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EDITOR

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**CHANGES TO FORMULARY**

Additions

1. **Sertraline 25mg, 50mg, 100mg capsules (Zoloft<sup>®</sup>)**  
-selective serotonin reuptake inhibitor used as an anti-depressant  
-cost: \$ 0.8-2.0/day

it is unclear whether they are intended for activation or merely as suggestions awaiting acceptance by the consulting physician. Please note that suggestions or recommendations should be written only in the history section of the health record or on consult forms. The words "suggest" and "recommend" should be omitted from physicians' orders intended for immediate activation.

**UPDATED POLICY AND PROCEDURES**

1. **"Suggest" Orders**

Several physicians have been writing "suggest" or "recommend" orders directly on the physician's orders section of the patient's health record. These orders pose a dilemma as

## The Calcium Channel Blocker Controversy: Why All the Fuss?

### Introduction

Recently, there has been much debate on the safety of calcium channel blockers (CCBs) with a special emphasis on nifedipine (Adalat®). The controversy revolves mainly around the results of two case control studies<sup>1,2</sup> and a meta-analysis<sup>3</sup> supporting an increased risk of myocardial infarction and mortality in patients receiving CCBs for hypertension or coronary artery disease. There are differences amongst health practitioners in the interpretation of these studies and, as expected, there is confusion and anxiety in the general public due to media hype. In light of this controversy, the Health Protection Branch (HPB) recently mailed a "Dear Doctor" letter to all physicians addressing the safety and role of CCBs in the treatment of hypertension and coronary heart disease.<sup>4</sup> In their letter, the Ad Hoc Committee convened by HPB recommended that CCBs as a class not be used as first line agents in hypertension and chronic stable angina, and that "particular prudence is suggested with the short acting dihydropyridines, particularly short acting nifedipine, which should be used with great caution, if at all". The calcium channel blockers available in Canada for the treatment of cardiovascular diseases are summarized in Table 1.

Table 1. Calcium Blockers for Cardiovascular Diseases

Classification	Drug	Comments
Dihydropyridine	nifedipine* nicardipine amlodipine* felodipine	-potent peripheral vasodilating properties -reflex tachycardia (more frequent with short-acting preparations) -least negative inotropic effects
Benzothiazepine	diltiazem*	-increases AV node conduction time and refractory period -negative inotropic effects -peripheral vasodilator
Phenylalkylamine	verapamil*	-as diltiazem except has greater negative inotropic potential

\* Formulary at VHHSC

### Review of the studies

The first trial published that sparked a controversy was a retrospective population-based case-control study by Psaty et al.<sup>1</sup> The objective of this study was to assess the relationship between antihypertensive therapy and incidence of first myocardial infarction. The cases (n=623) were enrollees in a Group Health Cooperative (GHC) between the ages of 30-79 years who were receiving drug therapy for hypertension and sustained a first myocardial infarction (MI). Controls (n=2032) were a random sample of GHC enrollees frequency matched to the treatment cases according to sex, age and calendar year. These subjects received pharmacological treatment for hypertension but had not experienced an MI.

An initial analysis of the relationship between MI and antihypertensive drug therapy was restricted to 335 cases and 1395 controls who were free of cardiovascular disease. The adjusted risk ratios (95% confidence interval) were 1.0 for diuretics (reference antihypertensive), 1.58 (1.04-2.39) for CCBs alone and 1.70 (0.97-2.99) for CCBs in combination with diuretics. A dose-response analysis showed increasing risk of MI with increasing doses of CCBs reaching statistical significance at high doses. High doses of CCBs were defined as daily doses greater than 30mg of nifedipine, 180mg of diltiazem and 240mg of verapamil. The second analysis included 384 cases and 1108 controls who were taking either a CCB or a  $\beta$ -blocker and were stratified according to the presence or absence of clinical cardiovascular disease. The use of CCBs compared with  $\beta$ -blockers (reference) was associated with an adjusted risk ratio for MI of 1.57 (95% CI 1.21-2.04). This increased risk of MI in association with CCB use was present in both groups of patients with and without cardiovascular disease. A dose-response analysis revealed that while higher doses of  $\beta$ -blockers further reduced the risk of MI, higher doses of CCBs were associated with a greater MI risk.

In this study, only short-acting CCBs were used and it is not possible to single out an individual CCB in association with MI risk. As a class, the CCBs were associated with a 60%

(RR = 1.6) increase in risk of first MI in hypertensive patients compared to patients treated with diuretics. Of note, a comparison of baseline characteristics (cholesterol level, smoking status, presence of diabetes or angina) indicated that the cases were significantly sicker than the controls. Hence, it is possible that CCBs in high doses were simply a marker for sicker patients rather than a true risk factor for MI. Also, since antihypertensive therapy was selected by physicians and patients, this self-selection process may have introduced bias in the study results. At best, this case-control study raises a suspicion that short-acting CCBs, especially in high doses, may be associated with an increased risk of MI.

Pahor et al.<sup>2</sup> conducted a prospective cohort study of subjects (n=906) identified from three communities of the Established Populations for Epidemiologic Studies of the Elderly (EPESE)<sup>5</sup>. The objective of the study was to determine if there was a difference in risk of all cause mortality amongst older hypertensive patients treated with CCBs or angiotensin converting enzyme inhibitors (ACE-I) versus those receiving  $\beta$ -blockers. Patients receiving combinations of a  $\beta$ -blocker, CCB, or ACE-I were excluded due to the suspected high risk nature of these patients. The authors specified that the sustained release preparations of nifedipine were not used but did not provide information about the formulation of the other CCBs used in the study. After

adjusting for potential confounding factors (age, gender, comorbid conditions), the results demonstrated that treatment with short-acting nifedipine in elderly hypertensive patients was associated with a 70% (RR=1.7, 95% CI 1.1-2.7) increased risk of all-cause mortality compared with the use of  $\beta$ -blockers. There was no significant difference in mortality when subjects receiving diltiazem, verapamil or ACE-I were compared with those using  $\beta$ -blockers. Similar results were seen when the analysis was stratified according to presence of coronary heart disease at baseline. In a dose-response analysis, higher doses of nifedipine were associated with a significant increase in risk of death. While a similar association was not seen with verapamil, a nonsignificant trend to higher mortality rates was seen with higher doses of diltiazem. High doses were defined as daily doses greater than 160mg of verapamil, 90mg of diltiazem and 20mg of nifedipine.

Like any observational study, this one suffers the usual major weaknesses pertaining to the presence of selection and confounding biases. Of note, the risk ratio for nifedipine was derived from a much smaller sample size (n=74) compared with the  $\beta$ -blocker group (n=515) hampering reliable interpretation of the results.

Furberg et al. conducted a meta-analysis to assess the effect of the dose of nifedipine on the increased risk

of mortality seen in the trials in patients with coronary heart disease.<sup>3</sup> This analysis included 16 randomized secondary-prevention trials which had mortality data available; twelve trials randomized patients with MI, three trials included patients with unstable angina, and one trial included patients with stable angina. A total of 8350 patients were evaluated and daily doses of nifedipine ranged from 30-120mg. Nifedipine capsules (short-acting formulation) were used in 11 of the 16 trials while information on the formulation used in the remaining 5 trials was lacking. For all trials combined, nifedipine use was associated with a significant increase in the risk of mortality compared with placebo (RR 1.16; 95% CI 1.01-1.33). In a formal test of dose-response, the risk of mortality was strongly associated with the dose of nifedipine (p=0.01). The data suggested a sharp increase in mortality risk when nifedipine doses of 80mg or more were used in the trials.

There are several limitations to the interpretation of this meta-analysis study. It has been criticized for the authors' biased selection of data for analysis.<sup>6</sup> Other limitations relate to the inclusion of heterogeneous patient populations, lack of uniformity in concurrent medication usage, and inclusion of studies that started nifedipine treatment both early and late after the MI.<sup>7</sup> The latter has raised the question as to whether the increase in mortality demonstrated in the meta-

analysis might be related to the timing of nifedipine administration post-MI rather than the dose. Some clinicians may even argue that a 95% confidence interval of 1.01 to 1.33 for the combined risk ratio may not be clinically significant.

### **Summary and recommendations**

Interpretation of the above studies has ranged from identifying short-acting nifedipine as the principle culprit, to including other short-acting dihydropyridines and non-dihydropyridines (diltiazem and verapamil) as potential causes of an increase in the risk of MI and mortality in patients with hypertension or coronary heart disease. Some clinicians may even associate these adverse outcomes with long-acting formulations of nifedipine and the CCBs as a class.

It is important to realize that case-control and meta-analysis studies cannot establish a cause and effect relationship and are not a substitution for randomized and controlled clinical trials. They do raise suspicion and are definitely hypotheses generating. A number of inherent weakness, biases and confounding factors exist in the design of the above studies. Nevertheless, these studies represent the limited safety data that we currently have available for calcium channel blockers. Until definitive data becomes available, the following recommendations can be considered:

1. **Hypertension.** Diuretics or  $\beta$ -blockers are encouraged as first line agents as they have proven benefits in reducing morbidity and mortality in

hypertensive patients.<sup>8</sup> If these agents are contraindicated or not tolerated, then consider an ACE-I; many of these agents have proven benefits in patients with congestive heart failure and post-MI, conditions which are often present in hypertensive patients. Vasodilators, long-acting CCBs, or alpha-blockers may be considered as third line agents. Use of short-acting nifedipine as a temporary measure for blood pressure reduction in patients with hypertensive crises is probably safe.

2. **MI and unstable angina.** Short-acting nifedipine should be avoided in the early period post-MI and in patients with unstable angina. The safety of longer acting formulations of nifedipine and of the newer long-acting dihydropyridines is unknown; these preparations would be best avoided until data on their safety is available.

3. **Stable angina.** It is unclear whether CCBs have a negative impact when used to treat stable angina. Based on available data, it would seem prudent to avoid use of short-acting nifedipine especially at high doses (greater than 60mg per day). Nitrates and  $\beta$ -blockers can be recommended as first-line agents. CCBs, preferably diltiazem or verapamil, could be used if the first-line agents are ineffective, contraindicated or not tolerated. In patients with poor left ventricular function, amlodipine may be a safer alternative based on results of the PRAISE study demonstrating no harm when used in patients with congestive heart failure.<sup>9</sup>

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