Calcium Channel Blockers as Inhibitors of Drug Metabolism*

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Calcium channel blockers have risen to a position of prominence in clinical medicine. Current applications include treatment of hypertension, supraventricular arrhythmias, angina pectoris, and peripheral vasospastic disease. In addition, the calcium channel blockers show promise for use in certain pulmonary diseases, GI disorders, seizure disorders, and migraine headache. With this broad range of clinical applications and widespread use comes the potential risk for adverse drug interactions between the calcium channel blockers and concomitant drug therapies employed in the treatment of these or other disease states.

Many case reports have surfaced recently regarding interactions between the calcium channel blockers and drugs which undergo hepatic metabolism. Although some of these reports have been well documented, others have not. Controlled studies have been conducted to determine the nature, extent, and clinical significance of the observed interactions, often with conflicting results. Our purpose is to critically review the reports and studies concerning the effects of calcium channel blockers on hepatic drug metabolism. An additional goal is to provide guidance for the clinician faced with the need for concomitant drug therapy with the calcium channel blockers.

The heterogeneous compounds classified as calcium channel blockers are chemically dissimilar but share the property of inhibiting calcium ion flux through slow-channels in myocardial, smooth muscle, and specialized conductive tissues. Currently, only diltiazem, nifedipine, verapamil, and nitrendipine are approved for use in the United States, and the majority of reports concern these agents.

MARKER COMPOUNDS

Several studies have been conducted to characterize the effects of the calcium channel blockers on liver blood flow and hepatic enzyme activity, the two main determinants of hepatic drug metabolism. These studies have involved the coadministration of the various calcium channel blockers and indocyanine green (ICG) or antipyrine, marker compounds for liver blood flow and hepatic oxidative enzyme activity, respectively.

The disposition of drugs with large hepatic extraction ratios may be significantly altered by increases in liver blood flow during the absorption phase, resulting in increased bioavailability through reduction of the first-pass effect. Increased blood flow will also increase the systemic clearance of these drugs. Studies indicate that nifedipine, nisoldipine, and verapamil produce increases in liver blood flow of approximately 30 percent and consequently might alter the disposition of highly extracted drugs, while diltiazem has no significant effect on liver blood flow. The clinical importance of these changes in liver blood flow has not been clearly established.

Antipyrine studies with calcium channel blockers have shown no change in antipyrine oxidation as a result of nifedipine coadministration. Diltiazem and verapamil were both shown to decrease total clearance of antipyrine (diltiazem 13 to 28 percent; verapamil 12 to 33 percent) and to increase its elimination half-life (diltiazem 12 to 44 percent; verapamil 15 to 50 percent). Diltiazem and verapamil have been further studied and shown to decrease the formation of the three major antipyrine metabolites. Data from studies by Bauer et al., Abernethy et al., and Botteroff et al. suggest that diltiazem and verapamil exhibit dose-dependent inhibition of antipyrine elimination. Diltiazem doses of 120 mg/day, 270 mg/day,

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and 360 mg/day produced antipyrene clearance decreases of 13 percent, 18 percent, and 28 percent, respectively. Likewise, verapamil doses of 240 mg/day and 480 mg/day were associated with decreases in antipyrene clearance of 13 percent and 30 percent, respectively.

These studies indicate that nifedipine has little or no measurable effect on hepatic oxidative enzyme activity (as assessed by antipyrene disposition). Diltiazem and verapamil, on the other hand, produce significant inhibition of these enzymes, particularly at higher levels of dosing, which may provide a basis for clinically significant interactions with drugs eliminated by oxidative metabolism.

Theophylline

Theophylline metabolism is known to depend on hepatic oxidative enzyme activity, which may be altered by calcium channel blockers. Early case reports implicating verapamil and nifedipine as agents interacting with theophylline elimination were inadequately documented. Subsequent controlled studies involved single-dose and multidose therapy with theophylline in combination with nifedipine, verapamil, and diltiazem.

Nifedipine has been shown to change theophylline clearance in a range from −9 to +10 percent in three controlled trials. These equivocal findings suggest no clinically significant interaction.

Two controlled studies with verapamil and theophylline in healthy non-smoking subjects showed a decrease in theophylline clearance of 14 percent and 18 percent, both resulting in a uniform depression of all measured theophylline metabolites. Changes in theophylline disposition due to diltiazem coadministration were studied in two healthy subject trials with decreases in mean theophylline clearance of 12 percent and 21 percent.

While some studies have shown statistically significant decreases in theophylline clearance and increases in theophylline concentrations as a result of coadministration of verapamil and diltiazem, the increases would generally not be of clinical concern. However, in patients maintained on theophylline concentrations in the upper therapeutic range, initiating therapy with a calcium channel blocker should be done with caution. It is also unclear what effect calcium channel blockers may have when administered to patients with other "risk factors" for decreased theophylline elimination (cimetidine, liver disease, etc). Table 1 provides some perspective on the relative effects of the calcium channel blockers and other medications on theophylline clearance.

<table>
<thead>
<tr>
<th>Inhibiting Compound</th>
<th>% Decrease in Clearance (Mean)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxacin</td>
<td>64</td>
<td>45</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>26-40</td>
<td>46, 47</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>28</td>
<td>49</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>26-40</td>
<td>49, 50</td>
</tr>
<tr>
<td>Verapamil</td>
<td>14-18</td>
<td>13, 16</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>12-21</td>
<td>13, 14</td>
</tr>
</tbody>
</table>

Quinidine

Effects of calcium channel blockers on the disposition of quinidine have been studied. Changes in serum quinidine concentrations have been reported, with increases of up to 135 percent on discontinuation of nifedipine therapy in patients with heart failure previously showing unusually low serum quinidine concentrations despite large doses of quinidine. Munder et al studied 12 patients to test the hypothesis that in patients with depressed left ventricular ejection fraction, nifedipine may increase quinidine clearance, possibly as a function of enhanced cardiac output. A change in quinidine clearance was seen in only one of the twelve, that patient having a normal ejection fraction. No correlation was found between depressed left ventricular ejection fraction and a nifedipine-quinidine interaction, nor was the interaction proven reproducible in this population.

Guengerich et al studied the metabolism of quinidine and nifedipine in human liver cytochrome P450 samples, concluding that the P450n (nifedipine oxidase) isozyme is responsible for greater than 90 percent of both quinidine and nifedipine metabolism. Although competitive inhibition at this common site of metabolism is theoretically possible, the only published trial showed an insignificant effect of nifedipine on quinidine disposition.

Trohman et al reported a case of a patient receiving verapamil and quinidine over the course of one week leading to quinidine concentrations above the desired range. Later withdrawal of verapamil was accompanied by decreasing quinidine concentrations. The investigators then undertook a controlled trial with this subject, determining quinidine pharmacokinetic parameters alone and following five doses of verapamil. Following verapamil, quinidine elimination half-life and steady-state concentration increased by 83 percent and 47 percent, respectively, while clearance decreased by 51 percent.

Edwards et al studied the effect of verapamil coadministration at two dose levels (80 mg and 120 mg orally three times daily) on quinidine disposition in six healthy subjects. They found similar decreases of approximately 33 percent in quinidine oral clearance at both 80 mg and 120 mg verapamil doses, as
Table 2—Influence of Calcium Channel Blockers on Hepatic Drug Metabolism

<table>
<thead>
<tr>
<th>Drug</th>
<th>CCB</th>
<th>Cl</th>
<th>AUC</th>
<th>Css</th>
<th>Clinical Significance</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline</td>
<td>VER</td>
<td>-18</td>
<td></td>
<td></td>
<td>Usually none</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>DTZ</td>
<td>-12</td>
<td></td>
<td></td>
<td>Usually none</td>
<td>13</td>
</tr>
<tr>
<td>Quinidine</td>
<td>VER</td>
<td>-33</td>
<td></td>
<td></td>
<td>Possible toxicity</td>
<td>22</td>
</tr>
<tr>
<td>Propranolol</td>
<td>VER</td>
<td>+66</td>
<td></td>
<td></td>
<td>Usually none</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>DTZ</td>
<td>+29</td>
<td></td>
<td></td>
<td>Usually none</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>NIS</td>
<td>+43</td>
<td></td>
<td></td>
<td>Usually none</td>
<td>29</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>VER</td>
<td>+33</td>
<td></td>
<td></td>
<td>Usually none</td>
<td>26</td>
</tr>
<tr>
<td>Prazosin</td>
<td>VER</td>
<td>+84</td>
<td></td>
<td></td>
<td>Increased hypotension</td>
<td>32</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>VER</td>
<td>+27</td>
<td></td>
<td></td>
<td>Usually none</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>DTZ</td>
<td>+21</td>
<td></td>
<td></td>
<td>Usually none</td>
<td>34</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>DTZ</td>
<td>+50</td>
<td></td>
<td></td>
<td>Possible neurotoxicity</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>VER</td>
<td>+46</td>
<td></td>
<td></td>
<td>Possible neurotoxicity</td>
<td>37</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>NIC</td>
<td>+110</td>
<td></td>
<td></td>
<td>Possible nephotoxicity</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>DTZ</td>
<td>+49</td>
<td></td>
<td></td>
<td>Possible nephotoxicity</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>VER</td>
<td>+100</td>
<td></td>
<td></td>
<td>Possible nephotoxicity</td>
<td>44</td>
</tr>
</tbody>
</table>

*CCB = calcium channel blocker; VER = verapamil; DTZ = diltiazem; NIS = nisoldipine; NIC = nicardipine; Cl = clearance; AUC = area under the concentration-time curve; Css = steady-state concentration.

well as increases of about 30 percent in quinidine elimination half-life. Urinary recovery of quinidine and 3-OH-quinidine following verapamil revealed a significant decrease in 3-OH-quinidine formation and an increase in unchanged quinidine versus control. Renal clearance of quinidine did not change significantly. There was no change in quinidine unbound fraction between treatments. The authors concluded that the interaction between verapamil and quinidine is due to inhibition of quinidine oxidation. The reduction in quinidine clearance found in the study ranged from 20 to 50 percent, potentially clinically significant due to the narrow therapeutic range of quinidine.

Clinicians should be aware of the potential for adverse interactions between verapamil and quinidine. While diltiazem has not been reported to interact with quinidine and reports of a nifedipine-quinidine interaction have not been verified in controlled trials, cautious coadministration of all these agents is, nevertheless, advisable due to potential toxicity or loss of antiarrhythmic effect at initiation or discontinuation of calcium channel blocker therapy.

**β-blockers**

Use of β-blockers with calcium channel blockers is increasingly common in clinical practice. Several investigations have established the safety and efficacy of concurrent β-blocker and calcium channel blocker treatment when used appropriately with careful monitoring. However, there is some evidence to suggest that the calcium channel blockers may decrease the hepatic metabolism of certain β-blockers.

In controlled trials, nifedipine has been shown to produce no significant changes in the pharmacokinetics of propranolol, metoprolol, or atenolol given in commonly prescribed doses.22,24

Verapamil has been shown to affect the clearance of the lipophilic β-blockers, propranolol25 and metoprolol26,27 (both metabolized in the liver), but to have no effect on the pharmacokinetics of atenolol,22 a hydrophilic compound excreted unchanged in the urine. McCourty et al25 found increases in mean propranolol maximum serum concentrations (Cmax) and area under the concentration-time curve (AUC) of 94 percent and 66 percent, respectively, during chronic verapamil coadministration. However, no significant changes in propranolol pharmacodynamic effects were noted.

Keech et al26 studied nine patients receiving a broad range of verapamil and metoprolol doses in a crossover trial of verapamil with metoprolol or metoprolol alone. They found variable but statistically significant increases in the mean Cmax (42 percent) and AUC (53 percent) for metoprolol with coadministration of verapamil. There appeared to be a positive correlation between the dose of verapamil and the extent of interaction between the two agents.

Dimmitt et al27 studied 14 healthy volunteers to determine the effects of diltiazem (180 mg/day) on propranolol pharmacokinetics and found increases in propranolol Cmax and steady-state AUC of 15 percent and 28 percent, respectively. This effect was less than that previously described for verapamil,26 however, it is possible that larger diltiazem doses may produce greater inhibition.

Levine et al28 studied the effect of nisoldipine on propranolol disposition in a blinded, placebo-controlled, randomized trial with 12 healthy volunteers.
A single oral dose of nisoldipine was followed after 1 h by an oral dose of propranolol. The investigators found significant increases in propranolol AUC (43 percent) and Cmax (68 percent) which resulted in a higher degree of β-blockade as assessed by isoproterenol stimulation. A transient increase in liver blood flow caused by nisoldipine during the absorption phase of propranolol may have caused the increase in bioavailability. However, the need for longterm dosing studies of this interaction for clinical application was recognized by the investigators.

In summary, the hepatic metabolism of the lipophilic β-blockers propranolol and metoprolol may be affected by coadministration of verapamil, diltiazem, and possibly nisoldipine. In most patients, the clinical significance of these pharmacokinetic interactions appears to be minimal; however, due to additive pharmacodynamic effects, clinicians should be aware of the potential for increased cardiodepressant activity during the coadministration of calcium channel blockers and β-blockers.

**Prazosin**

Calcium channel blockers are commonly employed in combination therapy for hypertension. One such combination, prazosin and nifedipine, resulted in marked hypotension which was attributed to the additive vasodilating effects of nifedipine.29 Pasanisi et al29 assessed both pharmacodynamic and pharmacokinetic parameters in eight normotensive subjects following acute administration of prazosin, verapamil, and their combination. With combined treatment, they found an earlier and greater hypotensive effect vs either treatment alone and a decrease in tachycardia vs that caused by prazosin alone. No changes in verapamil disposition were found during combination therapy; however, prazosin Cmax increased by 84 percent and AUC increased by 62 percent during coadministration of verapamil.

Similarly, Elliott et al30 studied 12 patients with essential hypertension in a placebo-controlled, randomized, crossover trial of both single-dose and chronic administration of verapamil and prazosin. When added to verapamil, first-dose prazosin caused a more rapid fall in systolic blood pressure than when given alone. In addition, the prazosin AUC increased by 82 percent during verapamil coadministration. Similarly, chronic dosing of verapamil and prazosin produced a greater hypotensive effect than either drug alone and led to increases of 84 percent and 103 percent in prazosin AUC and Cmax, respectively. No change in prazosin elimination half-life was seen.

No studies of a diltiazem-prazosin interaction have been reported to date; however, as with nifedipine and verapamil, clinicians should be aware of the potential for an enhanced hypotensive effect when prazosin and the calcium channel blockers are coadministered.

**Digitalis Glycosides**

Interactions between calcium channel blockers and digoxin, extensively studied by many investigators, have been reviewed in great detail by DeVito et al.33 While the elevations in serum digoxin concentrations seen with verapamil (60 to 80 percent) and diltiazem (33 percent) coadministration may be clinically significant, these interactions are reportedly caused predominantly by changes in the renal clearance of digoxin. Consequently, in keeping with our intent to review only those calcium channel blocker effects attributable to changes in hepatic metabolism, studies of these interactions will not be further considered here.

Digoxin has been studied at steady-state by Kuhlmann et al34 with concomitant verapamil, diltiazem, and nifedipine. Verapamil coadministration resulted in an increase in mean digoxin concentrations of 27 percent over two to three weeks. Renal digoxin excretion was unchanged. Total and nonrenal clearance of digoxin was reduced by 27 percent and 29 percent, respectively. Diltiazem effects on digoxin disposition in ten patients were equivocal. Only five of ten subjects experienced any increase in steady-state digoxin trough concentrations with a mean increase of 21 percent for those five subjects. Studies with nifedipine showed no effect on digoxin steady-state concentrations, renal excretion, or nonrenal clearance.

Verapamil may be expected to increase digoxin trough concentrations at steady-state by approximately 30 percent, while diltiazem appears to have a minimal but less predictable effect on digoxin disposition. Overall, an interaction with verapamil or diltiazem would usually produce no clinically significant problems.

**Carbamazepine**

Carbamazepine undergoes extensive hepatic oxidation via the cytochrome P450 system. Carbamazepine neurotoxicity as a result of interactions with diltiazem and verapamil has been reported. Following initiation of diltiazem, Brodie et al35 and Eimer et al36 have reported single cases of increases in carbamazepine concentrations of 40 percent and 50 percent, respectively, leading to neurotoxicity. In both cases, withdrawal of diltiazem was accompanied by a return of carbamazepine concentrations to pretreatment levels. When Eimer et al36 rechallenged the patient with diltiazem, an increase in carbamazepine concentration of approximately 50 percent was again seen, requiring a 62 percent reduction in the dose of carbamazepine to maintain concentrations in the desired range.
Brodie et al. followed diltiazem treatment in their patient with a trial of nifedipine and found no resultant change in carbamazepine concentrations.

MacPhee et al. studied six otherwise healthy patients with seizure disorders receiving stable doses of carbamazepine and other anticonvulsants for three months prior to the study period. Addition of verapamil 120 mg three times a day for seven days produced a mean increase of 46 percent in plasma carbamazepine concentrations (evaluable in only five subjects) and clinical signs of neurotoxicity in all subjects. No changes were noted in plasma concentrations of carbamazepine-10,11-epoxide, the major metabolite formed. Following a seven-day verapamil washout, carbamazepine concentrations had returned to approximately pretreatment values in all subjects. Two subjects rechallenged with verapamil 240 mg/day for two days showed increases of 37 percent and 70 percent in carbamazepine concentrations compared with their baseline values. Of additional interest was an increase in phenytoin and valproic acid concentrations in two subjects during verapamil coadministration, suggesting the potential for interactions with anticonvulsant drugs not yet studied. MacPhee et al. also reported a case of a seven-day withdrawal of verapamil from a patient, leading to declining carbamazepine and increasing carbamazepine-10,11-epoxide concentrations. The patient experienced a seizure following verapamil reintroduction when carbamazepine levels were still below the desired range. Within three days, carbamazepine concentrations had risen and carbamazepine-10,11-epoxide concentrations fallen to prewithdrawal levels.

While these reports seem to be well documented, certainly, more controlled studies need to be conducted regarding the effects of the calcium channel blockers on commonly used anticonvulsants. Most anticonvulsants undergo significant hepatic metabolism and increase intrinsic hepatic enzyme activity. Pending further study, it would be wise to carefully monitor carbamazepine concentrations during the initiation or withdrawal of diltiazem or verapamil therapy. If clinically indicated, nifedipine may prove to be a safer choice of calcium channel blocker, having less apparent effect on hepatic oxidative enzyme activity.

**Cyclosporine**

Cyclosporine undergoes extensive first-pass metabolism through multiple hydroxylation pathways following oral administration. Several clinicians have reported a pharmacokinetic interaction occurring with coadministration of the calcium channel blockers, leading to a twofold or greater increase in serum cyclosporine concentrations, which may carry risks for nephrotoxicity. Bourbigot et al. retrospectively reviewed cyclosporine serum concentration data for nine patients receiving concomitant nifedipine, five of whom were changed from nifedipine due to peripheral edema. Their findings showed a mean increase in cyclosporine steady-state concentrations of 110 ± 92 percent following the introduction of nifedipine. However, because this was a retrospective and uncontrolled review of patient data, interpretation of the data must be made with caution.

Pochet et al. report a case of diltiazem interaction with cyclosporine followed by rechallenge and recurrence of the increase in cyclosporine serum concentrations (26 percent and 49 percent). Grino et al. report a similar experience in a single patient leading to a 279 percent increase in cyclosporine blood concentration. Realizing that steady-state cyclosporine concentrations had probably not been reached at the time of the suspected interaction, the investigators rechallenged the patient a month later with IV cyclosporine therapy and the same diltiazem oral dose. After three days, blood samples were collected to determine cyclosporine AUC and clearance. Diltiazem was then discontinued, and four days later cyclosporine AUC was decreased by 69 percent and total clearance was increased by 222 percent. Oral dosing of cyclosporine was later resumed at one-third the original level with diltiazem coadministration in order to achieve therapeutic trough cyclosporine blood concentrations.

Neumayer et al. considered this interaction from the standpoint of a reduced dosage requirement for cyclosporine, with diltiazem coadministration having favorable economic consequences. Ptachinski et al. sought to exploit this interaction in order to elevate cyclosporine blood concentrations in patients with unusually low concentrations following high oral dosing. These studies seem to indicate a reproducible and, to the investigators, desirable drug interaction between diltiazem and cyclosporine. However, consideration of potential side effects from the use of diltiazem is necessary when judging potential benefits of this therapy.

Robson et al. reported a single case where verapamil induced a greater than twofold increase in steady-state cyclosporine concentration. Verapamil withdrawal and introduction of nifedipine resulted in a fall in cyclosporine concentration to preverapamil treatment levels over the ensuing two weeks. This report would suggest a lack of effect of nifedipine on cyclosporine clearance, a finding also noted by Bourbigot et al. Lindholm et al. carried out a trial of verapamil in five patients with hypertension receiving cyclosporine for renal transplant. They, too, found statistically significant increases in steady-state cyclosporine concentrations for all subjects treated.

Although most of these reports are well docu-
mented, few are the products of controlled trials. Therefore, further research is needed to fully characterize this interaction between cyclosporine and the calcium channel blockers. Nevertheless, it seems that caution should be exercised when coadministration of cyclosporine and diltiazem, verapamil, or nicardipine are initiated in order to avoid potential nephrotoxicity due to elevated cyclosporine concentrations. Compared with other calcium channel blockers, the use of nifedipine, where indicated, may be preferred for patients on stable cyclosporine regimens.

**CONCLUSION**

It is now clearly established that verapamil and diltiazem inhibit the hepatic metabolism of several drugs, while nifedipine has little or no effect on hepatic drug disposition. In time, it is probable that verapamil and diltiazem will be shown to alter the disposition of many other drugs, as well. While some of these reported interactions are clinically significant, others have been found to be statistically significant in investigative trials, but are probably not important in the clinical setting. Although specific interactions have been reviewed here (Table 2), the clinician should carefully consider the potential for interactions between verapamil and diltiazem and any coadministered drug undergoing oxidative hepatic metabolism as its predominant route of elimination.

**ADDENDUM**

Since the preparation of this manuscript, two new dihydropyridine derivative calcium channel blockers, nicardipine and nimodipine, have been approved for marketing by the FDA.

**REFERENCES**

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