Clopidogrel: Some Drugs May Reduce Its Effectiveness

John R. Horn, PharmD, FCCP, and Phillip D. Hansten, PharmD

Drs. Horn and Hansten are both professors of pharmacy at the University of Washington School of Pharmacy. For an electronic version of this article, including references if any, visit www.hanstenandhorn.com.

In October 2003, this column discussed the potential interaction between clopidogrel (Plavix) and atorvastatin. At that time, it was concluded that this interaction was unlikely to cause a risk to patients. Multiple studies in the past few years have confirmed that view.

Clopidogrel represents a rather unique risk for drug interactions, however. It is a prodrug that requires metabolic conversion to a thiol metabolite that binds to the platelet adenosine diphosphate receptor and reduces the ability of platelets to aggregate. The antiplatelet effect is useful to prevent blood clots in the arterial system and in patients with coronary artery stents.

CYP3A4 Inhibitors

It is believed that cytochrome P (CYP) enzymes CYP3A4 and CYP2C19 are involved in the conversion of clopidogrel to its active metabolite. Previously, CYP3A4 inhibitors such as erythromycin and ketoconazole (Nizoral) have been demonstrated to reduce clopidogrel antiplatelet activity. All drugs that possess at least modest CYP3A4 inhibitory activity should be considered to interact with clopidogrel and may reduce its therapeutic effectiveness.

Thus, it is very important for pharmacists to review the drug therapy of patients prescribed clopidogrel. One should look for any concomitant drug known to be an inhibitor of CYP3A4. Other common CYP3A4 inhibitors include clarithromycin (Biaxin), fluconazole (Diflucan), itraconazole (Sporanox), posaconazole (Noxafil), voriconazole (Vfend), diltiazem (Cardizem), verapamil (Calan), and the chronic consumption of grapefruit juice.

CYP2C19 Inhibitors

Recently, omeprazole (Prilosec), an inhibitor of CYP2C19, has been reported to reduce the activity of clopidogrel.[1,2] In both observational and placebo-controlled trials, patients receiving omeprazole with clopidogrel had a greater likelihood of inadequate antiplatelet response. The odds ratio of being a poor responder to clopidogrel when taking concomitant omeprazole was estimated to be 4.3.[2]

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The mechanism of omeprazole-induced reduction in antiplatelet activity of clopidogrel has not been defined. It may be due to omeprazole's inhibition of CYP2C19. If this is true, esomeprazole (Nexium) would be expected to interact in a similar manner.

It is important to note that none of the other proton pump inhibitors (eg, lansoprazole [Prevacid], rabeprazole [Aciphex], pantoprazole [Protonix]) inhibit CYP2C19 and may not interact with clopidogrel. In addition to omeprazole and esomeprazole, fluvoxamine (Luvox), voriconazole, and cimetidine (Tagamet) have been noted to inhibit CYP2C19 activity. Until data are available showing a lack of interaction with these drugs, patients taking clopidogrel should avoid drugs that inhibit CYP2C19 activity.

CYP2C19 metabolic activity is genetically determined, with 10% to 30% of patients having reduced CYP2C19 activity. Patients who are genetically poor metabolizers (PMs) for CYP2C19 may not have an adequate response to clopidogrel treatment. Patients of Asian descent are more commonly found to be PMs for CYP2C19.

The antiplatelet activity of clopidogrel has been reported to predict the ability of clopidogrel to prevent cardiovascular events. Reduced antiplatelet activity has been associated with the occurrence of recurrent coronary events and stent thrombosis.[3] Several studies have reported resistance to clopidogrel's effects in up to 30% of patients treated with the drug. Unfortunately, these studies did not control for the patient's CYP2C19 phenotype or for concurrent drug therapy that might affect clopidogrel's conversion to its active metabolite via CYP3A4 or CYP2C19.

Rifampin (Rifadin), rifapentine (Priftin), carbamazepine (Tegretal), barbiturates, and St. John's wort are known to induce the activity of CYP3A4 and will enhance the antiplatelet effect of clopidogrel. For that reason, patients taking clopidogrel should be advised to avoid St. John's wort, and clopidogrel doses may need to be reduced if a CYP3A4 inducer is coadministered.

By careful monitoring of patients prescribed clopidogrel, drugs likely to reduce its effectiveness can be avoided, and perhaps fewer patients will be resistant to its beneficial therapeutic effects. PT

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