Are calcium antagonists safe?

THREE RECENT studies[1-3] have raised concerns about the safety of calcium antagonists (calcium-channel blockers). The ensuing media coverage, which was intense and not always accurate, frightened many patients, leading to frantic phone calls to their physicians. For this reason, the National Heart, Lung, and Blood Institute (NHLBI) convened an ad hoc panel to advise physicians about how these reports should influence the appropriate use of calcium antagonists. This editorial reviews the data from those studies, along with the NHLBI report, and provides some perspectives on the use of calcium antagonists.

THE STUDIES

Psaty study: increased MI risk in hypertensive patients

Psaty et al,[1] in an observational (case-control) study, assessed the risk of fatal and nonfatal myocardial infarction (MI) in patients with hypertension who took antihypertensive drugs of different classes. Two main comparisons were carried out: calcium antagonists vs diuretics in patients free of cardiovascular disease according to the medical record, and calcium antagonists vs beta-blockers in patients both with and without cardiovascular disease (but not a previous MI or heart failure).

The results showed a 60% higher risk of MI in patients receiving calcium antagonists compared either with diuretics or with beta-blockers. Further, the higher the calcium antagonist dose, the greater the relative risk of MI compared with each of the other drugs. (The difference was statistically different only with the highest doses of calcium antagonists compared with either diuretics or beta-blockers.) On the other hand, there was a progressive *decrease* in the risk of MI as the dose of beta-blockers increased. Consequently, the greatest contrast in the occurrence of MI was between high-dose calcium antagonists and high-dose beta-blockers.

Patients both with and without diagnosed cardiovascular disease had a higher risk with calcium antagonists than with beta-blockers. The MI risk was higher with all calcium antagonists studied—nifedipine (31% higher), diltiazem (63% higher), and verapamil (61% higher)—but the increased risk was statistically significant only for the latter two drugs. *All of the calcium antagonists in this study were in short-acting formulations.* The results with diltiazem and verapamil were at odds with those of randomized trials in post-MI populations, a group at high risk for recurrent MI, in which diltiazem and verapamil have had either no effect on events or have shown a favorable trend.[4-6] The different results could reflect the different populations, or failure to adjust fully for coronary risk factors. As in all observational studies, physicians originally prescribed particular drugs for each patient on the basis of relevant clinical factors, probably including risk factors for MI, the outcome addressed by the study. Then, after the fact, the investigators attempted to extract information on such confounding factors from the medical records and control for them in their analyses. However, there is always some question about how well investigators were able to control for confounding factors in retrospective studies.

Furberg study: increased mortality risk in CAD

Furberg et al[2] reviewed previous meta-analyses[4-6] to determine the effect of dosage of nifedipine on mortality rates in patients with symptomatic coronary artery disease, many with acute ischemic syndromes. Patients taking low doses of the short-acting formulation of nifedipine (30 to 60 mg/day) had a slightly higher death rate than did patients receiving placebo, but the difference was not statistically

significant. The risk ratio jumped to 2.83 (95% confidence interval 1.35–5.93) at a dosage of 80 mg/day, and to 2.20 (0.69–6.99) at more than 100 mg daily. Overall, the risk ratio was 1.16 (1.01–1.33) for patients taking any dosage of nifedipine.

Pahor study: increased mortality risk in elderly

Another observational study,[3] conducted by Pahor and colleagues at the National Institute of Aging, estimated the risk of mortality in elderly patients taking single drugs for hypertension and compared individual short-acting calcium antagonists with beta-blockers. The risk was significantly higher with nifedipine, increased but not significantly so with diltiazem, and not increased with verapamil. Here also, the investigators adjusted for other cardiovascular risk factors as much as possible.

POSSIBLE MECHANISMS OF ADVERSE EFFECTS

Calcium antagonists have a number of effects that could, in theory, increase the risk of adverse cardiovascular outcomes. The shorter-acting drugs can cause reflex sympathetic stimulation, leading to increased myocardial oxygen demand and potentiating arrhythmogenesis.[7] All calcium antagonists have negative inotropic effects.[8] Some calcium antagonists have antiplatelet actions, an effect generally viewed likely to reduce MI risk. However, this action, together with vasodilatation, could have led to the excess of hemorrhagic complications in a recent trial in cardiac surgery patients.[9] Finally, there is evidence that calcium antagonists dilate collateral vessels more than stenotic coronary arteries, leading to a "coronary steal syndrome," with redistribution of blood flow from stenotic to collateral vessels.[10]

RECOMMENDATIONS OF THE NHLBI AD HOC PANEL ON CALCIUM ANTAGONISTS

Millions of patients in the United States and other countries take calcium antagonists. These drugs effectively relieve certain cardiac disorders such as angina pectoris (especially variant angina) and some arrhythmias, and they are effective, well-tolerated agents for blood pressure reduction. Like most drugs, however, calcium antagonists have multiple effects. It is therefore important to establish whether their known benefits are accompanied by significant risks, and whether they reduce major morbidity and mortality. The following conclusions seem prudent and consistent with available information.

Although the two observational studies in hypertensive patients probably contained biases, the apparent concordance of findings from these studies and from randomized trials in patients with primary acute MI and unstable angina suggests that short-acting nifedipine should be used with great caution (if at all), especially at higher doses, in the treatment of hypertension, angina, and MI.

Whether this conclusion should be generalized to any other classes of calcium antagonists, to other short-acting dihydropyridines such as isradipine, or to longer-acting dosage forms of nifedipine or other dihydropyridines is unclear. Verapamil and diltiazem were associated with significantly increased MI risk in the case-control study by Psaty et al[1] in patients with hypertension, but not in other studies, including well-designed clinical trials in patients with MI, a group at high risk of recurrent MI.

Further large-scale randomized clinical trials (some of which are underway) in people with hypertension will be absolutely essential to the ultimate resolution of these extremely important issues of safety and efficacy. For example, in the ongoing Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[11] a risk as large as that seen with calcium antagonists in the study by Psaty et al[1] could, if present, be detected after only a few years of follow-up.

Other agents proven effective

Practitioners should remember that there are other drugs that do unequivocally increase survival and provide other benefits after MI and in hypertension. Certain beta-blockers reduce mortality and reinfarction in post-MI patients[12]; in contrast, controlled trials of adequate size have not revealed such a benefit for calcium antagonists, and there is no reason to use them in the post-infarction setting except to treat symptoms. Similarly, in hypertension, diuretics and beta-blockers have reduced major cardiovascular events and mortality in well-controlled trials, while other agents have not been adequately tested. For this reason, the fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommended diuretics and beta-blockers as preferred drugs for treating hypertension.[13]

Uncertainties about the choice of drugs for the treatment of hypertension should not detract from efforts to achieve optimal blood pressure control, because lowering blood pressure is clearly an effective strategy for preventing stroke, MI, and other cardiovascular sequelae of hypertension.

OTHER RECOMMENDATIONS

On the same day that the report of the NHLBI ad hoc panel was released, the American Heart Association issued a press release stating that patients who are concerned about possible adverse effects of calcium antagonists should not stop taking their medications but should consult their doctors.

The NHLBI ad hoc panel did not directly address the issue of using short-acting nifedipine in the management of Raynaud's phenomenon and hypertensive urgencies.

Most patients with Raynaud's phenomenon are young women with few if any risk factors for coronary disease; therefore, doses of short-acting nifedipine of 10 mg three times daily should not be hazardous when long-acting preparations are not effective. Higher doses should be used with caution, especially for patients who have hypertension or symptomatic coronary disease.

The indiscriminate use of 10-mg capsules of nifedipine, either orally or sublingually, to control severe hypertension, should be discouraged.[14,15]

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