Hotline Editorial

Calcium antagonism in perspective: new data on diltiazem in unstable angina

A case-control study by Psaty and colleagues\(^1\) has triggered a vigorous discussion on the use of calcium antagonists for the treatment of various cardiovascular diseases. The study observed that rates of myocardial infarction were higher among hypertensive patients taking a calcium antagonist than among those on beta-blocker or diuretic. In addition, a few months later the same group published a meta-analysis on the use of calcium antagonists, in particular short-acting nifedipine, in patients with coronary artery disease\(^2\). They concluded that the use of short-acting nifedipine in moderate to high dose causes an increase in mortality. The analysis included 16 secondary prevention clinical trials for which mortality data are available. Twelve trials randomized patients with acute myocardial infarction, three trials included patients with unstable angina and one trial evaluated patients with stable angina. The results of all these trials were first published in the 1980s. This study was linked with the earlier debate on calcium antagonism in hypertensive patients.

Against this background of retrospective analyses, the study by Göbel \textit{et al.}, recently published in the \textit{Lancet}\(^3\), is important, since it produces interesting prospective data on the use of the calcium antagonist, diltiazem, in unstable angina. In a randomized, double-blind trial diltiazem was compared with nitroglycerin, both given intravenously to 129 patients with unstable angina. The outcome event was refractory angina or myocardial infarction, each individually and as a composite endpoint.

Refractory angina as well as the composite endpoint of myocardial infarction and refractory angina occurred significantly less in the diltiazem group. The incidence rates during the period that patients were on study medication (per protocol analysis) were: refractory angina 6(10-0\%) vs 17(27-8\%), relative risk 0-36, \(P=0-02\), and refractory angina and myocardial infarction: 9(15-0\%) vs 23(37-7\%), relative risk 0-40, \(P=0-007\). An intention to treat analysis over the total 48 h observation period revealed comparable results: refractory angina 8(13-3\%) vs 18(29-5\%), relative risk 0-45, \(P=0-03\), and refractory angina and myocardial infarction 12(20-0\%) vs 25(41-0\%), relative risk 0-49, \(P=0-02\). Consequently, patients in the diltiazem group showed a significantly \((P<0-05)\) improved event free survival on study medication. The incidence of differences in side effects were as expected: atrioventricular conduction disturbances occurred in 5(8-3\%) patients in the diltiazem group but not in the nitroglycerin group \((P=0-03)\); headache, resulting in addition of an analgesic or dose adjustment of study medication, occurred significantly more in the nitroglycerin group: 15(24-6\%) vs 3(5-0\%), relative risk 5-00 \((P<0-004)\). A possible explanation for these observations may be that the heart rate pressure product was only reduced significantly by diltiazem \((P<0-05)\). It was concluded that intravenous diltiazem, compared with intravenous nitroglycerin, significantly reduces ischaemic events and can be used safely in patients with unstable angina.

The data of this study reminds us again that calcium antagonists are a very heterogeneous group. On the basis of many trials performed in the 1980s (largely the studies Furberg used for his analysis\(^2\)) it was concluded that first-generation dihydropyridines should not be used in acute ischaemic syndromes. The last study performed in unstable angina was the Dutch HINT study which supported this conclusion\(^4\). Subsequent trials were small and inconclusive. It is the strength of the present study with diltiazem that after almost ten years of absence of new data on this topic we have evidence that calcium antagonists are indeed a heterogenous group and that conclusive data in regard to dihydropyridines may not be true for other classes of calcium antagonists. Moreover, it underscores one of the conclusions by Opie and Messerli in the debate on calcium antagonism: 'Clearly, what is needed is a more thorough prospective database and fewer meta-analyses\(^5\).

How can we explain this beneficial effect against the earlier findings with the dihydropyridine calcium antagonists? Several mechanisms may be suggested. Firstly, the haemodynamic differences between the calcium antagonists. Nifedipine monotherapy in acute ischaemia is associated with a higher incidence of myocardial infarction, probably because of a reflex tachycardia due to a decrease in blood
The results of the present trial with diltiazem show a significant decrease in heart rate as well as heart rate pressure product in the diltiazem group. This could explain the beneficial effects in contrast to reported studies with nifedipine. In contrast to diltiazem, the nitroglycerin group showed no significant change in the heart rate pressure product, since the observed rise in heart rate was associated with a decrease in blood pressure. Interestingly, 30% of the study population was on beta-blockade. It appeared that the beneficial effect of diltiazem was comparable between patients with or without beta-blocker. This suggests that the effect of diltiazem adds to beta-blockade and thus could be used in addition to beta-blockade in unstable angina.

The second, probably less important, explanation for the differences between the various calcium antagonists in unstable angina is a pharmacokinetic effect. Absorption, volumes of distribution, and clearance of the diverse calcium channel blockers is variable when these agents are given orally or sublingually. Intravenous preparation may permit the more effective use of diltiazem in patients with unstable angina.

In conclusion, the present study with diltiazem is important in itself since it shows for the first time in a large randomized double blind study design a beneficial effect of a calcium antagonist in unstable angina without the prerequisite of beta-blockade. In a broader perspective, it teaches us again that final conclusions may only be based on prospectively tested hypotheses and not on emotional debates based on retrospective data arranged in an arbitrary way. Finally, in every discussion on calcium antagonists we should clearly define what kind of calcium antagonism is intended and even more importantly which type of patient is being treated.

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References