How Do Calcium Channel Blockers Prevent Cardiovascular Events
Are They All Alike?

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Summary

The calcium channel blockers (calcium antagonists) have vasodilatory and cardiodepressant effects. These pharmacological properties explain, to a large extent, the antihypertensive, antianginal, and antiarrhythmic effects of these agents. Pharmacological differences between members of this class, e.g. differences in vascular selectivity, are well documented and can be exploited clinically.

The efficacy of calcium channel blockers in the prevention of cardiovascular events may depend on factors other than their vasodilatory and cardiodepressive effects. Much interest, for example, has been shown in their possible antiatherosclerotic effects. It is, however, at present not possible to ascertain how important these and other ancillary effects (such as plaque stabilisation) are for the putative cardioprotective effects of calcium channel blockers. There are, moreover, few in vitro or in vivo (animal or clinical) studies allowing valid comparison of the different calcium channel blockers with regard to these ancillary properties.

As a class, the calcium channel blockers (calcium antagonists) are a heterogeneous group of compounds with diverse pharmacological and physiological characteristics. Recent interest in this group of drugs has focused on their potential role in the prevention of cardiovascular events. In this respect, it is important to define what the mechanisms underlying their putative cardioprotective effects are likely to be, and whether any differences exist between the various calcium channel blockers. In particular, much emphasis has been placed on the differences between these drugs regarding sympathetic activation consequent to the peripheral vasodilatation. The time-course of this vasodilatation can, indeed, vary from agent to agent; sympathetic activation is, moreover, influenced by the drug’s cardioprotective effect. Other ancillary properties of interest include the influence of calcium channel blockers on endothelial function.
1. Limitations of the Data

In any discussion of the potential role of calcium channel blockers in the prevention of cardiovascular events, the following points need to be considered:

- Relevant studies have evaluated the effects of calcium channel blockers at different experimental levels: cellular pharmacology, molecular biology, \textit{in vitro} and \textit{in vivo} animal pharmacology, clinical pharmacology (e.g. angiographic data), and clinical efficacy studies. Although preclinical data or intermediary end-points are of interest and can provide an indication of the potential clinical usefulness of the drug or drug class being investigated, clinical efficacy data are ultimately needed. The recent controversy surrounding the use of calcium channel blockers in patients with coronary disease (discussed below) highlights the need for conclusive outcome data.

- Cardiovascular events (such as unstable angina and myocardial infarction, congestive heart failure, and sudden coronary death) targeted for prevention may be disparate. A property that is characteristic of calcium channel blockers or of a specific drug in this class could be advantageous in one condition, but may not be useful or may even be deleterious in another condition.\textsuperscript{11} Even for a given disease, e.g. unstable angina, the risk-benefit ratio of a given class or a given drug can differ greatly from one patient to another, depending on the haemodynamic situation of the individual.

- Although the clinical relevance of the pharmacological differences between compounds with regard to efficacy and tolerability are well documented for the vasodilatory and cardiodepressant properties of the calcium channel blockers, no comparative studies are available for these agents in the prevention of cardiovascular disorders.

2. Vasodilatation and Reflex Sympathetic Activation

There are important pharmacological differences between the calcium channel blockers, which have led to differences in the use of these agents in hypertension, angina and arrhythmias; these differences are also reflected in their adverse event profiles.\textsuperscript{11} The dihydropyridine calcium channel blockers, typified by nifedipine, have greater vascular selectivity than diltiazem or verapamil, i.e. for a given degree of vasodilatation, there is less cardiac depression.\textsuperscript{12,3}

A recent meta-analysis of secondary prevention trials of nifedipine suggests that short-acting nifedipine used in moderate to high doses may be associated with increased total mortality in patients with coronary disease.\textsuperscript{14} The authors postulate that intermittent reflex increases in sympathetic activity, occurring with short-acting formulations of nifedipine, are responsible for this increased mortality risk. If this is verified, long-acting dihydropyridines, such as amlodipine,\textsuperscript{15} and long-acting sustained release formulations of nifedipine, may be preferable in these patients. For agents such as verapamil and diltiazem, cardiac sympathetic activation is counteracted by the cardiodepressive effects of these drugs.\textsuperscript{12,3} Data from a population-based case-control study showed that the risk of first myocardial infarction was higher in hypertensive patients treated with calcium channel blockers than in patients treated with other antihypertensive drug classes; this effect was observed for nifedipine, diltiazem and verapamil.\textsuperscript{16} These studies\textsuperscript{4,6} have elicited much controversy.\textsuperscript{7,8} On the basis of available data definitive conclusions cannot, however, be made regarding the potential role of these various agents in the prevention of cardiovascular events. It appears, in the meantime, better to avoid agents and formulations which, through important fluctuations in blood pressure, lead to repeated sympathetic activation.