Clopidogrel–Proton Pump Inhibitor Interaction: An Update

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In April 2008, this column discussed the potential interaction between clopidogrel (Plavix) and proton pump inhibitors (PPIs). Since that time, several additional studies on this interaction have been published. This update will attempt to place the newer data into perspective. Because this is a complex interaction, it is important to consider the issues discussed below as new trials are presented.

Clopidogrel is a prodrug that requires metabolic conversion to a thiol metabolite. Recent data have identified that several enzymes, including CYP2C19, CYP3A4, CYP1A2, CYP2C9, and CYP2B6, are involved in the conversion of clopidogrel to its active metabolite.[1] Inhibition of any of these pathways could reduce the antiplatelet activity of clopidogrel. Omeprazole (Prilosec), an inhibitor of CYP2C19, has been reported to reduce the activity of clopidogrel when platelet function is measured.[2] In addition, CYP2C19 metabolic activity is reduced in 10% to 30% of patients who are genetically poor metabolizers (PMs) for CYP2C19. The effect of CYP2C19 inhibitors on clopidogrel would be expected to be greater in patients who are rapid metabolizers of clopidogrel and be diminished in PMs of clopidogrel.

Although the effect of omeprazole on the antiplatelet activity of clopidogrel has been consistently demonstrated, the effect of this change on the clinical efficacy of clopidogrel is still being debated. One problem is that no standard exists for the degree of platelet inhibition required to produce a clinical benefit and thus no agreement exists on how much diminution in effect is clinically significant. Several retrospective studies have reported reduced clinical efficacy, based on cardiovascular events, of clopidogrel in patients taking PPIs.[3-6] Most of these studies are burdened by differences in confounding variables between the patients receiving PPIs and those who do not. For example, disease states (eg, diabetes, hyperlipidemia, heart failure), genetics (rapid or slow CYP2C19 metabolizers), and drugs (eg, aspirin, beta-blockers, statins, calcium channel blockers) can independently affect patient outcomes. None of the retrospective trials have adequately matched for these variables. Two trials that compared well-matched groups of patients taking clopidogrel found no effect of PPIs on cardiovascular outcomes.[7,8] The only prospective, double-blind trial reported to date also found no difference in cardiovascular outcomes when PPIs were administered with clopidogrel.[9] It is important to note that although this trial did not show any influence of PPI on clopidogrel outcomes, patients not taking PPIs had an increased risk of gastrointestinal bleeding. Thus, there appears to be a definite risk associated with withholding PPIs from patients who have an indication for them.

The FDA recently reported the results of a trial that again demonstrated the effect of omeprazole on clopidogrel's antiplatelet activity.[10] This trial compared the antiplatelet activity of clopidogrel 300 mg followed by 75 mg daily for 4 days administered alone and together with 80 mg of omeprazole daily for 5 days taken concurrently or 12 hours after the clopidogrel dose. The maximum platelet inhibition of clopidogrel was modestly reduced by omeprazole from 38% to 30% and from 54% to 47% with concurrent PPI administration and 12-hour dose separation, respectively. The study did not examine the potential for PPIs to reduce the clinical effect of clopidogrel. Based on these data, the FDA notice reported that: "Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction."[10] The use of an 80-mg dose of omeprazole would produce an estimated plasma concentration of omeprazole 10 to 12 hours after administration that would be similar to that observed 2 to 3 hours after a 20-mg dose, however. Following a usual 20-mg dose of omeprazole, plasma concentrations are nearly undetectable after 8 hours. Therefore, this trial does not provide convincing evidence that separation of the PPI and clopidogrel dose in patients taking usual omeprazole doses would not minimize the magnitude of the interaction.

It appears clear that some PPIs reduce the antiplatelet activity of clopidogrel in some patients. The question is whether this is of clinical importance. Further well-designed and -controlled studies are necessary to define the best approach to patients requiring these drugs. For patients with an indication for PPI therapy, it is important to consider the risk (gastrointestinal bleeding) of withholding a PPI. Until definitive studies are available, separating the dose of omeprazole from clopidogrel may help. For example, administering the PPI 1 hour before breakfast and the clopidogrel at bedtime will provide 14 to 18 hours of separation. While data are limited, selecting a PPI other than omeprazole (or esomeprazole) may also be appropriate. ■

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