Clinical Pharmacology of Calcium Antagonists
Satellite Symposium on Calcium Antagonists

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SUMMARY A new class of agents has been made available for the treatment of hypertension. These calcium antagonists have rapid bioavailability and dramatic antihypertensive effects through reduction of total peripheral resistance and the vascular resistance of the major target organs of the body. These changes are usually associated with unchanged cardiac output, preserved organ blood flows, maintained organ function, and preserved reflex responses without fluid retention in long-term treatment. These drugs do not stimulate plasma renin activity and aldosterone levels. Thus they fulfill many of the major criteria for an ideal antihypertensive agent.

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KEY WORDS • calcium entry blockers • hemodynamics • pharmacokinetics •
nifedipine • diltiazem • verapamil • nitrendipine • antihypertensive drugs

HYPERTENSION in its various clinical forms and degrees of severity is manifested by an increased total peripheral resistance that is more or less uniformly distributed throughout the various vascular territories.1-2 In response to the increased ventricular afterload imposed on the heart, myocardial oxygen demand on the heart increases as the ventricle adapts by the process of concentric hypertrophy.3-4 The blood vessels also respond by a thickening of the media, thereby increasing the wall-to-lumen ratio of the arterioles.3-6 It follows that the ideal antihypertensive drug should control arterial pressure through a reduction in the total peripheral resistance and resistance to blood flow, at least in the circulation to the major organs that are the primary targets of hypertensive vascular disease.2-3 Furthermore, this reduction in pressure should be achieved without secondary retention of fluid that expands intravascular volume9-10 and without inordinate reflexive stimulation of the heart in response to the pressure reduction sensed by the arteriolar baroreceptors. In recent years we have come to look for a regression of cardiovascular structural changes, as long as this is not associated with an impairment of organ function.10-14

Basic Pharmacology

The calcium antagonists (also called slow-channel calcium blockers or calcium entry blockers) have been under active study for over 20 years.15 Four of the more commonly employed compounds worldwide are diltiazem, nifedipine, nitrendipine, and verapamil. These agents differ vastly in their clinical characteristics and their physiological effects.16-17 They inhibit the intracellular movement of calcium ions from extracellular sites through voltage-sensitive calcium channels. As a result, less calcium is available for interaction with the actin and myosin filaments that are responsible for smooth muscle contraction. It is important to remember that intracellular calcium migration is promoted by stimulation of α-adrenotropic receptors, and that β-receptor stimulation facilitates the outward movement of calcium from the cell. Calcium movement may also be dependent on sodium-calcium and potassium-calcium exchange channels. Moreover, although the greatest effect of the calcium antagonists is exerted by diminishing intracellular calcium influx through voltage-sensitive calcium channels, they also seem to block calcium influx stimulated by postjunctional α₂-adrenergic receptors. In contrast, stimulation of postjunctional α₁-adrenergic receptor–mediated calcium influx does not seem to be blocked completely by calcium antagonists.18-19

This overview is further complicated by the interference of some calcium antagonists with the intracellular action of calmodulin, the binding of calcium ions with cytoplasmic and sarcoplasmic calcium stores.
Pharmacokinetics

Of the four cited calcium antagonists, all are maximally absorbed through the gastrointestinal tract and have prompt onset of action—in less than 1 hour. Nifedipine seems to have the quickest onset of action (within 20 minutes), and verapamil and diltiazem within 30 minutes. In its present formulation, upwards of 70% of nifedipine becomes bioavailable, whereas less than 20% of the other three agents is available. The calcium antagonists demonstrate quite variably the so-called first-pass phenomenon after gastrointestinal absorption. Thus, verapamil is extensively lost on its first pass through the liver, whereas there seems to be relatively little first-pass disappearance of the dihydropyridine derivatives. Over 90% of the administered drug is bound to protein. Most of these agents have a 3- to 5-hour terminal plasma half-life; nifedipine has a longer half-life of 12 hours (Table 1).

Hemodynamics

All of the calcium antagonists reduce arterial pressure through a fall in total peripheral resistance. Initially, however, there may be a significant reflex increase in heart rate and cardiac output with nifedipine, that can be blocked by the β-blocking agent propranolol.

Verapamil, having a different cardiac action than the other calcium antagonists, slows cardiac conduction from the sinoatrial node with prolonged treatment. Nevertheless, after intravenous administration it also causes a significant increase in heart rate and cardiac output as arterial pressure and total peripheral resistance decrease. Diltiazem and nitrendipine also produce an initial increase in heart rate and cardiac output, and both of these responses to intravenous administration are associated with a significant increase in circulating catecholamine levels. With more prolonged therapy, some authors have demonstrated a persistent increase in circulating norepinephrine levels with nifedipine, but this has not been documented in all reports. The increase in catecholamine levels with diltiazem has been shown only after intravenous administration and not with prolonged therapy.

Renal hemodynamics in patients with hypertension have been studied primarily with verapamil, diltiazem, and nitrendipine. In these studies renal flow is increased with diltiazem but remains unchanged in association with unchanged cardiac output with nitrendipine and verapamil. The result is a fall in renal vascular resistance with all calcium channel blocking drugs studied, and this has been associated with an unchanged glomerular filtration rate. That renal blood flow increases with diltiazem unassociated with a changed glomerular filtration rate indicates a reduced filtration fraction that can only be explained by efferent as well as afferent glomerular arteriolar dilatation. Thus, calcium channel blocking drugs all have provided reduced renal vascular resistance without any decrease in glomerular filtration rate. In response to all calcium antagonists, plasma renin activity and circulating aldosterone levels remain unchanged and plasma volume fails to expand significantly.

Structural Changes

Although ventricular structure and function have not been shown to change significantly with nifedipine, left ventricular mass decreases significantly within 4 weeks with diltiazem and within 8 to 12 weeks with verapamil. No decrease in ventricular wall thicknesses has been associated with these changes, nor have there been changes in circumferential fiber shortening and ejection fraction.

Large Vessel Distensibility

A decrease in large artery compliance and an increase in vascular distensibility have been demonstrated in single-dose studies with diltiazem and nitrendipine. These changes were observed at a time when plasma norepinephrine levels were increased, suggesting a strong direct effect of these two calcium antagonists not only in dilating the arterioles and decreasing total peripheral resistance but also in reducing the compliance of the larger arteries.

References

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TABLE 1. Pharmacokinetics of Calcium Antagonists

<table>
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<th>Verapamil</th>
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<tr>
<td>Absorption (%)</td>
<td>&gt;90</td>
<td>&gt;90</td>
<td>&gt;90</td>
<td>&gt;80</td>
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<td>Onset of action (min)</td>
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<td>&lt;30</td>
<td>&lt;30</td>
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<td>&lt;20</td>
<td>16</td>
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<td>Metabolites</td>
<td>Inert free acid; lactone</td>
<td>First-pass extraction (&lt;70%)</td>
<td>Deacetylated</td>
<td>Dehydrogenation &amp; glucuronide conjugates in bile</td>
</tr>
<tr>
<td>Therapeutic plasma concentrations (pg/ml)</td>
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<td>30-120</td>
<td>5-140</td>
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<tr>
<td>Protein binding (%)</td>
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<td>90</td>
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<tr>
<td>Terminal (hr)</td>
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