Side Effects of Calcium Channel Blockers

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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 vasodilation, 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]: H-42-11^4, 1988)

KEY WORDS • nifedipine • nitrendipine • verapamil • diltiazam • 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. 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. 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 heterogeneity of

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interaction with cardiac glycosides

| 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.
recently at the Second International Nitrendipine Symposium held in Lisbon, Portugal, on April 17-19, 1986. Weber 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. 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. 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%. According to Subramanian and Raftery, 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-
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Hypertension. 1988;11:II42
doi: 10.1161/01.HYP.11.3_Pt_2.II42

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