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.5-6 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.7-8 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

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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. Nevertheless, after intravenous administration it also causes a significant increase in heart rate and cardiac output as arterial pressure and total peripheral resistance decrease.23,29 All of the calcium antagonists reduce arterial pressure through a fall in total peripheral resistance.23,29 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.24

Verapamil, having a different cardiac action than the other calcium antagonists, slows cardiac conduction from the sinoatrial node with prolonged treatment.28 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.28 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.23,24 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.

Renal hemodynamics in patients with hypertension have been studied primarily with verapamil, diltiazem, and nitrendipine. In these studies renal flow is increased with diltiazem25,26 but remains unchanged in association with unchanged cardiac output with nitrendipine29,31 and verapamil.24 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.29,32 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.29,33 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

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Pharmacokinetics

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