Fortnightly Review

Short acting dihydropyridine (vasodilating) calcium channel blockers for hypertension: is there a risk?

D G Beevers, P Sleight

There is a wide choice of drugs for hypertension. To date, however, only thiazide diuretics and β blockers have been shown to prevent myocardial infarction and stroke and reduce mortality in properly randomised and blinded studies. The efficacy of newer drugs in these respects (the calcium channel blockers and angiotensin converting enzyme inhibitors) has not been proved because no comparative trial in hypertensive patients has been conducted. It is much more difficult and expensive to conduct trials of these newer drugs. Giving a placebo to controls is no longer ethical, and new trials must therefore be enormous if they are to have the power to detect any differential effect.

Surrogate end points of trials are not enough

Calcium channel blockers and angiotensin converting enzyme inhibitors are expensive and are not more effective at lowering blood pressure, but they have some theoretical advantages. The current licensing and clinical use of these newer drugs have been based on surrogate end points such as reduction of blood pressure or left ventricular hypertrophy, or both, or reduction of microproteinuria or macroproteinuria.

A major clinical trial concerned with mortality has been started in the United States to compare the safety and effectiveness of newer versus older drugs but is having difficulty recruiting patients.¹ In any case, evidence will not be available until the year 2000 at the earliest. Attempts by the British Hypertension Society to mount a similar trial comparing the main therapeutic classes of antihypertensive agents have so far been unsuccessful owing to lack of support from industry in this fiercely competitive and commercially sensitive topic.

Preliminary data from two unpublished trials of dihydropyridine calcium channel blockers in hypertension have been presented at meetings. The multi-centre isradipine-diuretic atherosclerosis study was designed to monitor the progression or regression of carotid artery atherosclerosis over three years in almost 900 hypertensive men and women with ultrasonic evidence of mild to moderate carotid artery disease.² Mortality was not the primary end point, but there were more deaths in the isradipine group than in the group given hydrochlorothiazide.

A Chinese study of nifedipine versus placebo in 1797 elderly hypertensive patients showed a significant reduction in all cause mortality (P Hamet, paper presented at meeting of the European Society of Hypertension, Milan, 1995). However, coronary deaths were fewer than 10 and balanced; there was a significant reduction in stroke deaths. These data from

Summary points

- Only thiazide diuretics and β blockers have been shown to prevent myocardial infarction and stroke in properly randomised and blinded studies in patients with hypertension
- The efficacy of calcium channel blockers and angiotensin converting enzyme inhibitors in preventing myocardial infarction and stroke and reducing mortality in hypertensive patients has not been studied
- The current licensing and clinical use of calcium channel blockers and angiotensin converting enzyme inhibitors in hypertension have been based on surrogate end points such as reduction of blood pressure or left ventricular hypertrophy, or both, or reduction of microproteinuria or macroproteinuria
- Observational data on short acting dihydropyridine calcium channel blockers are worrying; there is urgent need for proper large scale randomised trials of calcium channel blockers in hypertension
- Trials in ischaemic heart disease suggest that in the absence of left ventricular dysfunction verapamil and diltiazem are preferred choices if a calcium, channel blocker is needed in the non-acute setting

a population with a very low incidence of ischaemic heart disease may not be readily applicable to Western populations. In addition, the study used an inexpensive Chinese preparation of nifedipine, which had a longer duration of action than standard nifedipine.

Unreliability of observational and case-control studies

In the absence of published randomised trials, retrospective or prospective pharmacosurveillance studies aim at determining whether hypertensive patients treated with one particular class of drug have more or fewer adverse events (for example, heart attacks or death) than patients given other drugs. These studies may try to balance the patients for other known risk factors, such as age, sex, blood pressure, and so on (when they are called case-control studies).

Non-randomised outcome studies can be biased so that they are very unreliable, even when obvious confounding factors are allowed for. But in the absence

City Hospital, Birmingham
B18 7QH
D G Beevers, *president,*
British Hypertension Society

John Radcliffe Hospital,
Oxford OX3 9DU
P Sleight, *past president,*
British Hypertension Society

Correspondence to:
Professor Sleight.

BMJ 1996;312:1143-5

of large randomised trials (which eliminate bias) they may be the only source of data available. When surveillance or case-control studies throw up evidence of possible harm we should not rely on surrogate end points but should press for mortality data from randomised trials. A recent retrospective case-control study of patients with hypertension showed that those treated with calcium channel blockers had more heart attacks than those treated with a β blocker.³ Release of prepublication data from that trial generated a great deal of anger and distress in the United States and received much media attention, which also spread to the United Kingdom.

The study was confined to hypertensive patients receiving drug treatment in a group health cooperative in the Seattle area. The cases comprised 623 treated hypertensive men and women aged 30-79, who were matched (by age and sex) to 2032 randomly selected hypertensive controls who had not had a myocardial infarction while receiving drug treatment for hypertension. Patients were excluded if they had started drug treatment only in the last month before any event or index date. Data were also collected on other risk factors for myocardial infarction in order to adjust for these.

The modal daily doses of drugs were 30 mg for nifedipine (all short acting formulations), 180 mg for diltiazem, 240 mg for verapamil, 80 mg for propranolol, 100 mg for metoprolol, 80 mg for nadolol, and 50 mg for atenolol. In a subanalysis of 335 cases and 1395 controls who had no prior clinical cardiovascular disease (adjusted for all known confounding factors) the use of calcium channel blockers compared with a diuretic was associated with a 58-70% increase in the risk of having a myocardial infarction. When the cases were divided (about equally) into three dose levels of calcium channel blockers there was a significant trend for higher risk with higher doses. With increasing doses of β blockers the risk of myocardial infarction decreased. There were no significant differences in risk with different calcium channel blockers, though numbers and hence power to detect differences were small. When patients taking calcium channel blockers were compared with those taking β blockers the risk ratio for myocardial infarction was increased by 17% for low dose and 72% for high dose calcium channel blockers.

Nifedipine unpromising in ischaemic heart disease

The case against some calcium channel blockers (particularly short acting formulations of nifedipine) in ischaemic heart disease (rather than hypertension) was further developed in a meta-analysis of randomised trials which looked at the dose related risks of nifedipine in patients with established coronary heart disease.⁴ The authors found a dose related excess mortality associated with short acting nifedipine. This second analysis is perhaps less surprising, as there was already considerable evidence from properly randomised trials that nifedipine may be associated with an excess of reinfarction and deaths in patients with established ischaemic heart disease.⁵ (Two of these nifedipine studies were stopped early by the safety committees.)

Nifedipine in elderly hypertensive patients

The reports by Psaty *et al*⁶ and Furberg *et al*⁷ of increases in myocardial infarction and deaths, respectively, with calcium channel blockers and particularly short acting nifedipine were followed by a report by Pahor *et al*, who had very similar findings but gave more specific information on individual drugs.⁶ Pahor *et al* studied four year survival in a prospective cohort

study of 906 elderly (aged 71 and over) patients treated for hypertension. Funded by the United States National Institute of Ageing, this was part of a large cohort study of older people from New Haven, Connecticut; east Boston; and two counties of Iowa.⁷ Patients with heart failure were excluded, as were patients taking only diuretics (a low risk group) and patients taking combination therapy (a high risk group). The main end point was all cause mortality between 1988 and 1992. The 906 patients were divided into mutually exclusive categories by drug use—namely, β blockers (515), verapamil (77), diltiazem (92), nifedipine (74), and angiotensin converting enzyme inhibitors (148). The relative risks for all cause mortality after adjusting for confounding variables and taking β blockers as 1.0 were verapamil 0.8 (NS), diltiazem 1.3 (NS), nifedipine 1.7 ($P=0.016$), and angiotensin converting enzyme inhibitors 0.9 (NS).

A separate analysis which excluded patients with ischaemic heart disease, diabetes, claudication, and chronic pulmonary disease (which might have influenced drug choice) found a similar significant excess risk with nifedipine compared with β blockers (relative risk 4.2; 95% confidence interval 1.1 to 16.1).

The doses of drugs used could be analysed in the subgroup from Iowa and east Boston, and as before (compared with β blockers) the higher dose of nifedipine (>20 mg daily) was associated with higher risk compared with <20 mg nifedipine daily (relative risk 3.1 *v* 1.4). Though the prospective nature of the study and the adjustments for known confounders were strengths, the study was more likely to be biased than a randomised trial. These three non-randomised studies were also likely to present problems from publication bias—that is, similar studies showing no excess mortality with a particular drug would not excite interest in either authors or journals.

National Heart, Lung and Blood Institute warning

Data from the three reports caused the United States National Heart, Lung and Blood Institute to issue a warning statement to all physicians on 1 September 1995 on the safety of short acting dihydropyridine calcium channel blockers.⁸ This balanced report acknowledged the problems with such observational studies but stated that short acting nifedipine should be used with caution (if at all). It also stated there was a need for proper mortality trials with the newer calcium channel blockers. The report reminded physicians of the wealth of data on the benefits of β blockers and diuretics for hypertension.

A later advisory committee to the United States Food and Drug Administration decided that most calcium channel blockers are safe to use in patients with hypertension.⁹ The panel recommended strengthening the labelling to indicate that short acting nifedipine should not be used in hypertension or unstable angina (though many doctors still use it for these indications).

Not all calcium channel blockers are the same

An unpublished meta-analysis of published trials of verapamil (a non-dihydropyridine calcium channel blocker) presented to the panel showed that verapamil reduced mortality and coronary events compared with placebo in patients with ischaemic heart disease.⁹ The committee called for more data from randomised controlled trials to compare calcium channel blockers with each other and with other agents of proved efficacy.

As stated above, these observational data are inherently unreliable.¹⁰ Despite every endeavour to collect data scrupulously and to adjust for obvious

confounding variables, unmeasured or unmeasurable biases may completely overwhelm modest differences between different agents. Even if the association is real is it biologically plausible and therefore more likely to be causal? Some calcium channel blockers have negative inotropic and chronotropic effects; others—particularly the short acting calcium channel blockers like nifedipine—may provoke potentially harmful reflex catecholamine surges associated with the rapid vasodilatation. Calcium channel blockers have also both antiplatelet and antispasm effects which may lead to excessive bleeding in patients having surgery¹¹ or in patients with coexisting lesions such as gastritis, ulcer, or cancer.¹² This bleeding risk seems to be a feature of all calcium channel blockers. Proischaemic effects may result from a coronary steal phenomenon.¹³

Unlike β blockers, calcium channel blockers show substantial differences between each other. The non-dihydropyridine calcium channel blockers diltiazem and, particularly, verapamil do not increase heart rate and seem safer in patients with ischaemic heart disease.^{5 14-17} Psaty *et al*, however, found no differences in their small study, in which verapamil was non-significantly worse.³ Nifedipine in these observational studies was used largely in 10 mg capsule or tablet formulation and in some cases in unusually large doses (up to 180 mg daily). Whether these worrying data can be extrapolated to the newer long acting calcium channel blockers, longer acting formulations of existing calcium channel blockers like nifedipine gastrointestinal transmission system—slow release, or even to lower doses of short acting dihydropyridines is not clear. One unpublished study of the long acting dihydropyridine amlodipine in patients with heart failure showed neither excess nor decrease in mortality but possible beneficial effects in patients with non-ischaemic cardiomyopathy (M Packer, paper presented to meeting of the American Heart Association, Anaheim, California, November 1995).

Advice for clinicians

What should clinicians do while this debate continues? Firstly, it seems sensible to avoid using short acting formulations of calcium channel blockers such as nifedipine in high dose. Whether we should extend this caution to the newer formulations and second generation drugs is a matter of judgment until better data are available, particularly if proved agents such as low dose diuretics or β blockers are effective and tolerated. In patients for whom these proved agents are not adequate or appropriate (for example, with β blockers because of bronchospasm), then an angiotensin converting enzyme inhibitor or verapamil (in ischaemic patients) as monotherapy or added to a diuretic seems the safest current option.

Secondly, clinicians should remember that because these are observational and sometimes retrospective studies—not randomised placebo controlled trials—there may have been other reasons why the patients were being treated with calcium channel blockers rather than other drugs. Thirdly, calcium channel blockers (preferably verapamil or diltiazem) may still be necessary (but as second line treatment) in Afro-Caribbean and older patients. Fourthly, we do not recommend the use of sublingual nifedipine for hypertensive emergencies, as it may precipitate stroke or myocardial infarction.^{18 19} Fifthly, verapamil or diltiazem may be necessary to control angina in patients with both hypertension and ischaemic heart disease; of the newer agents, amlodipine (a long acting dihydropyridine) did not reduce mortality in patients with heart failure and ischaemic heart disease (Packer, 1995). Sixthly, dihydropyridine calcium channel blockers should not be given to patients with a recent

myocardial infarction. If other proved drugs are not sufficient, then verapamil or possibly diltiazem could be used in patients without left ventricular dysfunction.

The British Hypertension Society will continue to strive for a large scale mortality study comparing older and newer agents in hypertension through its sub-committee (chaired by Professor Peter Sever). It may be that the current debate will concentrate some minds. Such trials are imperative in the light of these worrying observational data.

- 1 Davis BR, Cutler JA, Gordon DJ, Furberg CD, Wright JT Jr, Cushman WC, *et al* for ALLHAT Research Group. Rationale and design for the antihypertensive and lipid lowering treatment to prevent heart attack trial (ALLHAT). *Am J Hypertens* (in press).
- 2 Borhani NO, Miller ST, Brugger SB, Schnaper HW, Craven TE, Bond MG, *et al*, on behalf of the MIDAS Research Group. MIDAS: hypertension and atherosclerosis. A trial of the effects of antihypertensive drug treatment on atherosclerosis. *J Cardiovasc Pharmacol* 1992;19(suppl 3):S16-20.
- 3 Psaty BM, Heckbert SR, Koepsell TD, Siscovick DS, Raghunathan TE, Wyss NS, *et al*. The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 1995;274:620-5.
- 4 Furberg CF, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995;92:1326-31.
- 5 Sleight P. Calcium channel blockers during and after myocardial infarction. *Drugs* 1996;51:216-25.
- 6 Pahor M, Guralnik JM, Corti M-C, Foley DJ, Carbonien P, Havlik RJ, *et al*. Long-term survival and use of antihypertensive medications in older persons. *J Am Geriatr Soc* 1995;43:1191-7.
- 7 Comoni-Huntley J, Ostfeld AM, Taylor JO, Blazer D, Berkman LF, Evans DA, *et al*. Established populations for epidemiologic studies of the elderly: study design and methodology. *Ageing (Milano)* 1993;5:27-37.
- 8 McCarthy M. US National Institute of Health issues warning on nifedipine. *Lancet* 1995;346:689-90.
- 9 Barnett AA. News. *Lancet* 1996;347:313.
- 10 Buring JE, Glynn RJ, Hennekens CH. Calcium channel blockers and myocardial infarction. A hypothesis formulated but not yet tested. *JAMA* 1995;274:654-5.
- 11 Wagenknecht LE, Furberg CD, Hammon JW, Legault C, Troost BT. Surgical bleeding: unexpected effect of a calcium antagonist. *BMJ* 1995;310:776-7.
- 12 Pahor M, Guralnik JM, Furberg CD, Carbonien P, Havlik RJ. Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old. *Lancet* (in press).
- 13 Waters D. Proischemic complications of dihydropyridine calcium channel blockers. *Circulation* 1991;8:2598-603.
- 14 Rehnqvist N, Hjemdahl P, Billing E, Björkander I, Eriksson SV, Forslund L, *et al*. Effects of metoprolol versus verapamil in patients with stable angina pectoris. *Eur Heart J* (in press).
- 15 Danish Study Group on Verapamil in Myocardial Infarction. Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish verapamil infarction trial II DAVIT II). *Am J Cardiol* 1990;66:779-85.
- 16 Yusuf S, Held P, Furberg C. Update of effects of calcium antagonists in myocardial infarction or angina in light of the second Danish verapamil infarction trial (DAVIT II) and other recent studies. *Am J Cardiol* 1991;67:1295-7.
- 17 Yusuf S. Verapamil following uncomplicated myocardial infarction: promising, but unproven. *Am J Cardiol* 1996;77:421-2.
- 18 O'Mallia JJ, Sander GE, Giles TD. Nifedipine associated myocardial ischemia or infarction in the treatment of hypertensive emergencies. *Ann Intern Med* 1987;107:185-6.
- 19 Messerli FH, Konrey P, Grodzicky T. Sublingual nifedipine for hypertensive emergencies. *Lancet* 1991;338:881.

ONE HUNDRED YEARS AGO

THE DUTIES OF THE GENERAL MEDICAL COUNCIL.

SIR,—I have long been of opinion and have advocated that the British Medical Association should be the medium for defence, and that an increased subscription should be paid by each member desiring to insure such benefits, and my views coincide mainly with the scheme proposed on p. 350 in the *BRITISH MEDICAL JOURNAL* of February 8th, but I do not think the prosecution of illegal practitioners should be necessarily included in this scheme, as it is to the General Medical Council we should look for such proceedings. I hope to see the time when the existing defence societies will amalgamate with the British Medical Association, and in this way one solid body be formed for the general benefit of the profession, which sorely needs it. I am not, however, in favour of the work being delegated as a rule to the Branches, but that it should be conducted by a Committee selected for the purpose.—I am, etc.,

HENRY HEMSTED.
(*BMJ* 1896;i:629.)

Whitchurch, Hants, Feb. 8th.