Calcium Channel Blockers
Potential Medical Benefits and Side Effects

Harriet P. Dustan

Calcium channel blockers are recently developed antihypertensive drugs. In terms of mechanisms of action, their specificity is not so well established as that of angiotensin converting enzyme inhibitors but is better understood than that for diuretics or adrenergic-inhibiting drugs. Calcium channel blockers were originally developed for treatment of angina but were found to lower arterial pressure as well. Three of them are now in wide use in the United States; their therapeutic spectrum in regard to type of hypertension is broad. Sublingual nifedipine has replaced intravenously administered vasodilators as immediate treatment of severe hypertension, and all three drugs, given orally, have been shown to be effective in mild, moderate, and severe hypertension. The three drugs available in this country are verapamil, diltiazem, and nifedipine. Pharmacological studies have shown that verapamil has the most negative chronotropic and inotropic effects of the three, with nifedipine producing the most vasodilation and having the potential for causing reflex tachycardia. Actually in practice, these various pharmacological differences have proved to have less significance than previously thought, and the drugs seem to have about equal antihypertensive effectiveness. Comparisons of calcium entry blockers with other drugs have shown them to be equally effective in whites as propranolol but more effective in blacks. Responsiveness appears to be related, as well, to pretreatment plasma renin activity and age. Thus, the antihypertensive effect is directly related to age and inversely related to plasma renin activity. The side effects mostly relate to vasodilation, reflex tachycardia, palpitations, headache, and edema; they are not frequent, and the drugs are well tolerated. (Hypertension 1989;13(suppl I):I-137-I-140)

As knowledge of biologic mechanisms has increased, calcium has come to be recognized as one of the most important ions in control of a large variety of functions. Relevant for hypertension are its roles in sympathetic neurotransmission, release of norepinephrine from nerve terminals, renal release of renin, aldosterone secretion, vascular smooth muscle tone, and responsiveness to adrenergic agonists. Thus, it is not surprising that drugs limiting the cellular influx of calcium have proved to be among the most interesting of antihypertensive agents—interesting because of the insight they seem certain to bring into mechanisms of vasoconstriction. This article reviews the usefulness of calcium channel blockers (CCBs) in the treatment of mild-to-moderate hypertension as well as their side effects.

In the United States, only three CCBs are available for general use: verapamil, diltiazem, and nifedipine. However, many other representatives of this class of drugs are under trial, and many will probably soon be approved for the treatment of hypertension.

These drugs represent a new approach to the treatment of hypertension, and the class has been variously named—calcium antagonists, CCBs, and calcium entry blockers. For this discussion, I have chosen the term CCB because it is the term most frequently used in this country.

Cardiovascular Pharmacology

Vasoconstriction, myocardial contractility, and cardiac automaticity depend on transmembrane calcium fluxes as well as release from and subsequent sequestration in intracellular storage sites. In regard to vascular smooth muscle (VSM), calcium enters cells by three mechanisms: a calcium leak down the considerable concentration gradient, through receptor-operated channels, and through channels activated by a change in membrane potential. Once inside the cell, calcium initiates VSM contraction by binding to calmodulin. This calcium—calmodulin complex activates myosin light chain kinase, which catalyzes the phosphorylation of the myosin light chain, thus initiating rapid shortening of contractile elements. Slower contraction and maintained tension are thought to result from catalysis by smooth muscle phosphatases. All these responses result from an increase in cytosolic calcium, which is dependent not
only on transport from extracellular fluid but also release from sarcoplasmic reticulum. In fact, van Breemen et al postulate that calcium entering VSM is taken up by the superficial sarcoplasmic reticulum and that release from this site is the major determinant of cytosolic calcium concentration. CCBs are thought to affect calcium influx through sarcolemmal channels, but van Zwieten et al have proposed that these drugs specifically interfere with calcium influx that is mediated by binding of the neurotransmitter, norepinephrine, to its receptor on VSM. In cardiac muscle, CCBs inhibit calcium transmembrane entry, thus modifying its contractile behavior; while in the specialized tissue of the sinoatrial and atrioventricular nodes, it reduces the slow inward current, thereby reducing automaticity.

Verapamil, diltiazem, and nifedipine are of markedly dissimilar structures, which probably is partly responsible for their different cardiovascular effects. Thus, verapamil has the greatest chronotropic and inotropic depressant actions while nifedipine has the least, with diltiazem's effect being intermediate (see McCall for review of CCB pharmacology). In contrast, nifedipine is the most potent vasodilator of the three, and the vasodilation is often accompanied by reflex tachycardia. The actions of these drugs, however, is dependent not only on their structure but also on interactions with other cardiovascular control mechanisms. Thus, whereas in isolated heart muscle, the relative negative inotropic potency—from the most potent to the least potent—is nifedipine, verapamil, and diltiazem, the clinical effects are different, with verapamil > diltiazem > nifedipine. Further, van Breemen et al have reviewed the evidence suggesting a heterogeneity of voltage-sensitive calcium channels in VSM. All these considerations give a glimpse of the complex direct and indirect actions of CCBs.

**Antihypertensive Effectiveness of Calcium Entry Blockers**

**Mild-to-Moderate Hypertension**

A large number of reports have described the antihypertensive efficacy of CCBs in mild-to-moderate hypertension, and to cite each one would entail a long bibliography. Therefore, reference will often be made to reviews in which the appropriate citations can be found.

Cubeddu has reviewed the effectiveness of verapamil. In comparison with the placebo, verapamil given to white patients produced significant reduction in arterial pressure although only 31% achieved diastolic pressures less than 90 mm Hg. In contrast, in three other non-placebo-controlled trials with the same dose (480 mg/day), the percent of responders ranged from 55% to 92%. Gould et al recorded intra-arterial pressure continuously over 24 hours in patients during placebo therapy and after verapamil treatment for 6 weeks. Mean daytime pressure was 158/79 mm Hg with verapamil versus 180/95 mm Hg with placebo, and the drug did not affect circadian changes in pressure.

Several studies have compared the antihypertensive effectiveness of verapamil and β-blockers. Cubeddu et al made this comparison in white and black patients with mild-to-moderate hypertension. Verapamil reduced pressure equally in the two groups, but propranolol was significantly less effective in blacks than in whites. Doyle compared pindolol with verapamil in a double-blind crossover trial in patients (presumably white) who continued to receive diuretic therapy although all other drugs had been discontinued for 4 weeks. Both drugs proved to be equally effective. Massie et al have recently reviewed seven reported comparisons of verapamil with β-blockers—propranolol, pindolol, and atenolol. With the exception of one study in which black patients participated, verapamil and β-blockers reduced arterial pressure equally.

Diltiazem's effectiveness has been compared with that of placebo, metoprolol, propranolol, and hydrochlorothiazide. The study of Pool et al showed it to reduce pressure significantly when compared with placebo. Cubeddu's review reports equal effectiveness for diltiazem and propranolol and for diltiazem and hydrochlorothiazide. Similarly, Massie et al found no difference in the antihypertensive effectiveness of diltiazem and propranolol.

Nifedipine's ability to reduce arterial pressure has been studied under a variety of circumstances. Eggertsen and Hansson found a significant effect of 12 weeks of treatment in comparison with placebo. Gould et al compared 24-hour intra-arterial ambulatory blood pressure measurements during placebo and after 6 weeks of nifedipine therapy. Arterial pressure was reduced from placebo values of 180/107 mm Hg to 146/88 mm Hg by drug treatment without modifying the circadian variations in pressure. Hallin et al randomized patients into two groups, one treated with nifedipine and the other with bendroflumethiazide, and found that 6 months of therapy resulted in equal reductions in arterial pressure. Massie et al have reviewed the trials comparing nifedipine with the β-blockers metoprolol and acebutolol and reported no differences between the CCB and the two β-blockers.

Unfortunately, there is very little information about the comparative effectiveness of CCBs. Clinical experience suggests little differences in antihypertensive actions, but to be certain, carefully controlled trials addressing comparative therapeutic value should be carried out. Another uncertainty is whether long-term blood pressure control with CCBs is as effective in preventing the complications of hypertension (strokes and heart failure) as the earlier drugs have been shown to be.

**Effects of Calcium Channel Blockers During Exercise**

All these three CCBs have been studied during dynamic exercise, and the data can be sum-
marized as follows: CCB therapy did not interfere with the exercise-induced rise in arterial pressure, but because the resting level was lowered by treatment, the maximal level achieved was less than that during the control period. When the effects of diltiazem and propranolol during dynamic exercise were compared, the pressure increases were similar, but the rise in heart rate was significantly less with propranolol than with diltiazem.8

Variables Affecting Arterial Pressure Responses

There is a growing body of evidence that certain demographic and biochemical characteristics of hypertensive patients affect responses to antihypertensive drugs.13 In regard to CCB therapy, these variables are age, race, and plasma renin activity. Bolli et al14 reported a positive correlation between age and the magnitude of arterial pressure reduction produced by nifedipine or nitrendipine. In contrast, the blood pressure-lowering effect of these drugs was inversely related to pretreatment plasma renin activity14 as Resnik15 had previously shown. The hypotensive effect of propranolol had the opposite correlations, being negatively associated with age and positively associated with pretreatment plasma renin activity. As noted above, verapamil had a greater antihypertensive effect in black patients than did propranolol probably because blacks tend to have lower plasma renin activity than whites.6

Side Effects

CCBs have a varying propensity for producing unwanted effects as detailed in the Physicians' Desk Reference for 1987. This source was chosen because those data represent the aggregate experience of the available CCBs. The most frequent reported was edema (2.4%), followed by headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), and asthenia (1.2%). Use of nifedipine, like verapamil, is associated with side effects more often than diltiazem. Those reported to occur in about 10% of patients are edema, dizziness, nausea, headache, flushing, and weakness. Transient hypotension has been reported as a side effect in about 5%, while symptoms occurring in 2% or less were palpitations, nasal congestion, constipation, diarrhea, shakiness, and dermatitis.

Clinical experience supports the reported incidence of adverse reactions in that constipation is frequent with verapamil, and edema, headache, and flushing with nifedipine, while diltiazem seems to be the best tolerated of the three drugs.

Calcium Channel Blockers as First-Line Therapy

The reports of the first three Joint National Committees on Detection, Evaluation, and Treatment of Hypertension established guidelines for therapy that have been widely used by American physicians for over 10 years. The first two reports recommended using a diuretic as the first-line drug in mild-to-moderate hypertension, and the third added a β-blocker to the first step as an alternative to a diuretic.

Since the 1984 report was issued, a change seems to have occurred in prescribing practices for first-line therapy. This has resulted for a variety of reasons: 1) the concerns over the potential for cardiovascular damage from the modest hypercholesterolemia and the hypokalemia that often accompany the use of diuretic drugs; 2) the lethargy and impotence that are frequent side effects of diuretics, centrally acting sympatholytics, and β-blockers; 3) the tolerability of the angiotensin converting enzyme inhibitors; and 4) the physician's wish to prescribe "modern" therapy as opposed to drugs that have been useful for many years but are now considered old hat. Thus, it is not uncommon for hypertension specialists to be referred patients in whom the newer drugs like the angiotensin converting inhibitors or CCBs have been ineffective although previous treatment with the "old-fashioned" drugs had maintained excellent blood pressure control for many years.

Table

Given these changes in prescribing practices, the natural question comes as to the role of CCBs as

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Cost per tablet (dollars)</th>
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<tr>
<td>Hydrochlorothiazide</td>
<td>0.01</td>
</tr>
<tr>
<td>Propranolol, long-acting</td>
<td>0.63</td>
</tr>
<tr>
<td>Verapamil SR</td>
<td>0.77</td>
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<tr>
<td>Nifedipine</td>
<td>0.35</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>0.44</td>
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Table 1. Pharmacists' Costs for Calcium Channel Blockers, Long-Acting Propranolol, and Hydrochlorothiazide
first-line therapy. Generally speaking, they are well tolerated, particularly diltiazem. They seem to be as effective as diuretic drugs in black and elderly patients; thus, for a large percentage of the hypertensive population, CCBs could be considered as ideal for first-line drugs. It is for the reasons of effectiveness and tolerability that the 1988 Joint National Committee report recommends CCBs as step-one therapy, along with diuretics, \( \beta \)-blockers, and angiotensin converting enzyme inhibitors. The main disadvantages of CCB therapy are the short durations of action of most of the available formulations and relatively high cost compared with the older drugs. The short half-lives, particularly that of nifedipine, require frequent dosing, which not only is inconvenient but also expensive. Part of this problem has been approached through development of sustained-release formulations that are now available for verapamil and soon to be released for nifedipine and diltiazem. CCBs are relatively expensive (Table I). Table I shows only the prices that the pharmacist must pay per tablet, so it does not reflect the patient’s cost, which could be substantially higher, and when several tablets per day are required, the monthly cost can be beyond the capability of many patients. Thus, as attractive as these drugs are as choices for a step-one drug in stepped-care guidelines, they are too expensive to recommend them for general use in the populations for which they could prove to be the most useful—the economically disadvantaged, black, and elderly patients.

References

**Key Words**
calcium channel blockers • hypertension treatment • antihypertensive agents
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