PPIs Seem Safe to Use With Antiplatelet Drugs

BY ROBERT FINN

A retrospective study involving 13,809 patients found no evidence that proton pump inhibitors interfere with the antiplatelet drugs clopidogrel and prasugrel in patients with acute cardiac syndrome. Existing guidelines, which endorse the content use of proton pump inhibitors with antiplatelet drugs in these patients, will therefore not need to be changed.

The results contrast with other recent studies suggesting that

Careful monitoring is necessary when patients with reduced response to thienopyridines take PPIs.

DR. KASTRATI

proton pump inhibitors (PPIs), especially omeprazole, might diminish the drugs' antiplatelet effects and clinical efficacy. The study, which was published online in the Lancet, was presented concurrently by Dr. Michelle L. O'Donoghue at the annual congress of the European Society of Cardiology in Barcelona.

Clopidogrel and prasugrel are in a class of drugs called thienopyridines. They are pro-drugs that are converted by the cytochrome P450 enzyme system into their active metabolites. It was thought that PPIs might interfere with this through their inhibition of a cytochrome P450 isozyme in the liver called 2C19. As a result of these concerns, and of earlier studies that seem to suggest problems, the Food and Drug Administration and the European Medicines Agency (EMEA) issued safety warnings discouraging the use of PPIs with clopidogrel unless absolutely necessary.

The new study involved a retrospective analysis of one large trial involving 13,608 patients and one small trial involving 201 patients. Both were randomized, controlled trials intended to compare clopidogrel with prasugrel in patients undergoing elective percutaneous coronary intervention. In both trials, the use of a PPI was at the discretion of the treating physician. At the time of randomization, 26% of patients in the smaller trial and 33% in the larger trial were taking PPIs.

The investigators, led by Dr. O'Donoghue of Brigham and Women's Hospital, Boston, adjusted their results for 28 potential confounders, including age; sex; ethnic origin; history of hypertension, hypercholesterolemia, heart failure, peptic ulcer disease, carotid or vertebral artery disease, or diabetes; previous MI; previous coronary artery bypass graft surgery (CABG); family history; and the use of a drug-eluting stent (Lancet 2009 [doi:10.1016/S0140-6736(09)61525-7]).

Although the investigators did find that PPIs were associated with a reduction in the antiplatelet effects of clopidogrel and prasugrel, this did not translate into any significant differences in clinical outcome. There were no significant differences in all cause death, cardiovascular death, MI, stent thrombosis, major or minor bleeding in thrombolysis-induced myocardial infarction, or net clinical outcome (a combination of death, MI, stroke, and major non-CABG bleeding).

In an accompanying editorial, the authors Dr. Dirk Sibbing and Dr. Adnan Kastrati of Technische Universität München (Munich) raised a number of questions. For example, they suggested that patient compliance with thienopyridines might be worse in real life than in the context of the clinical trials. Dr. Sibbing and Dr. Kastrati concluded that PPIs appear not to interact with clopidogrel or prasugrel in terms of clinical outcomes and that patients with a risk profile similar to that in the trials can be safely treated with a PPI (Lancet 2009 [doi:10.1016/S0140- 6736(09)61562-2]).

"However," they wrote, "caution is needed when prescribing PPIs for selected high-risk patients with an intrinsically reduced response to thienopyridines. … In all cases, careful monitoring of patients' compliance with a thienopyridine drugs is mandatory."

The original trials received grant funding from Eli Lilly & Co. and from Daiichi Sankyo. The investigators conducting the retrospective analysis stated that they received no external sources of funding.

Dr. Sibbing acknowledged receiving lecture fees from Dynabyte and fees for advisory board activities from Eli Lilly. Dr. Kastrati acknowledged receiving lecture fees from Bristol-Myers Squibb, Daiichi Sankyo, and Eli Lilly. ■

EXPERT OPINION

PPIs to Prevent NSAID-Induced GI Ulcers

BY JON O. EBBERT, M.D., AND ERIC G. TANGALOS, M.D.

The Problem

A 57-year-old man with a history of coronary artery disease and severe degenerative joint disease status post right shoulder rotator cuff tear repair, right total knee arthroscopy, left knee meniscal tear repair, and three spinal fusions presents to you for pain management issues. He is on long-term narcotics with oxycodone. He presented 3 months earlier to the emergency department (ED) with dysphagia and odynophagia. His hemoglobin level was normal, and he denied gastrointestinal bleeding. At the time of presentation, he was taking naproxen sodium (440 mg in the morning and 220 mg in the evening) for joint pain as he was trying to taper his narcotic regimen. Esophagogastroduodenoscopy (EGD) in the ED showed a normal-appearing esophagus with incidentally noticed gastric erosions. Esophageal biopsy revealed esophagitis. He was placed on omeprazole, instructed to discontinue the naproxen sodium, and dismissed. He improved over the next several months and became completely asymptomatic. He now presents with acute worsening of his shoulder pain and wishes to avoid increasing his dosage of narcotics because the drugs make him lethargic. He asks to go back on the naproxen for a short period of time. He remains on the omeprazole 20 mg per day and, given his recent history, you consider him to be at higher risk for GI complications. You are aware of data for the cytoprotective effects of misoprostol for NSAID-induced GI complications, but are not familiar with the data for proton pump inhibitors (PPIs) for primary prevention of GI complications from NSAIDs.

The Question

In patients requiring NSAID treatment who are at higher risk for GI complications, do PPIs prevent GI complications, compared with placebo?

The Search

You log on to PubMed (www.pubmed.gov) and find a relevant study. (See box at right.)

Our Critique

The major limitation of this study is the short duration of medication (6.5 days of therapy). However, the findings are consistent with earlier trials. The findings are useful and generalizable to patients seen in the primary care setting who are placed on short-term NSAIDs for acute complaints. Clinicians can recommend that these patients start an over-the-counter dose of omeprazole to prevent complications.

Clinical Decision

You discuss the information with the patient. You agree to restart the naproxen (220 mg once per day) and continue the PPI. He agrees to call you with any new symptoms, and to call you in 3 weeks with an update on his pain and gastrointestinal symptoms.

DR. EBBERT *and* DR. TANGALOS *are with the Mayo Clinic in Rochester, Minn. They have no conflict of interest to report.*

J.C. Desai, et al.

Primary prevention of adverse gastroduodenal effects from short-term use of non-steroidal anti-inflammatory drugs by omeprazole 20 mg in healthy subjects: A randomized, double-blind, placebo-controlled study.

Dig. Dis. Sci. 2008;53:2059-65.

► **Design:** Randomized, blinded, placebo-controlled clinical trial.

► **Setting:** Single academically affiliated, urban gastroenterology practice.

► **Subjects:** Potential subjects were eligible for inclusion if they were 50-75 years of age.

Subjects were excluded if they had: 1) use of any NSAID (including aspirin) within past 2 weeks or history of chronic NSAID use; 2) use of antacids, histamine$_2$ blocker within past 2 weeks, or PPI within past 30 days; 3) use of any corticosteroid within the past 60 days; 4) history of bleeding tendencies or warfarin use within the past 60 days; 5) history of previous bleeding ulcer; 6) consumption of three or more alcoholic beverages a day; 7) hypersensitivity or allergy to NSAIDs or omeprazole, or other contraindications to their use; 8) baseline abdominal pain, nausea, and/or cramping; or 9) the presence of one or more gastroduodenal mucosal breaks (erosions or ulcerations) at baseline endoscopy.

► **Intervention:** Eligible subjects were randomly assigned to 6.5 days of naproxen (NPX) 500 mg twice per day plus omeprazole (OMP) 20 mg daily; or NPX 500 mg twice per day plus placebo.

EGD was performed at baseline with biopsies for *Helicobacter pylori*. Study medication was started 7 days later to allow mucosa healing.

► **Outcomes:** The primary end point was the presence of any gastroduodenal ulceration on repeat EGD 14 days after randomization (and 7 days after EGD).

Secondary end points included erosions and NSAID-related GI symptoms. GI symptoms were assessed using the Severity of Dyspepsia Assessment consisting of three subscales: pain intensity, nonpain symptoms, and satisfaction with dyspepsia-related health.

► **Results:** In all, 70 patients were randomized (average age, 56 years). OMP was associated with fewer gastroduodenal ulcerations (NPX + OMP 11.8% vs. NPX + placebo 46.9%; relative risk, 0.25; $P = .002$).

OMP was also associated with fewer gastroduodenal ulcerations and/or a decreased risk of more than five erosions (38.2% vs. 81.3%; RR = 0.47; $P = .001$).

The NPX + placebo group was more likely to report increases in nonpain symptoms ($P = .01$).