross-over study. *J Cardiovasc Pharmacol* 1992; **19:** 670–3.

Hiccup. Hiccups (p.976) result from involuntary spasmodic contraction of the diaphragm. Intractable hiccups resolved completely with nifedipine 20 mg every 8 hours in a patient.[1] In a further 7 such patients,[2] nifedipine in doses of 20 to 80 mg daily stopped hiccups in 4 and improved them in another. Resolution of intractable hiccups has also been reported[3] in 2 patients given nimodipine; the drug was given orally in one patient and intravenously in the other.

For the treatment of hiccups in palliative care the *BNF* recommends nifedipine at a dose of 10 mg three times daily.

1. Mukhopadhyay P, *et al.* Nifedipine for intractable hiccups. *N Engl J Med* 1986; **314:** 1256.
2. Lipps DC, *et al.* Nifedipine for intractable hiccups. *Neurology* 1990; **40:** 531–2.
3. Hernández JL, *et al.* Nimodipine treatment for intractable hiccups. *Am J Med* 1999; **106:** 600.

High-altitude disorders. Nifedipine lowers pulmonary artery pressure and is one of several drugs that are used in high-altitude disorders (p.1168), success being reported for both the treatment[1,2] and prevention[2,3] of symptoms of pulmonary oedema. In a study conducted at 4559 m above sea-level[1] nifedipine 10 mg sublingually and 20 mg as a modified-release dosage form was given to 6 subjects with symptoms of high-altitude pulmonary oedema. The sublingual dose was repeated if tolerated after 15 minutes and the subjects subsequently received modified-release nifedipine 20 mg every 6 hours while they remained at high altitude. Symptoms of high-altitude pulmonary oedema were relieved within 1 hour of beginning nifedipine and radiographic signs of oedema regressed during treatment despite remaining at high altitude for 36 hours and participating in mountaineering activities. Raised pulmonary arterial pressure was also reduced to control values by nifedipine. Successful treatment of pulmonary oedema in a climber at 6550 m has been described with doses of 20 mg every 8 hours for 36 hours and such doses also prevented the development of symptoms in 2 climbers who had taken nifedipine from the start of the climb.[2] Doses of 20 mg every 8 hours have been reported to allow rapid ascent to 4559 m without development of pulmonary oedema in 9 of 10 subjects who received nifedipine compared with 4 of 11 who received only placebo.[3] However, the point has been made that although it is reasonable that many climbers carry nifedipine in case of an attack, prophylactic nifedipine should not be considered an alternative to slow ascent and acclimatisation.[4]

1. Oelz O, *et al.* Nifedipine for high altitude pulmonary oedema. *Lancet* 1989; **ii:** 1241–4. Correction. *ibid.* 1991; **337:** 556.
2. Jamieson A, Kerr GW. Treatment of high-altitude pulmonary oedema. *Lancet* 1992; **340:** 1468.
3. Bärtsch P, *et al.* Prevention of high-altitude pulmonary oedema by nifedipine. *N Engl J Med* 1991; **325:** 1284–9.
4. A'Court CHD, *et al.* Doctor on a mountaineering expedition. *BMJ* 1995; **310:** 1248–52.

Hyperinsulinaemic hypoglycaemia. Nifedipine may have effects on blood-glucose levels due to inhibition of insulin release[1] (see Effects on Carbohydrate Metabolism, under Adverse Effects, above). There have been reports[1-4] of the successful use of nifedipine to increase blood-glucose levels in infants with hyperinsulinaemic hypoglycaemia (see under Uses of Glucagon, p.1447), and it may have a role[5] as adjunctive therapy in such patients. The *BNFC* suggests that neonates with persistent hyperinsulinaemic hypoglycaemia may be given oral nifedipine in a dose of 100 to 200 micrograms/kg 4 times daily, increased to a maximum of 600 micrograms/kg 4 times daily if required.

1. Lindley KJ, *et al.* Ionic control of beta cell function in nesidioblastosis: a possible therapeutic role for calcium channel blockade. *Arch Dis Child* 1996; **74:** 373–8.
2. Eichmann D, *et al.* Treatment of hyperinsulinaemic hypoglycaemia with nifedipine. *Eur J Pediatr* 1999; **158:** 204–6.
3. Bas F, *et al.* Successful therapy with calcium channel blocker (nifedipine) in persistent neonatal hyperinsulinemic hypoglycemia of infancy. *J Pediatr Endocrinol Metab* 1999; **12:** 873–8.
4. Shanbag P, *et al.* Persistent hyperinsulinemic hypoglycemia of infancy—successful therapy with nifedipine. *Indian J Pediatr* 2002; **69:** 271–2.
5. Aynsley-Green A, *et al.* Practical management of hyperinsulinism in infancy. *Arch Dis Child Fetal Neonatal Ed* 2000; **82:** F98–F107.

Hypertension. Long-acting calcium-channel blockers are among the drug groups that may be used as first-line therapy in uncomplicated hypertension (p.1171); meta-analyses[1] and large studies[2] have shown them to be as safe and effective as other first-line antihypertensives and they are particularly recommended in older patients. Dihydropyridine calcium-channel blockers are also useful in patients who require combination therapy[3] and are particularly effective when given with a beta blocker or an ACE inhibitor. The use of short-acting calcium-channel blockers is not recommended since they may increase mortality (see under Adverse Effects, above).

Calcium-channel blockers may also be used in **hypertensive crises**, particularly in hypertensive urgencies where oral therapy is suitable. Nifedipine has been given sublingually, or by biting the capsule and swallowing the contents, but such use may cause dangerous hypotension and is no longer recommended. In hypertensive emergencies, where parenteral antihypertensives are required, intravenous nicardipine may be used. One study concluded that intravenous nicardipine was as effective as sodium nitroprusside in the treatment of postoperative hypertension.[4]

For **hypertension in pregnancy**, first-line treatment is usually methyldopa or a beta blocker but calcium-channel blockers may also be used. Nifedipine is reported to be teratogenic in *animals* and may inhibit labour, but it has been tried in a limited number of patients with pre-eclampsia. Although a high rate of caesarean deliveries, premature births, and small-for-date infants was reported[5] in patients given nifedipine as a second-line drug, assessment of the role of nifedipine is difficult because outcome is often poor in such severely compromised pregnancies.[6] Fetal nifedipine concentrations have been reported to be 75% of maternal values 2 to 3 hours after sublingual administration.[7] However, nifedipine in a single 20-mg oral dose lowered blood pressure without compromising blood flow in the fetus in 9 women in the third trimester with normal haemodynamics.[6] This is in line with other reports,[8] although there has also been a report[9] of severe hypotension and fetal distress after sublingual nifedipine administration. In a randomised controlled study,[10] nifedipine 10 to 30 mg sublingually followed by 10 mg as capsules by mouth every 6 hours increasing to 20 mg every 4 hours if necessary, was compared with hydralazine 12.5 mg intravenously as required followed by 20 to 30 mg orally every 6 hours, with added methyldopa if necessary. Both groups also received intravenous magnesium sulfate. Effective control of blood pressure was achieved in 23 of 24 patients given nifedipine compared with only 17 of 25 given hydralazine and 9 nifedipine patients achieved term delivery compared with only 2 of those receiving hydralazine. The average gestational age was greater in infants in the nifedipine group; hence these neonates weighed more and had fewer neonatal complications when compared with neonates from the hydralazine treated group.

1. Opie LH, Schall R. Evidence-based evaluation of calcium channel blockers for hypertension: equality of mortality and cardiovascular risk relative to conventional therapy. *J Am Coll Cardiol* 2002; **39:** 315–22. Correction. *ibid.*; 1409–10.
2. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid.*; **289:** 178.
3. Epstein BJ, *et al.* Dihydropyridine calcium channel antagonists in the management of hypertension. *Drugs* 2007; **67:** 1309–27.
4. Halpern NA, *et al.* Postoperative hypertension: a multicenter, prospective, randomized comparison between intravenous nicardipine and sodium nitroprusside. *Crit Care Med* 1992; **20:** 1637–43.
5. Constantine G, *et al.* Nifedipine as a second line antihypertensive drug in pregnancy. *Br J Obstet Gynaecol* 1987; **94:** 1136–42.
6. Hanretty KP, *et al.* Effect of nifedipine on Doppler flow velocity waveforms in severe pre-eclampsia. *BMJ* 1989; **299:** 1205–6.
7. Pirhonen JP, *et al.* Single dose of nifedipine in normotensive pregnancy: nifedipine concentrations, hemodynamic responses, and uterine and fetal flow velocity waveforms. *Obstet Gynecol* 1990; **76:** 807–11.
8. Pirhonen JP, *et al.* Uterine and fetal flow velocity wave forms in hypertensive pregnancy: the effect of a single dose of nifedipine. *Obstet Gynecol* 1990; **76:** 37–41.
9. Impey L. Severe hypotension and fetal distress following sublingual administration of nifedipine to a patient with severe pregnancy induced hypertension at 33 weeks. *Br J Obstet Gynaecol* 1993; **100:** 959–61.
10. Fenakel K, *et al.* Nifedipine in the treatment of severe preeclampsia. *Obstet Gynecol* 1991; **77:** 331–7.

Kidney disorders. Although nifedipine may adversely affect renal function (see under Adverse Effects, above) there is evidence that calcium-channel blockers may be of benefit in various forms of kidney disorder. Proteinuria is an important indicator of glomerular kidney disease (p.1504) of various causes and the effects of calcium-channel blockers on proteinuria and renal dysfunction have been studied in a variety of patients. Results have been mixed,[1-5] and it is not clear whether any protective effect of calcium-channel blockers on renal function is only due to their antihypertensive action or whether they also have additional effects. The benefits of ACE inhibitors in kidney disorders are much better established (see p.1199) and a study[6] in African American hypertensives was stopped early when treatment with ramipril was found to be superior to treatment with amlodipine. A further study[7] in patients with non-diabetic proteinuria found that addition of felodipine to ACE inhibitor therapy provided no additional benefit in terms of renal outcomes.

Nifedipine has also been used in the management of renal calculi (see below), and has been reported to protect against ciclosporin-induced nephrotoxicity in renal transplant patients (see Transplantation, below).

1. Demarie BK, Bakris GL. Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; **113:** 987–8.
2. Melbourne Diabetic Nephropathy Study Group. Comparison between perindopril and nifedipine in hypertensive and normotensive diabetic patients with microalbuminuria. *BMJ* 1991; **302:** 210–16.
3. Reams G, *et al.* The effect of nifedipine GITS on renal function in hypertensive patients with renal insufficiency. *J Clin Pharmacol* 1991; **31:** 468–72.
4. Abbott K, *et al.* Effects of dihydropyridine calcium antagonists on albuminuria in patients with diabetes. *J Clin Pharmacol* 1996; **36:** 274–9.
5. Bouhanick B, *et al.* Equivalent effects of nicardipine and captopril on urinary albumin excretion of type 2, non-insulin-dependent diabetic subjects with mild to moderate hypertension. *Therapie* 1996; **51:** 41–7.
6. Agodoa LY, *et al.* Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA* 2001; **285:** 2719–28.
7. Ruggenenti P, *et al.* Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet* 2005; **365:** 939–46.

Migraine and cluster headache. Drugs with calcium-channel blocking activity have been given in the management of headaches considered to have a vascular component such as migraine (p.616) and cluster headache (p.616).

In migraine prophylaxis, of those drugs with calcium-channel blocking activity studied, flunarizine (p.580) has the best documented efficacy, and verapamil may be useful. Other calcium-channel blockers such as diltiazem, nifedipine, and nimodipine have been tried, but results have been conflicting. Verapamil has also been used successfully in patients with hemiplegic migraine, both intravenously to abort attacks,[1,2] and orally for prophylaxis.[2]

Beneficial effects have been reported[3-6] with calcium-channel blockers in the prevention of cluster headache during cluster periods. Verapamil appears to have been the most widely used. In one double-blind study it was found to be of similar efficacy to lithium[7] and appeared to produce fewer adverse effects. There have also been reports[8] of the successful use of nimodipine in patients with thunderclap headache.

1. Ng TMH, *et al.* The effect of intravenous verapamil on cerebral hemodynamics in a migraine patient with hemiplegia. *Ann Pharmacother* 2000; **34:** 39–43.
2. Yu W, Horowitz SH. Treatment of sporadic hemiplegic migraine with calcium-channel blocker verapamil. *Neurology* 2003; **60:** 120–1.
3. Jónsdóttir M, *et al.* Efficacy, side effects and tolerance compared during headache treatment with three different calcium blockers. *Headache* 1987; **27:** 364–9.
4. Gabai IJ, Spierings ELH. Prophylactic treatment of cluster headache with verapamil. *Headache* 1989; **29:** 167–8.
5. Leone M, *et al.*. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. *Neurology* 2000; **54:** 1382–5.
6. Matharu MS, *et al.* Management of trigeminal autonomic cephalgias and hemicrania continua. *Drugs* 2003; **63:** 1637–77.
7. Bussone G, *et al.* Double blind comparison of lithium and verapamil in cluster headache prophylaxis. *Headache* 1990; **30:** 411–17.
8. Lu S-R, *et al.* Nimodipine for treatment of primary thunderclap headache. *Neurology* 2004; **62:** 1414–16.

Oesophageal motility disorders. Results from a number of studies have indicated that nifedipine, usually in doses of 10 to 20 mg sublingually, may be of benefit in patients with achalasia, reducing lower oesophageal sphincter pressure and producing some symptomatic improvement.[1-5] Nifedipine has a role when mechanical dilatation of the sphincter or surgery are not feasible (see Oesophageal Motility Disorders, p.1702).

See also Effects on the Oesophagus under Adverse Effects, above.

1. Bortolotti M, Labò G. Clinical and manometric effects of nifedipine in patients with esophageal achalasia. *Gastroenterology* 1981; **80:** 39–44.

2. Gelfond M, *et al.* Isosorbide dinitrate and nifedipine treatment of achalasia: a clinical, manometric and radionuclide evaluation. *Gastroenterology* 1982; **83:** 963–9.
3. Traube M, *et al.* Effects of nifedipine in achalasia and in patients with high-amplitude peristaltic esophageal contractions. *JAMA* 1984; **252:** 1733–6.
4. Román FJ, *et al.* Effects of nifedipine in achalasia and patients with high-amplitude peristaltic esophageal contractions. *JAMA* 1985; **253:** 2046.
5. Coccia G, *et al.* Prospective clinical and manometric study comparing pneumatic dilatation and sublingual nifedipine in the treatment of oesophageal achalasia. *Gut* 1991; **32:** 604–6.

Peripheral vascular disease. Vasospastic arterial disease (p.1178) is due to an inappropriate response to temperature, usually cold, when vasoconstriction and/or vasospasm occurs. The most important of these disorders is Raynaud's syndrome. Calcium-channel blockers have been of benefit in Raynaud's syndrome,[1] but it is not entirely clear which of their pharmacological actions is responsible. The most widely used and studied is nifedipine. Evidence of subjective benefit has been seen both in primary idiopathic disease[2-5] and in Raynaud's phenomenon secondary to systemic sclerosis,[3,4,6,7] systemic lupus erythematosus,[3,4] rheumatoid arthritis,[4] and cancer chemotherapy,[8] or associated with breastfeeding.[9-11] Objective improvement as demonstrated by evidence of improved digital blood flow has been demonstrated in some[5,6,12,13] but not all[7] studies. Doses have varied; 10 mg of nifedipine twice daily initially, increased after a week to a maximum of 20 mg twice daily has been suggested,[14] but in many studies doses of up to 60 mg daily have been used, although side-effects have proved intolerable in some patients given such doses.[7] A modified-release preparation has also been used[15] and may reduce the incidence of adverse effects.

Nifedipine in doses of 20 to 60 mg daily has also been reported to be of benefit in the treatment of another vasospastic condition, chilblains, both for established chilblains and in the prevention of relapse.[16]

1. Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud's phenomenon: a meta-analysis. *Rheumatology (Oxford)* 2005; **44:** 145–50.
2. Roath S. Management of Raynaud's phenomenon: focus on newer treatments. *Drugs* 1989; **37:** 700–12.
3. Smith CD, McKendry RJR. Controlled trial of nifedipine in the treatment of Raynaud's phenomenon. *Lancet* 1982; **ii:** 1299–1301.
4. Kahan A, *et al.* Nifedipine for Raynaud's phenomenon. *Lancet* 1983; **i:** 131.
5. Gasser P. Reaction of capillary blood cell velocity in nailfold capillaries to nifedipine and ketanserin in patients with vasospastic disease. *J Int Med Res* 1991; **19:** 24–31.
6. Thomas RHM, *et al.* Nifedipine in the treatment of Raynaud's phenomenon in patients with systemic sclerosis. *Br J Dermatol* 1987; **117:** 237–41.
7. Rademaker M, *et al.* Comparison of intravenous infusions of iloprost and oral nifedipine in treatment of Raynaud's phenomenon in patients with systemic sclerosis: a double blind randomised study. *BMJ* 1989; **298:** 561–4.
8. Hantel A, *et al.* Nifedipine and oncologic Raynaud phenomenon. *Ann Intern Med* 1988; **108:** 767.
9. Garrison CP. Nipple vasospasms, Raynaud's syndrome, and nifedipine. *J Hum Lact* 2002; **18:** 382–5.
10. Anderson JE, *et al.* Raynaud's phenomenon of the nipple: a treatable cause of painful breastfeeding. *Pediatrics* 2004; **113:** e360–4.
11. Page SM, McKenna DS. Vasospasm of the nipple presenting as painful lactation. *Obstet Gynecol* 2006; **108:** 806–8.
12. Nilsson H, *et al.* Treatment of digital vasospastic disease with the calcium-entry blocker nifedipine. *Acta Med Scand* 1984; **215:** 135–9.
13. Finch MB, *et al.* The peripheral vascular effects of nifedipine in Raynaud's disease. *Br J Clin Pharmacol* 1986; **21:** 100P–101P.
14. Grigg MH, Wolfe JHN. Raynaud's syndrome and similar conditions. *BMJ* 1991; **303:** 913–16.
15. Raynaud's Treatment Study Investigators. Comparison of sustained-release nifedipine and temperature biofeedback for treatment of primary Raynaud phenomenon: results from a randomized clinical trial with 1-year follow-up. *Arch Intern Med* 2000; **160:** 1101–8.
16. Rustin MHA, *et al.* The treatment of chilblains with nifedipine: the results of a pilot study, a double-blind placebo-controlled randomized study and a long-term open trial. *Br J Dermatol* 1989; **120:** 267–75.

Phaeochromocytoma. Pharmacological management of phaeochromocytoma (p.1179) is principally achieved by alpha-adrenergic blockade and tachycardia may subsequently be controlled by cautious addition of a beta blocker. There have also been some reports[1-4] of the use of nifedipine to treat cardiovascular symptoms in adults and children with phaeochromocytoma.

1. Serfas D, *et al.* Phaeochromocytoma and hypertrophic cardiomyopathy: apparent suppression of symptoms and noradrenaline secretion by calcium-channel blockade. *Lancet* 1983; **ii:** 711–13.
2. Lenders JWM, *et al.* Treatment of a phaeochromocytoma of the urinary bladder with nifedipine. *BMJ* 1985; **290:** 1624–5.
3. Favre L, Vallotton MB. Nifedipine in pheochromocytoma. *Ann Intern Med* 1986; **104:** 125.
4. Deal JE, *et al.* Phaeochromocytoma—investigation and management of 10 cases. *Arch Dis Child* 1990; **65:** 269–74.

Premature labour. Although beta$_2$ agonists or magnesium are the drugs that have been most commonly used as tocolytics to postpone premature labour (p.2003), there is increasing interest in calcium-channel blockers such as nifedipine, either given alone or added to other tocolytics, as first-line drugs. Labour was successfully postponed in a patient given nifedipine 20 mg three times daily and oral terbutaline.[1] Terbutaline by subcutaneous injection was also occasionally necessary. Nifedipine was given from the twenty-sixth week of pregnancy for 55 days. A normal, healthy infant was delivered in the thirty-sixth week of pregnancy. In a study[2] in 20 patients, oral nifedipine 30 mg initially, then 20 mg every 8 hours, was more effective in suppressing premature labour than ritodrine given intravenously or no treatment. However, a similar study[3] in 33 patients found nifedipine to be no more effective than ritodrine infusion, although associated with a lower incidence of adverse effects. Similar results have been reported with nicardipine.[4] Meta-analyses[5,6] have concluded that nifedipine is at least as effective as beta$_2$ agonists and is associated with fewer maternal adverse effects, and this was supported by the results of further studies.[7,8] The larger[7] of these involved 185 women using oral nifedipine in an initial dose of up to 40 mg followed by 60 to 160 mg daily, reduced after 3 days to a maintenance dose of at least 20 mg 3 times daily. However, a systematic review[9] which examined 31 studies of the effectiveness of nifedipine in premature labour concluded that their overall quality was poor. Others[10] have expressed concern about the safety of calcium-channel blockers, reviewing cases of dyspnoea and pulmonary oedema in particular. They suggest that these drugs should not be used with intravenous beta agonists, that high doses should be avoided in women with cardiovascular compromise or multiple gestations, and that blood pressure and fetal heart rate should be monitored during use of short-acting preparations, which should not be chewed.

1. Kaul AF, *et al.* The management of preterm labor with the calcium channel-blocking agent nifedipine combined with the β-mimetic terbutaline. *Drug Intell Clin Pharm* 1985; **19:** 369–71.
2. Read MD, Wellby DE. The use of a calcium antagonist (nifedipine) to suppress preterm labour. *Br J Obstet Gynaecol* 1986; **93:** 933–7.
3. Ferguson JE, *et al.* A comparison of tocolysis with nifedipine or ritodrine: analysis of efficacy and maternal, fetal, and neonatal outcome. *Am J Obstet Gynecol* 1990; **163:** 105–11.
4. Jannet D, *et al.* Nicardipine versus salbutamol in the treatment of premature labor: a prospective randomized study. *Eur J Obstet Gynecol Reprod Biol* 1997; **73:** 11–16.
5. Ray JG. Meta-analysis of nifedipine versus beta-sympathomimetic agents for tocolysis during preterm labour. *J Soc Obstet Gynaecol Can* 1998; **20:** 259–69.
6. Tsatsaris V, *et al.* Tocolysis with nifedipine or beta-adrenergic agonists: a meta-analysis. *Obstet Gynecol* 2001; **97:** 840–7.
7. Papatsonis DNM, *et al.* Nifedipine and ritodrine in the management of preterm labor: a randomized multicenter trial. *Obstet Gynecol* 1997; **90:** 230–4.
8. Van De Water M, *et al.* Tocolytic effectiveness of nifedipine versus ritodrine and follow-up of newborns: a randomised controlled trial. *Acta Obstet Gynecol Scand* 2008; **87:** 340–5.
9. Lamont RF, *et al.* Steering Group of the International Preterm Labour Council. The quality of nifedipine studies used to assess tocolytic efficacy: a systematic review. *J Perinat Med* 2005; **33:** 287–95.
10. Oei SG. Calcium channel blockers for tocolysis: a review of their role and safety following reports of serious adverse events. *Eur J Obstet Gynecol Reprod Biol* 2006; **126:** 137–45.

Pulmonary hypertension. Vasodilators have been tried in primary pulmonary hypertension (p.1179) on the premise that pulmonary vasoconstriction is an important component of the condition. Calcium-channel blockers are the most widely-used. Improved survival over a 5-year period has been noted in a study in patients treated with high doses of calcium-channel blockers (nifedipine or diltiazem).[1] However, treatment failures have occurred with nifedipine, and at least one death has been reported shortly after starting therapy.[2] Other reports have also stressed the potentially deleterious effects of nifedipine (or other vasodilator) therapy in pulmonary hypertension. Increased dyspnoea and a fall in arterial PO_2 have been reported in a patient with primary pulmonary hypertension given nifedipine, probably due to preferential vasodilatation of underventilated hypoxic tissues resulting in an increased physiological shunt.[3] Invasive investigations, notably blood-gas monitoring, are therefore recommended when giving nifedipine to these patients[2,3] and it has been advised that an acute response test should be performed before embarking on long-term treatment.[1]

1. Rich S, *et al.* The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992; **327:** 76–81.
2. McLeod AA, Jewitt DE. Drug treatment of primary pulmonary hypertension. *Drugs* 1986; **31:** 177–84.
3. Krol RC, *et al.* Primary pulmonary hypotension, nifedipine, and hypoxemia. *Ann Intern Med* 1984; **100:** 163.

Renal calculi. There is some interest in the possible use of drug treatment to ease the spontaneous passage of renal calculi (p.2181) in patients with uncomplicated lower ureteral stones. It has been suggested that the combination of a calcium-channel blocker (to reduce ureteral spasm) with a corticosteroid (to reduce oedema) may be useful. Small studies[1-3] have used modified-release preparations of nifedipine, given in oral doses of 30 mg daily for up to 28 days, with oral deflazacort 30 mg daily for up to 10 days. If the stone had not been expelled within 28 days, the patient was treated with extracorporeal shock wave lithotripsy or ureteroscopy. Treatment with nifedipine and deflazacort was found to improve the rate of stone expulsion and expulsion time, and to reduce analgesic requirements.

The use of a 10-day course of nifedipine and deflazacort has also been studied[4] as adjunctive therapy after lithotripsy. It was found to ease the passage of stone fragments, reduce analgesic requirements, and increase the number of patients who were stone-free after 45 days.

1. Porpiglia F, *et al.* Effectiveness of nifedipine and deflazacort in the management of distal ureter stones. *Urology* 2000; **56:** 579–83.
2. Porpiglia F, *et al.* Nifedipine versus tamsulosin for the management of lower ureteral stones. *J Urol (Baltimore)* 2004; **172:** 568–71.
3. Dellabella M, *et al.* Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureteral calculi. *J Urol (Baltimore)* 2005; **174:** 167–72.
4. Porpiglia F, *et al.* Role of adjunctive medical therapy with nifedipine and deflazacort after extracorporeal shock wave lithotripsy of ureteral stones. *Urology* 2002; **59:** 835–8.

Tardive dyskinesia. Calcium-channel blockers have been tried in the treatment of tardive dyskinesia (see under Extrapyramidal Disorders, p.971). However, a systematic review[1] concluded that their effects are unclear and they should not be used.

1. Soares-Weiser K, Rathbone J. Calcium channel blockers for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 28/03/06).

Transplantation. The main adverse effect of ciclosporin is reversible, dose-related nephrotoxicity. There is some evidence that nifedipine may be of value in protecting against this effect. Retrospective analysis[1] of 106 ciclosporin-treated renal transplant patients found that patients receiving nifedipine for hypertension had better graft function, despite having shorter graft duration and therefore requiring higher dosage of ciclosporin, than hypertensive patients receiving other drug treatment. Subsequent studies have similarly reported improved graft function[2] in patients receiving nifedipine and suggest that graft survival is also improved.[3,4] A nephroprotective effect has also been reported with nitrendipine,[5] felodipine,[6] isradipine,[7] and with the non-dihydropyridine diltiazem (see p.1267), although a study[8] with nicardipine failed to demonstrate any improvement in graft function.

For a report of adverse effects attributed to reduced metabolism of nifedipine in patients taking ciclosporin, see Immunosuppressants, under Interactions, above.

1. Feehally J, *et al.* Does nifedipine ameliorate cyclosporin A nephrotoxicity? *BMJ* 1987; **295:** 310.
2. Shin GT, *et al.* Effect of nifedipine on renal allograft function and survival beyond one year. *Clin Nephrol* 1997; **47:** 33–6.
3. Weinrauch LA, *et al.* Role of calcium channel blockers in diabetic renal transplant patients: preliminary observations on protection from sepsis. *Clin Nephrol* 1995; **44:** 185–92.
4. Mehrens T, *et al.* The beneficial effects of calcium channel blockers on long-term kidney transplant survival are independent of blood-pressure reduction. *Clin Transplant* 2000; **14:** 257–61.
5. Rahn K-H, *et al.* Effect of nitrendipine on renal function in renal-transplant patients treated with cyclosporin: a randomised trial. *Lancet* 1999; **354:** 1415–20.
6. Madsen JK, *et al.* The effect of felodipine on renal function and blood pressure in cyclosporin-treated renal transplant recipients during the first three months after transplantation. *Nephrol Dial Transplant* 1998; **13:** 2327–34.
7. van Riemsdijk IC, *et al.* Addition of isradipine (Lomir) results in a better renal function after kidney transplantation: a double-blind, randomized, placebo-controlled, multi-center study. *Transplantation* 2000; **70:** 122–6.
8. Kessler M, *et al.* Influence of nicardipine on renal function and plasma cyclosporin in renal transplant patients. *Eur J Clin Pharmacol* 1989; **36:** 637–8.

Urticaria. Oral antihistamines are the main drugs used in the management of urticaria (p.1584). Addition of a calcium-channel blocker, such as nifedipine, has been suggested for patients unresponsive to treatment with oral antihistamines alone, but results have been mixed.[1,2]

1. Lawlor F, *et al.* Calcium antagonist in the treatment of symptomatic dermographism: low-dose and high-dose studies with nifedipine. *Dermatologica* 1988; **177:** 287–91.
2. Bressler RB, *et al.* Therapy of chronic idiopathic urticaria with nifedipine: demonstration of beneficial effect in a double-blinded, placebo-controlled, crossover trial. *J Allergy Clin Immunol* 1989; **83:** 756–63.

Preparations

BP 2008: Nifedipine Capsules;
USP 31: Nifedipine Capsules; Nifedipine Extended-release Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Adalat; Nifecor†; Nifed Sol; Nifedel; Nifelat†; Prudencia†; ***Austral.:*** Adalat; Addos; Adefin; Nifecard; Nifehexal; Nyefax; Nypine; ***Austria:*** Adalat; Buconif; Fedip; Majolat; Nifal; Nifebene; Nifehexal; Nifestad; Ospocard; ***Belg.:*** Adalat; Hypan; ***Braz.:*** Adalat; Adalex†; Cardalin; Dilaflux; Dipinal; Loncord†; Neo Fedipina; Nifadil; Nifedax†; Nifedicard; Nifedin†; Nifehexal†; Nioxil; Normopres; Oxcord; Prodopina; ***Canad.:*** Adalat; Apo-Nifed; Novo-Nifedin†; Nu-Nifed; ***Chile:*** Adalat; Carbloc†; Cardicon; Coronovo; Nipress; Pabalat†; Sulotil; ***Cz.:*** Adalat; Aprical†; Cordafen†; Cordipin; Corinfar; Nifecard; Nifehexal†; Sponif†; Supracordin†; ***Denm.:*** Adalat; Hexadilat; Nifecodan; ***Fin.:*** Adalat; Nifangin; Nifdemin†; Nifecor†; ***Fr.:*** Adalate; Chronadalate; ***Ger.:*** Adalat; Aprical; Cordicant†; Corinfar; Dignokonstant†; duranifin†; Jedipin; Jutadilat; Nife; nife uno†; Nifeclair; Nifecor; Nifedipat†; Nifehexal; Nifelat; Nifical; Pidilat; ***Gr.:*** Adalat; Antiblut; Coracten; Flecor-N; Glopir; Macorel; Nefelid; Nifedicor; Nifedipat†; Viscard†; ***Hong Kong:*** Adalat; Cardilate MR†; Coracten†; Fenamon†; Nadipinia; Nifecard; Nifelat; Vidalat; Waridipin†; ***Hung.:*** Adalat; Cordaflex; Cordipin†; Corinfar; Nifecard; ***India:*** Calcigard; Calnif; Cardules; Depicor; Depin; Edip†; Myogard; Nicardia†; Nifedine; Nifelat; ***Indon.:*** Adalat; Calcianta; Carvas; Cordalat; Coronipin; Farmalat; Fedipin; Ficor; Nifedin; Vasdalat; Xepalat; ***Irl.:*** Adalat; Nifed; Nifelease†; Pinifed†; Systepin†; Vasofed†; ***Israel:*** Megalat†; Osmo-Adalat; Pressolat; ***Ital.:*** Adalat; Bionif†; Citilat; Coral; Euxat; Fenidina; Nifedicor; Nifedicron†; Nifedin†; Nifesal; Nipin; ***Jpn:*** Adalat; ***Malaysia:*** Adalat; Adifen†; Fenamon; Nifecip; ***Mex.:*** Adalat; Apo-

Fedipisal†; Atenses; Cordilat; Corogal; Corotrend; Fusepina; Gelprim; Nifedigel; Nifedipres; Nifezzard; Nifser; Noviken; **Neth.:** Adalat; **Norw.:** Adalat; **NZ:** Adalat; Adefin; Nyefax; **Philipp.:** Adalat; Calcheck; Calcibloc; Calcigard; Cardicap; Darat; Heblopin; Nelapine; Nifestad; Normadil; Odipin; Tensibloc; **Pol.:** Adalat; Cordafen; Cordipin; **Port.:** Adalat; Angipina; Meborilan; Medipina†; Nifedate†; Zenusin; **Rus.:** Adalat (Адалат); Calcigard (Кальцигард); Cordafen (Кордафен); Cordaflex (Кордафлекс); Cordipin (Кордипин); Corinfar (Коринфар); Depin-E (Депин-Е); Fenamon (Фенамон); Nicardia (Никардия); Nifecard (Нифекард); Osmo-Adalat (Осмо-Адалат); **S.Afr.:** Adalat; Cardifen; Cardilat†; Cipalat; Nifedalat; Vascard; **Singapore:** Adalat; Apo-Nifed; Calcigard; Cordipin; Fenamon; Nifecard†; Nifedi-Denk†; Nifelat†; Nipin; Stada Uno; Vasdalat†; **Spain:** Adalat; Dilcor; Pertensal; **Swed.:** Adalat; **Switz.:** Adalat; Aldipin†; Cardipin; Corotrend; Ecodipine; nife-basan†; Nifedicor; **Thai.:** Adalat; Calcigard; Coracten; Fenamon; Nelapine; Nifecard; Nifelat; Nifiran†; Nyefax; Stada Uno; **Turk.:** Adalat; Kardilat; Nidicard; Nidilat; **UAE:** Cardiopine; **UK:** Adalat; Adipine; Angiopine†; Calchan; Cardilate MR; Coracten; Corodaγ†; Fortipine; Hypolar Retard; Nifedipress; Nifopress; Slofedipine; Tensipine; **USA:** Adalat; Afeditab; Nifediac; Nifedical; Procardia; **Venez.:** Adalat; Conducil; Fedilex†; Nifal; Tensomax; Tensopin.

Multi-ingredient: **Arg.:** Atel N†; **Austria:** Beta-Adalat; Nif-Ten; Pontuc; **Belg.:** Beta-Adalat†; Tenif; **Braz.:** Nifelat; **Fin.:** Nif-Ten; **Fr.:** Beta-Adalate; Tenordate; **Ger.:** AteNif beta; Belnif; Bresben; duranifin Sali†; Nif-Ten; Nifatenol; Sali-Adalat; Tredalat; **Hong Kong:** Nif-Ten; **India:** Beta Nicardia†; Cardules Plus; Depten; Nifetolol; Presolar; Tenofed; **Indon.:** Nif-Ten; **Irl.:** Beta-Adalat; Nif-Ten; **Ital.:** Antrolin; Mixer; Nif-Ten; **Mex.:** Plenacor; **Neth.:** Nif-Ten†; **Philipp.:** Nif-Ten; **Singapore:** Beta Nicardia; Nif-Ten; Nifetex; **Switz.:** Beta-Adalat; Nif-Atenil; Nif-Ten; **UK:** Beta-Adalat; Tenif.

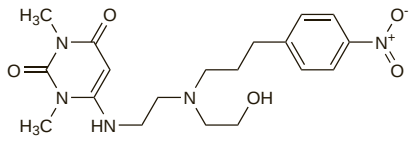
Nifekalant Hydrochloride *(rINNM)*

Hidrocloruro de nifekalant; MS-551; Nifékalant, Chlorhydrate de; Nifekalanti Hydrochloridum. 6-[(2-{(2-Hydroxyethyl)[3-(*p*-nitrophenyl)propyl]amino}ethyl)amino]-1,3-dimethyluracil hydrochloride.

Нифекаланта Гидрохлорид

$C_{19}H_{27}N_5O_5,HCl$ = 441.9.

CAS — 130636-43-0 (nifekalant); 130656-51-8 (nifekalant hydrochloride).



(nifekalant)

Profile

Nifekalant is a class III antiarrhythmic (p.1153) used intravenously as the hydrochloride in the management of life-threatening ventricular arrhythmias (p.1160).

◊ References.

1. Katoh T, *et al.* Emergency treatment with nifekalant, a novel class III anti-arrhythmic agent, for life-threatening refractory ventricular tachyarrhythmias: post-marketing special investigation. *Circ J* 2005; **69:** 1237–43.

Effects on the heart. A woman who had been receiving intravenous nifekalant continuously for 10 months was found[1] to have a round mass in the right atrium. This was resected and shown to be a fibrin thrombus containing a large amount of nifekalant in the form of needle crystals.

1. Okamura H, *et al.* Crystals in the heart. *Heart* 2004; **90:** 1106.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Shinbit.

Nilvadipine *(USAN, rINN)*

CL-287389; FK-235; Nilvadipidiini; Nilvadipidin; Nilvadipidinum; Nilvadipin; Nilvadipino; Nilvadipinum; Nivadipine; SKF-102362. 5-Isopropyl 3-methyl 2-cyano-1,4-dihydro-6-methyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate.

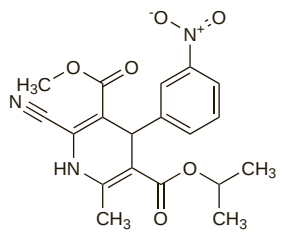
Нильвадипин

$C_{19}H_{19}N_3O_6$ = 385.4.

CAS — 75530-68-6.

ATC — C08CA10.

ATC Vet — QC08CA10.



Pharmacopoeias. In *Jpn.*

Profile

Nilvadipine is a dihydropyridine calcium-channel blocker with general properties similar to those of nifedipine (p.1350). It is used in the management of hypertension (p.1171). Nilvadipine is given orally, usually as a modified-release preparation, in a dose of up to 16 mg daily.

◊ Reviews.

1. Brogden RN, McTavish D. Nilvadipine: a review of its pharmacodynamic and pharmacokinetic properties, therapeutic use in hypertension and potential in cerebrovascular disease and angina. *Drugs Aging* 1995; **6:** 150–71. Correction. *ibid.*; **7:** 116.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Tensan; **Cz.:** Escor; **Fin.:** Escor; **Ger.:** Escor; Nivadil; **Gr.:** Peroma; **Irl.:** Nivadil; **Jpn:** Nivadil; **Port.:** Nivadil; **Switz.:** Nivadil†; **Turk.:** Nilvadis.

Nimodipine *(BAN, USAN, rINN)*

Bay-e-9736; Nimodipiini; Nimodipin; Nimodipinas; Nimodipino; Nimodipinum; Nimodypina. Isopropyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate.

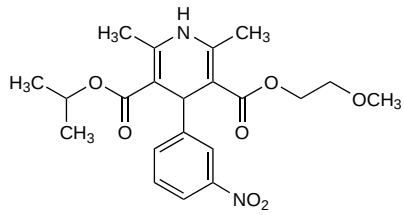
Нимодипин

$C_{21}H_{26}N_2O_7$ = 418.4.

CAS — 66085-59-4.

ATC — C08CA06.

ATC Vet — QC08CA06.



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

Ph. Eur. 6.2 (Nimodipine). A light yellow or yellow crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in ethyl acetate. Exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Solutions should be prepared in the dark or under light of wavelength greater than 420 nm, immediately before use. Protect from light.

USP 31 (Nimodipine). A light yellow or yellow crystalline powder, affected by light. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in ethyl acetate. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Licensed product information states that solutions of nimodipine are incompatible with some plastics, including PVC, and that the only plastics suitable for use are polyethylene and polypropylene.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1350).

Nimodipine should be used with caution in patients with cerebral oedema or severely raised intracranial pressure.

Effects on the heart. Marked bradycardia developed in a patient with acute ischaemic stroke during treatment with nimodipine and was suspected to be related to the drug therapy.[1]

1. Fagan SC, Nacci N. Nimodipine and bradycardia in acute stroke—drug or disease? *DICP Ann Pharmacother* 1991; **25:** 247–9.

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1352).

Pharmacokinetics

Nimodipine is rapidly absorbed from the gastrointestinal tract after oral doses but undergoes extensive first-pass metabolism in the liver. The oral bioavailability is reported to be about 13%. Nimodipine is more than 95% bound to plasma proteins. It crosses the blood-brain barrier, but concentrations in CSF are lower than those in plasma. Nimodipine is extensively metabolised in the liver. It is excreted in faeces via the bile, and in urine, almost entirely as metabolites. The terminal elimination half-life is reported to be about 9 hours but the initial decline in plasma concentration is much more rapid, equivalent to a half-life of 1 to 2 hours.

Uses and Administration

Nimodipine is a dihydropyridine calcium-channel blocker that has the general properties of nifedipine (p.1354), but acts particularly on cerebral blood vessels. It is used in cerebrovascular disorders (see below), particularly in the prevention and treatment of ischaemic neurological deficits after aneurysmal subarachnoid haemorrhage.

To reduce the incidence and severity of neurological deficit after aneurysmal haemorrhage nimodipine is given orally in a dose of 60 mg every 4 hours. Treatment should begin within 4 days of onset of haemorrhage and should continue for 21 days. In patients with hepatic impairment the dose may be reduced (see below) and blood pressure should be closely monitored.

If cerebral ischaemia occurs or has already occurred, neurological deficit may be treated by intravenous infusion of nimodipine. It should be given via a bypass into a running intravenous infusion into a central vein. The initial dose should be nimodipine 1 mg/hour for 2 hours, increased (provided that no severe decrease in blood pressure occurs) to 2 mg/hour. The starting dose should be reduced to 500 micrograms/hour, or even lower if necessary, in patients weighing less than 70 kg and in those with unstable blood pressure; a similar reduction in dosage has been suggested in hepatic impairment, and blood pressure should be closely monitored. Treatment should be started as soon as possible and continued for at least 5 and no more than 14 days; if the patient has already received oral nimodipine, the total duration of nimodipine use should not exceed 21 days.

Administration in hepatic impairment. The clearance of nimodipine is reduced in patients with cirrhosis, and blood pressure should be closely monitored in such patients. US licensed product information recommends that the oral dose of nimodipine should be halved to 30 mg every 4 hours in patients with hepatic cirrhosis. Some manufacturers have also suggested a reduction in the initial intravenous dose to 500 micrograms or less per hour.

Cerebrovascular disorders. Nimodipine is used orally and intravenously in the prevention and treatment of ischaemic neurological deficits caused by arterial vasospasm after aneurysmal subarachnoid haemorrhage (see Stroke, p.1185), although the evidence for benefit after intravenous use is limited.[1] Nimodipine has also been used for traumatic subarachnoid haemorrhage,[2] but results have been mixed.[3,4] In addition to dilating cerebral blood vessels and improving cerebral blood flow, nimodipine may also prevent or reverse ischaemic damage to the brain by limiting transcellular calcium influx.

These effects have led to the investigation of nimodipine in other conditions associated with cerebral ischaemia. Studies[5,6] of nimodipine given orally after ischaemic stroke have produced conflicting results. A meta-analysis[7] of controlled studies suggested that nimodipine is beneficial if given within 12 hours of stroke onset but a further study[8] failed to confirm these findings. In a controlled study[9] of 155 patients suffering a cardiac arrest, nimodipine was given by intravenous infusion for 24 hours. Nimodipine had no effect on overall survival, although it did improve survival of patients in whom advanced life support was delayed for more than 10 minutes after arrest. Nimodipine has also been tried in dementia (p.362). Two multicentre studies[10] involving a total of 755 patients with dementia of vascular or degenerative origin given nimodipine for up to 6 months reported improvements in cognitive function and disability, and a systematic review[11] concluded that nimodipine could be of some benefit in patients with various forms of dementia.

1. Dorhout Mees SM, *et al.* Calcium antagonists for aneurysmal subarachnoid haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 12/03/08).
2. Harders A, *et al.* Traumatic subarachnoid hemorrhage and its treatment with nimodipine. *J Neurosurg* 1996; **85:** 82–9.
3. Langham J, *et al.* Calcium channel blockers for acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 12/03/08).
4. Vergouwen MDI, *et al.* Effect of nimodipine on outcome in patients with traumatic subarachnoid haemorrhage: a systematic review. *Lancet Neurol* 2006; **5:** 1029–32.
5. Gelmers HJ, *et al.* A controlled trial of nimodipine in acute ischemic stroke. *N Engl J Med* 1988; **318:** 203–7.
6. Trust Study Group. Randomised, double-blind, placebo-controlled trial of nimodipine in acute stroke. *Lancet* 1990; **336:** 1205–9.