Calcium channel blockers are commonly prescribed to treat several cardiovascular diseases and may be helpful in other conditions, such as migraine and bipolar disorder. These agents are associated with numerous clinically significant drug interactions. While some of these interactions, such as the effect of verapamil on serum digoxin concentrations, are well-known, others are not widely recognized—yet warrant attention.

My aim here is to heighten your awareness of these interactions to ensure optimal management as well as patient safety. I emphasize pharmacokinetic interactions.

### Table 1 —Examples of interactions with diltiazem and verapamil that increase serum concentrations of other drugs*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Monitor carbamazepine levels when using this drug with diltiazem or verapamil; carbamazepine levels increase approximately 50%; neurotoxicity has been reported when carbamazepine was taken with diltiazem or verapamil</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Both diltiazem and verapamil can increase cyclosporine levels; some clinicians consider this interaction desirable as a strategy to decrease the cyclosporine dose</td>
</tr>
<tr>
<td>Drug</td>
<td>Effects/Interactions</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Monitor digoxin levels; anticipate need to reduce digoxin dose (e.g., by 50%) within the first week of initiation of verapamil therapy; effect is greater with concurrent cirrhosis; diltiazem may also elevate digoxin levels but usually not to a clinically significant degree</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Diltiazem can greatly increase methylprednisolone levels, which can result in adrenocortical suppression; this effect usually becomes clinically significant only during long-term methylprednisolone therapy</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Monitor phenytoin levels when giving concomitant verapamil or diltiazem; phenytoin toxicity is not as well documented as carbamazepine toxicity but is possible</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Monitor quinidine levels; interaction with verapamil causes a 33% decrease in oral quinidine clearance</td>
</tr>
<tr>
<td>Statins (HMG-CoA reductase inhibitors)</td>
<td>Diltiazem and verapamil increase serum concentrations of simvastatin/simvastatin</td>
</tr>
</tbody>
</table>
INHIBITION OF DRUG METABOLISM

Diltiazem and verapamil inhibit the metabolism of several drugs; examples of these interactions are listed in Table 1. These 2 calcium channel blockers inhibit the cytochrome P-450 isoenzyme CYP 3A4\(^1\)\(^2\) as well as drug transport via P-glycoprotein. The latter effect results in increased serum concentrations of drugs such as digoxin. Dihydropyridine calcium channel blockers (eg, nifedipine) generally do not inhibit the metabolism of other drugs.
Table 2 — Examples of drug interactions that decrease calcium channel blocker levels

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>20-22 Serum felodipine and nisoldipine concentrations dramatically reduced in patients receiving phenytoin; felodipine levels also decreased with carbamazepine and phenobarbital; avoid these combinations if possible; anticipate need for higher doses of felodipine or nisoldipine and monitor response to therapy if phenytoin, carbamazepine, or phenobarbital must be given concurrently; possible reduction in verapamil concentrations caused by phenytoin requires further investigation</td>
</tr>
<tr>
<td>Rifampin</td>
<td>23 Verapamil and diltiazem serum concentrations are dramatically reduced (below the level of detection) for typical oral dosage range; nifedipine levels and pharmacologic effects are also greatly reduced†; other appropriate cardiovascular agents are preferred when rifampin is required</td>
</tr>
</tbody>
</table>

*Examples only; consult references cited
Calcium Channel Blocker-Drug Interactions: Strategies for Avoiding Untoward Effects

and other dihydropyridines.†

†Studies of interaction with other dihydropyridines are needed; anticipate that the effect of the calcium channel blocker will be markedly decreased because of rifampin.

Table 3 — Examples of drug interactions that increase calcium channel blocker levels*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>1,2 Monitor for heightened effects, especially with dihydropyridine calcium channel blockers; in some patients, the dose of the calcium channel blocker may need to be reduced</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>24 Felodipine levels increase; monitor blood pressure and be alert for adverse effects; anticipate need to reduce felodipine dose; note that grapefruit juice or unprocessed grapefruit also raises felodipine levels, especially in elderly patients</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>28 Felodipine levels increase; monitor blood pressure and heart rate; anticipate need to reduce dose of felodipine or other dihydropyridines with concurrent administration of itraconazole and possibly other azole antifungals (eg,</td>
</tr>
</tbody>
</table>
**EFFECTS OF OTHER DRUGS ON CALCIUM CHANNEL BLOCKERS**

Inducers of drug metabolism, such as rifampin, increase the clearance of verapamil, diltiazem, and dihydropyridine calcium channel blockers (Table 2). On the other hand, inhibitors of drug metabolism (eg, erythromycin) may decrease the clearance of calcium channel blockers (Table 3).

**PHARMACODYNAMIC INTERACTIONS**

Although the emphasis here is on pharmacokinetic interactions, pharmacodynamic interactions also deserve mention. Abernethy and Schwartz have provided a useful summary of pharmacodynamic interactions.

If other cardiovascular drugs are used concomitantly with calcium channel blockers, be alert for additive pharmacologic effects. For example, the use of verapamil or diltiazem concurrently with amiodarone inhibits atrioventricular conduction and sinusnode function more than therapy with either calcium channel blocker alone.

References:

REFERENCES:

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