How safe are the CALCIUM ANTAGONISTS?

Dr Henry Purcell

Introduction

The calcium antagonists are among the most widely prescribed drugs for the treatment of hypertension and angina worldwide. Until recently, there has been something of a cloud hanging over the calcium antagonists. However, new data were presented during the recent European Society of Hypertension (ESH) meeting in Milan and the European Society of Cardiology (ESC) in Stockholm which appear to support their use in patients who are among those at the highest cardiovascular risk.

The three classes of calcium antagonists are structurally, haemodynamically and pharmacologically very different to one another (Figure 1), particularly in terms of effects on heart rate and cardiac contractility and their selectivity for cardiac versus vascular tissue. Used appropriately, heart rate lowering agents such as diltiazem and verapamil are highly efficacious in angina, but must be avoided in patients with heart failure because of their cardiac depressant properties. Similarly, short-acting dihydropyridine preparations should no longer be used because of their side effects and the likelihood of them causing tachycardia. Long-acting preparations of nifedipine and amlodipine lower blood pressure (BP) effectively, but it may be necessary to combine them with a beta blocker to control exertional angina in some patients.

Hypertension in the elderly

Hypertension contributes to all major cardiovascular diseases, increasing risk on average 2 to 3-fold. The elderly are among the most susceptible to sustained arterial pressures, and have the most to gain from treatment in terms of absolute risk reduction of the complications of hypertension. This appears to be a message which has been slow to sink in however, as some doctors still harbour doubts about the benefits of treating high BP in older patients, and they even subscribe to the myth that older persons need higher pressures to perfuse narrowed vessels. Yet "it is very clear that we all have a responsibility to identify and treat the elderly population, but in many places this is not done, even as well as the younger patient population" said Dr Norman Kaplan, one of the great 'gurus' of BP, from Dallas, Texas. Speaking at a Bayer symposium during the ESH meeting, he said that BP control in general is poor, especially among the elderly, in whom "treatment is essential". He described the structural changes occurring with age. Stiffening of the arteries and a widening of the pulse pressure (the difference between systolic and diastolic pressure, which is the most sensitive indicator of prognosis) are a consequence of ageing, and "atherosclerotic rigidity". Well over half the individuals from 60 years onwards in developed countries are hypertensive. Findings from the Framingham Heart Study show that about 2 out of 3 of these individuals develop pure isolated systolic hypertension (ISH), "this is the most common nature of the BP which we identify in the elderly, and there is a clear straight increase relationship of morbidity and mortality with the rising systolic pressures that occur with age", said Dr Kaplan.

Meta-analysis of trials of treatment of ISH in the elderly clearly show that complications such as heart attack, stroke, cardiac failure and so forth are "significantly reduced by the treatment of hypertension". These "very impressive" reductions in events also apply to very elderly patients, over 80 years in many cases. The next question is, exactly how should we lower BP in these patients? Outcome data invariably point in the same direction, to low-dose diuretics or calcium antagonists, as seen in the SHEP trial (trial acronyms are explained on page 34) which used chlorthalidone, and in SYST-EUR with nitrendipine as the primary therapy. This latter trial also showed a significant decrease in dementia. These findings are likely to be a reflection of the better antihypertensive efficacy of these two drug classes in the elderly, who seem to have lower renin-angiotensin activity. This may be why ACE (angiotensin-converting enzyme) inhibitors and beta blockers are less effective in this population, according to Dr Kaplan; "without overstating the evidence… calcium antagonist-based therapy, without question, has been shown to be particularly effective in the elderly in reducing stroke". It can also regress left ventricular hypertrophy – an independent cardiovascular risk factor. The PREVENT trial with amlodipine suggests that some calcium antagonists may slow the progression of atherosclerosis in the carotid vessels. Another 'niche' for these drugs is that they seem to be the only antihypertensives whose efficacy is not impaired by the use of non steroidal anti-inflammatory drugs (NSAIDs). Dr Kaplan concluded by saying

that the calcium antagonists have been available for about 30 years, and in his view they are safe and effective, but "they are not for all patients". All antihypertensives have a place, "but there is a niche for the use of calcium antagonists in the treatment of hypertension".

Professor Lars Lindholm from Umea University in Sweden made the point that when treating the elderly we must "do as little harm and as much good as possible". He provided data from the STOP-2 trial which randomised 6614 hypertensive patients aged 70-84 years to treatment with older agents such as diuretics or beta blockers, or newer drugs such as calcium antagonists or ACE inhibitors for 5.3 years. Results showed that that the older and the newer types of drugs were similarly effective in preventing cardiovascular events; such was also the case in the 719 patients with diabetes at baseline. Overall, about 9% of patients developed cancer during the study period, but there was no difference in the frequency of cancer between any treatment group, data which Professor Lindholm finds "very, very reassuring", and which were published recently (Lindholm L.H., et al. *Lancet* 2001;358:539-44). Professor Lindholm has recently undertaken a cost-effectiveness study on behalf of the Swedish Government and has found that it is "very cost-effective to treat elderly patients with high blood pressure".

Meta-analysis on outcomes with antihypertensives

Professor Stephen MacMahon, University of Sydney, Australia summarised the findings from the Blood Pressure Lowering Trialists Collaboration, looking at the effects of calcium antagonists, ACE inhibitors and other agents on mortality and cardiovascular morbidity (*Lancet* 2000;355:1955-64). This overview involved large-scale prospective randomised trials, which were required to have a minimum of 1000 patient years of follow-up in each randomised group. In the two trials of calcium antagonists versus placebo (PREVENT and SYST-EUR), in 5520 patients, drug treatment was associated with a 39% reduction in strokes and a 28% reduction in major cardiovascular events. There was "no clear reduction in risk of coronary heart disease", but there was a trend towards benefit, said Professor MacMahon, and the inclusion of data from many on-going trials of calcium antagonists and ACE inhibitors will allow more precise estimates of the effects of these agents in broader patient groups. Further analysis suggests that there was a lower risk of stroke and a greater risk of coronary heart disease (CHD) when comparing calcium antagonists with diuretics and beta blockers. However, there is uncertainty about the size of the differences between these agents, and in Professor MacMahon's view "the data are probably insufficient to recommend changes to current practice".

INSIGHT on hypertension

One of the largest trials to be included in the meta-analysis was INSIGHT. This trial randomised 6321 hypertensive patients aged 55-80 years, who had at least one additional risk factor, to treatment with nifedipine GITS or diuretic treatment. After 4.5 years, results showed that both therapies were equally effective in preventing overall cardiovascular and cerebrovascular complications. Professor Giuseppe Mancia, St Gerado Hospital, Monza, Italy, commented that a clinical interpretation of this finding was that whatever protection was derived from conventional treatment, "was also obtained by treatment based on nifedipine slow-release". In his view, from further analysis of INSIGHT (as per ISH/WHO guidelines), first-line treatment should not be restricted to diuretics and beta blockers.

A sub-study using 24-hour ambulatory BP monitoring confirmed the effective reduction in pulse pressures as a result of a greater fall in systolic pressures, without any heart rate increases with either treatment group. Professor Mancia pointed out that in INSIGHT, 70% of patients, regardless of therapy, achieved BP control with monotherapy. This even applied to just over 50% of the diabetic patients, in whom combination therapy is invariable warranted. In all patients, regardless of the sub-group, BP control was impressive, with pressures coming down to around 141/83 mmHg on average. However, BP control "could not zero the original risk of the patients"; that is, those with previous myocardial infarction (MI), proteinuria and dyslipidaemia for example (in addition to their hypertension), all of whom maintained an elevated risk. "This is strong evidence that even effective antihypertensive treatment may not be enough, and that in the future we may move towards multifactorial intervention and antihypertensive drugs with drugs of other types", said Professor Mancia. He suggested that we really need trials of much longer duration to see whether we can differentiate between short-term (acute) and longer-term benefits with different drugs.

Carotid disease

As well as hard-end points, there is much current interest in sub-clinical target organ damage, such as changes in carotid intima-media thickness (IMT), which serves as a "new marker of atherosclerosis", according to Professor A Simon, Hopital Broussais, Paris, who presented details of an INSIGHT sub-study looking at 439 hypertensive patients who underwent serial carotid ultrasonography. Calcium antagonist-treated patients were observed to have a significantly lower IMT progression rate (mm/year) and a lower IMT change from baseline at the end of a 4-year follow-up compared to diuretic-treated patients. There were no differences in either group in terms of BP control, and Professor Simon postulates that the beneficial arterial changes are due to "a direct action of nifedipine on the arterial wall, which may be either an anti-atherogenic effect on the intima and/or an anti-proliferative effect on the media – unfortunately we cannot discriminate between these two mechanisms at present". One can only speculate that the change in IMT progression may be related to long-term complications and in Professor Simon's view, a longer trial is needed to demonstrate this.

Diabetes and renal disease

In INSIGHT, a significantly larger number of patients developed diabetes with diuretic compared with calcium antagonist treatment. Cardiovascular disease is at least 2-4

times more common among diabetic patients and the diabetic with hypertension is at a high risk of developing diabetic nephropathy, which is the commonest cause of end-stage renal disease. Professor Luis Ruilope, Hospital 12 de Octubre, Madrid, said that in daily clinical practice, if increased creatinine, decreased creatinine clearance or microalbuminuria/proteinuria are present, these are high-risk patients who need aggressive treatment and that "we must lower blood pressure as much as possible… to values below 130/85 mmHg". In his opinion, "treatment with nifedipine GITS results in better maintenance of renal function as compared to the diuretic combination employed in the INSIGHT study". Dr Kaplan commented that the majority of diabetics will require "multiple drugs" and in his opinion, "in most diabetics, the initial drug will likely be an ACE inhibitor or an AII blocker". In addition to that, he added, in order to achieve adequate BP (control), a calcium antagonist will often be indicated, which is no problem in regards to safety and has a very definite benefit.

Dr Kjeldsen, Ullevaal University Hospital, Oslo, underlined the BP treatment challenge stating that, "maybe three or even four drugs may be needed in type 2 diabetics with hypertension. There is still no consensus on first choice, which may possibly be clarified from some of the on-going trials which have randomised a large number of type 2 diabetics, although I'm not really sure whether it matters, because these patients probably need all the drugs we have to control their blood pressure", he concluded.

Diltiazem – current role

A Sanofi-Synthelabo symposium at the ESC afforded an opportunity to review some of the latest diltiazem data. The NORDIL trial in 108,881 hypertensive patients showed that diltiazem was as effective as treatment based on diuretics and beta blockers in preventing stroke, MI and other cardiovascular deaths. Diltiazem gave an additional benefit of a reduction in cerebral stroke in the most severe hypertensives. The INTERCEPT trial looked at dilitazem or placebo randomised treatment in 874 patients (without heart failure) administered within 36-96 hours following thrombolysis for acute MI. No major safety issues were encountered. Diltiazem did not reduce the primary end-point, the cumulative occurrence of cardiac death, non-fatal reinfarction or refractory ischaemia during 6-month follow-up, but it did reduce the composite end-points of non-fatal cardiac events, especially the need for revascularisation (by 42%). These findings suggest that the use of diltiazem can also be used to reduce cardiac and cerebrovascular events in selected high-risk patients.

Conclusions

Calcium antagonists have been used clinically for almost 35 years, but we still have much to learn about this diverse drug class. While huge outcome studies such as ALLHAT, which compares different classes of antihypertensives, will provide more detailed insights, the available evidence suggests that, when used appropriately, that calcium antagonists are safe and effective drugs for a wide range of cardiovascular patients.

Trial acronyms explained

Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)
Swedish Trial in Old Patients with Hypertension-2 Study (STOP-2)
International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT)
Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis post-Thrombolysis (INTERCEPT)
Nordic Diltiazem Study (NORDIL)
Prospective Randomised Evaluation of the Vascular Effects of Norvasc Trial (PREVENT)
The Systolic Hypertension in the Elderly Programme (SHEP)
Systolic Hypertension Europe (SYST-EUR).

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Figure 1.

Cardiovascular effects of calcium antagonists

	Amlodipine	Diltiazem	Verapamil
Heart rate	↔	↓	↓
AV node conduction	↔	↓	↓
Myocardial contractility	↔	↓↓	↓↓↓
Peripheral vasodilation	↑↑	↑	↑
Myocardial O_2 demand	↓	↓	↓

↑, increase; ↓, decrease; ↔, unchanged; AV, atrioventricular.

Cardiovascular effects of calcium antagonists. Adapted from: Angina, a systematic guide to investigation and treatment. Eds. Purcell H, Kaddoura S. Mosby Publishers, London 2001.