- 4 Tchirkow GT, Lavery IC, Fazio VW. Crohn's disease in the elderly. *Dis Colon Rectum* 1983;26:177-81.
- 5 Goligher JC. Crohn's disease (granulomatous enteritis). In: Goligher JC, de Dombal FT, Watts J McK. *Surgery of the anus, rectum and colon*. 4th ed. London: Baillière, Tindall, 1980:827-57.
- 6 Kyle J. An epidemiological study of Crohn's disease in north east Scotland. *Gastroenterology* 1971;61:826-33.
- 7 Brahme F, Lindstrom C, Wenckert A. Crohn's disease in a defined population. *Gastroenterology* 1975;69:342-51.
- 8 Hellers G. Crohn's disease in Stockholm County 1955-1974. *Acta Chir Scand* 1979;490(suppl): 1-84.
- 9 Mayberry J, Rhodes J, Hughes LE. Incidence of Crohn's disease in Cardiff between 1934 and 1977. *Gut* 1979;20:602-8.
- 10 Elliott PR, Ritchie JK, Lennard-Jones JE. Prognosis of colonic Crohn's disease. *Br Med J* 1985;291:178.
- 11 Mayberry JF, Newcombe RG, Rhodes J. Mortality in Crohn's disease. *Q J Med* 1980;193:63-8.
- 12 Prior P, Gyde S, Cooke WT, Waterhouse JAH, Allan RN. Mortality in Crohn's disease. *Gastroenterology* 1981;80:307-12.
- 13 Truelove AC, Pena AS. Course and prognosis of Crohn's disease. *Gut* 1976;17:192-201.
- 14 Ritchie JK, Lennard-Jones JE. Crohn's disease of the colon and its distinction from diverticulitis. *Scand J Gastroenterol* 1976;11:433-6.

Regular Review

Calcium channel blocking agents and the heart

JOHN KENNY

The advent of calcium channel blocking agents was a substantial advance in cardiovascular therapeutics. In the four years since the last editorial in the *BMJ* on this subject the number of agents available has risen¹ and clinical experience with the existing drugs has increased; with that experience the range of therapeutic indications has widened.

What these drugs have in common is the ability to modify the transmembrane transport of calcium ions in different tissues, but the group is heterogeneous.² Calcium channel blocking agents differ from each other in their chemical structure, their mechanism of action at a cellular level, and their pharmacological effects. Far from being a disadvantage, this heterogeneity gives the group of drugs a distinct advantage over the β adrenergic blocking drugs.

Verapamil, nifedipine, and diltiazem are the three front line calcium channel blocking agents available, and these three agents have been the most extensively evaluated in clinical practice. Drugs such as prenylamine, perhexiline maleate, and lidoflazine also achieve their effects by actions on the calcium channel, but experience with these and other agents is more limited, and in some cases their use is also restricted by serious adverse effects.

The cellular mechanism of action of calcium channel blocking agents is complex.³ Calcium is vital in the genesis of the cardiac action potential, regulation of myocardial contractility, and contraction of smooth muscle. Calcium channel blocking agents interfere with the entry of calcium ions into the cell and so may reduce the formation and conduction of the cardiac impulse, reduce myocardial contractility, and produce vasodilatation. Nifedipine, a dihydropyridine derivative, produces coronary and systemic vasodilatation but in vivo has no effect on the cardiac conducting system. In contrast, both verapamil, a phenylalkylamine derivative, and diltiazem, a benzothiazepine derivative, produce less vasodilatation than nifedipine but impair sinoatrial and atrioventricular nodal conduction. In studies on dogs nifedipine has the most negatively inotropic effect, diltiazem having the least.⁴ In vivo, however, this negative inotropic effect of the calcium channel blocking

agents is offset by systemic vasodilatation and reflex sympathetic stimulation.

Coronary artery spasm

Dynamic coronary obstruction—coronary artery spasm—plays an important part in the pathogenesis of angina (and particularly angina at rest), not only in patients with normal coronary arteries but also in patients with fixed arterial stenoses due to coronary artery disease. Calcium channel blockade with nifedipine provides symptomatic relief in this condition, reducing the frequency of angina and the consumption of glyceryl trinitrate.⁵ Similar results have been obtained with verapamil and diltiazem. Long term treatment of coronary artery spasm with diltiazem also reduces cardiovascular "events" such as myocardial infarction, sudden death, and admission to hospital for prolonged pain.⁶ Nitrates and calcium channel blockade are equally effective in the condition, but patients seem to prefer treatment with calcium channel blockers.⁷

Stable angina pectoris

The main indication for the use of calcium channel blocking agents is chronic stable angina. Used alone, all the calcium channel blocking agents are effective in stable angina; they improve exercise tolerance and prolong both the time to the onset of angina and the time to the onset of ST segment depression during exercise testing.⁸⁻¹⁰ These beneficial effects appear to be sustained with long term treatment.¹¹ Although calcium channel blocking agents are said to achieve their beneficial effects in stable angina by increasing coronary blood flow, the evidence for this is not convincing,¹² and the more likely mechanism is a reduction in myocardial oxygen consumption. Indeed, most studies have shown that calcium channel blocking agents do reduce the rate pressure product and thus the myocardial oxygen consumption at submaximal exercise. They may also have an

effect on myocardial cells unrelated to their effects on systemic and coronary haemodynamics, and this, too, may delay or reduce the consequences of ischaemia.

Used alone, both verapamil and diltiazem are as effective as propranolol in prolonging exercise tolerance and the time to angina.^{13 14} Propranolol appears, however, to reduce ST segment depression during exercise induced ischaemia more than verapamil or diltiazem. This is because propranolol decreases the rate pressure product more than the calcium channel blocking agents. Nifedipine should be used alone with caution in the treatment of stable angina: responses by patients are variable and in some it increases angina.^{15 16} In part these adverse effects of nifedipine may be related to its action in increasing the heart rate—and this may also explain the findings of a study that showed that verapamil was superior to nifedipine in the treatment of stable angina.¹⁷

Nifedipine, diltiazem, and verapamil all produce an added beneficial effect when combined with β adrenergic blockade in the treatment of stable angina.¹⁸⁻²⁰ When given in this way, however, verapamil and diltiazem may produce adverse effects from their depression of the cardiac conducting system. Indeed, in stable angina high doses of diltiazem may be as effective as combined treatment with diltiazem and propranolol and the single drug may cause fewer side effects than the combination treatment.²¹

In patients with angina pectoris the first treatment should be with a short acting nitrate. Next, β blockade remains the prophylactic treatment of choice in stable angina for many reasons. These include the vast clinical experience of its use in angina, its cardioprotective effect after myocardial infarction, and its ability to produce a greater reduction in ischaemic ST depression. In the many patients unable to tolerate β blockade or in whom its use is contraindicated, however, treatment with verapamil or diltiazem appears to be an effective alternative. Few direct comparisons have been made between long acting nitrates and calcium channel blocking agents in the treatment of angina. In favour of the use of calcium channel blocking agents is the maintenance of their beneficial effects with long term use, whereas there are serious doubts about the long term efficacy of long acting nitrates.²² Nifedipine is safe and effective when added to the treatment of a patient whose symptoms persist despite his taking an adequate dose of a β blocking drug. If this combination does not provide adequate relief then β blockade combined with verapamil or diltiazem may be more effective, but patients should be monitored carefully for adverse effects, with particular attention to the heart rate.²³

Unstable angina

The pathogenesis of unstable angina is complex, but the consensus is that its initial treatment should consist of bed rest and medical treatment. When unstable angina is associated with pain at rest increased coronary vasomotor tone is almost certainly an important factor.²⁴ As might be expected, therefore, calcium channel blocking agents have proved extremely effective in this condition. They provide valuable symptomatic relief, and when added to conventional antianginal treatment they reduce the incidence of sudden death, myocardial infarction, and the need for coronary artery surgery.^{25 26} If calcium channel blocking agents are used alone in the treatment of unstable angina then diltiazem or verapamil may be preferable because of the increased risk of adverse effects associated with the use of nifedipine.²⁷

Hypertension

As might be predicted on the basis of their action as peripheral vasodilators, calcium channel blocking agents are effective in systemic hypertension. Possibly they may also correct the defect in leucocyte sodium transport that occurs in hypertension.²⁸ Nifedipine is simple, safe, and effective in the management of hypertensive emergencies and as a third line agent in the treatment of hypertension.^{29 30} Diltiazem is as effective as hydrochlorothiazide and may have advantages because of its low incidence of side effects.³¹ Verapamil is also effective in hypertension, producing a consistent reduction in blood pressure over 24 hours.³² It is difficult, however, to define the precise place of calcium channel blocking agents in the "stepped care" approach to the management of hypertension.³³

Cardiac arrhythmias

Verapamil and diltiazem impair atrioventricular and sinoatrial conduction. This action contributes to some of their adverse effects, but it also makes them effective agents in the management of certain arrhythmias. The important cardiac arrhythmias that are dependent on the slow inward calcium current include sinus and atrioventricular nodal re-entry tachycardias.³⁴ Intravenous verapamil is the treatment of choice in supraventricular tachycardias, up to 85% of patients reverting to sinus rhythm.³⁵ Though verapamil is effective in terminating the reciprocating tachycardia of the Wolff-Parkinson-White syndrome when one of the pathways incorporates the atrioventricular node, it should not be used if atrial fibrillation is present because of the risk of accelerated antegrade conduction through the bypass tract and thus of ventricular fibrillation.³⁴ In atrial fibrillation both parenteral verapamil given short term and long term oral treatment will reduce the ventricular response, though conversion to sinus rhythm is rare.³⁵ Similar effects occur in atrial flutter. Verapamil and digoxin are effective when combined together if either proves inadequate in controlling the ventricular response.^{36 37} Intravenous diltiazem is also effective and well tolerated in the management of paroxysmal supraventricular tachycardias.³⁸ Calcium channel blocking agents are regarded as not having any useful part to play in the treatment of ventricular arrhythmias, but verapamil may possibly be effective in certain specific types of ventricular tachycardia.³⁹

Other indications

Other indications for the use of calcium channel blockers in heart disease include hypertrophic cardiomyopathy and pulmonary hypertension. These drugs produce important symptomatic and haemodynamic improvements in patients with hypertrophic cardiomyopathy, but there is no evidence that they reduce the incidence of sudden death.⁴⁰ They are useful in the management of pulmonary hypertension because of their vasodilating properties, but their long term efficacy and safety have yet to be established.⁴¹ They may also be used as afterload reducing agents in heart failure, though this use is limited because of their negative inotropic effects.⁴² Calcium channel blocking agents may have a cardio-protective effect in patients with coronary heart disease, but this needs to be confirmed in practice—as was done for β blocking agents by a large double blind trial.⁴³ They may also

possibly modify experimental atherosclerosis, perhaps by interfering with platelet function.⁴⁴

Unwanted effects

Many of the unwanted effects of the calcium channel blocking agents may be predicted from their pharmacological actions. Their most serious adverse effects are related to disturbances of conduction. Atrioventricular block and asystole have been reported in patients given verapamil or diltiazem.^{45,46} Most such reports have been in patients with pre-existing sinoatrial or atrioventricular node disease or those receiving concurrent β adrenergic blockers. Parenteral verapamil or diltiazem should not be given to such patients, though it may be possible to give intravenous diltiazem to patients already taking oral β blockers.⁴⁷ By mouth, diltiazem or verapamil may be combined with a β blocker but the dose should be titrated carefully and the heart rate monitored to detect any substantial bradycardia.^{19,20} Nifedipine does not have any adverse effects on the conducting system. Because of their negative inotropic effects calcium channel blocking agents may produce heart failure or impair left ventricular function, particularly if they are used in combination with β

blockers in patients with pre-existing left ventricular dysfunction.^{48,49} Nifedipine is generally well tolerated, though symptoms related to vasodilatation may occur—such as headache, flushing, dizziness, palpitations, ankle oedema, and rarely hypotension.⁵⁰ Verapamil may produce hypotension after parenteral use, which is usually transient. Other unwanted effects of verapamil include dizziness, headaches, and constipation. Diltiazem appears so far to have a low incidence of adverse effects. Calcium channel blocking agents may have adverse effects on glucose and potassium homeostasis, producing hyperglycaemia and hypokalaemia.^{30,51}

The experience of calcium channel blocking agents so far indicates that they are effective and safe in many cardiovascular disorders. As newer agents with greater tissue selectivity are developed the indications for this exciting and important group of drugs should increase further.

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- Anonymous. Calcium antagonists and the heart [Editorial]. *Br Med J* 1981;282:89-90.
- Henry PD. Comparative pharmacology of calcium antagonists: nifedipine, verapamil and diltiazem. *Am J Cardiol* 1980;46:1047-58.
- Braunwald E. Mechanism of action of calcium-channel-blocking agents. *N Engl J Med* 1982;307:1618-27.
- Walsh RA, Badke FR, O'Rourke RA. Differential effects of systemic and intracoronary calcium channel blocking agents on global and regional left ventricular function in conscious dogs. *Am Heart J* 1981;102:341-50.
- Antman E, Muller J, Goldberg S, et al. Nifedipine therapy for coronary artery spasm. *N Engl J Med* 1980;302:1269-73.
- Schroeder JS, Lamb IH, Bristow MR, Ginsburg R, Hung J, McAuley BJ. Prevention of cardiovascular events in variant angina by long-term diltiazem therapy. *Journal of the American College of Cardiology* 1983;1:1507-11.
- Ginsburg R, Lamb IM, Schroeder JS, Hu M, Harrison DC. Randomized double-blind comparison of nifedipine and isosorbide dinitrate therapy in variant angina due to coronary artery spasm. *Am Heart J* 1982;103:44-8.
- Mueller HS, Chahine RA. Interim report of multicenter double-blind, placebo-controlled studies of nifedipine in chronic stable angina. *Am J Med* 1981;71:645-57.
- Subramanian VB, Lahiri A, Paramasivan R, Raftery EB. Verapamil in chronic stable angina. *Lancet* 1980;i:841-4.
- Hossack KF, Bruce RA. Improved exercise performance in patients with stable angina pectoris receiving diltiazem. *Am J Cardiol* 1981;47:95-101.
- Petru AM, Crawford MH, Kennedy GT, Amon KW, O'Rourke RA. Long term efficacy of high-dose diltiazem for chronic stable angina pectoris: 16 month serial studies with placebo controls. *Am Heart J* 1985;109:99-103.
- Kenny J, Daly K, Bergman G, Kerkez S, Jewitt DE. Beneficial effects of diltiazem in coronary artery disease. *Br Heart J* 1984;52:53-6.
- Subramanian VB, Bowles MJ, Davies AB, Raftery EB. Calcium channel blockade as primary therapy for stable angina pectoris. A double-blind placebo-controlled comparison of verapamil and propranolol. *Am J Cardiol* 1982;50:1158-63.
- O'Hara MJ, Khurmi NS, Bowles MJ, Subramanian VB, Dore CJ, Raftery EB. Comparison of diltiazem at two dose levels with propranolol for treatment of stable angina pectoris. *Am J Cardiol* 1984;54:477-81.
- Deanfield J, Wright C, Fox K. Treatment of angina pectoris with nifedipine: importance of dose titration. *Br Med J* 1983;286:1467-70.
- Jariwalla AG, Anderson EG. Production of ischaemic cardiac pain by nifedipine. *Br Med J* 1978;ii:1181-2.
- Subramanian VB, Bowles MJ, Khurmi NS, Davies AB, Raftery EB. Randomized double-blind comparison of verapamil and nifedipine in chronic stable angina. *Am J Cardiol* 1982;50:696-703.
- Lynch P, Dargie H, Krikler S, Krikler D. Objective assessment of antianginal treatment: a double blind comparison of propranolol, nifedipine, and their combination. *Br Med J* 1980;281:184-7.
- Kenny J, Kiff P, Holmes J, Jewitt DE. Beneficial effects of diltiazem and propranolol, alone and in combination, in patients with stable angina pectoris. *Br Heart J* 1985;53:43-6.
- Subramanian B, Bowles MJ, Davies AB, Raftery EB. Combined therapy with verapamil and propranolol in chronic stable angina. *Am J Cardiol* 1982;49:125-32.
- Hung J, Lamb IH, Connolly SJ, Jutzy KR, Goris ML, Schroeder JS. The effect of diltiazem and propranolol alone and in combination, on exercise performance and left ventricular function in patients with stable effort angina: a double blind, randomized, and placebo controlled study. *Circulation* 1983;68:560-7.
- Parker JO, Fung HL, Ruggirello BS, Stone JA. Tolerance to isosorbide dinitrate: rate of development and reversal. *Circulation* 1983;68:1074-80.
- Winniford MD, Fulton KL, Corbett JR, Croft CH, Hillis LD. Propranolol-verapamil versus propranolol-nifedipine in severe angina pectoris of effort: a randomized, double-blind, crossover study. *Am J Cardiol* 1985;55:281-5.
- Oliva PB. Unstable rest angina with ST-segment depression. Pathophysiologic considerations and therapeutic implications. *Ann Intern Med* 1984;100:424-40.
- Mehta J, Pepine CJ, Day M, Guerrero JR, Conti CR. Short-term efficacy of oral verapamil in rest angina. *Am J Med* 1981;71:977-82.
- Gertensblith G, Ouyang P, Achuff SC, et al. Nifedipine in unstable angina. A double-blind randomized trial. *N Engl J Med* 1982;306:885-9.
- Zelis R. Calcium-blocker therapy for unstable angina pectoris. *N Engl J Med* 1982;306:926-8.
- Gray HH, Poston L, Hilton PJ, Smith SJ, Markandu ND, MacGregor GA. Reversal by verapamil of defect in sodium transport in leucocytes in essential hypertension. *Br Med J* 1984;288:673-5.
- Bertel O, Conen D, Radu EW, Muller J, Lang C, Dubach UC. Nifedipine in hypertensive emergencies. *Br Med J* 1983;286:19-23.
- Murphy MB, Scriven AJ, Dollery CT. Role of nifedipine in treatment of hypertension *Br Med J* 1983;287:257-9.
- Inouye IK, Massie BM, Benowitz N, Simpson P, Loge D. Antihypertensive therapy with diltiazem and comparison with hydrochlorothiazide. *Am J Cardiol* 1984;53:1588-92.
- Gould BA, Mann S, Kiesio H, Subramanian VB, Raftery EB. The 24-hour ambulatory blood pressure profile with verapamil. *Circulation* 1982;65:22-7.
- Breckenridge A. The third drug in hypertension. *Br Med J* 1984;289:859-60.
- Gilmour RF, Zipes DP. Slow inward current and cardiac arrhythmias. *Am J Cardiol* 1985;55:89-101B.
- Talano JV, Tommaso C. Slow channel calcium antagonists in the treatment of supraventricular tachycardia. *Prog Cardiovasc Dis* 1982;25:141-56.
- Winniford MD, Fulton KL, Hillis LD. Long-term therapy of paroxysmal supraventricular tachycardia: a randomized, double-blind comparison of digoxin, propranolol and verapamil. *Am J Cardiol* 1984;54:1138-9.
- Schwarz JB, Keefe D, Kates RE, Kirsten E, Harrison DC. Acute and chronic pharmacodynamic interaction of verapamil and digoxin in atrial fibrillation. *Circulation* 1982;65:1163-70.
- Betriu A, Chaitman BR, Bourassa MG, et al. Beneficial effect of intravenous diltiazem in the acute management of paroxysmal supraventricular tachyarrhythmias. *Circulation* 1983;67:88-94.
- Belhassen B, Harowitz LN. Use of intravenous verapamil for ventricular tachycardia. *Am J Cardiol* 1984;54:1131-3.
- Goodwin JF. The frontiers of cardiomyopathy. *Br Heart J* 1982;48:1-18.
- Packer M. Therapeutic application of calcium-channel antagonists for pulmonary hypertension. *Am J Cardiol* 1985;55:196-201B.
- Josephson MA, Singh BN. Use of calcium antagonists in ventricular dysfunction. *Am J Cardiol* 1985;55:81-8B.
- Kendall MJ, Horton RC. Are calcium antagonists cardio-protective? *J R Coll Physicians Lond* 1985;19:85-9.
- Parmley WW, Blumlein S, Sievers R. Modification of experimental atherosclerosis by calcium-channel blockers. *Am J Cardiol* 1985;55:165-71B.
- Hossack KF. Conduction abnormalities due to diltiazem. *N Engl J Med* 1982;307:953-4.
- Benaim ME. Asystole after verapamil. *Br Med J* 1972;iii:169-70.
- Kenny J, Daly K, Bergman G, Kerkez S, Jewitt DE. Beneficial effects of diltiazem added to beta-blockade in coronary artery disease. *Eur Heart J* (in press).
- Robson RH, Vishwanath MC. Nifedipine and beta-blockade as a cause of cardiac failure. *Br Med J* 1982;284:104.
- Oesterle SN, Schroeder JS. Calcium-entry blockade, beta-adrenergic blockade and the reflex control of circulation. *Circulation* 1982;65:669-70.
- Opie LH. Calcium antagonists: mechanisms therapeutic indications and reservations: a review. *Q J Med* 1984;103:1-16.
- Bhatnagar SK, Amin MMA, Al-Yusuf AR. Diabetogenic effects of nifedipine. *Br Med J* 1984;289:19.