

Side Effects of Calcium Channel Blockers

R. PATTERSON RUSSELL

SUMMARY Calcium channel blocking drugs are a chemically heterogenous group, so it might be expected that their effects on vascular smooth muscle, cardiac contractility, and conduction tissue may differ. However, the majority of adverse reactions are predictable from their pharmacological actions and may be conveniently grouped in the following categories: 1) vasodilatation, 2) negative inotropic effects, 3) conduction disturbances, 4) gastrointestinal effects, 5) metabolic effects, and 6) drug interactions. Vasodilatory symptoms, namely, dizziness, headaches, flushing sensation, and palpitation, are more likely with nifedipine. Peripheral edema is also common with nifedipine, but the mechanism is uncertain. For a given degree of vasodilatation, the greatest negative inotropic effect is seen with verapamil first, diltiazem second, and nifedipine last. Calcium channel blocking drugs are contraindicated in hypertensive patients with second and third degree heart block, sick sinus syndrome, and severe heart failure. Verapamil and diltiazem have a significant effect on cardiac conduction, whereas nifedipine, in therapeutic doses, does not. Local gastrointestinal symptoms, such as nausea and constipation, are common with verapamil. None of the calcium channel blocking drugs have been reported to adversely affect lipid or protein metabolism. However, nifedipine, verapamil, and diltiazem in high doses may inhibit liberation of insulin. The significance of this finding needs to be explored further in hypertensive diabetics. Serum digoxin levels have been shown to increase after administration of verapamil and nifedipine, but there is no evidence that this change has any clinical relevance. The combination of calcium channel blocking drugs and β -blockers may be beneficial in hypertensive patients with normal heart function but should be avoided in the presence of cardiac function impairments. (*Hypertension* 11 [Suppl II]: II-42-II-44, 1988)

KEY WORDS • nifedipine • nitrendipine • verapamil • diltiazem • side effects

SINCE the hemodynamic hallmark of essential hypertension is an increased total peripheral resistance, the logical treatment choice is a drug that promotes arteriolar vasodilatation. Calcium entry blockers all reduce the entrance of calcium ions into vascular smooth muscle cells, and their antihypertensive effect has been documented since 1968.¹ However, these agents are heterogenous, differing in chemical structure and intracellular actions as well as in physiological effects. Over three dozen of these compounds are either being prescribed for patients worldwide or are under active clinical investigation; though at present, verapamil is the only calcium channel blocking drug that has received FDA approval for the treatment of hypertension in the United States.

Despite the long-standing use of these agents, it is difficult to compare quantitatively the adverse reactions experienced individually because the recording of side effects has not been standardized and because there have been few direct comparisons between the

agents.² One additional problem that confounds this reviewer's task is that the cumulative frequency of adverse effects of calcium channel blocking drugs more often than not is derived from studies in patients with coronary artery disease, and it may not be justifiable to compare side effects of different drugs in different diseases. Recognizing these limitations and the fact that essential hypertension is often an asymptomatic disease, the frequency of adverse effects may actually be greater in hypertensive patients as compared with the reported frequency in patients with coronary insufficiency.

Calcium channel blocking drugs may be divided into two pharmacological classes: 1) those that possess both vasodilating and cardiodepressing actions, such as verapamil, diltiazem, bepridil, gallopamil, perhexiline, and tiampamil; and 2) those that possess vasodilating but not cardiodepressing actions, such as dihydropyridines, including nifedipine, nitrendipine, nisoldipine, nicardipine, and felodipine, and cinnarizine, flunarizine, and lidoflazine.

The structures of three of the most commonly used calcium channel blockers are shown in Figure 1.

The majority of adverse reactions to calcium channel blockers are predictable from their pharmacological actions. Moreover, because of the heterogenicity of

From the Renal Division, Good Samaritan Hospital, Baltimore, Maryland.

Address for reprints: R. Patterson Russell, M.D., Renal Division, Good Samaritan Hospital, 5601 Loch Raven Boulevard, Baltimore, MD 21239.

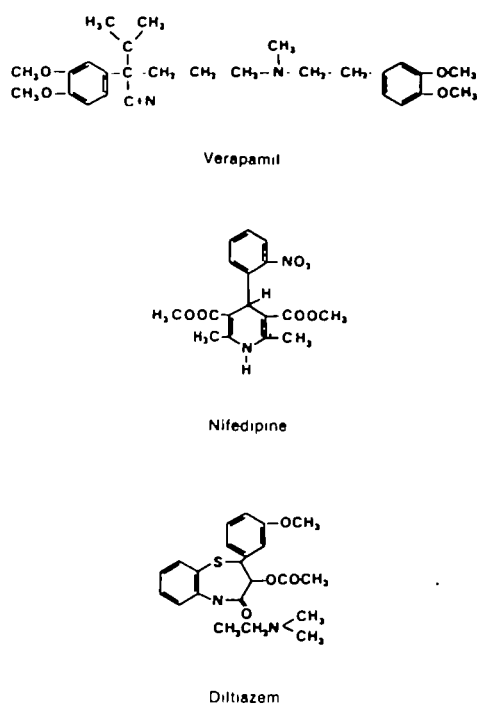


FIGURE 1. Structures of calcium channel blockers.

these compounds, they differ in their effects on vascular smooth muscle, cardiac contractility, and conduction tissue.

Major adverse reactions associated with calcium channel blocking drugs may be conveniently grouped in the following categories: 1) vasodilation that is characterized by headaches, flushing, palpitations, peripheral edema, and hypotension; 2) negative inotropic effects that contraindicate the use of some calcium channel blockers in the presence of severe left ventricular dysfunction or sick sinus syndrome and second or third degree atrioventricular block; 3) conduction disturbances, specifically supraventricular tachyarrhythmia; 4) gastrointestinal effects, such as constipation, diarrhea, and nausea; and 5) metabolic effects; and drug interactions associated with 6) cardiac glycosides and 7) β -blockers. Table 1 ranks the three most commonly used calcium channel blockers used in the United States, nifedipine, verapamil, and diltiazem, with regard to each of the above mentioned categories of adverse reactions.

Nifedipine has the strongest vasodilatory effect for

TABLE 1. Ranking of Adverse Effects of Calcium Antagonists*

Adverse effect	Ranking
Vasodilatation	N>D>V
Negative inotropic effects	V>D>N
Conduction disturbances	V>D>N
Gastrointestinal effects	V>D>N
Impaired glucose tolerance	N>V>D
Interaction with cardiac glycosides	V>N>D
Interaction with β -blockers	V>N>D

*N = nifedipine; D = diltiazem; V = verapamil.

coronary artery disease and seems to be dependent on the dose and rate of absorption. Whether this is also true for hypertension has not been established. Verapamil, for a given degree of vasodilation, has the greatest negative inotropic effect and effect on cardiac conduction. A high frequency of constipation has been attributed to verapamil, ranging from 12 to 42%, though a few patients have discontinued the drug for this reason. Edema is a common side effect of the calcium antagonists, particularly with nifedipine. While the mechanism has not been defined precisely, it is believed that this is on the basis of precapillary dilatation and postcapillary reflexive constriction. None of the calcium channel blocking drugs have been reported to adversely affect lipid or potassium metabolism. All three agents in high dose may inhibit liberation of insulin, though basal insulin secretion in healthy volunteers is not significantly influenced by diltiazem, nifedipine, or verapamil. A reversible hyperglycemia has been reported in patients with maturity onset diabetes mellitus treated with nifedipine, and short-term administration of nifedipine to subjects with a normal glucose tolerance resulted in significant glucose intolerance.³ However, Schulte and associates⁴ were unable to find any significant changes in serum glucose or insulin in nondiabetic hypertensive subjects treated for 8 weeks with nifedipine and diltiazem.

There are two areas of interest with regard to potential drug interactions. In patients treated with digoxin, the serum digoxin level is raised after administration of verapamil or nifedipine. While the effect of verapamil is dose dependent and greater than nifedipine, there is no evidence that the increase in digoxin level by verapamil or nifedipine has any clinical relevance. Second, in patients whose disease is not adequately controlled by β -blockers alone, the addition of a calcium channel blocker may be beneficial. This is particularly true for nifedipine but may be contraindicated for verapamil. Even though beneficial effects of the latter combination have been reported, administration of verapamil to patients treated with β -blocking drugs has the potential for causing severe conduction disturbances as well as negative inotropic effects. Additional long-term studies are needed to resolve this drug interaction issue.

Table 2 is adapted from McMahon⁵ and depicts the overall incidence of adverse reactions for nifedipine, verapamil, and diltiazem and lists the leading reactions associated with each drug(s). The data in this table are based upon experience with 2100 patients studied for coronary insufficiency. The same patient may be counted under one or more reactions, and it should be emphasized that these were patients with coronary insufficiency. There is currently very little data that permit one to compare directly the effects of these three calcium channel blockers in treatment of patients with essential hypertension.

Data concerning adverse reactions occurring in hypertensive patients treated with another calcium channel blocking drug, nitrendipine, a dihydropyridine derivative similar in action to nifedipine, were presented

TABLE 2. Percentage of Adverse Reactions to Calcium Channel Blockers*

Adverse effect	Nifedipine	Verapamil	Diltiazem
Overall incidence	17.0	8.0	4.0
Dizziness or light-headedness	10	3.6	—
Peripheral edema	10	1.7	2.4
Headache	10	1.8	2.0
Flushing or heat sensation	10	—	—
Transient hypotension	5	2.9	—
Nausea	10	1.6	2.7
Constipation	—	6.3	—
Bradycardia	—	1.1	2.0
Rash	—	—	1.8

*Based upon 2100 patients studied for angina. Adapted from McMahon⁵ with permission.

recently at the Second International Nitrendipine Symposium held in Lisbon, Portugal, on April 17–19, 1986. Weber⁶ reported on 1 year's experience with a multicenter study with nitrendipine in 329 patients with essential hypertension. Diastolic blood pressure was recorded as less than 105 mm Hg in 256, between 105 and 114 mm Hg in 77, and greater than 115 mm Hg in 2 patients. Forty-five patients, or 14%, did not complete the study, but only one third or 4.7% were discontinued because of adverse reactions. Corsing et al.⁷ reported a total of 105 side effects in 61 of 211 hypertensive patients treated with nitrendipine for 300 or more days. Headache was seen most frequently in 14.5% followed by symptoms related to vasodilation in 6.1% and palpitations in 4.7%. Table 3 presents the four most common, adverse reactions with nitrendipine in the treatment of essential hypertension from five separate studies totaling 344 patients.^{7–11} The similarity to the side effects profile with nifedipine in coronary insufficiency is apparent.

Unlike nifedipine and nitrendipine, the major side effect with verapamil is constipation. This is not considered to be a common cause for withdrawal of treatment, but the incidence is generally reported in excess of 30%.¹² According to Subramanian and Raftery,¹³ the most common major side effects seen in 250 patients on long-term therapy with verapamil at 360 mg daily being treated for chronic stable angina and hypertension are a prolongation of the PR interval greater than 0.24 seconds (3.2%), junctional escape rhythm (1.6%), and intraventricular conduction defect (1.2%). However, only five patients had to be withdrawn from treatment because of these side effects.

Of the three calcium channel blocking drugs available in the United States, diltiazem appears to have the fewest reported adverse effects. However, an idiosyn-

TABLE 3. Adverse Effects in 344 Hypertensive Patients Treated with Nitrendipine

Adverse effect	n	%
Headaches	48	13.9
Flushing	25	7.3
Palpitation	18	5.2
Ankle swelling	8	2.3

Data taken collectively from References 7–11.

cratic rash has been reported to occur in approximately 2% of patients treated with diltiazem. Other problems have usually been restricted to patients with bradycardia, first degree heart block, or sick ventricles.

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Hypertension. 1988;11:II42

doi: 10.1161/01.HYP.11.3_Pt_2.II42

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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