

Calcium channel blockers in the management of arterial hypertension

Theodore Thomas, MD
Donald G. Vidt, MD

The calcium channel blockers are a new class of vasodilators that are effective in treating arterial hypertension. They may be particularly effective in black hypertensives, in the elderly, and in patients with alpha-adrenergic-mediated vasoconstriction. Three agents, nifedipine, verapamil, and diltiazem, are currently available in the United States. Nifedipine, in particular, rapidly reduces blood pressure in severe hypertension or in hypertensive urgencies. These agents have cardioprotective effects, and do not affect lipid metabolism, the pulmonary system, nor the central nervous system. As additional calcium channel blockers are developed, and as more sustained release forms become available, the current disadvantages of short duration of action and high cost should be overcome, making these agents a logical alternative choice for both initial and additive therapy of arterial hypertension.

Index terms: Calcium channel blockers • Hypertension

Cleve Clin J Med 1987; 54:529-536

The calcium channel blockers are currently approved in the United States for treating angina pectoris and selected cardiac arrhythmias. The potent vasodilatory effects of calcium channel

blockers observed in hypertensive patients has focused attention on using this class of compounds to treat arterial hypertension. The major hemodynamic abnormality in most patients with essential hypertension is increased total peripheral vascular resistance, mediated, at least in part, by abnormal transmembrane fluxes of calcium, leading to increased intracellular concentrations of free calcium.¹ The ability of calcium channel blockers to impede the influx of calcium into cardiac and vascular smooth muscle cells is responsible for the demonstrated efficacy of this class of agents in the treatment of hypertension and angina pectoris.

Currently, three calcium channel blockers are available in the United States—nifedipine, verapamil, and diltiazem. At this time, only verapamil has been approved for treating hypertension; however, approval of nifedipine and diltiazem is expected shortly. These agents inhibit calcium influx across potential-dependent channels, blunt intracellular calcium release, and stimulate calcium efflux from cells.² Nifedipine appears to act at a receptor site specific to this agent, enabling it to block selected channels. Verapamil and diltiazem act at receptor sites close to, but distinct from, the nifedipine binding sites.³

Mechanism of action

Calcium ions play an important role in vascular smooth muscle contraction.^{4,5} Calcium serves as

Department of Hypertension and Nephrology, The Cleveland Clinic Foundation. Submitted Feb 1987; accepted May 1987.

0891-1150/87/06/0529/08/\$3.00/0

Copyright © 1987, The Cleveland Clinic Foundation

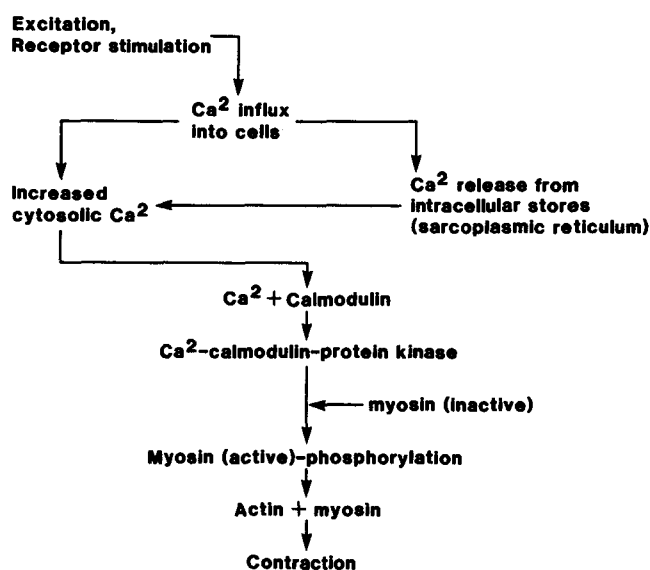


Fig. Excitation-contraction coupling in smooth muscle.

the key intracellular messenger in excitation-contraction coupling (Fig.). Calcium is noted within cell membranes, sarcoplasmic reticulum, mitochondria, and intracellular fluid. Calcium ions enter cells through receptor-operated (fast) or potential-dependent (slow) channels. Calcium channels may be opened by depolarization or receptor activation by selected chemical transmitters or hormones. Calcium entry into cells stimulates release of calcium from intracellular stores (sarcoplasmic reticulum); this release is not affected by calcium channel blockers. It is likely that other mechanisms can initiate the cellular entry of activator calcium. Current evidence suggests that calcium channel blockers specifically inhibit channel-mediated entry of calcium across cell membranes.⁶

Regardless of the process, increased cytosolic free calcium binds with high affinity to a protein, calmodulin. The calcium-calmodulin complex causes calcium-dependent protein kinases to catalyze the phosphorylation of the light chain protein, myosin. This phosphorylation initiates the interaction of smooth-muscle myosin with actin, leading to contraction.^{4,5} Although this regulation by calmodulin-induced phosphorylation is the most commonly accepted theory to explain excitation-contraction coupling in smooth muscle, it is but one of a number of possible explanations for smooth-muscle activation (Fig.).^{7,8}

The calcium channel blockers are an extremely complex group of agents. While these drugs do inhibit calcium entry into cells to modify excita-

tion-contraction coupling, the precise mechanism of calcium channel inhibition is unknown, and the question of intracellular effects remains unresolved.

Calcium channel blockers differ from arterial vasodilators (hydralazine, minoxidil, diazoxide) in their ability to counteract the hemodynamic effect of compensatory homeostatic mechanisms. In response to vasodilation induced by arterial vasodilators, reflex stimulation of the sympathetic nervous system and renin-angiotensin-aldosterone system occurs.⁹ Alpha-adrenergic-mediated vasoconstriction is induced, beta-adrenergic-mediated tachycardia and increased contractility occur, and sodium and fluid retention occur along with angiotensin-II-mediated vasoconstriction. These homeostatic mechanisms operate together to counteract the beneficial antihypertensive effect of arterial vasodilators. The calcium channel blockers possess negative inotropic activity (except nifedipine) and alpha-adrenergic-inhibitory action. Evidence has suggested that the nonselective alpha-2 receptor stimulation by endogenous catecholamines is mediated by an influx of extracellular calcium ions and can be inhibited by calcium channel blockers.¹⁰ The calcium channel blockers interfere with angiotensin-II-induced vasoconstriction and these agents also have demonstrated natriuretic activity.^{11,12} These pharmacologic properties enable the calcium channel blockers to counteract homeostatic mechanisms and contribute to their effective function as antihypertensive agents. While clinical experience with the calcium channel blockers in the United States is limited, extensive clinical trials in other countries suggest that these agents will be useful in the management of arterial hypertension. Several excellent reviews are available on the cellular actions and pharmacology of the calcium channel blockers.^{4-6,9} Table 1 lists the cardiovascular actions of the currently available calcium channel blockers. Table 2 summarizes the pharmacokinetic properties of these agents.

Nifedipine

Nifedipine is currently available in liquid-filled capsule form. It is well absorbed following sublingual or oral administration, is metabolized rapidly and completely, and is heavily bound to plasma proteins. The average plasma half-life of nifedipine ranges from two to five hours. Peak plasma concentrations of nifedipine are achieved within 30 to 60 minutes after oral administration

and 15 to 30 minutes following sublingual administration.⁶ Antianginal effects result from dilatation of the main coronary arteries and arterioles in both normal and ischemic myocardium, permitting increased oxygen delivery to the myocardium. Nifedipine reduces blood pressure and peripheral resistance, and reduces cardiac afterload and myocardial oxygen requirements. Nifedipine also exerts a vasodilatory effect on the pulmonary vasculature and capacitance vessels to reduce preload. While nifedipine does have modest negative inotropic effects, the combined preload and afterload reduction is associated with reflex activation of the sympathetic nervous system and a reflex increase in heart rate.

Clinical administration

Oral or sublingual nifedipine has been effective in treating severe arterial hypertension of varying etiology, including hypertension complicated by encephalopathy, left ventricular failure, and intracerebral or subarachnoid hemorrhage. The blood pressure reduction ranges from 20% to 36% and correlates with the pretreatment level of blood pressure.¹³ Since the drug increases reflex cardiac activity, it is not recommended as the sole agent for hypertension complicated by a dissecting aortic aneurysm. The hemodynamic responses to nifedipine include a significant reduction in peripheral vascular resistance, decreased pulmonary wedge and arterial pressures, and an increased cardiac index.¹⁴

Nifedipine should be used with extreme caution when severe hypertension is complicated by cerebrovascular insufficiency, since the precipitous, marked reduction in blood pressure may compromise cerebral blood flow. This may occur

Table 1. Cardiovascular effects of calcium channel blockers

Effect	Nifedipine	Diltiazem	Verapamil
Peripheral vasodilation	+++	++	++
Reflex sympathetic stimulation	++	0-+	0-+
Bradyarrhythmias			
SA node	0	++	+
AV node	0	+	++
Negative inotropic effect	0-+	+	++

Key: 0 = rare; + = uncommon; ++ = occasional; +++ = common (>20%).

despite the fact that studies have indicated increased cerebral blood flow with nifedipine.¹⁵ The risk of cerebral compromise may be enhanced by concomitant diuretic therapy and hypovolemia. Nifedipine may be effective when hypertension is complicated by left ventricular failure since the agent reduces left ventricular filling pressure, systemic vascular resistance, and afterload. Stroke volume is increased and left ventricular function may be improved.¹⁶ However, nifedipine should not be used as a sole agent to decrease afterload in patients with congestive heart failure.

In our experience, nifedipine has not been suitable for treatment as monotherapy in mild or moderate hypertension, due largely to its rapid absorption, significant dose-related responses in blood pressure, and its relatively short duration of action. For prolonged therapy in hypertension it has been most effective when used in combination with an oral diuretic and an adrenergic blocking agent. When used this way, it has been effective in adults with resistant hypertension¹⁷

Table 2. Pharmacokinetics of the calcium channel blockers*

	Diltiazem	Nifedipine	Verapamil
Drug absorption (PO)	90%	90%	90%
Bioavailability	40%	65-70%	10-20%
Protein binding	70-80%	90%	90%
Elimination:			
Metabolism	hepatic (50% first-pass metabolism)	hepatic	hepatic (85% first-pass metabolism)
Urinary excretion of unchanged drug	2-4%	trace	3-4%
Active metabolites†	yes	no	yes
Half life‡	3-5 hr	2-5 hr	3-7 hr

* Pharmacokinetic data utilize both demonstrated facts and inferred assumptions about drug absorption, metabolism, distribution, and elimination. Much information is from single-dose studies in normal volunteers.

† Clinical implications of active metabolites are not well understood.

‡ Half life may be increased in cirrhosis and multiple dosing, necessitating a decrease in dose.

and in hypertension associated with chronic renal insufficiency.¹⁸ While not approved for use in severe hypertension in children¹⁹ or in hypertension associated with pregnancy,²⁰ nifedipine has been used effectively in both conditions. In pregnancy-related hypertension, uterine activity has been seen to decrease with minimal maternal and no fetal adverse reactions.

To treat acute hypertension, one or two 10-mg capsules may be administered orally, or perforated and given sublingually, resulting in a prompt but relatively brief reduction in blood pressure. For prolonged treatment of hypertension, the usual dose is 10 to 30 mg in capsular form every six to eight hours. Again, in the chronic treatment of hypertension, we have found the agent most useful when combined with an oral diuretic and a beta-adrenergic blocking agent.

Adverse effects

The most common adverse effects are light-headedness, headache and flushing, ankle and occasional periorbital edema, and a burning sensation in the lower extremities. Short-term administration of nifedipine is associated with increased urine flow and sodium excretion despite no significant effects on either glomerular filtration rate or renal plasma flow. These changes are not sustained with long-term administration.¹¹

Hypokalemia has been reported with nifedipine administration without changes in potassium excretion. Vasodilatation may promote increased sympathetic nervous system activity and beta-2-mediated potassium influx into cells.¹⁷ Hypokalemia may be enhanced by the concurrent administration of kaluretic diuretics.

Edema and fluid retention occur without significant changes in body weight and are probably the result of increased capillary hydrostatic pressure and fluid transudation.²¹ Significant hypotension, cardiac failure, or ischemic myocardial changes are rarely seen in association with nifedipine therapy.

A recent report has suggested that nifedipine can cause acute, reversible deterioration in renal function in patients with existing renal insufficiency.²² Altered intrarenal effects of angiotensin II and epinephrine on regulation of renal blood flow and glomerular filtration rate or inhibition of compensatory synthesis of vasodilatory prostaglandin-E₂ may have accounted for the acute changes. Abrupt discontinuation of nifedipine

does not appear to cause rebound hypertension, but in patients with ischemic heart disease, signs and symptoms of myocardial ischemia may be precipitated. These adverse changes can be reversed by restarting nifedipine therapy.²³

Drug interactions

A synergistic antihypertensive effect may be observed by combining nifedipine with oral diuretics or adrenergic blocking agents. The combination of propranolol with nifedipine provides more effective blood pressure reduction than either drug alone and the beta blockade effectively eliminates the tachycardia associated with nifedipine administration.²⁴ Nifedipine combined with captopril has been effective in the therapy of hypertension,²⁵ whereas acute hypotension has been reported when nifedipine is given to patients concurrently treated with prazosin.²⁶ Cimetidine and ranitidine increase plasma concentrations of nifedipine and may enhance its hypotensive response. Changes in hepatic microsomal enzyme activity and hepatic blood flow may be responsible for the alteration in nifedipine pharmacokinetics.²⁷ Nifedipine, by improving hepatic blood flow, may decrease the serum concentration of a drug metabolized by the liver, such as quinidine.²⁸

Available preparations:

Adalat (Miles), capsules 10 mg
Procardia (Pfizer), capsules 10 mg

Verapamil

Verapamil is water soluble, well absorbed after oral administration, and is highly bound to plasma proteins. It demonstrates antianginal effects similar to those of nifedipine and is effective in patients with both stable and unstable angina. Verapamil slows atrioventricular conduction by prolonging the effective refractory period within the AV node, and may interfere with sinus node impulse generation, causing sinus arrest in patients with sick sinus syndrome. Verapamil undergoes extensive first-pass metabolism in the liver, resulting in limited bioavailability (approximately 10–20% of an administered dose). With initial administration, the duration of action of verapamil ranges from three to seven hours, but is prolonged with continued administration due to effective reduction in first-pass metabolism. The effective half-life is prolonged with administration of a recently approved sustained release (SR) preparation, mainly due to slower absorp-

tion following oral administration. Significant hepatic dysfunction decreases the clearance of verapamil and extends the duration of action to several times normal.⁶ Pharmacologic effects are seen within three to five minutes following intravenous administration, and a duration of action of two to five hours is observed. When given by intravenous injection, verapamil is best administered slowly over several minutes. The effective plasma concentration for prolonged control of blood pressure appears to be in the range of 100 to 300 ng/mL, a level achieved in most patients with a dosage of 360 to 400 mg per day.²⁹

Clinical administration

Verapamil effectively lowers peripheral vascular resistance and has been effective in the therapy of mild to moderate arterial hypertension. When used as monotherapy, verapamil appears to have antihypertensive effects comparable to beta-adrenergic blockers or diuretics, without many of the adverse effects noted with these latter agents.^{30,31} Verapamil lowers blood pressure in both the supine and the standing positions, does not usually cause orthostatic hypotension, and is effective in both white and black hypertensive patients. The usual effective dose of verapamil in mild to moderate hypertension ranges from 320 to 480 mg per day given in three divided doses. The recently introduced sustained-release forms are administered as 240-mg caplets, once or twice per day. Neither short-term nor long-term oral administration of verapamil has any significant effect on urine flow or sodium excretion in hypertensive patients, and long-term administration is not associated with significant changes in serum electrolytes, plasma volume, or body weight. Verapamil attenuates the intrarenal effects of angiotensin II and norepinephrine, and has no short-term or long-term effects on renal function.³²

Intravenous verapamil, although not approved for use in hypertension in the United States, has proved extremely effective by injection or continuous infusion for the control of severe hypertension or hypertensive emergencies. Blood pressure reduction following intravenous administration is similar in magnitude to that observed with sublingual or oral nifedipine administration.

Adverse effects

Verapamil is well tolerated, the most common side effect being constipation. Vasodilatory side

effects such as vertigo, flushing, headache, and orthostatic hypotension are less common than those noted with nifedipine. Prolongation of the PR interval, AV block, pedal edema, and congestive heart failure have occurred occasionally. Verapamil should be avoided in patients with sick sinus syndrome, second- or third-degree AV block, and congestive heart failure.

Drug interactions

Verapamil should be used with caution in combination with beta-adrenergic blocking agents because of significant negative inotropic and chronotropic effects of this combination.³³ These agents have been used in combination but should probably be avoided in patients with compromised left ventricular function or AV conduction disorders. Increased serum levels of digoxin, ranging from 35% to 70%, have been reported after patients already receiving digoxin received verapamil.³⁴ Elevated prazosin concentrations and an enhanced hypotensive response may occur during concurrent administration. The increased prazosin bioavailability results from its reduced first-pass hepatic metabolism.³⁵ Verapamil appears to reduce the clearance of quinidine and may produce clinically important increases in serum quinidine levels and hypotension.³⁶ Verapamil may cause an elevation in hepatic enzyme levels, although hepatocellular damage rarely occurs.³⁷ Rifampin, and probably other enzyme-inducing drugs, reduces the bioavailability of verapamil by increasing its metabolism. Cimetidine may reduce its clearance.³⁸

Available preparations:

Calan (Searle), tablets 80 and 120 mg
Calan SR (Searle), caplets 240 mg
Isoptin (Knoll), tablets 80 and 120 mg
Isoptin SR (Knoll), caplets 240 mg

Diltiazem

Diltiazem is effective therapy for angina and dilating epicardial and subendocardial coronary vessels, and increases exercise tolerance by decreasing myocardial oxygen demand. Diltiazem is water soluble, well absorbed from the gastrointestinal tract, and highly bound to plasma proteins. First-pass hepatic metabolism of approximately 40% occurs after oral dosing, however, saturation of metabolic pathways and an increased plasma half-life may occur with repeated higher doses.⁶ Only the oral form of diltiazem is available in the United States. Following oral

administration, peak plasma levels occur within two to three hours, with a duration of action of three to five hours. Its negative inotropic and vasodilatory effects appear to be intermediate compared with other calcium channel blockers. The negative inotropic effects of diltiazem can be observed in the treatment of hypertension, because peripheral vasodilatation and blood pressure reduction are not usually associated with reflex tachycardia.³⁹ The negative inotropic effects of diltiazem become more prominent in patients with compromised left ventricular function or in patients receiving other negative myocardial depressant drugs.

Clinical administration

Oral doses of 180 to 360 mg daily of diltiazem have been used in the therapy of mild to moderate hypertension, with observed reductions of 10% to 15% noted in diastolic blood pressures. Diltiazem has not been extensively studied in treating severe hypertension or hypertensive urgencies, but intravenous diltiazem has been effective in these situations without causing major adverse effects or significant alterations in cardiac function. Diltiazem as monotherapy has demonstrated effectiveness comparable to hydrochlorothiazide or propranolol in patients with mild to moderate arterial hypertension.^{40,41}

Adverse effects

The incidence of adverse effects with diltiazem appears to be low, although bradycardia, dizziness, weakness, flushing, and pedal edema have been occasionally observed. Symptomatic sinus bradycardia, hypotension, and congestive heart failure have been observed during combined treatment with a beta-adrenergic blocker. Asymptomatic elevations of hepatic enzymes have also been observed.

Drug interactions

Diltiazem's interactions are similar to those reported with verapamil, including significant reduction of the heart rate and force of contraction when diltiazem is used in combination with beta-adrenergic blockers. Digoxin plasma levels may increase significantly when diltiazem is added.⁴² Concurrent use of diazepam may reduce diltiazem plasma levels by 20% to 30% by decreasing the bioavailability of diltiazem. Diltiazem may increase carbamazepine levels⁴³ and may inhibit cyclosporine clearance, with observed increases in cyclosporine plasma concentrations.⁴⁴

Available preparations:

Cardizem (Marion), tablets 30 and 60 mg

Newer calcium channel blocking agents

A number of newer calcium channel blockers are currently undergoing clinical trials.^{45,46} Nifedipine, in doses of 20 to 40 mg daily, has significant antihypertensive action, although higher doses may induce tachycardia. Nicardipine, 20 mg three times daily, lowers blood pressure in patients with mild to moderate hypertension. Niludipine, 20 mg daily, as a single dose, has effectively lowered blood pressure by 10 to 15% in patients with chronic renal failure and maintained on dialysis. Cinnarizine and flunarizine have been demonstrated to induce vasodilatation without stimulating reflex cardiac activity. A dihydropyridine derivative, isradipine, is relatively free of negative inotropic activity and has the advantage of a prolonged duration of action.

Role of calcium channel blockers in hypertension

Calcium channel blockers are effective in hypertension of all degrees of severity, especially, perhaps, in patients with low-renin hypertension (blacks or the elderly), and in those patients with alpha-adrenergic-mediated vasoconstriction. Diuretics are the most commonly used antihypertensive agents in blacks and the elderly, and are also effective in patients with low-renin hypertension. Diuretics, however, have been implicated in hyperuricemia, hyperglycemia, hypokalemia, and increased triglycerides and low-density lipoproteins.⁴⁷ Calcium channel blockers have no effect on lipid metabolism, and, in addition, have antiarrhythmic, cardioprotective properties that may be preferred over diuretics in selected patients with cardiac disease. The calcium channel blockers may be combined with diuretics, and together give an additive effect on blood pressure reduction.

Beta-adrenergic-blocking agents are useful antihypertensives and also offer cardioprotection. Studies suggest that beta blockers may be more effective in younger hypertensives and those with high plasma renin activity.⁴⁸ Beta blockers prove difficult to use in patients with bronchospastic disease, congestive heart failure, or symptomatic peripheral vascular disease. Calcium channel blockers may be used safely in these subgroups, while possibly offering cardioprotection. Use of beta-blocking agents with nifedipine

has eliminated many of the latter drug's undesirable adverse effects, but beta blockers must be used cautiously in combination with verapamil or diltiazem, both of which have negative inotropic activity.

Calcium channel blockers may be administered safely to hypertensive patients with renal disease.⁴⁹ There appears to be an inverse correlation between the maximal effect of nifedipine on diastolic blood pressure and creatinine clearance. This fall in blood pressure was independent of pretreatment blood pressures. Although nifedipine kinetics differ in those with renal failure, this does not seem to explain the greater antihypertensive effect.⁵⁰ Patients with severe renal dysfunction exhibit a reduction in the apparent volume of distribution and a decrease in total body clearance of verapamil and its metabolites. A decrease in the doses of verapamil in those with renal failure has been proposed, but no set standard dosage regimen has been established.⁵¹ The manufacturer of the sustained-release verapamil recommends a 50% dosage reduction in those with renal disease and gradual increases until the desired effect is obtained. No dose adjustments of diltiazem in renal failure have been proposed.

Adverse effects common to the centrally acting antihypertensive agents, such as sexual dysfunction, fatigue, drowsiness, or dry mouth, are not generally observed with calcium channel blockers. They induce less fluid retention than do other vasodilators such as hydralazine or minoxidil, and they may be used selectively as monotherapy. Calcium channel blockers must be used cautiously with alpha blocking agents or central alpha agonists, because the combination may induce significant symptomatic orthostatic hypotension. The calcium channel blockers have been used effectively in hypertensive patients with ischemic heart disease, migraine headache, congestive heart failure (nifedipine), supraventricular tachycardia, and esophageal motility disorders. Their major current disadvantages are a relatively high cost and a short duration of action, which usually necessitates three or more doses daily. The recent introduction of a sustained-release preparation of verapamil offers effective once or twice daily administration.

Summary

The calcium channel blockers represent a new class of agents effective in the therapy of arterial hypertension. Three agents, nifedipine, verapa-

mil, and diltiazem, are currently available in the United States. While effective in the treatment of mild, moderate, or severe hypertension, these agents may be particularly efficacious in black hypertensives and in the elderly, and in those with alpha-adrenergic-mediated vasoconstriction. Nifedipine, in particular, induces rapid blood pressure reduction in patients with severe hypertension or hypertensive urgencies. Their cardioprotective effects and lack of effects on lipid metabolism suggest that they may be appropriate alternatives to other agents in selected patients. Absence of adverse effects on the pulmonary system and the central nervous system has also proved to be a potential advantage in selected patients. As additional calcium channel blockers are developed, and as more sustained-release forms become available, the current potential disadvantages of short duration of action and high cost should be overcome, making these agents a logical alternative choice for both initial and additive therapy in arterial hypertension.

Donald G. Vidt, MD

Chairman, Department of Hypertension and Nephrology
The Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, Ohio 44106

References

1. Bohr DF, Webb RC. Vascular smooth muscle function and its changes in hypertension. *Am J Med* 1984; **77**:3-16.
2. Van Breemen C, Lukeman S, Cauvin C. A theoretic consideration on the use of calcium antagonists in the treatment of hypertension. *Am J Med* 1984; **77**:26-30.
3. Schramm M, Thomas G, Towart R, Franckowiak G. Novel dihydropyridines with positive inotropic action through activation of calcium channels. *Nature* 1983; **303**:535-537.
4. Braunwald E. Mechanism of action of calcium-channel-blocking agents. *N Engl J Med* 1982; **307**:1618-1627.
5. Katz AM, Hager WD, Messineo FC, Pappano AJ. Cellular actions and pharmacology of the calcium channel blocking drugs. *Am J Med* 1984; **77**:2-10.
6. Kates RE. Calcium antagonists, pharmacokinetic properties. *Drugs* 1983; **25**:113-124.
7. Bolton TB. Mechanisms of action of transmitters and other substances on smooth muscle. *Physiol Rev* 1979; **59**:606-718.
8. Silver PJ, Stull JT. The role of calcium in the contraction of vascular smooth muscle. [In] Flaim SF, Zelis R, eds. *Calcium Blockers: Mechanisms of Action and Clinical Applications*. Baltimore, Urban and Schwarzenberg, 1982, pp 37-51.
9. Lam YW, Giard MJ, Warren JB. Calcium channel blockers and treatment of hypertension. *Drug Intell Clin Pharm* 1986; **20**:187-198.
10. van Zweiten PA, Timmermans PBMWM, Thoolen MJMC, Wilffert B, De Jonge A. Inhibitory effect of calcium antagonist drugs on vasoconstriction induced by vascular alpha-2-adrenoreceptor stimulation. *Am J Cardiol* 1986; **57**:11D-15D.
11. Bauer JH, Sunderrajan S, Reams G. Effects of calcium entry

- blockers on renin-angiotensin-aldosterone system, renal function and hemodynamics, salt and water excretion and body fluid composition. *Am J Cardiol* 1985; **56**:62H-67H.
12. de Leeuw PW, Birkenhager WH. Effects of verapamil in hypertensive patients. *Acta Med Scand* 1984; **681(suppl)**:125-128.
 13. Beer N, Gallegos I, Cohen A, Klein N, Sonnenblick E, Frishman W. Efficacy of sublingual nifedipine in the acute treatment of systemic hypertension. *Chest* 1981; **79**:571-574.
 14. Bartorelli C, Magrini F, Moruzzi P, et al. Haemodynamic effects of a calcium antagonistic agent (nifedipine) in hypertension: Therapeutic implications. *Clin Sci & Molecular Med* 1978; **55(suppl)**:291S-292S.
 15. Bertel O, Conen D, Radü EW, Müller J, Lang C, Dubach UC. Nifedipine in hypertensive emergencies. *Br Med J* 1983; **286**:19-21.
 16. Polese A, Fiorentini C, Olivari MT, Guazzi MD. Clinical use of a calcium antagonistic agent in acute pulmonary edema. *Am J Med* 1979; **66**:825-830.
 17. Murphy MB, Scriven AJI, Dollery CT. Efficacy of nifedipine as a step 3 antihypertensive drug. *Hypertension* 1983; **5(suppl 2)**:118-121.
 18. Kubo K, Shiraishi K, Muto H, Suzuki T, Sugino N. Treatment of hypertension in hemodialysis patients with nifedipine. *Hypertension* 1983; **5(suppl II)**:109-112.
 19. Dilmen U, Caglar MK, Senses DA, Kinik E. Nifedipine in hypertensive emergencies of children. *Am J Dis Child* 1983; **137**:1162-1165.
 20. Walters BNJ, Redman CWG. Treatment of severe pregnancy-associated hypertension with the calcium antagonist nifedipine. *Br J Obstet Gynaecol* 1984; **91**:330-336.
 21. Muesan G, Agabiti-Rosei E, Castellano M, et al. Antihypertensive and humoral effects of verapamil and nifedipine in essential hypertension. *J Cardiovasc Pharm* 1982; **4(suppl 3)**:S325-S329.
 22. Diamond JR, Cheung JY, Fang LST. Nifedipine-induced renal dysfunction. *Am J Med* 1984; **77**:905-909.
 23. Engelman RM, Hadji-Rousou I, Breyer RH, Whittredge P, Harbison W, Chircop RV. Rebound vasospasm after coronary revascularization in association with calcium antagonist withdrawal. *Ann Thorac Surg* 1984; **37**:469-472.
 24. Yagil Y, Kobrin I, Stessman J, Ghanem J, Leibel B, Benl-Ishay D. Effectiveness of combined nifedipine and propranolol treatment in hypertension. *Hypertension* 1983; **5(suppl II)**:113-117.
 25. Guazzi MD, De Cesare N, Galli C, et al. Calcium-channel blockade with nifedipine and angiotensin converting-enzyme inhibition with captopril in the therapy of patients with severe primary hypertension. *Circulation* 1984; **70**:279-284.
 26. Jee LD, Opie LH. Acute hypotensive response to nifedipine added to prazosin in treatment of hypertension. *Br Med J* 1983; **287**:1514.
 27. Kirch W, Janisch HD, Heidemann H, Ramsch K, Ohnhaus EE. Influence of cimetidine and ranitidine on the pharmacokinetics and antihypertensive effect of nifedipine. *Dtsch Med Wochenschr* 1983; **108**:1757-1761.
 28. Farringer JA, Green JA, O'Rourke RA, Linn WA, Clementi WA. Nifedipine-induced alterations in serum quinidine concentrations. *Am Heart J* 1984; **108**:1570-1572.
 29. Frishman WH, Klein NA, Klein P, et al. Comparison of oral propranolol and verapamil for combined systemic hypertension and angina pectoris. *Am J Cardiol* 1982; **50**:1164-1172.
 30. Halperin AK, Gross KM, Rogers JF, Cubeddu LX. Verapamil and propranolol in essential hypertension. *Clin Pharmacol Ther* 1984; **36**:750-758.
 31. Bühler FR, Hulthén UL, Kiowski W, Müller FB, Bolli P. The place of the calcium antagonist verapamil in hypertensive therapy. *J Cardiovasc Pharmacol* 1982; **4(suppl 3)**:350-357.
 32. Kubo SH, Cody RJ, Covit AB, Feldschuh J, Laragh JH. The effects of verapamil on renal blood flow, renal function and neurohormonal profiles in patients with moderate to severe hypertension. *J Clin Hypertens* 1986; **3**:38S-46S.
 33. Packer M, Meller J, Medina N, Yushak M, Smith H, Holt J. Hemodynamic consequences of combined beta-adrenergic and slow calcium channel blockade in man. *Circulation* 1982; **65**:660-668.
 34. Klein HO, Lang R, DiSegni E, Kaplinsky E. Verapamil-digoxin interactions. *N Engl J Med* 1980; **303**:160.
 35. Pasanisi F, Elliott HL, Meredith PA, McSharry DR, Reid JL. Combined alpha adrenoceptor antagonism and calcium channel blockade in normal subjects. *Clin Pharmacol Ther* 1984; **36**:716-723.
 36. Maisel AS, Motulsky HJ, Insel PA. Hypertension after quinidine plus verapamil: Possible additive competition at alpha-adrenergic receptors. *N Engl J Med* 1985; **312**:167-170.
 37. Stern EH, Pitchon R, King BD, Wiener I. Possible hepatitis from verapamil. *N Engl J Med* 1982; **306**:612-613.
 38. Smith MS, Benyunes MC, Björnsson TD, Shand DG, Pritchett ELC. Influence of cimetidine on verapamil kinetics and dynamics. *Clin Pharmacol Ther* 1984; **36**:551-554.
 39. Klein W, Brandt D, Vrecko K, Härringer M. Role of calcium antagonists in the treatment of essential hypertension. *Circ Res* 1983; **52(suppl 1)**:1174-1181.
 40. Yamakado T, Oonishi N, Kondo S, Noziri A, Nakano T, Takezawa H. Effects of diltiazem on cardiovascular responses during exercise in systemic hypertension and comparison with propranolol. *Am J Cardiol* 1983; **52**:1023-1027.
 41. Inouye IK, Massie BM, Benowitz N, Simpson P, Loge D. Antihypertensive therapy with diltiazem and comparison with hydrochlorothiazide. *Am J Cardiol* 1984; **53**:1588-1592.
 42. Kuhlmann J. Effects of nifedipine and diltiazem on plasma levels and renal excretion of beta-acetyldigoxin. *Clin Pharmacol Ther* 1985; **37**:150-156.
 43. Brodie MJ, MacPhee GJA. Carbamazepine neurotoxicity precipitated by diltiazem. *Br Med J* 1986; **292**:1170-1171.
 44. Pochet JM, Pirson Y. Cyclosporin-diltiazem interaction. *Lancet* 1986; **1**:979.
 45. Ram CVS. Calcium antagonists in the treatment of hypertension. *Am J Med Sci* 1985; **290**:118-133.
 46. Lewis JG. Adverse reactions to calcium antagonists. *Drugs* 1983; **25**:196-222.
 47. Flamenbaum W. Metabolic consequences of antihypertensive therapy. *Ann Intern Med* 1983; **98(part 2)**:875-880.
 48. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Comparison of propranolol and hydrochlorothiazide for the initial treatment of hypertension: 1. Results of short-term titration with emphasis on racial differences in response. *JAMA* 1982; **248**:1996-2003.
 49. Bennett WM. Update on drugs in renal failure. *Adv Neph* 1986; **15**:379-394.
 50. Kleinbloesem CH, van Brummelen P, van Harten J, Danhof M, Breimer DD. Nifedipine: Influence of renal function on pharmacokinetic/hemodynamic relationship. *Clin Pharmacol Ther* 1985; **37**:563-574.
 51. Storstein L, Larsen A, Midtbo K, Saevareid L. Pharmacokinetics of calcium blockers in patients with renal insufficiency and in geriatric patients. *Acta Med Scand* 1984; **681(suppl)**:25-30.