EDITORIAL COMMENT

Anti-Ischemic Properties of Calcium-Channel Blockers
Lessons From Cardiac Surgery*

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Calcium-channel blocking agents (CCBs) (or calcium antagonists) were originally introduced to counteract myocardial ischemia and, in particular, angina pectoris. It was only later that their antihypertensive qualities came to be understood and commercially exploited. About 25 years ago, when the calcium-induced coronary spasm theory of unstable angina was dominant, short-acting CCBs were among the most widely used antianginal agents in the world. Gradually, arguments for evidence-based medicine were coming. In a decisive trial, the Holland Inter-university Nifedipine Trial (HINT) study in unstable angina (1), therapy by short-acting nifedipine led to an increased rate of recurrent myocardial infarction (MI), so the trial was stopped. However, in a tantalizing way, the beta-blocker arm of the study did not show a significant improvement, and it was only the combination of the two different classes of drugs that gave the desired decrease in repeat MI.

Thereafter, it was clearly unethical to use this subtype of CCBs, namely the short-acting dihydropyridines (DHPs), without concurrent beta-blockade for unstable angina. With the non-DHPs such as diltiazem and verapamil, which also slowed the heart rate, the situation was different in that a number of smaller trials showed benefit (2). Taking together the available studies, there were good arguments for two different types of antianginal mechanisms: beta-blockade, acting chiefly by the inhibitory effects on heart rate and cardiac contractility, with CCBs acting chiefly as coronary vasodilators and the non-DHPs having intermediate properties (3).

Major surgery is an inevitably stress-provoking procedure with increased adrenergic discharge, as shown by the beneficial effects of beta-blocker therapy covering noncardiac surgery (4). Many episodes of perioperative ischemia are silent and occur especially in the postoperative period, often with a tachycardia (5). Therefore, logically, the anti-ischemic agents of choice should be beta-blockers. Regarding the non-DHP calcium channel blockers, their use in the perioperative period is logical considering that they have heart rate reducing properties and, like beta-blockers, have negative inotropic and dromotropic effects. The DHPs, on the other hand, lack these properties, and in fact, some may increase the heart rate. Thus, it could be argued that DHPs should not give perioperative protection. However, they do have coronary vasodilatory properties with the potential for perioperative protection.

QUALITY OF THE PRESENT STUDY

Therefore, the studies by Wijeysundera et al. (6) in the issue of the Journal are of special interest. They searched the literature for randomized controlled trials (RCTs) relating to CCBs and their effects on complications of cardiac surgery such as death, MI, ischemia, and supraventricular tachycardias. Their literature search for data to include in this meta-analysis followed the Quality of Reporting of Meta-analyses (QUOROM) guidelines destined to improve the quality of reports of meta-analyses (7). Out of the potential 1,813 studies, they eventually selected 41 studies for their meta-analysis. Of these, 28 studies related to intraoperative complications or those occurring during the first postoperative day. Other studies were for longer periods. Approximately one-half were given DHP therapy, mostly intravenous nifedipine or nicardipine; the rest were given either diltiazem or verapamil.

The rigorous inclusion process relied on quality grading using the Jadad et al. (8) scoring system, which assesses the quality of RCTs chiefly on three prime qualities: 1) the adequacy of randomization; 2) the quality of the double-blinding; and 3) the exactness of follow-up, with particular reference to withdrawals and dropouts (Table 1). Thus, patients included in any given study but not completing the observation period or those who are not included in the analysis must be described. The number and reasons for withdrawal in each group must also be stated. To enter the present study required a minimum Jadad score of 1. The primary analyses were approached in a conventional way, with secondary analyses for each CCB class, with comparisons of CCBs versus nitroglycerine and for those who underwent CABG alone. Thereafter followed sensitivity analyses by successively withdrawing trials of the most favorable CCB treatment effects. Furthermore, the authors repeated the meta-analyses for different Jadad scores, and funnel tests were performed to counter any possible publication bias.

Using all these precautions, CCBs reduced MI with an odds ratio (OR) of 0.58 and confidence interval (CI) of 0.37 to 0.91. They reduced ischemia with an OR of 0.53 and CI of 0.39 to 0.72. Non-DHPs reduced supraventricular tachycardias with an OR of 0.60 and CI of 0.41 to 0.93.
Regarding the small numbers of deaths, there was no trend to increased mortality, but rather towards a decrease.

Where does this place us at a time when beta-blockers are generally thought to be the agents of choice to cover perioperative ischemia (4)? Before making such comparisons, we are entitled to ask how convincing this new evidence is.

THE STRENGTH OF A META-ANALYSIS

Even RCTs and meta-analyses are not free of defects and need careful design and critical appraisal. A meta-analysis is only as good as the studies that it analyzes, even when full precautions to obtain best results have been taken, as in the present study. Yet despite all the efforts of the authors, and including the QUOROM and Jadad criteria, the present study does fall short of the ideal (Table 1), chiefly because of the nature of the limited database. Of note, in none of the individual studies in the present meta-analysis were more than 221 subjects studied. Ideally, to achieve a satisfactory meta-analysis requires studies each with 1,000 patients or more (9). Most of the studies are much smaller, and in the present one, in total, there were only 480 patients with high Jadad scores (3 or more). Therefore, although a major contribution, this meta-analysis does not clearly and unequivocally show that CCBs confer benefits when given in association with cardiac surgery. The authors are quite correct in emphasizing that further prospective studies are needed to determine the true effects of CCBs on outcome measures, particularly including perioperative mortality. Postoperative atrial fibrillation should be a further specific outcome measure, especially bearing in mind the documented success of beta-blockers in preventing this complication (10).

Regarding items 4 and 5 of the ideal meta-analysis as shown in Table 1, two major publications have had statistical errors that, although not wrong regarding the direction of change, did mislead readers regarding the magnitude of the change (11,12). Both required corrections. I must confess to being author of one of the articles with errors (12), after having criticized another article for the exact same reason (11). Also, in any controversial area, such as safety or efficacy of the CCBs, personal bias may creep in, so that the technique of blinded assessment of data in various studies as recommended by Jadad et al. (8) and as used by the present authors seems ideal. However, the complete ideal would be to have the final statistics and data checked by an external blinded statistician.

CCBs AS ANTI-ANGINAL AGENTS

Although CCBs were originally introduced for angina, their use has suffered with the advance of beta-blockade. The present studies show clearly that they have anti-ischemic properties. When the American College of Cardiology/American Heart Association Committee drew up its recommendations on drug use for angina (13), in my opinion, it short-changed the CCBs and, in particular, virtually ignored amlodipine (14). Of the 74 trials in the Stanford meta-analysis (15) that the Committee cited and heavily relied on, hardly any related to amlodipine, arguably the most widely used of the CCBs. If CCBs are such effective anti-ischemic drugs as the present meta-analysis would suggest, then their role in stable-effort angina may need to be reconsidered (14). In general, the important study by

Table 1. Properties of an Ideal Meta-Analysis

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<th>Ideal Requirements</th>
<th>Present Study</th>
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<tr>
<td>1. Database</td>
<td>Based on an adequate number of randomized controlled trials, each having 1,000 or more subjects.</td>
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<tr>
<td>2. Overall quality of meta-analysis</td>
<td>QUOROM recommendations for trial flow and inclusion and exclusion of studies (7).</td>
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<tr>
<td>3. Specific requirements for included data</td>
<td>High Jadad score chiefly based on three requirements (8). First, the adequacy of randomization; second, high quality double-blinding; third, exact follow-up with particular reference to withdrawals and dropouts.</td>
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<tr>
<td>4. Conflicts of interest</td>
<td>The authors of meta-analyses should be nonbiased and have minimal or no conflicts of interest in controversial areas.</td>
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<tr>
<td>5. Check on statistics presented</td>
<td>Authors must take responsibility for statistical accuracy; ideally need independent blinded check. Readers take results on trust.</td>
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Rinaldi et al. (16) seems to have been overlooked. In that study, not only was the antianginal effect of the CCB amlopidine versus nitrate on the onset of effort angina evaluated and found equal, but particular attention was paid to the post-ischemic recovery after exercise cessation.Delayed recovery is an index of post-ischemic stunning with a temporary fall in cardiac output and transiently impaired exercise capacity. At 30 min after exercise, amlopidine attenuated stunning with increased shortening and ejection fraction and with more rapid isovolumic relaxation. The anginal attack is not over until the patient can again exercise normally. Yet postexercise recovery is very seldom an end point of anginal studies. Data with amlopidine suggest that enhanced postischemic recovery is a property of CCBs and an important although neglected aspect of antianginal therapy.

Of course, short-term benefit against angina does not equal long-term outcome benefit. The Stanford meta-analysis had to acknowledge that there were no good long-term data to distinguish between beta-blockers and calcium blockers (15). That meta-analysis, based on the small number of hard outcome events in stable angina, could not exclude a long-term benefit or harm of CCBs versus beta-blockers. Recently, the CCB lacidipine was compared with atenolol, the entry point being carotid disease (an index of generalized arterial disease) in the presence of hypertension (17). Again, outcome data, although limited, suggested equality between these two types of drugs with, in this case, possibly better outcome with the CCB.

GENERAL COMMENTS ON SAFETY AND EFFICACY OF CCBs

In general, CCBs have gone through different phases. First they were hailed as very effective antianginals and then as equally effective antihypertensives. However, the reflex tachycardia induced by short-acting nifedipine was ignored and is the probable explanation for the adverse effects found by Furberg et al. (11) when they studied the effects on mortality of short-acting nifedipine given in very high doses to patients largely with unstable coronary disease. Although his results were disputed by many, including myself and Messerli (18), and although there were indeed errors in the calculation, nonetheless Furberg et al. (11) correctly pointed out the need for large RCT studies with CCBs. Some of those studies have now come in: for example, the Intervention as a Goal in Hypertension Treatment (INSIGHT) study, comparing long-acting slow-release nifedipine versus a potassium-retaining diuretic in the management of hypertension (19). There were approximately equal primary outcome benefits, although the CCBs gave rise to less diabetes, gout, and cholesterol elevation, whereas the diuretic gave rise to less heart failure.

Regarding angina, the results of the ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine GITS) study are still to come (20). This study evaluates the effect of added long-acting nifedipine to pre-existing therapy in angina of effort. So far a large number of patients have been enrolled, more than 6,000, and the safety committee has allowed the study to proceed. Likewise in the giant study ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) (21), the CCB arm gave overall results similar to the diuretic. This study has given further insights into the efficacy and safety of the DHF CCBs, at least in high-risk hypertension. Yet the comparison between amlopidine and chlorthalidone in ALLHAT gave results similar to that between long-acting nifedipine and amiloride-thiazide in INSIGHT (19). In both studies more heart failure with the CCB was balanced by less new diabetes.

Thus, the present surgical study fits into a general pattern: CCBs have anti-ischemic properties for which they can safely be used, without there being sufficient long-term hard outcome data to be sure of effects on mortality. Such data are going to be hard to harvest. It is appropriate to recall that among three major meta-analyses of outcome when CCBs were used for hypertension, all agree that there were no differences in major cardiac events or total mortality when CCBs were compared with conventional therapy by diuretics and/or beta-blockers (12,22,23). Thus, jumping from the present surgical study to the wider implications, this meta-analysis provides further data favoring the view that CCBs are both effective and safe drugs when correctly used with due respect for their properties, indications, and limitations. The specific message of the present meta-analysis is quite clear: CCBs may be safer and have more benefit in cardiac surgery than often supposed.

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REFERENCES


