Coadministration of clopidogrel and proton pump inhibitors

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TO THE EDITOR: Thank you for the excellent review on proton pump inhibitors (PPIs) in the January 2011 issue.[1] I would like to make the following comments about Dr. Madanick's suggested algorithm (see **FIGURE 2** in the article) for deciding whether to use a PPI in patients requiring clopidogrel:

A posting dated October 27, 2010, on the Web site of the US Food and Drug Administration (FDA) states the following: "With regard to the proton pump inhibitor (PPI) drug class, this recommendation [against the concomitant use of Plavix (clopidogrel) and omeprazole (Prilosec)] applies only to omeprazole and not to all PPIs. Not all PPIs have the same inhibitory effect on the enzyme [CYP2C19] that is crucial for conversion of Plavix into its active form. Pantoprazole (Protonix) may be an alternative PPI for consideration. It is a weak inhibitor of CYP2C19 and has less effect on the pharmacological activity of Plavix than omeprazole."[2] Thus, when it is deemed necessary to coadminister clopidogrel with a PPI, pantoprazole appears to be the preferred PPI.

If the patient is taking clopidogrel for stroke prophylaxis, one can consider switching to Aggrenox (aspirin plus extended-release dipyridamole), which has no warnings regarding coadministration with PPIs.

Patients taking aspirin plus clopidogrel may benefit by the addition of misoprostol (Cytotec), which is indicated for reducing the risk of aspirin-induced gastric ulcers in patients at high risk of complications from gastric ulcer.

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REFERENCES

1. **Madanick RD**. Proton pump inhibitor side effects and drug interactions: much ado about nothing? Cleve Clin J Med 2011; 78:39–49.
2. **US Food and Drug Administration**. FDA reminder to avoid concomitant use of Plavix (clopidogrel) and omeprazole. www.fda.gov/Drugs/DrugSafety/ucm231161.htm. Accessed March 23, 2011.

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IN REPLY: I thank Dr. Keller for his interest in my review on the side effects and drug interactions of proton pump inhibitors (PPIs).[1] In particular, the concern about the potentially increased risk of a cardiovascular event in patients taking a PPI while on clopidogrel is a matter of active research. Since the prevention of death, myocardial infarction, or stroke is the desired outcome in patients receiving antiplatelet therapy, any reduction in the antiplatelet effect of clopidogrel could put patients at increased risk. Because of the enormous number of patients on both PPIs and clopidogrel, investigators are studying the effect of PPIs on clopidogrel to determine the true significance in day-to-day practice. We should expect that the data will continue to evolve in the coming years as more research is done on this important interaction.

The FDA Web site that Dr. Keller brings up[2] was posted a few months after the submission of my manuscript. But even with the FDA's cautionary words, it is important to realize that the risk that purportedly exists with the interaction of omeprazole and clopidogrel and the suggestion for the alternative use of pantoprazole are both based on pharmacokinetic, pharmacodynamic, and epidemiologic studies, not on clinical outcome data.

As much as we would like to rely on such studies, pharmacokinetic and pharmacodynamic studies do not address clinical outcomes, and observational studies cannot account for every confounder, because patients in these studies are not randomly assigned to the intervention, which is the rationale behind the necessity for a prospective trial. The Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) study,[3] a prospective randomized controlled trial with 3,761 analyzed patients, found no differences in adjudicated cardiovascular outcomes between groups

who received a clopidogrel plus omeprazole vs clopidogrel alone.[3] Although the COGENT study ended prematurely because of bankruptcy of the funding source, these outcomes represent the only randomized prospective data that can be found to date on PubMed. With such large numbers of patients in each group (1,876 and 1,885, respectively) and no differences in outcomes, it stands to reason that only a study with massive sample sizes would be able to detect a statistically significant difference. Differences between clopidogrel-treated patients taking and not taking omeprazole are likely be found in a well-designed prospective trial; however, it would be virtually impossible to find differences among PPIs.

To make matters even less convincing that therapy should be altered, the Working Group on High On-treatment Platelet Reactivity stated in their recent consensus paper that there are "limited data to support that alteration of therapy based on platelet function measurements actually improves outcomes."[4] Additionally, a recent multisociety Expert Consensus Document discussing the concomitant use of PPIs and thienopyridine drugs to reduce gastrointestinal complications further supports this argument.[5] Therefore, it is difficult to justify a marked increase in cost of the PPI selected (pantoprazole costs nearly seven times more per dose than omeprazole, according to one Web site[6]) for a benefit that is supported only by theoretical and observational data, not by outcome data.

As Dr. Keller also mentions, Aggrenox can be used for secondary stroke prophylaxis, but a discussion about a therapeutic exchange between clopidogrel and other antiplatelet agents was beyond the scope of my review. A recently published joint guideline of the American Heart Association and the American Stroke Association guideline should be consulted for further information.[7]

Other gastroprotective therapies are available. However, misoprostol (as mentioned) is associated with significant gastrointestinal side effects and must be taken four times a day. H2-receptor antagonists are not considered to be as effective as PPIs.[8,9]

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REFERENCES

1. **Madanick RD**. Proton pump inhibitor side effects and drug interactions: much ado about nothing? Cleve Clin J Med 2011; 78:39–49.
2. **US Food and Drug Administration**. FDA reminder to avoid concomitant use of Plavix (clopidogrel) and omeprazole. www.fda.gov/Drugs/DrugSafety/ucm231161.htm. Accessed March 23, 2011.
3. **Bhatt DL, Cryer BL, Contant CF, et al**. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med 2010; 363:1909–1917.
4. **Bonello L, Tantry US, Marcucci R, et al**. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol 2010; 56:919–33.
5. **Abraham NS, Hlatky MA, Antman EM, et al**. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. Am J Gastroenterol 2010; 105:2533–2549.
6. **HealthWarehouse**. www.healthwarehouse.com. Accessed March 23, 2011.
7. **Furie KL, Kasner SE, Adams RJ, et al**. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011; 42:227–276.
8. **Bhatt DL, Scheiman J, Abraham NS, et al**. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation task force on clinical expert consensus documents. Circulation 2008; 118:1894–1909.
9. **Lanza FL, Chan FK, Quigley EM, et al**. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol 2009; 104:728–738.

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