CCBs and CYP3A4 Inhibitors: Watch Out for Enhanced Cardiovascular Response

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Calcium channel blockers (CCBs) are widely used for their vasodilatory activity in the treatment of hypertension and angina. Additionally, diltiazem (Cardizem) and verapamil (Calan) exert a negative dromotropic effect (slow conduction through the atrioventricular node) that makes them effective for the treatment of supraventricular arrhythmias. The CCBs are primarily metabolized by cytochrome P450 (CYP) 3A4. Some of them have extensive first pass metabolism (eg, nisoldipine [Sular], felodipine [Plendil], isradipine [DynaCirc]) that limits their bioavailability. Thus, the combination of CYP3A4 inhibitors with CCBs is likely to enhance the pharmacologic activity of the CCB, potentially resulting in hypotension or bradycardia.

EVIDENCE OF AN INTERACTION

A publication recently described a study that included patients at least 66 years of age who were taking CCBs and were subsequently admitted to the hospital with hypotension or shock.[1] On average, these patients had been taking CCBs for 2 years prior to the hypotensive episode. The risk of hypotension was estimated by comparing each patient's exposure to a macrolide antibiotic (azithromycin [Zithromax], clarithromycin [Biaxin], or erythromycin [E-mycin]) during the 7 days prior to admission and during a 7-day period 30 days prior to the hypotensive event. Out of the study population of nearly a million patients taking a CCB, 7100 were admitted to the hospital for hypotension over the 15-year study period. Diltiazem, amlodipine (Norvasc), and nifedipine (Procardia) accounted for nearly 90% of the CCBs prescribed to the patients.

After controlling for patient characteristics, including the administration of other CYP3A4 inhibitors, a significant association between macrolide antibiotic use and admission for hypotension was found for erythromycin (odds ratio 5.8) and clarithromycin (odds ratio 3.7), but not for azithromycin. The lack of an association with azithromycin is likely due to its lack of CYP3A4 inhibition, whereas both erythromycin and clarithromycin are known inhibitors of CYP3A4.

Several case reports have appeared describing CCB-induced side effects during concurrent administration of erythromycin, clarithromycin, and other CYP3A4 inhibitors.[2-5] Case reports typically describe patients who are stabilized on chronic CCB therapy when the macrolide is introduced. The maximal inhibition of erythromycin and clarithromycin will occur over several days, and one would expect a similar gradual increase in the response to the CCB.

The risk of an adverse event occurring will depend on the CCB being administered, the doses of both the CCB and CYP3A4 inhibitor, and the patient's specific demographics. For example, CCBs with high first pass metabolism will have a potentially greater increase in CCB plasma concentration during CYP3A4 inhibitor administration. Elderly patients may be at increased risk for adverse reactions due to a reduced ability to compensate for increased vasodilation or bradycardia.

OTHER CYP3A4 INHIBITORS

In addition to erythromycin and clarithromycin, there are many CYP3A4 inhibitors that would be expected to interact with CCBs. Commonly prescribed CYP3A4 inhibitors include azole antifungal drugs, such as fluconazole (Diflucan), itraconazole (Sporanox), ketoconazole (Nizoral), and voriconazole (Vfend). Protease inhibitors (eg, atazanavir [Reyataz], darunavir [Prezista], fosamprenavir [Lexiva], indinavir [Crixivan], and ritonavir [Norvir]) are effective inhibitors that are often administered for longer periods than macrolide antibiotics.

The antiarrhythmic drugs amiodarone (Cordarone) and dronedarone (Multaq) inhibit CYP3A4 and may also enhance the effects of diltiazem and verapamil on cardiac conduction. Bradycardia may be a more likely outcome in patients receiving combinations of these drugs.

MANAGEMENT STRATEGIES

Patients who are stabilized on a CCB should be monitored for increased pharmacologic response when a drug known to inhibit CYP3A4 is added to their regimen. The increased response will occur as the inhibitor reaches steady-state plasma levels. For most inhibitors this will occur within a week. Inhibitors with long half-lives (eg, amiodarone, fluoxetine [Prozac]) will require a longer period to develop the maximum response. If a patient is already receiving an inhibitor and then the CCB is added to their therapy, monitor closely for the desired response, and be alert to the potential for lower than usual doses of the CCB to be effective.

Minimization of the interaction magnitude could be attempted by selecting CCBs that do not have a large first pass metabolism, but some patients may still develop adverse effects and all patients should be monitored. Avoidance of the interaction could be achieved by selecting a noninhibiting antibiotic, such as azithromycin, when it is appropriate. Avoiding CCBs by using other classes of antihypertensive agents that are not substrates for CYP3A4 may be appropriate in patients requiring long-term administration of inhibitory drugs. ***PT***

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