Pharmacology notes

Calcium channel blocker review

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The calcium channel blocker (CCB) class comprises 4 categories of compounds: phenylalkylamines, benzothiazepines, tertralols, and dihydropyridines. Phenylalkylamine, verapamil, and the benzothiazepine diltiazem are the only agents in this class that have a Food and Drug Administration (FDA) indication for the treatment of supraventricular arrhythmias. Formulary considerations for these agents deal with dosage formulations for the various brands available. Nimodipine, a dihydropyridine, is the only CCB that is indicated for the treatment of subarachnoid hemorrhage. A tertralol, mibefradil, has been withdrawn from the US market. Six dihydropyridines (amlodipine, felodipine, isradipine, nicardipine, nifedipine, and nisoldipine) were considered for formulary inclusion and will be discussed in this review. Bepridil will not be discussed in this review because of the incidence of arrhythmias associated with the use of this drug. The Table summarizes the approved indications for each agent (1, 2).

<table>
<thead>
<tr>
<th>Agent (brand; generic availability)</th>
<th>Hypertension</th>
<th>Subarachnoid hemorrhage</th>
<th>Supraventricular tachycardia</th>
<th>Arrhythmia</th>
<th>Unstable angina</th>
<th>Vasospastic angina</th>
<th>Chronic stable angina</th>
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<tbody>
<tr>
<td>Norvasc: amlodipine</td>
<td>X</td>
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<td>Vascor: bepridil</td>
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<td>Cardizem: diltiazem</td>
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<td>Cardizem SR, Cardizem CD, Dilacor XR: diltiazem SR</td>
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<td>Cardizem: diltiazem (injection)</td>
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<td>Plendil: felodipine</td>
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<td>DynaCirc: isradipine</td>
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<td>Posicor: mibefradil</td>
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<td>Cardene: nicardipine</td>
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<td>Cardene SR: nicardipine SR</td>
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<td>Cardene: nicardipine injection</td>
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<td>Adalat, Procardia: nifedipine</td>
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<td>Adalat CC, Procardia XL: nifedipine SR</td>
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<td>Nimodipine</td>
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<td>Sular: nisoldipine</td>
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<td>Calan, Isoptin: verapamil</td>
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<td>Calan SR, Covera-HS, Isoptin SR, Venelan, verapamil SR</td>
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<td>Isoptin: verapamil injection</td>
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Dihydropyridine CCBs inhibit both calcium uptake into smooth muscle cells and mobilization from intracellular stores. This leads to vasodilation by inhibiting the coupling of myocardial excitation to contraction in peripheral vascular smooth muscles. By this mechanism, these CCBs decrease peripheral vascular resistance and decrease blood pressure. Activity is primarily in the peripheral vasculature for these agents (1, 3).

PHARMACOKINETICS

In general, dihydropyridine CCBs are well absorbed after oral administration but have a low bioavailability because of significant first-pass metabolism. Most are cleared hepatically, with <5% being excreted unchanged in the urine. Dosage adjustments may be necessary in patients with hepatic impairment. These drugs are highly protein bound.

Two formulations of sustained-release nifedipine currently are available: Procardia XL, which is a gastrointestinal transport system, and Adalat CC, which is a coated core system. These 2 products are not considered therapeutically equivalent by the FDA (1–4).

COMPARATIVE EFFICACY STUDIES

For the treatment of hypertension

Overall, studies have shown that amlodipine is equivalent to felodipine in the treatment of hypertension. One study suggested that amlodipine may be more potent than felodipine, whereas another revealed that amlodipine had fewer adverse effects. When using the kinetic-based study, amlodipine was found to have a more consistent antihypertensive effect over the day, thus maintaining the patient in a lower blood pressure range (5–8). One trial compared amlodipine and felodipine extended release. The blood pressure–lowering effect was equal at equivalent doses, although amlodipine had a higher incidence of undesirable side effects (9).

Efficacy for nicardipine and nifedipine was found to be similar in the treatment of hypertension, although nifedipine had a higher incidence of pedal edema and tachycardia. Also, the duration of nicardipine sustained release was found to be <12 hours. Both studies had a small number of subjects enrolled, thus limiting the utility of the data collected.

For the treatment of angina

Nifedipine and amlodipine are the only dihydropyridines with an FDA indication for vasospastic and chronic stable angina. Nicardipine is only indicated for chronic stable angina.

The literature contains data from a trial that compared extended release felodipine (given once daily) with immediate-release nifedipine (given 4 times daily) in patients with vasospastic angina. The 2 regimens had comparable efficacy, but because the sample size was small, conclusions from this study are of limited utility (10).

Various forms of nifedipine were compared with isradipine in 3 studies (11–13). The drugs were shown to have comparable efficacy for reductions of blood pressure and heart rate, as well as for
improvements in exercise tolerance (the time until ST-segment depression). One study found nifedipine to be associated with fewer incidences of angina but with greater side effects (11–13). Two studies used the immediate-release formulation of both nicardipine and nifedipine. Although the 2 agents produced a similar effect on exercise tolerance and a delay of ischemia onset, nicardipine caused a significant increase in heart rate (14, 15).

**DRUG INTERACTIONS AND ADVERSE EFFECTS**

The major adverse effect of dihydropyridine CCBs is that of peripheral vasodilation. Adverse events can be lessened by using the longer-acting formulations. There is no clinically significant difference in the adverse effect profiles of these drugs. Some recent studies have suggested that the adverse effect profile of CCB use may include adverse cardiovascular events, bleeding, and colon cancer (16–18).

**SUMMARY OF FORMULARY DECISIONS**

In the phenylalkylamine category, generic verapamil has been chosen for the immediate-release and intravenous verapamil. The oral formulation is bioequivalent to the immediate-release Isoptin and Calan brands of verapamil. When considering the sustained-release products available for verapamil, Isoptin SR and Calan SR are bioequivalent, whereas Covera HS and Verelan are not. When compared, Isoptin SR and Verelan have equal bioavailability and produce an overall reduction in blood pressure that is comparable. Isoptin SR has a shorter time to peak level. Verelan’s effects last longer. The Verelan capsule can be opened, without destroying its sustained-release properties, to administer to patients who have difficulty swallowing. There are no comparative data with Covera HS. Based on these data, Verelan has been chosen for addition to the BUMC formulary (19–23).

In the benzothiazepine category, generic diltiazem (oral) immediate-release and intravenous formulations also have been chosen for formulary inclusion. They are bioequivalent to the corresponding Cardizem brand of diltiazem.

Dilacor XR, Cardizem CD, and Tiazac are not bioequivalent diltiazem products. Tiazac has been chosen for the diltiazem extended-release preparation because it has superior bioavailability compared with Dilacor XR and Cardizem CD. It has been shown to have equivalent reductions in mean systolic and diastolic blood pressures and heart rate compared with Cardizem CD, while being less expensive. Tiazac also has an adverse effect profile similar to placebo (24, 25).

All members of the dihydropyridine class are equivalent in efficacy and safety for treating hypertension and angina. Formulary decisions are driven by cost and compliance issues. Once-a-day dosing is considered advantageous. Nifedipine and amlodipine are the only 2 drugs with all 3 FDA-approved indications. For these reasons, Adalat CC (nifedipine) and Norvasc (amlodipine) have been chosen as the formulary agents. An alternative agent included is felodipine, because it has similar pharmacology to amlodipine and is a less expensive agent. Nicardipine injection will be included as an injectable formulation from this class.
References


